Patient-Reported Outcomes in Cancer Clinical Trials: Measuring Symptomatic Adverse Events With the National Cancer Institute's Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE)

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OVERVIEW

Systematic capture of the patient perspective can inform the development of new cancer therapies. Patient-reported outcomes (PROs) are commonly included in cancer clinical trials; however, there is heterogeneity in the constructs, measures, and analytic approaches that have been used making these endpoints challenging to interpret. There is renewed effort to identify rigorous methods to obtain high-quality and informative PRO data from cancer clinical trials. In this setting, PROs are used to address specific research objectives, and an important objective that spans the product development life cycle is the assessment of safety and tolerability. The U.S. Food and Drug Administration's (FDA) Office of Hematology and Oncology Products (OHOP) has identified symptomatic adverse events (AEs) as a central PRO concept, and a systematic assessment of patient-reported symptomatic AEs can provide data to complement clinician reporting. The National Cancer Institute's Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) is being evaluated by multiple stakeholders, including the FDA, and is considered a promising tool to provide a standard yet flexible method to assess symptomatic AEs from the patient perspective. In this article, we briefly review the FDA OHOP's perspective on PROs in cancer trials submitted to the FDA and focus on the assessment of symptomatic AEs using PRO-CTCAE. We conclude by discussing further work that must be done to broaden the use of PRO-CTCAE as a method to provide patient-centered data that can complement existing safety and tolerability assessments across cancer clinical trials.

The intent of this educational manuscript is to discuss the importance of PRO assessments in cancer trials, identify strengths and limitations of currently used PRO strategies, and focus on the potential utility of a rigorous and systematic assessment of symptomatic AEs as a component of a broader PRO strategy.

As part of this effort, we have been fortunate to have a patient advocate included to introduce the manuscript by providing her personal perspective on the inclusion of PROs in cancer trials. Diana Chingos is a 20-year survivor of early onset breast cancer whose advocacy work extends to membership on the National Cancer Institute's (NCI) Investigational Drugs Steering Committee and the National Clinical Trials Network's Core Correlative Sciences Committee, as well as participation on a data and safety monitoring board for the California Cancer Consortium (a phase I/II clinical trials group) and an institutional review board. Her experience as a patient and caregiver coupled with extensive work as an advisor to cancer studies brings a unique combination of patient focus and understanding of the complexities of clinical trial design and conduct.

THE PATIENT PERSPECTIVE ON PATIENT-REPORTED OUTCOMES IN CANCER TRIALS

Patients, and human beings more generally, are accustomed to providing our views in many aspects of our lives. Until recently, the act of seeking out feedback from those who use the health care system was rare. One can argue that the health care user experience should reign supreme over all other contexts, when the quality and quantity of our lives is at stake, sometimes at great financial and logistical expense.

Gratefully, at least from this patient's view, PRO questionnaires have been developed to bring our perspective

into the research setting more systematically. In my opinion, soliciting patient reports espouses equity and autonomy, enabling patients to speak for themselves, without the filter of health care providers. Capturing a patient's self-report using well-validated measures offers a direct indicator of change in symptoms, function, or well-being during treatment, providing additional information to supplement the clinician's evaluation of tumor response and toxicity.

Many patients with cancer are willing to play their part in research through answering questionnaires. Unless patients are very ill and/or have cognitive deficits, many patients with cancer like the opportunity to contribute to research, especially meaningful research that can improve care for patients in the future. It can be difficult for some patients to assess the value of specific research studies, but everyone understands treatment toxicity and side effects. You live it and usually have something to say about it.

From the informed patient's perspective, the patient's voice has been a key missing element in the current system of drug safety assessment. Assessing patient-reported symptomatic AEs can fill this need. Published studies have demonstrated discordance between physician and patient reports, with underreporting of patients' symptoms and their severity being common.[1,2] Something is getting lost in the translation. PRO measures provide an opportunity for the patient to directly report side effects and their intensity from the perspective of the person experiencing it. The PRO-CTCAE has generated considerable interest in the broader stakeholder community as a PRO tool that could be used across the therapeutic development process to address important questions related to the tolerability profile of a specific therapy.

I welcome the ability to report the side effects I have experienced, and I encourage others to do so. However, it is important to mention that although most patients want to describe their experiences, it can become tedious, depending on the time required. Survey fatigue is real and is magnified by medication-related fatigue, cancer-related fatigue, and the unfortunate synergy of physical, emotional, psychologic, and environmental strains involved with being a patient with cancer undergoing therapy. Given this, it is important to consider the length of the survey, the relevance of the questions, and the time points for assessment, while trying to reduce the redundancy of questions.

Some patients need encouragement and validation to participate in this process, that their voice is valued and integral to the clinical trial. Patient engagement helps the system—it does not hinder it. Empowering patients to articulate their experiences can provide value to those who develop cancer therapies by more accurately characterizing a drug's effect on the patient and also may enhance research participation, a necessity if we are to speed up the rate of knowledge generation.

Past Efforts at Collecting Patient-Reported Outcomes in Cancer Trials

To date, the most common PRO strategy for oncology has been to assess the broad multidomain concept of health-related quality of life (HRQOL), utilizing instruments largely developed in a different therapeutic era.[3–5] These existing HRQOL measures have strengths, including translations across multiple languages and a familiarity with their use among the cancer therapeutic development community. Many instruments have also been expanded to include disease-specific modules in an effort to better capture disease- and treatment-related symptoms.[6,7] Substantial data have been accumulated using many of these measures, and some offer the advantage of well-established cut scores, minimally important difference thresholds, and normative values that can aid in interpretation.

However, although the PRO measures commonly used in oncology trials to date address a broad range of important and common symptoms and functional domains, they typically include the same questions irrespective of disease stage or the therapy under study. This can lead to questions that may be less relevant to the trial context and/or miss the assessment of important symptoms (e.g., toxicities not currently included in existing static instruments). This limitation is becoming more evident in the current drug development era of molecularly targeted agents with wide-ranging side effect profiles. Investigators could benefit from a more flexible toolbox of PRO measures that can adapt to differing disease and treatment contexts.

From the FDA OHOP perspective, all PRO data will be taken into consideration as part of the overall data package to inform the benefits and risks of a therapy under review. However, not all data reviewed in an application can be included in the FDA drug label. The FDA is tasked with

providing information in the product label that is useful to prescribers in treating their patients and must ensure that the information is easily interpreted, unbiased, and not misleading. Broad concepts such as HRQOL are more challenging to define, with some domains such as social well-being farther removed from a therapy's direct effect on the patient. Submitted HRQOL data can be further complicated by trial design limitations, missing data, and lack of pre-specified analyses. For this reason, PRO data have rarely been included in FDA labeling of cancer therapies. When PRO data have been included in the FDA product label for cancer products, it has predominantly relied on well-defined measures of specific symptoms or functional measures that relate directly to the disease under study.[8]

There continues to be wide variability in the type and quality of PRO data acquired from cancer trials. This lack of standardization includes heterogeneity in the PRO instruments used, as well as the assessment frequencies, and the approach to data analysis and reporting. High levels of missing data have also been a common challenge that can adversely affect the interpretability of PRO findings. Many stakeholders, including the FDA OHOP, have actively engaged the oncology drug development community to evaluate existing instruments and identify emerging opportunities to improve the PRO strategy in cancer trials to provide more rigorous patient-centered data to all those who weigh the risks and benefits of cancer therapies.[9]

FOCUSING ANALYSES ON CORE PATIENT-REPORTED OUTCOME CONCEPTS INCLUDING SYMPTOMATIC ADVERSE EVENTS

In most late-phase randomized clinical trials, concepts such as HRQOL and social, emotional, and cognitive domains are expected by many stakeholders to provide a reasonably comprehensive picture of the patients' experience of their disease and treatment. These data will be reviewed by FDA's OHOP as important supportive data. However, in an effort to increase the amount of patient-centered data in FDA labeling, OHOP has recently proposed that our key PRO analyses focus on three core symptom and functional concepts (Fig. 1).[10] Symptomatic AEs, physical function, and disease-related symptoms are considered by OHOP to be more well-defined and closer to the effect of a therapy on the patient and their disease. The careful collection and analysis of these core concepts can provide PRO data that may be more consistent with FDA requirements for labeling.

It should be acknowledged that cancer trials are designed for differing purposes along the therapeutic development continuum from first in-human exploration of dose and safety, to exploratory therapeutic trials, to trials designed to demonstrate substantial evidence of safety, tolerability, and efficacy to support a regulatory submission. Whereas a comprehensive PRO strategy may be expected to address the needs of multiple stakeholders in the later phases of therapeutic development, a focused

PRO strategy may be more appropriate and efficient in early clinical development. This is an important distinction, as the classic phases of drug development are blurring, and precision medicine trials may have multiple study arms designed to simultaneously gauge antitumor activity[11] with some single-arm cohorts potentially demonstrating notable antitumor activity suitable for accelerated approval.[12] Safety is an important trial objective in all phases of therapeutic product development. Inclusion of a PRO measure of symptomatic AEs can improve our understanding of safety, tolerability, and dose selection and thus is applicable to a broad range of clinical trial contexts.

THE USE OF PATIENT-REPORTED OUTCOMES TO INFORM TREATMENT TOLERABILITY

Safety assessment in cancer clinical trials has been standardized through the use of the CTCAE.[13] Currently, in version 4, the CTCAE provides a widely accepted lexicon and associated criteria for grading AEs of cancer treatment. CTCAE is routinely updated and used in conjunction with the Medical Dictionary for Regulatory Activities by regulatory agencies. Using CTCAE, AEs are graded on a scale from grade 1 to 5, in which, by convention, grade 5 is death, and grade 4 reflects toxicities that are life-threatening and warrant urgent intervention. Grades 1–3 represent progressive worsening in severity or frequency of the toxicity, interference with self-care and the performance of daily activities, and the need for clinical intervention. Although this method of safety reporting provides for standardization and efficiency in data collection and analysis, the assessment of AEs using CTCAE is elicited by health care providers, including symptomatic AEs such as nausea or sensory neuropathy. It has been stated by the FDA and others that the patient is best positioned to report his or her own symptoms.[14] Thus, the systematic assessment of symptomatic AEs using a PRO provides additional information that is complementary to existing safety assessments reported by clinicians using the CTCAE.

The assessment of symptomatic AEs may be of increasing importance as we enter into a new therapeutic era in malignant hematology and oncology. An expanding number of mechanistic drug classifications have produced a more diverse range of potential toxicities.[15] Many of the molecularly targeted agents are administered orally, often require prolonged treatment duration, and may produce less severe but more chronically bothersome side effects.[16] A systematic longitudinal assessment of relevant symptomatic AEs using a PRO measure may provide informative patient-centered data on symptomatic side effects that may otherwise have been considered low grade by standard clinician report.[17]

Existing HRQOL measures and their disease modules evaluate a more limited range of side effects, many of which were selected based on therapies that were used at the time they were developed (e.g., cytotoxic chemotherapies). Given the different therapeutic landscape

FIGURE 1. U.S. Food and Drug Administration Core Concepts for Patient-Reported Outcomes Analysis in Cancer Trials
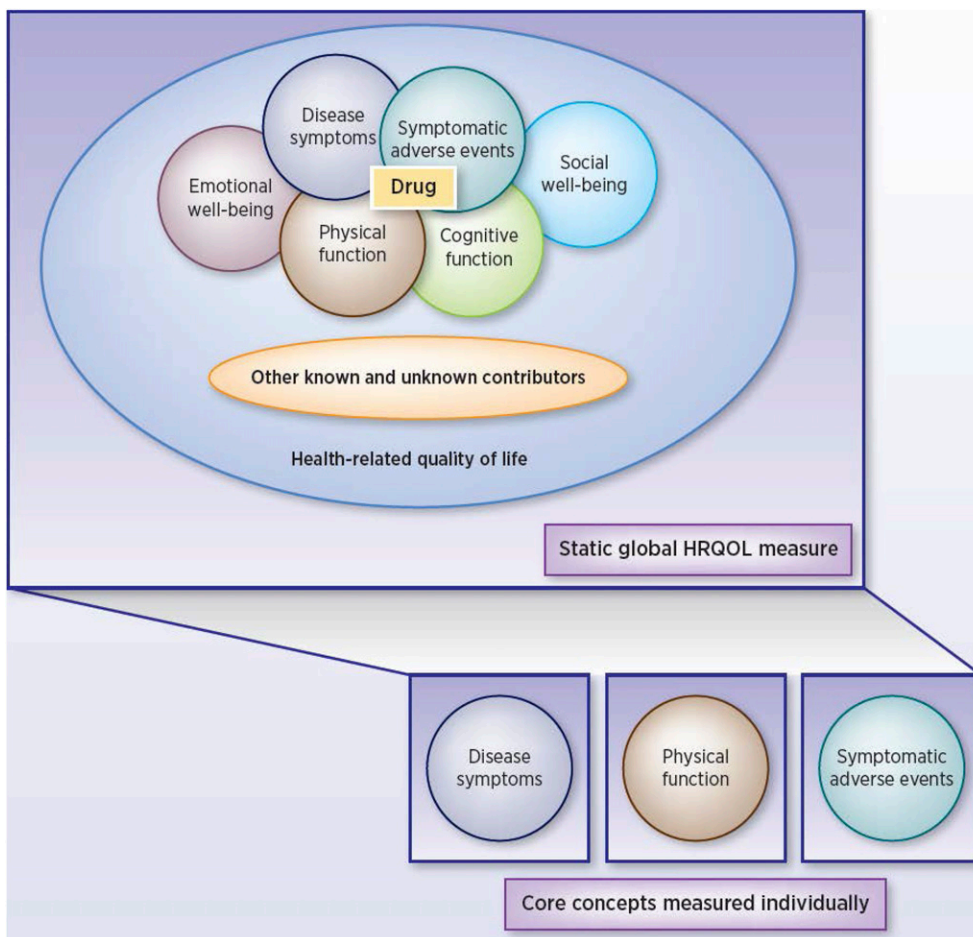
In an effort to increase the amount of informative patient-centered data in product labeling, FDA OHOP focuses its PRO analyses on the core concepts of symptomatic AEs, physical function, and disease-related symptoms. Although these well-defined concepts are more in line with the regulatory framework of the FDA for labeling considerations, all submitted PRO data will be taken into consideration as important supportive data. The three core concepts are not the only PRO measures to assess in a trial to support drug approval, as broader domains and HRQOL remain important exploratory measures. Reprinted from Kluetz et al.[10]
Abbreviations: OHOP, Office of Hematology and Oncology Products; PRO, patient-reported outlets; AEs, adverse events; HRQOL, health-related quality of life.

today, this can lead to measurement of irrelevant symptoms not considered part of the toxicity profile of the newer drug and/or potentially miss the assessment of important unique side effects of contemporary therapies. Furthermore, the limited assessment frequency used to date in many PRO corollary studies may not be optimal to adequately gauge tolerability.

Contemporary drug development requires a more flexible PRO approach to ensure an unbiased assessment of the most important symptomatic treatment side effects based on the anticipated toxicity profile of the therapies under study. Selection of symptomatic AEs from a large library of options would therefore be desirable. Recently, the NCI has developed and tested a measurement system to capture symptomatic toxicities directly from patients.[18] Comprised of both a library of 124 questions reflecting 78 symptomatic toxicities drawn from the CTCAE and an electronic system for survey administration, reminders, central monitoring, and alerts, NCI PRO-CTCAE is designed

to provide a standard yet flexible tool to assess symptomatic AEs.

Development of the NCI PRO-CTCAE Measurement System

The PRO-CTCAE measurement system has been developed by NCI as a companion to the CTCAE. It was designed to improve the validity, reliability, and precision with which symptomatic adverse effects of treatment are evaluated in patients on cancer clinical trials. PRO-CTCAE was developed by a multidisciplinary team of trialists, methodologists, clinicians, informatics experts, patients, and regulators[18] and has been tested and refined in a consortium of academic and community-based cancer-treatment sites and in the NCI-sponsored clinical trials network (NCI contracts HHSN261200800043C and HHSN261200800063C) and by more than 120 early adopters in 10 countries. The PRO-CTCAE item library consists of 124 discrete items representing 78

symptomatic AEs that are common in oncology clinical trials and included in the CTCAE. PRO-CTCAE items were created with substantial input from patients, clinicians, and PRO methodologists and underwent refinement through cognitive interviews with patients to establish content validity.[19] Subsequently, the quantitative measurement properties, including validity, reliability, and responsiveness, were evaluated in a large and diverse sample of patients receiving cancer treatment in six sites around the United States.[20]

Each of the 78 symptom terms included in the PRO-CTCAE item library is assessed relative to one or more distinct attributes, including presence/absence, frequency, severity, and/or interference with usual or daily activities.[18] Responses are provided on a five-point Likert scale. The generic PRO-CTCAE item structures for the frequency, severity, and interference attributes are listed below:

- Frequency item: How **OFTEN** did you have _____ ? (Never / Rarely / Occasionally / Frequently / Almost constantly)
- Severity item: What was the **SEVERITY** of your _____ at its WORST? (None / Mild / Moderate / Severe / Very severe)
- Interference item: How much did _____ **INTERFERE** with your usual or daily activities? (Not at all / A little bit / Somewhat / Quite a bit / Very much)

The standard PRO-CTCAE recall period is the past 7 days. A recent study suggests that longer recall periods (2-, 3-, or 4-week recall) are associated with small but successively increasing measurement error, which must be considered if recall periods longer than 1 week are used in a trial for logistical reasons (TR Mendoza, AV Bennett, SA Mitchell et al, unpublished data, March 2016). Administration of PRO-CTCAE via different modes including web, interactive voice response, and paper offers flexibility for patients and study operations personnel, and there is psychometric evidence to justify comparison of results and pooled analyses across studies that use different PRO-CTCAE modes of administration.[21] A pediatric version of PRO-CTCAE is also currently in development.[22] For more information about PRO-CTCAE, visit http://healthcaredelivery.cancer.gov/pro-ctcae.

Early Adoption of PRO-CTCAE and Lessons Learned

The PRO-CTCAE has been implemented in multiple cancer clinical trials. Patients are generally willing and able to self-report this information weekly via the web or automated telephone systems though electronic reminders; central monitoring and personnel for backup data collection were also needed to optimize response rates. Clinicians note finding this information to be meaningful and valuable for clinical decision-making and AE reporting.[23]

Selecting which symptomatic AEs to assess and determining the time points for measurement are critical trial-design decisions. In trials developed to date, items from the PRO-CTCAE and time points of measurement have generally been specified using an approach similar to that used to define the AE surveillance plan for the trial more broadly. That is, the study team reviews published data, as well as data from earlier phase trials or animal models, if available, and incorporates information about the known or anticipated on- and off-target effects of agents in a similar mechanistic class to identify those symptomatic AEs likely to be associated with the regimens in the trial.[24] PRO-CTCAE items corresponding to these symptomatic AEs are loaded into a software platform. Patients are trained to use the software and are asked to self-report either from home on a regular basis or at clinic visits. After establishing a pretreatment baseline, more frequent PRO-CTCAE administration is generally warranted during the first few cycles of therapy (e.g., weekly reporting during the initial several months of therapy). Thereafter, the assessment intervals may be extended (e.g., monthly or quarterly, depending on the regimen under study), particularly in trial contexts in which the duration of investigational treatment is prolonged. However, the time points of measurement should reflect the anticipated pattern of toxicity and scientific objectives of the trial.

Moving forward, several challenges and knowledge gaps must be addressed. Although multiple translations are in progress (for example, Italian, Korean, Chinese, and Swedish), and linguistically validated language versions are available in Spanish, German, Japanese, and Danish,[25-27] translation and linguistic validation of the PRO-CTCAE item library in other languages is needed. Second, as is the case for the collection of PRO data in any trial, there are personnel and infrastructure requirements. Investments will be required to develop and refine strategies that achieve efficient PRO data collection and ensure data completeness (e.g., central monitoring and backup data collection). Potential concerns about workload for clinical research staff will also need to be addressed, and analyses are in progress that will yield specific estimates of the resource requirements associated with collecting and analyzing PRO-CTCAE data in NCI-sponsored clinical trials. Third, there is limited experience with respect to how to optimally analyze and interpret patient-reported symptomatic AE data. Efforts are underway to determine how PRO-CTCAE scores should be interpreted to assign a corresponding CTCAE grade. Additional work will be required to identify the most informative ways to display symptomatic toxicity scores descriptively alongside CTCAE grades in both published reports as well as potential product labels.

Notably, FDA OHOP is committed to working with the NCI as well as commercial sponsors early in programs to identify opportunities to include PRO-CTCAE in clinical trials. Data generated using PRO-CTCAE offer complementary descriptive patient-reported information about symptomatic side effects that may further inform patients and providers. There is also interest in using PRO-CTCAE as a component to support comparative tolerability trial designs. More work must be done to explore this

opportunity, including identifying an appropriate approach to capture the overall side effect burden of treatment. In addition, FDA OHOP, in collaboration with Clinical Outcome Assessment staff and the Office of Biostatistics, has initiated several internal working groups to explore different analysis and data presentation methods.

There is a reasonable concern that stacking new instruments on top of existing lengthy HRQOL and disease modules as well as utility measures could lead to duplication and pose additional respondent burden. FDA OHOP is fostering international collaboration to review existing HRQOL instruments and their disease modules to identify a collection of new and existing or modified existing instruments to meet the needs of all those who will use these data to make treatment, regulatory, and health policy decisions. The goal remains to identify approaches that increase the relevance and interpretability of PRO data while minimizing the burden to patients to ensure that the patient can be queried at an assessment frequency that provides the best picture of the patient experience while on therapy.

There has been a call to improve the quality of PRO data captured from cancer clinical trials and integrate more of these data in the FDA product label.[28] To realize this goal, more attention must be paid to PRO measures in both trial design and conduct to improve overall data quality, regardless of the symptoms or domains being measured. The assessment of symptomatic AEs using a rigorously developed item library such as the PRO-CTCAE can increase the likelihood of inclusion of descriptive patient-centered data

in product labels, complementing the standard safety assessment of a therapy.

CONCLUSION

Patients and their clinicians would benefit from improved data about the effects of anticancer therapy on how an individual feels and functions. Traditional PRO strategies are being revisited as patient-focused drug development has generated multistakeholder interest to optimize the collection and interpretation of PRO data to satisfy the needs of the many end users of this information. As a key component of a broader PRO strategy, the systematic longitudinal assessment of patient-reported symptomatic AEs can provide additional complementary tolerability data to inform dose selection and the overall benefit: risk assessment of a cancer therapy. The PRO-CTCAE has been developed as a standardized measurement system that can provide a flexible fit-for-purpose approach to assess relevant symptomatic AEs across a broad range of cancer therapies. It is anticipated that the NCI PRO-CTCAE item library will continue to be iteratively refined as novel symptomatic toxicities are identified and a deeper understanding of its measurement properties emerges. There is vigorous and ongoing international collaboration among trialists, methodologists, regulators, and patients to address these and other challenges in study design, implementation, and interpretation to evolve a standard method to obtain well-defined, descriptive patient-centered data on the safety and tolerability of cancer therapies.

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