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Use of PRO Measures to Inform Tolerability in Oncology Trials: Implications for Clinical Review, IND Safety Reporting, and Clinical Site Inspections

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Abstract

Cancer therapeutics frequently lead to symptomatic adverse events (AE) that can affect treatment tolerability. The NCI has developed the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) to assess symptomatic AEs by direct patient self-report. Although longitudinal assessment of patient-reported symptomatic AEs holds promise to better inform treatment tolerability, using patient-reported outcome (PRO) measures to assess symptomatic AEs has raised several regulatory and good clinical practice issues among those who conduct cancer clinical trials. These include concerns regarding trial monitoring, clinical review of PRO results by investigators and delegated clinical staff, whether PRO data on symptomatic AEs require investigational new drug (IND) safety reporting, and how the trial conduct and resultant PRO data will be assessed during clinical investigator site inspections. This article addresses current thinking regarding these issues in cancer clinical trials from the FDA, the NCI, and the Office for Human Research Protections. PRO measures, such as PRO-CTCAE, that assess symptomatic AEs in cancer trials are considered similar to other PRO assessments of symptoms, function, and health-related quality of life and can generate complementary data that may inform tolerability. Clarity on operational concerns related to incorporating PRO measures to inform tolerability is critical to continue the advancement of rigorous PRO assessment in cancer clinical trials. *Clin Cancer Res; 24(8); 1780–4. ©2017 AACR.*

See related commentary by Nipp and Temel, p. 1777

Introduction

Integrating the patient voice in cancer drug development is of increasing interest to the FDA and others who make decisions regarding the risks and benefits of a cancer treatment. The FDA has embarked on multiple patient-focused drug development (PFDD) initiatives, and the newly formed FDA Oncology Center of Excellence has identified PFDD as one of its initial programs (1). One important aspect of PFDD is the use of patient-reported outcome (PRO) data to inform the scientific regulatory review of cancer therapeutics. PRO measures can provide a better understanding of treatment outcomes from the patient's perspective. FDA Guidance for Industry has advised using a PRO measure when the concept of interest is best known by the patient [e.g., a nonobservable symptom such as a symptomatic adverse event (AE); ref. 2].

Although a variety of study objectives can be addressed by PRO measures in cancer clinical trials, the FDA Office of Hematology and Oncology Products has identified symptomatic AEs, disease symptoms, and physical function as three core concepts of interest to focus its PRO analyses for potential product labeling (3). A particularly promising use of PRO measures is the assessment of symptomatic AEs to inform the tolerability of a cancer therapeutic.

Historically, the most commonly used PRO measures in cancer trials have been multidimensional self-reported questionnaires intended to assess health-related quality of life (HRQL) and accompanying disease modules that assess common disease symptoms and toxicities for different cancer types. These tools often include a standard selection of the most commonly encountered symptomatic AEs of cancer treatments (e.g., fatigue, nausea, vomiting, and diarrhea) and pain. In recent years, the diversity of novel drug classes has led to a wide variety of toxicities, making a "one-size-fits-all" approach to the use of static HRQL instruments problematic.

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One way to address increasing heterogeneity in the toxicity profile of cancer therapies is to select a panel of symptomatic AEs relevant to a particular trial context from a library of well-defined symptom questions. Although several symptom libraries exist, the NCI has developed a measurement system called the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) that is specifically designed to capture symptomatic AEs by patient self-report as a companion to standard clinical CTCAE assessment (4, 5). Given the importance of AEs in the assessment of a cancer therapy's benefits and risks, the FDA has identified PRO-CTCAE as a promising tool and has worked with the NCI and others to explore its use (6).

Although many PRO measures used in cancer trials capture some aspects of drug toxicity, PRO-CTCAE was specifically developed to assess symptomatic AEs by direct patient report. The typical PRO strategy in cancer trials involves the collection of PRO data with monitoring for data compliance (completion of questionnaires) conducted during the trial to minimize missing data. An aggregate review of PRO results is then performed at study completion. The collection of symptomatic AEs using PRO-CTCAE has led those designing and conducting clinical trials to ask for clarity on how inclusion of PRO measures of symptomatic AEs might affect the way in which PRO data are reviewed and reported in cancer trials. Is it necessary for clinical investigators or their designated staff to review patient responses to PRO questions during trial conduct to ensure patient safety? How will PRO results regarding symptomatic AEs affect FDA safety reporting? How will the FDA look at discrepancies between standard CTCAE safety reporting and PRO measures of the same or similar symptomatic AEs during clinical investigator site inspections?

In this article, we bring together representatives from relevant FDA offices, the NCI, and the Office for Human Research Protections to provide our current perspective on these issues. Although not regulatory guidance, we hope to clarify current thinking to facilitate the continued exploration of the use of PRO measures to assist us in assessing the safety, efficacy, and tolerability of cancer therapies.

Although PRO measurement is incorporated into clinical trials across many therapeutic areas, the scope of this article is limited to cancer clinical trials. Different approaches to clinical monitoring of PRO data may be warranted in other therapeutic areas, or where clinical review and interpretation of PRO results during trial conduct are needed to meet the specific objectives of a study. In all cases, patient safety must be monitored by clinical investigators and their delegated clinical staff. In addition, all patients must be clearly informed and reminded regularly if, when, and how the results of their PRO assessments are being shared with their treatment team.

Clinical Review of PRO Data during the Conduct of Oncology Clinical Trials

Although PRO data are collected prospectively in cancer trials, they are typically analyzed in aggregate at trial completion, examining trends over the treatment course and comparing effects between the different treatment arms. In most trials, investigators or their delegated clinical staff do not review patient-level PRO responses to HRQL, functional, and symptom measures, even if a patient reports severe symptoms or functional decline on his or her PRO questionnaire. Rather, patients participating in cancer clinical trials are evaluated at regular intervals by clinical staff and are expected to communicate with their health care team any concerning signs or symptoms as they normally would irrespective of the completion of PRO assessments.

Although the issues described in this article apply to all modes of PRO collection (paper, Web-based, interactive voice response systems, etc.), there is increased interest in employing electronic PRO (ePRO) assessment in clinical trials. Advantages of ePRO data capture over the traditional paper mode of administration include the ability to collect data between clinical visits and the immediacy and potential availability of the information. As such, there is growing interest in using ePRO assessments to assist in the communication and management of symptoms in the clinical care setting (7, 8). Although sponsors may consider incorporating PRO results into the clinical care of their trial patients (regardless of the mode of collection), investigator use of PROs to monitor and facilitate clinical decision-making is not standard or required in cancer trials. Unless the communication of PRO results to clinical investigators is specified in the study protocol, there is no regulatory requirement for the clinical review of PRO data or implementation of alerts for severe symptoms in the cancer clinical trial setting, even when PROs are being collected to inform tolerability, as is the case with PRO-CTCAE.

Although there is no standard method for ongoing clinical review of PRO results during trial conduct, several options can be considered. For instance, Kyte and colleagues described four strategies ranging from blinding all research personnel to PRO data during trial conduct to active PRO monitoring in real time with alerts for severe symptoms (9). The degree to which PRO data are clinically reviewed during trial conduct is the purview of the sponsor and the institutional review board (IRB). Whether or how PRO data are reviewed during the trial should be clearly defined by the protocol and monitoring plan and be dependent on the context of the clinical trial, including study population and investigational therapy. Regardless, whether PRO measures are employed, the Common Rule and FDA regulations require that, when appropriate, a clinical safety plan should be in place to ensure that the study protocol makes adequate provision for monitoring the data collected to ensure the safety of subjects (10). FDA regulations require sponsors to ensure that the FDA and all participating investigators are promptly informed of potential serious risks from clinical trials or any other source (10–13). In oncology clinical trials, monitoring and investigator reporting of AEs to sponsors has long been satisfied by investigator assessment and reporting of AEs, including symptomatic AEs, as assessed and graded by clinicians using standard clinician-reported CTCAE.

Where PRO assessments are employed, clinical trial participants should be fully informed regarding if and how PRO information will be shared with their clinical care team (site investigator and delegated clinical staff) during a trial. Details as to how PROs are reviewed and acted upon should be outlined in the protocol and clearly described to study participants as part of the informed consent process prior to enrollment. In addition, if PRO information will not be shared with the clinical care team, it is important to remind patients regularly to call their health care provider for any concerning signs or symptoms, and that their responses to PRO measures are not being shared with members of their health care team. Considerations regarding the monitoring of PRO completion rates and the degree of clinical review that should be employed for PRO measures of symptomatic AEs are summarized in Table 1.

Table 1. Current thinking on trial monitoring and clinical review of PRO symptomatic AE responses during the conduct of oncology clinical trials

Topics of concern	Current thinking
What degree of trial monitoring should be employed to ensure completion of PRO measures?	
Ongoing review of compliance with PRO measure completion	• Completion rate should be reviewed by the sponsor regularly throughout clinical trial conduct, with prospective procedures put in place to minimize missing data. • Reasons for missing PRO data should be captured to the extent possible.
What level of clinical review should be employed during trial conduct for PRO measures of symptomatic AEs in cancer clinical trials?	
Clinical review of individual patient-level PRO data by clinical investigators and delegated clinical staff during trial conduct	• The degree of real-time clinical review of individual patient-level PRO data by clinical investigators during trial conduct is the decision of the sponsor (as defined by the protocol and monitoring plan), IRB, and the data and safety monitoring board (DSMB). • The degree of clinical review is informed by the clinical trial context (e.g., regimen and patient population). • A rationale should be provided in the monitoring plan for the degree of clinical review of PRO data employed to ensure patient safety for the trial context. • The informed consent document should clearly state if and when PRO data will be shared with clinical investigators during the clinical trial. • If PRO data are not shared with clinical investigators in real time, patients should be reminded of this as they complete each PRO assessment and instructed to contact their treating clinician for any concerning sign or symptom. • Although not currently standard practice, use of PRO measures to inform clinical evaluation for symptom management is a promising area of active investigation.

Implications for Investigational New Drug Safety Reporting

The FDA relies, in part, on investigational new drug (IND) safety reporting to assess and monitor the risks of a therapeutic intervention in a clinical trial. Accurate reporting of AEs to the FDA, clinical sites, and IRBs is vital to the safe conduct of cancer clinical trials. Guidance has been written to help sponsors and investigators comply with the IND safety reporting requirements (12). For example, sponsors are required to submit IND safety reports of serious and unexpected suspected adverse reactions to the FDA and all participating investigators as soon as possible but no later than 15 calendar days after the sponsor determines that the information qualifies for reporting. The sponsor also must notify the FDA of unexpected fatal or life-threatening suspected adverse reactions as soon as possible but no later than 7 calendar days following the sponsor's initial receipt of the information (13). Sponsors should have a systematic approach for safety surveillance to assess a drug product's risks during development. The U.S. Department of Health and Human Services (HHS) regulations for the protection of human subjects and FDA regulations also require that any unanticipated problems involving risks to subjects or others be reported to the IRB, FDA, and Office for Human Research Protections (OHRP), among other entities (14–17). The HHS human subject protection regulations may not apply to all trials, and details regarding which studies are subject to those regulations are outside the scope of this article.

Investigators are required to immediately report to the sponsor any serious AE and must include an assessment of whether there is a reasonable possibility that the drug caused the event (18). In oncology trials, clinical investigators or their delegated clinical staff review events as they unfold and use clinical judgment to attribute the likelihood that the AE is attributable to the investigational agent. The events are coded into AE terms and assigned a grade using the clinician-reported CTCAE, which has provided a standardized approach to AE reporting and safety labeling in the United States (19). Thus, the investigator's determination of severity and causality are important for the sponsor to consider when determining whether the safety information meets the IND safety reporting criteria.

In contrast to clinician-reported CTCAE safety data, patient-reported symptom results from the PRO-CTCAE are generated by patients without interpretation by clinicians or other health care providers. Thus, it is anticipated that there will be a difference between a PRO-CTCAE *score* for diarrhea and the CTCAE grade of diarrhea reported by an investigator after clinical assessment and interpretation. Although questions assessing symptoms in the PRO-CTCAE library were phrased to correspond to specific CTCAE terms, they are similar to other PRO measures that have been incorporated into cancer trials for decades. Clinicians use medical judgment to assign a single CTCAE grade to a symptomatic AE. In contrast, patient responses to PRO-CTCAE items are scored on a 0 to 4 scale with respect to one or more attributes (frequency, severity, and/or interference) for a particular PRO-CTCAE item. Although PRO-CTCAE and other PRO measures may assist in the overall understanding of a therapy's safety and tolerability, PRO data without clinical interpretation are not considered safety data, and there is no expectation that PRO data be reported to the FDA directly as safety data in cancer trials. Even in situations where there is a plan in place to clinically review PRO data during trial conduct, the PRO data would be used to trigger a clinical assessment. It is the clinical assessment of CTCAE grade and attribution (not the PRO data itself) that would form the safety data considered for IND safety reporting (Table 2).

Expectations during Clinical Investigator Site Inspections

The NCI PRO-CTCAE measurement system is increasingly being incorporated in oncology clinical trials that use standard clinical monitoring with routine clinical visits and clinician-

Table 2. Current thinking on IND safety reporting of PRO symptomatic AE results in oncology clinical trials

Topic of concern	Current thinking
Do PRO measures of symptomatic AEs in cancer clinical trials require IND safety reporting?	• For FDA purposes, IND safety reporting is currently based on clinical evaluation and standard clinician-reported outcome (ClinRo) CTCAE data. • There is no U.S. regulatory requirement that PRO data be directly reported as safety events to the FDA.

Table 3. Current thinking on clinical investigator site inspections and the potential for discrepant PRO and clinician-reported outcome symptom results

Issue	Current thinking
Would discrepancies between patient (e.g., PRO-CTCAE) and clinical investigator/clinician (CTCAE) results for a particular symptomatic AE affect FDA clinical investigator site inspection findings?	• PRO (e.g., PRO-CTCAE) data are complementary to clinical investigator/clinician CTCAE data but are expected to differ and may not correlate. • PRO symptomatic AE results should not inform gaps or errors in CTCAE reporting during clinical investigator site inspection.

generated CTCAE safety reporting. Results can therefore be generated for the same symptomatic AE (e.g., nausea) but from the clinical investigator/clinician (CTCAE) and patient (PRO-CTCAE) perspective. As previously discussed, oncology clinical trials report safety findings to the FDA using standard AE reporting based on clinical investigator–reported CTCAE grades. Each CTCAE term has associated criteria for assigning a grade, typically ranging from 0 to 5, which requires clinical interpretation and represents the severity of the AE. In contrast, a PRO-CTCAE result represents the patient's perception of the symptom (frequency, severity, and/or interference) without interpretation by a clinician or anyone else. PRO-CTCAE scores range from 0 to 4 and do not have a corresponding "grade." Thus, patient-reported PRO-CTCAE results are complementary to clinician-reported CTCAE data but are different information and not designed for direct comparison when capturing symptomatic AEs.

Multiple studies have demonstrated that PRO symptom data may provide different results than CTCAE data for the same or similar symptom (20, 21). A patient's perception of their symptoms may differ from their clinician's interpretation, and PRO data are more systematically assessed and often may ask about different aspects of the symptom than what CTCAE grading may capture. The FDA recognizes a clear distinction between these different sources of data (PRO vs. clinician-reported outcome). The data are complementary but are expected to differ and may not correlate. Unless otherwise detailed in the clinical protocol or monitoring plan, PRO results from cancer clinical trials should not inform gaps or errors in CTCAE reporting or other clinician toxicity grading during clinical investigator site inspections at this time (Table 3).

Conclusions

Detection and grading of AEs by clinical staff have long formed the cornerstone of clinical trial safety monitoring and description of the toxicity of an investigational therapy. In addition to clinical evaluation and CTCAE reporting, assessing the patient's own perception of his or her symptoms using PRO measures, such as PRO-CTCAE, can complement our understanding of toxicity and inform tolerability. The authors acknowledge the important questions raised by sponsors and investigators regarding good clinical practice and the protection of the safety and well-being of study participants when PRO measures are incorporated to assess symptomatic AEs. There are several approaches to the clinical review of individual patient-level PRO results during trial conduct, and the FDA does not require any particular clinical review strategy provided that patient safety is adequately addressed. Regardless of the clinical review strategy the sponsor elects to use, patients must be informed and reminded regularly regarding how their PRO results will be used and urged to call their health care provider for any concerning sign or symptom. As PRO data on symptomatic AEs are assessed and scored differently than clinician-assessed CTCAE safety, the FDA does not expect that PRO data from cancer trials would be reported as safety events without interpretation by the clinical care provider. Finally, the FDA discriminates between PRO data and CTCAE safety data; they are different but complementary. They are expected to differ in both incidence and severity; therefore, without specific rationale provided in protocol or monitoring plan documents, PRO data should not inform gaps or errors in CTCAE reporting during clinical investigator site inspections. The FDA, NCI, and OHRP welcome continued collaboration with investigators, patients, other government agencies, and industry to support the advancement of patient-outcome research.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

This article reflects the perspectives of the individual authors in an evolving area of regulatory science and health care policy. The article should not be construed to represent official views or policies of the FDA, NCI, Office for Human Research Protections, or Department of Veterans Affairs.

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