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Capturing Symptomatic Adverse Events From the Patients' Perspective: The Potential Role of the National Cancer Institute's PRO-CTCAE Measurement System

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Introduction

Oncology patients commonly experience significant symptom burden related to both their underlying disease as well as to anti-cancer treatments. This symptom burden can have a significant impact on treatment adherence, health service utilization, functional status (e.g. physical functioning and ability to perform activities of daily living), and overall health-related quality of life.[1] There is growing evidence in oncology (and healthcare more generally) that symptoms are under-reported by clinicians and that many of these symptoms—including mucositis, fatigue, pain, dysphagia, and nausea—are best captured directly from patients, rather than being gathered by clinicians or other intermediaries. [2,3] The systematic assessment of patient-reported symptomatic treatment toxicities, using patient-reported outcome (PRO) measures, can provide patients, clinicians, sponsors, and regulators with a more complete picture of the impact of treatment, and can assist in optimizing treatment dose and/or schedule, characterizing benefits and risks, and evaluating different treatment options.

PRO measures are increasingly being used in drug development trials, and their importance in oncology drug development in particular has been further underscored by the emergence of research and policy initiatives, such as the National Cancer Institute's Healthcare Delivery Research Program, the Patient-Centered Outcomes Research Institute, and the US Food and Drug Administration's (FDA) Patient-Focused Drug Development Initiative. However, oncology drug labeling in the United States rarely includes PRO data, although FDA finalized guidance on the documentation and level of evidence required to support such claims in 2009.[4,5] Patient reporting of symptomatic treatment toxicities represents an important area where rigorously collected data can play an important role in drug development and regulatory review. These data can also be directly communicated to patients to inform treatment decision-making.

Mechanisms to promote PRO development and standardization

There are ongoing efforts to optimize the collection and interpretation of PRO and other clinical outcome assessments in cancer clinical trials in order to provide data suitable for inclusion in FDA product labeling. Several methodological, operational, and communication-related challenges hinder progress towards this goal, both at the sponsor-level and regulatory-level (Table 1). Among these, the need to improve standardization of PRO data collection and reporting is particularly important. At present, there is substantial variation in the concepts that are being targeted, the instruments that are being used to collect data, the approaches to their

implementation in oncology trials, and the ways in which the resulting data are analyzed and presented, both in FDA regulatory submissions and in the literature.

Over the long-term, addressing these challenges will require a range of approaches, among them being the development of new instruments that can better capture those concepts that are most pertinent to oncology. There are, however, several near-term steps the field may consider. For example, the ability to utilize flexible contemporary instruments could be facilitated through an increased focus on the individual assessments of three 'core' concepts that are key components of health related quality of life, and are impacted by treatment benefit and toxicity: 1) **disease-related symptoms**, 2) **treatment-related symptoms** (i.e., symptomatic adverse events/toxicities), and 3) **functioning** (e.g. physical functioning and activities of daily living).

Table 1: Barriers to PRO measure implementation and use in oncology[1]

- Lack of prioritization by sponsors and regulators of PRO measures
- Increasingly small samples sizes for targeted oncology therapeutics that may make randomized comparison of PRO endpoints challenging
- A limited number of existing PRO instruments that meet the criteria in FDA's current application of established FDA guidance
- A lack of a standardized approach for identifying relevant PROs and corresponding PRO instruments for use in clinical trials
- Difficulty in aligning PRO instrument development timelines with clinical development programs, particularly under the expedited review process in oncology
- Difficulty in operationalizing PRO tools across multinational settings
- Trial designs that are often not optimized for the inclusion and interpretation of PROs (e.g. open-label and single arm studies which can be used for accelerated approval)
- PRO data that is infrequently assessed and/or incomplete (e.g. missing data due to inadequate PRO data collection or limited compliance)
- Lack of standardization in data analysis and presentation, both in product labels and in the published literature, which undermines credibility and usability
- Resource constraints in PRO expertise within statistical, clinical and psychometric review teams within oncology
- Potential for patient burden from inclusion of multiple instruments used to satisfy needs of various PRO stakeholders including FDA, international regulators, health technology assessors, academia and others
- Perception that PRO reports may be biased in unblinded studies

Panel Focus: Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events

This panel has focused on the recently developed National Cancer Institute's "Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events" (PRO-CTCAE); a tool developed to measure symptomatic adverse events related to cancer treatment from the patient perspective. The PRO-CTCAE represents a near-term opportunity to incorporate self-reporting of symptomatic toxicity data in a standardized fashion across the drug development spectrum. The following sections will explore: 1) the potential for the PRO-CTCAE instrument to capture symptomatic treatment toxicities across multiple contexts, 2) outstanding methodological and operational issues in implementing this tool to address varying research questions, 3) recommended approaches to analysis and reporting, 4) regulatory considerations in interpreting and reporting these data, and 5) next steps that can help broaden its use.

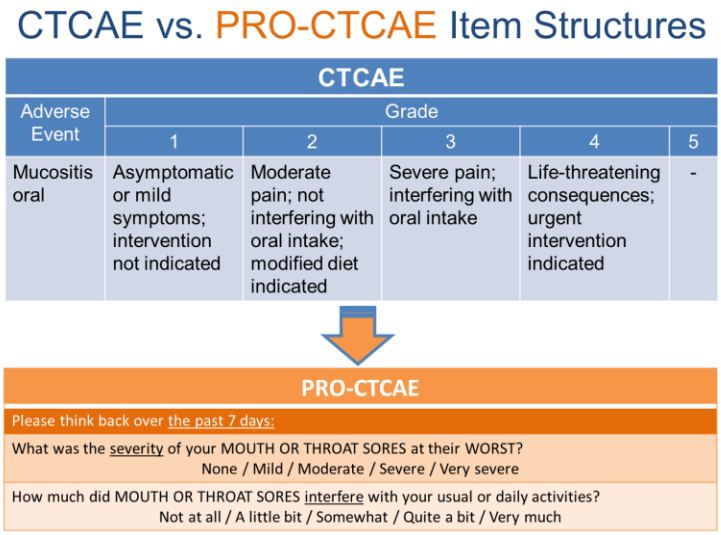
Development of the National Cancer Institute's PRO-CTCAE instrument

Currently, adverse events in cancer clinical trials are assessed and reported by health care providers using a standard method developed by the National Cancer Institute (NCI) known as the Common Terminology Criteria for Adverse Events (CTCAE). The NCI CTCAE system for grading and reporting adverse events (AE) is used widely during drug development, and the incidence and severity of important and/or frequent adverse events are provided in the FDA label following approval to inform patients and providers of the adverse effects of cancer treatments reported during the trial. The CTCAE contains approximately 800 individual adverse events that are graded for severity and impact on a scale of 1-5, anchored to discrete clinical phenomena (with 1 generally representing mild magnitude and no interference, and 5 representing death). These items are divided into three broad categories: 1) laboratory-based adverse events such as white blood cell count, 2) observable/measurable events such as blood pressure, and 3) symptomatic events such as pain or nausea.[6] The current standard of practice is for research staff to report on all three categories of adverse events using CTCAE.

Despite patients' willingness and ability to self-report, there is substantial evidence that clinicians under-detect the prevalence and severity of subjective symptoms such as pain and fatigue, and that clinicians' failure to note these symptoms can result in unnecessary harm to patients.[7,8] To improve the precision and patient-centeredness of the existing AE reporting system, a consortium of research centers, oncology practice sites, and PRO instrument developers was assembled by the NCI to develop and test a PRO measurement system to be used as a companion to the CTCAE. The development team included scientific staff from the NCI, FDA staff, as well as clinical investigators, methodologists, and patient representatives. As a first step, 78 symptomatic AEs drawn from the CTCAE were identified as amenable to patient reporting. These events were subsequently developed into a library of 124 PRO items, which were then refined through cognitive interviewing and determined to have acceptable measurement properties in a large validation study in a diverse sample of cancer patients receiving treatment.[6,9,10]

Figure 1 highlights how one particular symptomatic adverse event item in CTCAE (version 4.0) compares to the PRO-CTCAE item structure. In the CTCAE item, severity and interference are considered together in making a safety determination for the grade of the item. The PRO-CTCAE item has been broken into independent questions to allow for the separate scoring of severity and interference.

Figure 1: CTCAE vs. PRO-CTCAE Item Structures



Prior evaluations have found that the PRO-CTCAE items are well-understood by patients undergoing a range of different treatments, and demonstrate favorable validity, reliability, and responsiveness in large and diverse patient groups. Efforts are underway to develop optimal methods to incorporate PRO-CTCAE information into different study designs across the drug product lifecycle and to establish the logistical approaches to implementing in NCI-sponsored clinical trials. More than 150 early adopters in industry and academia have also incorporated PRO-CTCAE into their observational studies and clinical trials.

The PRO-CTCAE has also been integrated into two NCI-supported multicenter controlled trials to evaluate the feasibility and value of the instrument, including a study in the NRG/RTOG cooperative group (a chemoradiation trial in lung cancer), and one in the Alliance cooperative group (a multimodality therapy trial in rectal cancer, as well as two additional ongoing trials in breast cancer).[11,12] These evaluations have found that most patients will self-report using the PRO-CTCAE during active treatment, with more than 90% reporting compliance via an automated telephone system with human backup for patients who miss their scheduled calls (compliance was slightly lower at 86% when using tablet computers at clinic visits without backup data collection). PROs were also better at detecting baseline symptoms compared to clinician reporting, thus leading to a more comprehensive understanding of pre-existing symptoms versus those that emerge during treatment.[12] The ability to delineate toxicities between study arms may also be enhanced with patient reporting in addition to clinician reporting, as opposed to clinician reporting alone.

Capturing patient-reported treatment side effects throughout the drug product lifecycle

The PRO-CTCAE item library has several potential uses, and can be employed across cancer treatment modalities (i.e. chemotherapy, radiation, and surgery) to evaluate both acute and chronic toxicity. Given that the CTCAE system is already in wide use across both research and practice settings, the PRO-CTCAE item library is particularly well-placed to be integrated across the entire drug development spectrum and thus serve as an example of a standard method for patient self-reporting of symptomatic toxicities. Importantly, PRO-CTCAE provides the ability to select items from the library that are relevant to the adverse event profile of the regimen under study. This ability to adapt to a specific therapeutic context is lacking in most existing HRQOL disease modules that assess a static set of common adverse events regardless of the therapeutic context.

In designing a study that would include PRO-CTCAE, an investigator selects for surveillance those symptomatic toxicities that are most bothersome to patients, and anticipated to be meaningful and relevant based on prior knowledge of the agent, or knowledge of the on- and off-target symptomatic effects of the drug class. Input from patients should be obtained where feasible. The PRO-CTCAE system also encourages the collection of free-text narratives of additional symptoms that the patient is experiencing, to allow for the capture of unanticipated events. It should be recognized that the PRO-CTCAE is not a measure of treatment burden, disease burden, or treatment efficacy and further work must be done to provide a well-defined and reliable endpoint to assess treatment burden.

Potential uses of the PRO-CTCAE item library include:

- In early-phase trials, the instrument could help provide initial information about the side effect profile of an agent, provide context to establish dosing and schedule, and inform PRO-CTCAE item selection and standardized supportive care for later-phase studies. Identification of severely bothersome symptomatic adverse events may even inform decisions regarding which agents to advance in development.
- In expansion cohorts, PRO-CTCAE could help to elaborate on toxicity in broader populations, refine dosing, identify chronic symptomatic toxicities that may impair adherence, generate data to power clinical outcome assessments and explore approaches (e.g. alternate schedules/dosing, supportive care) to reduce or mitigate symptomatic AEs.

- In both early and late-phase trials, the library could be used to improve characterization of symptoms at baseline. In late-phase trials, PRO-CTCAE contributes to developing a profile of the symptomatic adverse effects of treatment that can be generalized to a wider population, inform assessments of overall benefits and risks, and provide data for comparative tolerability assessments.
- In post-market studies, particularly for accelerated approvals that usually involve randomized trial commitments, it could aid assessment of longer-term impacts of the treatment, and may be particularly valuable in tailoring regimens for vulnerable sub-populations. It could also inform safety surveillance activities, comparative effectiveness research, and clinical management during routine oncology practice.

While PRO-CTCAE data have not yet been used to inform a regulatory decision, PRO data submitted to FDA, including PRO-CTCAE, would be reviewed as part of the overall assessment of a treatment's safety and efficacy. As use of PRO-CTCAE increases, the drug development community can iteratively improve the tool and the analysis of the data it produces, increasing the likelihood of future inclusion of descriptive patient-reported symptomatic adverse event data in the FDA label. It is anticipated that this data will be complimentary to ClinRO CTCAE data. Optimal item selection and trial design would be facilitated by incorporating PRO-CTCAE early into a treatment's development program. A sound rationale for the objective selection of adverse events to be measured, the approach to scoring, the handling of missing data and other key aspects of trial conduct will be critical, and early interaction with FDA regarding the PRO-CTCAE strategy is recommended.

Operationalizing PRO-CTCAE in drug development

PRO-CTCAE has two primary components: 1) the symptom library itself, already available for use by investigators; and 2) the electronic architecture that is used to capture and store the information collected. The electronic architecture is being developed for NCI clinical trial networks with the goal of being integrated into other NCI data collection tools. Those industry partners that are using the PRO-CTCAE item library have developed their own electronic tools for collection of the data.

Several methodological and operational issues will need to be addressed in order to ensure optimal and broad utility of the item library (Table 2). These operational issues—and the extent to which they represent a challenge for investigators—are influenced by how the instrument and the information generated from it are used in the study design. For example, if PRO-CTCAE is used to collect descriptive data that is captured, stored, and analyzed once the trial is completed, then the operational considerations are straightforward. However, one of the potential uses of patient-reported symptomatic adverse events is the real-time use of the data generated to better inform clinical decision making during the conduct of a trial. Additional work is required to determine how best to implement the instrument and the information generated from it for such purposes. In order to realize the full potential of PRO-CTCAE, an iterative approach will be needed to incorporate the tool into trials and evaluate its performance over time.

Approaches to analyzing and standardizing PRO-CTCAE information

As PRO-CTCAE is more commonly incorporated into clinical trials, optimal approaches to analyze, interpret, and present the collected data in a rigorous and standard manner are urgently needed. Below are major considerations and potential approaches to address these issues (Table 3).

Table 2: Strategies for operationalizing PRO-CTCAE in drug development

Issues	Potential solutions
Item selection	Develop consensus recommendations on approach to selecting items for particular contexts of use.
Considerations for item 'write-in' by patients	Develop consensus on approaches to enabling, coding, and analyzing patient write-in responses. The PRO-CTCAE software hosted at the NCI incudes a free text capability for write-ins.
Linguistic and quantitative validation	Many more languages are needed to include this in a global trial. There needs to be a process and plan for cooperative investment in linguistic and quantitative validation of the language versions to assure measurement equivalence and justify pooled analyses.
Obtaining permission to use the item library	Open access with an online registration system to enable documentation and tracking of users.
Minimizing patient burden in trials	Identify strategies for incorporating different PRO questions while minimizing duplicative and redundant questions to patients.
Minimizing duplication	PRO-CTCAE questions may overlap with existing measures from HRQOL and other assessments. Engagement with international regulatory and payer entities is necessary to reduce duplication of concepts being assessed while ensuring the PRO strategy meets the evidentiary needs of all stakeholders.
Mechanisms for sharing results with clinicians and patients	Consensus on how to represent the data in publications and drug labels is needed. Further workshops are planned beginning in 2016 to address data analysis and other operational issues utilizing experience gained from early adopters.

Table 3: Major considerations and possible approaches to data analysis and reporting

Considerations for analysis/reporting	Possible approaches
Displaying data in longitudinal v. frequency tables	Standard AE tables including PRO-CTCAE data as well as CTCAE data, stacked bar charts/histograms displaying symptom attributes (frequency, severity, interference) at each measurement, plots of longitudinal trajectories for selected AEs of interest.
Missing data	Backup data capture strategies must be integrated into trials. Data quality should be monitored prospectively. Frequency and reasons for missing data should be reported. Clinician reporting is the basis for capturing all adverse events when patients are too ill to report, or unable to report due to cognitive or language barriers.
Treatment of baseline events	PRO-CTCAE improves the capture of baseline symptom status, and baseline values should be incorporated into interpretations of change over time.

Conclusion

Work is already underway to address a number of priority methodological and operational issues related to PRO-CTCTAE, including additional translation and linguistic validation to enable multinational trials, enabling open access without requiring permission, and mapping PRO-CTCAE scores to CTCAE grades. Experts from across the PRO field continue to discuss data collection and interpretation, impact on industry and regulatory frameworks, and other barriers that may hinder broader inclusion of PROs in trials of new cancer therapies. PRO-CTCAE can play an important role in improving the quality, reliability, and completeness of patient-reported symptomatic adverse event data collected during cancer clinical trials. Continued refinement of the PRO-CTCAE measurement system and its systematic use in clinical trials could lead to inclusion of descriptive PRO-CTCAE data in the FDA label that is complimentary to ClinRO data. This would ultimately provide both patients and clinicians with useful and reliable information on the impact of treatment reported by patients themselves.

PRO-CTCAE could also form one key component in comparing the side effect profile and its burden between two different therapies in the clinical trial setting. Such a "comparative tolerability" trial design will require further dedicated efforts to identify optimal approaches, including the potential creation and inclusion of a measure of "overall treatment burden". This has been attempted in the past with prospective interventional patient preference studies, and could be an interesting area for investigation in ‘chronic’, maintenance or adjuvant indications requiring long periods of treatment. Finally, it remains critically important to involve all those who utilize PRO data to inform regulatory and payment decision-making to work toward a common framework of PRO measures and endpoints that provide the most accurate data to address the needs of all, while reducing burden and duplication.

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