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Policy Perspective:

Informing the Tolerability of Cancer Treatments Using Patient-Reported Outcome (PRO) Measures: Summary of an FDA and Critical Path Institute Workshop

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DISCLAIMER

This article summarizes topics addressed at the FDA-Critical Path Institute workshop. The views of the authors represent their own and should not be interpreted to reflect the official policy of the U.S. FDA, National Cancer Institute, Critical Path Institute or any of the author's respective institutions.

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ABSTRACT

Objective: The U.S. Food and Drug Administration and the Critical Path Institute's PRO Consortium convened a co-sponsored workshop on the use of patient-reported outcome (PRO) measures to inform the assessment of safety and tolerability in cancer clinical trials.

Study Design: Open Public Workshop

Methods: A broad array of international stakeholders involved in oncology product development and PRO measurement science provided perspectives on the role of PRO measures to provide complementary clinical data on the symptomatic side effects of anti-cancer agents.

Results: Speakers and panelists explored the utility of information derived from existing and emerging PRO measures, focusing on the PRO version of the National Cancer Institute's Common Terminology Criteria for Adverse Events (PRO-CTCAE™). Panelists and speakers discussed potential ways to improve the collection, analysis, and presentation of PRO data describing symptomatic adverse events in order to support product development and better inform regulatory and treatment decisions. Workshop participants concluded the day with a discussion of possible approaches to the patient-reported assessment of an investigational product's overall side effect burden as a potential clinical trial endpoint.

Conclusions: FDA reiterated its commitment to collaborate with international product development stakeholders to identify rigorous methods to incorporate the patient perspective into the development of cancer therapeutics.

INTRODUCTION

The newly formed FDA Oncology Center of Excellence (OCE) has identified patient-focused drug development (PFDD) as one of its important initial programs to advance cancer therapeutic development. [1] One of the priority areas for the OCE is to foster scientific outreach and investigation into the use of patient-reported outcomes (PRO) and other clinical outcome assessments (COA) in cancer clinical trials. When reviewing clinical trials supporting the safety and efficacy of cancer therapeutics, the FDA has recently described its perspective on the current opportunities and challenges with the use of PRO measures, placing initial focus for product labeling on analysis of PRO measures of disease- and treatment-related symptoms and physical function. [2] FDA has reiterated that while symptoms and physical function will be the initial focus of FDA analyses for product labeling purposes, other aspects of the patient experience may also be important to measure, and all submitted PRO data will be taken into account during product review. [3]

Newer products approved for the systemic treatment of cancer have increasingly diverse mechanisms of action and are frequently administered orally and on a daily schedule. Unprecedented efficacy seen with targeted and immune-based therapies has led to a longer more chronic course of anti-cancer treatment with accompanying heterogeneous side effect profiles. These contemporary therapies stand in sharp contrast to the cytotoxic, intravenous, fixed-duration regimens that have been the backbone of most cancer therapy for decades. Characteristic toxicities observed with cytotoxic therapies are being replaced with an array of different types, severities and duration of symptomatic side effects. While the advances seen with these new therapies are

welcome, prolonged treatment necessitates a closer look at low grade but potentially burdensome symptomatic side effects that can decrease quality of life and adversely impact long-term adherence. [4]

The U.S. Food and Drug Administration (FDA) partnered with the Critical Path Institute's PRO Consortium to conduct a public workshop on April 25, 2017 in Bethesda, MD to explore the use of PRO measures to inform tolerability in cancer clinical trials. [5] Speakers, panelists and participants represented diverse stakeholder groups, including patients, clinicians, clinical investigators, industry representatives and international regulators involved in oncology drug development. In this meeting report, we summarize the four sessions of this public workshop and identify areas of future research and development.

Exploring the Concepts of Safety and Tolerability – Incorporating the Patient Voice

The first session explored the concepts of safety and tolerability from the perspective of patients, international regulators, academic clinical trialists and the biopharmaceutical industry. The panel reviewed a common definition of safety and tolerability provided in the International Conference for Harmonisation E9 guideline **(Figure 1)**. [6] The panel clarified that safety and tolerability are related but distinct from one another. Safety reflects the *medical risk* to the patient, frequently involves clinical judgment, and incorporates the overall adverse event profile of the product including both symptomatic and asymptomatic laboratory, radiographic, and clinical events, as well as symptomatic side effects. Tolerability reflects the extent to which overt adverse effects impact the patient's willingness to remain on the current treatment dose. Key contributors to tolerability include those effects that are symptomatic and bothersome to the patient (as compared to laboratory abnormalities which can commonly go unnoticed). The panel generally agreed that whereas the assessment of safety requires clinical judgment relying on clinical assessment of the patient, the ability to continue a therapy at its recommended dose (tolerability) could be informed by patient assessment of symptomatic side effects.

Panelists commented that in addition to better communicating a drug's side effect profile, there are other potential benefits of using PRO measures to improve the understanding of a drug candidate's tolerability. For example, improved characterization of tolerability during early phase trials could inform dose selection for later phase trials. Moreover, tolerability is the ability to continue to adhere to the prescribed dose and schedule of a

therapy; therefore any efficacy resultant from drug exposure is reliant to some degree on tolerability. Better methods to understand tolerability could inform both safety and efficacy and could be valuable to inform decision making for all drug stakeholders.

Panelists noted that current information informing tolerability (e.g. dose modification and discontinuation and CTCAE information on worst grade adverse events) was considered limited. Patient panelists in particular noted that simply knowing how many patients were dose reduced or discontinued therapy, while important, does not provide information regarding how patients experience treatment and which bothersome symptoms, if any, may be impacting those treatment decisions. Consistent with a survey of academic, patient and FDA stakeholders reported by Bruner and colleagues[7], the panel agreed that assessment of symptomatic adverse events using patient-reported measures could be useful.

Assessment of Safety and Tolerability – Emerging Patient-Reported Methods

The second session brought together experts from the National Cancer Institute (NCI), industry and academia to discuss current developments in the use of patient-reported outcome (PRO) measures to inform tolerability in cancer trials. Currently, safety is predominately based on clinician evaluation of adverse events and is documented using the Common Terminology Criteria for Adverse Events (CTCAE), a grading system used across all cancer clinical trials to ensure consistent severity scoring.[8] These clinician-reported outcomes are important to monitor the safety of trial participants, and are included in FDA product labeling as descriptive data to represent the overall safety of the treatment regimen. CTCAE data includes both symptomatic adverse events (e.g. nausea, fatigue), together with laboratory, radiographic, or clinical AEs, and the AE is then interpreted and graded by clinicians using the CTCAE criteria. Recognizing that symptomatic adverse events may not be observable and are best quantified by the patients themselves, the NCI developed a patient-reported outcome (PRO) version of the CTCAE entitled the PRO-CTCAE™. [9] [10] [11]

The panel reviewed the development of the PRO-CTCAE measurement system to date, and highlighted the fact that it has been adopted for use in more than a dozen countries and has been in multiple academic and pharmaceutical industry-sponsored cancer clinical trials. PRO-CTCAE has been publicly available on the NCI-PRO-

CTCAE website since April of 2016. [11] The measurement system is still relatively early in its evolution and there are a number of measurement, interpretation, and implementation considerations to be addressed to support further adoption in global cancer trials. Several industry panelists discussed their early experience with using the PRO-CTCAE and provided an update from the multi-stakeholder PRO-CTCAE Industry Working Group on progress made to address internal and external barriers to adoption in multinational trials. **(Table 1)** Topics discussed included translation and cross-cultural adaptation efforts as well as sharing best practices for data-driven methods for item selection and the standardized collection, analysis and presentation of data. The panel noted that continuing to update item libraries with new symptoms would be important as novel toxicities are encountered during drug development. It was generally agreed that systematic assessment of PRO measures informing tolerability could be useful for drug development, and that PRO-CTCAE could be one important tool to achieve this trial objective.

The session concluded with a discussion of how safety and tolerability are currently analyzed and presented in most publications and FDA-approved product labeling. Adverse event tables included in product labeling typically present the incidence rate and severity of an adverse event observed at any time during the course of the trial. While there are benefits to such an approach including simplicity and familiarity to clinicians, such an approach does not provide information regarding the trajectory of adverse events or information on their burden to patients. As such, there is growing interest in exploring longitudinal approaches to present safety and tolerability data. [4] The panel discussed several longitudinal methods that could be used to analyze clinician-reported outcomes (CTCAE) or patient-reported outcomes. Panelists agreed that clinician and patient-reporting of symptomatic AEs are complementary, and that PRO measures provide a strategy to directly capture the frequency, severity and impact of symptoms directly from patients without interpretation by clinicians. (Table 2). Panelists noted that CTCAE remains the standard for grading symptomatic adverse events in cancer clinical trials. However, capture of symptomatic adverse events using a PRO measure offers valuable information to improve our precision in gauging symptoms that can affect the tolerability of treatment, particularly in contexts where symptomatic adverse events are common, tend to be low grade, and when treatment is given over the long term. The session concluded with calls to advance our understanding of the longitudinal analysis of symptomatic adverse events using PRO measures.

Analysis and Display of PRO-Based Tolerability Data – Metrics and Paths Forward

Building from the prior session, the third panel brought together researchers with expertise in data analytics to review longitudinal methods to analyze and present PRO data capturing symptomatic adverse events. A simulated data set with variables that included PRO-CTCAE was provided to panelists. Panelists evaluated various approaches to data analysis and characterization of missing data. Several different visualization techniques were presented that could be used to summarize data, and each had strengths and limitations.

Analytic and graphical methods explored included stacked bar charts of response over time by treatment arm, stacked bar charts of response over time by treatment arm and baseline, heat maps of response over time by treatment arm, area under the curve, line graphs depicting the proportion of any level of response at each assessment by treatment arm, and latent class trajectory analysis which groups patients into different patterns of symptom trajectory ("latent classes"). The panel also discussed tabular presentations of the data as a way to summarize PRO-based symptomatic adverse event data. For example, rates of each symptomatic adverse event across post-baseline assessments grouped by treatment arm or cumulative incidence across post-baseline PRO assessments can be displayed in tables. A revision of a previously proposed method to adjust for baseline scores[12] was also discussed as a way to present the data, which displays only those symptomatic adverse events that worsened from an existing baseline score. There was consensus that carefully defining the research objective (e.g. describing specific symptoms for those on treatment) and defining the analysis population (e.g. the at-risk population who are receiving therapy and offered PRO assessments) is the first step in selecting the appropriate analytic strategy.

The panel identified several key issues to consider when analyzing and describing longitudinal descriptive symptomatic adverse event data **(Table 3)**. The session concluded by noting that there was no single analysis or representation of data that will address all study aims, but that standard principles and analyses must be developed, and a consistent method to summarize longitudinal data graphically that finds the balance between the strengths and limitations of the various methods would be useful. Approaches to the analysis of longitudinal symptomatic adverse events data continues to be actively investigated.

From Individual Symptoms to Overall Side Effect Burden

The final session explored different methods to assess overall symptomatic side effect burden. A more global impression of the impact of symptomatic adverse events would be useful for patients, clinicians and from a regulatory and drug development standpoint. For instance, if one is assessing 6 different symptomatic side effects, it is unclear whether all important side effects were assessed, and what weight patients apply to each side effect based on its impact on their daily lives. Hence, a patient-reported global measure of the overall side effect burden may be useful that takes into account the perceived overall burden to the patient of all the symptoms of a drug's particular adverse event profile. **(Figure 2)**

The panelists discussed several methods and existing tools that could provide a summative measure of overall side effect burden. Where scores are available for patient-reported severity of multiple symptomatic adverse events, one method would be to add or average the unweighted scores into a total symptom score for the symptomatic adverse events assessed. Similar methods have been used in multi-item disease symptom scales for efficacy assessment such as the development of a disease symptom measure for myelofibrosis. [13] Summary scores have also been used for health-related quality of life tools (HRQL) and their functional domains such as physical function. [14,15] Adding or averaging unweighted scores from a set of symptomatic adverse events assessed in a trial would provide an overall symptomatic adverse event score, but this method has limitations and care must be taken that potentially important side effects are not missed or diluted by the addition of irrelevant symptoms. Additionally, different patients may apply different weight to the occurrence of one symptom over another and this method does not take this into account.

The panel also discussed assessing overall side effect burden using a single question. An example was taken from the Functional Assessment of Cancer Therapy- General (FACT-G). [14] The FACT-G GP5 item, "I am bothered by side effects of treatment" has strengths including simplicity and the ability of individual patients to internally weight what was most important to them. Preliminary unpublished exploratory analyses of existing trial data were presented during the workshop suggesting that higher levels of self-reported side-effect bother can be associated with higher maximum grade CTCAE-reported toxicities and lower utility-based health status scores. The panel

acknowledged the challenges associated with single item measures of a global concept and more work must be done to evaluate the acceptability and responsiveness of a single global item as an endpoint to summarize overall side effect burden.

In addition to exploring the value of a summary measure of side effect bother, the panel also examined the potential utility of a summary measure of how side effects interfere with usual and daily activities. The panel considered the interference scale from the MD Anderson Symptom Inventory (MDASI). [16] The panel was not intended to arrive at consensus on the optimal method to assess overall side effect burden, but rather to begin a substantive dialogue. While the MDASI interference scale is not specific to symptomatic adverse events, but rather symptoms in general, the importance and utility of such a measure was acknowledged, and panelists noted that further study is warranted.

A PRO measure of overall side effect burden could complement information about the specific profile of symptomatic side effects captured using a PRO tool such as PRO-CTCAE, and could be used as key supportive data in trial designs that aim to distinguish the profile and consequences of symptomatic adverse events. Such a measure could aid in providing a range of side effect burden that could inform various levels of tolerability, thereby informing conclusions about the comparative tolerability of two similarly effective agents. In addition to a specific PRO measure of overall side effect burden, symptomatic adverse events can affect functioning and health related quality of life, and while these more distal concepts are influenced by more than the side effect profile of the drug alone, a description of physical function and other aspects of HRQL assessed in the trial can also provide complementary information on the overall impact of the side effect profile of a cancer therapy on the patient.

Conclusion

The U.S. Food and Drug Administration (FDA) and Critical Path Institute conducted a public workshop exploring the use of PRO measures to complement existing clinical safety assessments and inform cancer treatment tolerability. This workshop highlighted several areas of opportunity to systematically gather information about symptomatic adverse events using PRO measures, and communicate it to patients, clinicians and regulators in interpretable and meaningful ways. The assessment of safety and tolerability is critical at all stages of drug development, and

tolerability is influenced by overt symptomatic side effects. The use of a PRO measure has been recommended when a trial endpoint is a concept that is best known by the patient and can be validly and reliably captured by self-report. This workshop supports systematic assessment of patient-reported symptomatic adverse events using an item library such as the PRO-CTCAE to provide complementary data to existing measures of safety. Work is underway to address barriers to wider adoption of the PRO-CTCAE and other measures of symptomatic adverse events in international clinical trials. Sustained international collaboration on trial design, analysis methods and measurement of overall side effect burden is ongoing.

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TABLES:

Table 1: Update from the PRO-CTCAE Industry Working Group

Roadmap of PRO-CTCAE Industry Working Group Activities		
	Task	Completion Time Frame
Completed Activities		
Licensing Process	Assess NCI's on-line registration platform launched in April 2016 to evaluate whether it addresses current access barriers	WG pleased with functionality and convenience of on-line process
Item Selection- Early Stage Trials	Develop consensus recommendations on item selection approaches for early-stage cancer trials	Item selection process for early stage studies was reviewed by WG; ISOQOL 2016 abstract on general approach for early phase trials was published (18)
Ongoing Activities		

Item Selection- Registration Trials	Develop consensus recommendations on item selection approaches for registration trials	Item selection process for late stage studies was reviewed by WG in Feb 2017; Ongoing work underway to create objective methods for unbiased item selection in registration trials
Translation and Linguistic Validation	Develop proposal for translation and linguistic validation of PRO-CTCAE into more languages	Industry-sponsored collaboration between NCI and Corporate Translations Inc. to translate and linguistically validate PRO-CTCAE in 12 additional languages. This work is anticipated to be completed by December 2017
Data Collection Standards	Develop consensus recommendations on approaches to enabling, coding, + analyzing patient write-in responses	Initiated work in Sept 2016 and discussed approaches with WG in Sept 2016; on-going review of proposal
Data Analysis and Presentation Standards	Develop consensus recommendations on data scoring/analysis, and data presentation formats	Initiated work in August 2016; on-going development and review of proposals
Remaining Activities		
Data Collection Standards	Develop consensus recommendations on: - Clinical monitoring of PRO-CTCAE data - Consistency of platforms for	Short-term activity for 2017. Discussed clinical monitoring of PRO-CTCAE data with FDA and NCI in Q1. NCI and FDA are working with the Clinical Data Interchange Standards

	electronic administration	Consortium (CDISC) to develop PRO-CTCAE data standards
Data Analysis Standards	Develop consensus recommendations for standardized data scoring/analysis methods	Long-term activity; will be informed by data gathered from utilizing instrument on a wider scale
Data Presentation Standards	Share best practices for presenting data in submissions, manuscripts, drug label	Short/long-term activity; development of data presentation examples underway

Table 2: Complementary information on drug safety and tolerability provided by conventional CTCAE reporting and longitudinal analysis of both clinician- and patient-reported data sources.

	Conventional maximum grade CTCAE analysis	Longitudinal toxicity analysis of CTCAE data	Longitudinal toxicity analysis of PRO-CTCAE data
Describes non-symptomatic AEs	✓	✓	✗
Documents UNEXPECTED AEs	✓	✓	✗/✓*
Incidence / severity (high grades)	✓	✓	✓
Duration / trajectory / resolution	✗	✓	✓
Burden of chronic low grade AEs	✗	✓	✓
Direct patient perspective	✗	✗	✓
Systematic assessment that includes baseline	✗	✗	✓

* PRO-CTCAE does include the option for a patient to "write-in" a symptom they are experiencing that may allow for screening of unexpected symptomatic adverse events (AEs) from the patient perspective. [10,11]

Note: Conventional CTCAE clinician reported adverse events will remain the core of safety monitoring and reporting in cancer trials. Longitudinal analysis and use of PRO measures such as PRO-CTCAE can add important complementary information that may better inform tolerability.

Table 3: Considerations for analytic and visualization methods to describe longitudinal symptomatic adverse events assessed by PRO measures

Research objective	Clearly identify the research question to address • This workshop focused on describing symptomatic adverse events over time for patients undergoing anti-cancer therapy
Analysis population	Define the analysis population based on the research question • For this analysis we selected those patients who are on study and

	on treatment. The PRO symptomatic adverse event "at-risk" population. •
Completion rate (DataQuality)	Characterize the completion rate for those patients who were on study and scheduled to complete a PRO assessment. • Informs the quality of study conduct, study personnel training, and importance placed on data collection • Lower completion rates and missing observations can limit the interpretability, reproducibility, or generalizability of study results.
Missing data	Address uncertainty due to missing data • Collect specific reasons for missing observations
Account for baseline	Taking baseline into consideration provides additional information about safety and tolerability, and may inform AE attribution.
Data visualization	All analytic methods and visualizations will have strengths and limitations. No one method will satisfy all objectives. • A standard visualization is needed that leverages the benefits of longitudinal systematically assessed PRO data, takes baseline symptoms into account, and is interpretable to treating physicians and patients • Visualizations should have the intended audience in mind, and separate visualizations for clinicians and patients may be needed

Note: Identification of standard analysis and visualization methods for PRO data is an area of active regulatory science and international collaboration. [17]