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Policy Perspective

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

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A B S T R A C T

The US Food and Drug Administration and the Critical Path Institute's Patient-Reported Outcome (PRO) Consortium convened a cosponsored workshop on the use of PRO measures to inform the assessment of safety and tolerability in cancer clinical trials. A broad array of international stakeholders involved in oncology drug development and PRO measurement science provided perspectives on the role of PRO measures to provide complementary clinical data on the symptomatic side effects of anticancer agents. 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. Panelists and speakers discussed potential ways to improve the collection, analysis, and presentation of PRO data describing symptomatic adverse events to support drug 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 drug's overall side effect burden as a potential clinical trial end point. The Food and Drug Administration reiterated its commitment to collaborate with international drug development stakeholders to identify rigorous methods to incorporate the patient perspective into the development of cancer therapeutics.

Keywords: drug safety, oncology, patient-reported outcomes, PRO-CTCAE, tolerability.

This article summarizes topics addressed at the Food and Drug Administration (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 US FDA, the National Cancer Institute, the Critical Path Institute, or any of the authors' respective institutions.

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Introduction

The newly formed Food and Drug Administration (FDA) Oncology Center of Excellence has identified patient-focused drug development as one of its important initial programs to advance cancer therapeutic development [1]. One of the priority areas for the Oncology Center of Excellence is to foster scientific outreach and investigation into the use of patient-reported outcomes (PROs) and other clinical outcome assessments 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]. The FDA has reiterated that although 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 anticancer 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. Although 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 US 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 (Fig. 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

- **SAFETY:** The *medical risk* to the subject, usually assessed in a clinical trial by laboratory tests (including clinical chemistry and hematology), vital signs, clinical adverse events (diagnoses, signs and symptoms), and other specific diagnostic tests or evaluations (e.g. ECGs, visual field testing).
- **TOLERABILITY:** The degree to which *overt adverse effects* can be tolerated by the subject.

Fig. 1 – Definition for safety and tolerability adapted from the International Conference for Harmonisation (ICH) E9 guideline glossary [6].

(as compared with laboratory abnormalities that may go unnoticed by the patient). The panel generally agreed that although 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 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 Common Terminology Criteria for Adverse Events [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, although 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 et al. [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, industry, and academia to discuss current developments in the use of PRO measures to inform tolerability in cancer trials. Currently, safety is predominately based on clinician evaluation of adverse events and is documented using the 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. The CTCAE data include both symptomatic adverse events (e.g., nausea and fatigue) and laboratory, radiographic, or clinical adverse events, and the adverse event 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 National Cancer Institute developed a PRO version of the CTCAE titled the PRO-CTCAE™ [9–11].