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Commentary

Patient-Reported Outcomes in Oncology Clinical Trials: Stakeholder Perspectives from the Accelerating Anticancer Agent Development and Validation Workshop 2019

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Introduction

A patient-reported outcome (PRO) assessment is a measurement based on a report about the status of a patient's health condition that comes directly from the patient without amendment or interpretation of the patient's response by a clinician or anyone else [1]. PRO assessments in cancer clinical trials can be used to complement traditional safety and efficacy data by providing an accurate description of symptoms and their functional impacts experienced by patients undergoing anticancer therapy. There has been a substantial shift in oncology drug development in the last decade, with recognition that the measurement and analysis of patient experience data is important complementary information when assessing benefit–risk [2, 3]. Successful integration of PRO into cancer clinical trials is not accomplished by any one single drug development stakeholder. As previously described by Basch and colleagues, the Food and Drug Administration (FDA) and industry must collaborate closely to develop rigorous PRO endpoints and find opportunities to communicate the results, including potential inclusion of PRO information into FDA product labeling [4]. With an increasing amount of PRO being collected as part of cancer clinical trials, there are opportunities for PRO experts including patients, advocates, social scientists, statisticians, clinicians, and regulators to identify best practices to maximize the utility of this rich data source. The 2019 Accelerating Anticancer Agent Development and Validation (AAADV) Workshop assembled a panel to discuss "Patient-Reported Outcomes in Oncology Clinical Trials: Clinical Trial Design and Operational Issues Toward Regulatory Grade Clinical Experience." This session was a series of perspectives on the collection, interpretation, and analysis of rigorous patient-reported outcome data generated in cancer clinical trials, with an emphasis on the progress that has been made in the last 5 years.

Clinical Perspective

Study endpoints in late-phase clinical trials should be (a) consistently and readily measurable, (b) sensitive, (c) well defined and reliable, and importantly, (d) clinically meaningful. The measurement of symptoms and function using PRO assessments can serve as a direct evaluation of how a cancer therapy influences how patients feel and function.

Several issues require careful consideration when using PRO assessment(s) in cancer clinical trials. First, understanding whether measures have been studied in the specific population of interest and whether instruments have been rigorously developed with adequate measurement characteristics is crucial to allow for meaningful interpretation of the results [5]. An important challenge is heterogeneity in outcomes that are measured and how the clinical outcome data are analyzed. A core set of clinical outcomes that are meaningful to patients and clinicians and sensitive to the intervention and that isolate the effect of the drug has been proposed by FDA as an important starting point to generate data more useful for regulatory decision making across cancer clinical trials. This core outcomes set includes (a) symptomatic adverse events, (b) physical function, (c) impact on work and leisure activities (role function), (d) disease-related symptoms, and (e) overall side-effect

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Table 1. FDA reviewer approach to submitted patient-reported outcomes data

FDA review questions	Considerations
Which instruments are being used?	Are the instruments "fit for purpose" and well defined and reliable within the context of the clinical trial? Is there evidence of adequate measurement characteristics for the context of use?
Were PRO endpoints in the statistical hierarchy?	Were PRO objectives and endpoints stated clearly within the protocol and statistical analysis plan? Were endpoints clearly constructed based on the research objective?
How much data is missing?	Is data missingness due to technical limitations? Trial conduct? High attrition due to toxicity or disease progression?
Is the assessment timing reasonable given the drug(s) being tested?	Are PROs being assessed at times when symptomatic adverse event or physical function deterioration are most likely to occur in the treatment or disease course?
Can conclusions be made on the strength of results?	Are the results robust and clinically interpretable in order to inform the FDA benefit–risk determination?
What is the best way to share PRO results with the public?	Is the product labeling the most appropriate place for communication of complex PRO results?

Abbreviations: FDA, Food and Drug Administration; PRO, patient-reported outcome.

bother. This core outcomes set is not meant to discourage collection of other PRO measures; instead, these core outcomes can form a minimal expectation for measurement in cancer clinical trials. Assessment frequency is another area that would benefit from increased standardization. More frequent PRO assessment in the first few months of therapy can improve data quality, as the acute treatment phase is typically where the highest completion rate and least attrition are observed. A challenge with this frequent assessment approach may arise in terms of patient burden, but there are successful examples of frequent administration in commercial cancer trials. Like any clinical trial assessment, it is important for clinical trial staff to explain to patients the reasons for collecting these data, and that collection is typically less frequent after the initial treatment period. To further mitigate patient burden, core concepts that are expected to rapidly change (e.g., symptomatic adverse events) could be measured more frequently than other core outcomes such as physical or role function. This tailoring of the PRO strategy should fit the disease, treatment, and outcome being studied, as well as the PRO research objective.

Patient Advocate Perspective

Measuring what matters to patients is of critical importance in cancer clinical trials. Patients want their concerns to be heard and their symptoms and physical functioning to be included in their care decisions. Importantly, patient perceptions of their side effects and symptoms evolve throughout their treatment course and should be captured [6]. Beyond communicating PRO data to clinicians to support the individual's care, PROs can be used to share the patient experience for other patients considering their therapeutic options. A patient-reported research objective that is clinically meaningful and spans across disease areas is the description of an anticancer therapy's tolerability. The tolerability of a medical product has been defined as the degree to which symptomatic and nonsymptomatic adverse events associated with the product's administration affect the ability or desire of the patient to adhere to the dose or intensity of therapy [7]. Tolerability should include direct measurement from the patient on how they are feeling and functioning while on therapy. Patient-reported outcomes, including symptomatic adverse events and physical function, are direct measures of how a patient is feeling and functioning while on therapy and therefore are directly relevant to the measurement and interpretation of tolerability.

FDA Reviewer Perspective

A successful patient-focused approach would mean that treatments and clinical trials would address aspects of disease that are most important to patients, and that the information that comes out of trials is accurate, relevant, and interpretable to patients and providers to inform treatment decisions. In terms of PRO data collection, the FDA has frequently advised sponsors to focus on outcomes that are proximal to the disease and drug being studied such as disease symptoms, symptomatic adverse events, and physical function [8]. Assessment of outcomes outside of the core outcome set discussed above should have a sound scientific rationale for meeting research objectives in order to minimize patient burden and improve the quality of data collected.

In terms of timing, assessment frequency should be relevant and logical relative to the stated PRO research objectives and treatment cycle length. In essence, PRO assessments should capture symptoms and side effects and their impact on function and therefore would ideally be measured while these events are occurring, rather than during a washout period. For almost all oncologic conditions, more frequent assessment at the beginning of therapy (e.g., the first 6 months) increases the fidelity of symptomatic adverse event and physical function data during the time period that events are most likely to occur.

Regulatory review of PRO data includes psychometric, statistical, data quality, and interpretability considerations (Table 1) and frequently includes a multidisciplinary review team consisting of experts in their respective fields. To better answer the questions in Table 1 and improve the standardization of analytic methods, the Oncology Center of Excellence has created a consistent analytic approach to assist sponsors in organizing their PRO data in a way that is amenable to rigorous review. In collaboration with FDA statisticians, clinicians, and psychometricians, the Oncology Center of Excellence has

made considerable progress in formalizing the review of PRO data across our Oncology review divisions.

Trialists Perspective

The past decade has seen a tremendous acceleration in drug development in oncology with a shift in paradigm in conducting research and clinical trials. For instance, study designs have evolved toward tumor-agnostic basket studies, biomarker-selected populations, combination therapy (e.g., immunotherapy and chemotherapy), and a more systematic inclusion of patient-reported outcomes to inform patients' experience with treatment. Standardization of core concepts of data collection and analytical approaches of PROs should ultimately increase the quality of the data and therefore credibility in interpreting such data as part of the totality of evidence available to inform the assessment of a treatment's risk–benefit profile. Use of technology, such as electronic patient-reported outcomes (ePROs) data capture, holds great promise. For instance, PRO collection is moving beyond pen and paper questionnaires or provisioned clinical devices to novel approaches using patient-owned devices or mobile technology devices capturing patients' activity without the need for the patients to actively enter their data. These novel data collection methods have immense potential to improve compliance, efficiency, and reliability of data elements (e.g., improved PRO response time, ability to fill out PRO surveys outside of the clinical setting).

In this rapidly evolving environment, it is critical to maintain close collaboration among sponsors, trialists, patients, reviewers, and decision makers. There are some methodological challenges to consider. For instance, PROs are primarily used to complement traditional endpoints of efficacy (overall survival, progression-free survival) and therefore are often secondary or exploratory endpoints with limited opportunity for type I error control. In certain environments, blinding of the patients is either not feasible or unethical, increasing uncertainty regarding the reliability of the PRO data. To reduce completion burden and deliver on the core concepts, measures are more and more tailored to the treatments using symptoms from item libraries rather than static off-the-shelf instruments, prompting the need to provide evidence on the validity of this approach.

There are operational challenges to gathering PRO data electronically. Backup power sources should be made available to ensure that the data are collected without device error, and patients should be able to easily access technological support services. From a data management perspective, data integrity and protection of patient-level data must be considered in an ePRO data collection modality (e.g., password protection, fingerprint). Data management and security is mandated as part of the 21 CFR Part 11 requirement to mitigate potential contamination of clinical data sets [9].

Conclusion

The presentations and discussion at this important AAADV workshop session highlighted the need for reliable, sensitive, and fit-for-purpose PRO instruments as well as rigorous and pragmatic collection of PRO in cancer clinical trials. There was agreement among stakeholders that PROs should reflect things that matter to the patient, and measures of symptomatic adverse events, disease symptoms, and physical function could form a core outcome set that can inform the efficacy and tolerability of anticancer therapies. A focus on tolerability and development of a core outcome set that is focused on frequent measurement at the early portion of anticancer therapy could address the needs of patients, providers, sponsors, and regulators.

Although operational challenges were identified in obtaining regulatory-grade PRO data, multiple solutions to these barriers were identified and are actively being incorporated into clinical trials. Further work needs to be done to standardize PRO collection and analytical methods for regulatory purposes. Development of a core outcome set for regulatory purposes is one key step toward advancing that goal.

Disclosures

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