Commentary on King-Kallimanis et al.: Inadequate measurement of symptomatic adverse events in immunotherapy registration trials

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Symptomatic adverse events are common with cancer therapies, and provide key information about tolerability during development and regulatory review. After a therapy becomes available on the market, information about these adverse events is essential for patient and clinician decision-making. Historically, the standard approach for collecting symptomatic adverse events in trials depended on clinician reporting via the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE)—but this process was found to be unreliable and to miss about half of patients' symptoms.[1]

To address this problem, the NCI developed a patient-reported outcome (PRO) version of the CTCAE (called the "PRO-CTCAE"), to enable direct collection of this information from study participants. The NCI made this tool freely available without cost (downloadable at https://healthcaredelivery.cancer.gov/pro-ctcae). The Food & Drug Administration (FDA) and European Medicines Agency (EMA) have embraced the PRO-CTCAE as a standardized approach that can be applied across trials, and the FDA has convened multiple meetings to discuss methods for collecting, analyzing, and reporting symptomatic adverse events in drug applications and labeling.[2]

Yet, patient reporting of symptomatic adverse events remains inadequate in oncology trials, as illustrated by King-Kallimanis et al.[3] from the FDA in this issue of Clinical Trials. They focus specifically on the 28 registration trials submitted to the Agency for anti-PD-1/PD-L1 inhibitor therapies through the end of 2017. They identify common symptomatic adverse events known to be associated with these therapies (dyspnea, fatigue, cough, musculoskeletal pain, diarrhea, rash, and pruritis; they also include fever, which is not technically a PRO but is amenable to patient self-measurement). Analysis of the 28 trials finds a median of three of these adverse events assessed per trial via PRO questionnaires (range 3–5). Even the 18 trials that included well-established multi-item health-related quality of life questionnaires did not cover all of the common adverse events. None of the trials included PRO assessment of rash or pruritis.

Moving forward, product developers should identify those symptomatic adverse events known or suspected to be associated with a therapy, and include systematic collection of these via PRO questionnaires in trials. The PRO-CTCAE includes items for all of these adverse events except fever. Methods for selecting, collecting, analyzing, and reporting this information are available and are being refined through interactions between the FDA, NCI, and industry.[4] A multi-sponsor PRO-CTCAE working group meets regularly to compare approaches in a pre-competitive context. Sponsors including PROs in trials are encouraged to work with the FDA early in development on appropriate methods for collecting this information.

The authors demonstrate clearly that the traditional "one-size-fits-all" PRO approach in oncology clinical trials, that is, administering a generic multi-item health-related quality of life questionnaire is no longer adequate in the contemporary age of patient-focused drug development. Product developers need to prospectively identify PROs related to disease and to treatment, and systematically collect these in a targeted manner.[5] As noted by King-Kallimanis and colleagues, an open-ended question to capture unsolicited symptomatic adverse events should also be collected.

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The paper by King-Kallimanis et al. includes multiple additional gems that could only be gleaned by FDA insiders:

First, most of the trials included PROs (21/28 (75%) which reflects the FDA's and EMA's ongoing campaign to prompt sponsors to include PROs in registration trials. The majority with PROs administered both the EuroQoL EQ-5D questionnaire (largely used for economic analyses in Europe) and a multi-item health-related quality of life questionnaire (most commonly the EORTC QLQ-C30). About a third (9/28) included a disease-specific PRO. This is substantial progress,[6] and the FDA and EMA are to be particularly congratulated for consistently messaging to the industry that it is critical to include PROs in product development. Indeed, without this information, there is an inadequate characterization of the patient experience with treatment. Moreover, PROs are a central component of patient-focused drug development, which is a central tenet of the 21st Century Cures Act[7] (which charges the FDA to incorporate information about the patient experience in evaluations and documentation, and to report on use of this information in regulatory decision-making).

Second, completion rates of PROs are quite high, greater than 80% in these trials. This metric is consistent with another recent publication from these FDA authors using a different set of trials,[8] demonstrating that high levels of patient compliance with questionnaires should now be an expectation. Nonetheless, some trials have lower compliance, so sponsors need to make efforts in their study design and implementation to assure high compliance rates—emphasis with site staff and study participants that these are key endpoints; modes of questionnaire administration that are easy for patients; reminders to self-report; and backup data collection when patients miss a scheduled PRO report.[9]

Finally, the authors, and more broadly the FDA's Office of Hematology and Oncology Products, and the FDA's new Oncology Center of Excellence, should be congratulated for their ongoing efforts analyzing and publishing internal data to educate the product development community, advance regulatory science, and promote standardization of study methods. Industry product developers are also to be congratulated for increasing collection of PROs in oncology trials, which surely is improving our understanding of the patient experience with treatment. But we must now move into the next phase, using more targeted PRO tools beyond the traditional one-size-fits all, so that product development can truly become patient-centered.

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