High Compliance Rates With Patient-Reported Outcomes in Oncology Trials Submitted to the US Food and Drug Administration

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There is increasing interest in collecting patient-reported outcomes (PROs) in oncology drug development trials to understand how participants feel and function during treatment (1). PRO information can inform assessments of tolerability via patient self-reported symptomatic adverse events (eg, using the NCI's new Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse) and evaluations of efficacy by demonstrating improvements in disease-related symptoms or physical functioning. Well-established methods exist for developing PRO questionnaires, and for technologies to administer PRO questionnaires to patients electronically (2).

However, there are still skeptics, including many in the drug development community, who cite logistical barriers to collecting PROs as a rationale for omitting these metrics from trials. At a recent meeting of the Medicare Evidence Development & Coverage Advisory Committee (MEDCAC), which provides guidance to the Medicare program on scientific and clinical matters, several external presenters stated that they believe rates of patient compliance completing PROs are often low (3). This view, often articulated by investigators based on opinion or limited personal experiences, is refuted in this issue of the Journal, in which authors from the US Food and Drug Administration (FDA) mine internal data to put this question largely to rest (4).

Roydhouse et al. (4), from the FDA's Office of Hematology and Oncology Products, analyzed randomized controlled trials submitted to the FDA for malignant hematologic/oncologic conditions between 2007 and 2017 that contained PROs. Among 72 identified trials, 51 (71%) contained information about PRO completion rates [most trials without completion rate information were older, submitted prior to the 2009 issuance of a guidance on use of PROs from the FDA (5)]. The median PRO completion rates across trials were high: about 95% at baseline, and about 89% at six months.

The authors then conducted several interesting comparisons of PRO completion rates between investigational and control arms in these trials. Although rates were similar between arms for most trials, there were seven trials (14%) with gaps in completion rates of at least 10% between study arms (4). Curiously, completion rates were higher in control arms for blinded trials, but were higher in investigational arms for open-label trials. The authors postulated that knowledge of study arm allocation might influence patient enthusiasm to complete PROs (ie, participants in a control arm might be less prone to comply with study procedures such as PRO questionnaire completion). They emphasized that this observation is based on a small subset of trials, but that investigators nonetheless should strive to encourage participants in open-label trials to complete study procedures to avoid imbalances of data completeness between arms.

What methods can be used to optimize PRO questionnaire completion rates in clinical trials? As with any clinical research procedure, thoughtful and systematic implementation is a key. Table 1 provides a list of recommended best practices toward achieving high compliance rates, based on my research group's years of conducting these kinds of trials and analyses. These practices include assuring the simplicity of questionnaires and administration methods; emphasizing the importance of PROs with site study staff, participants, and caregivers; and real-time monitoring of compliance with automated and human backup data collection methods. Studies that do not elevate the importance of PROs sufficiently to consider these approaches may risk low completion rates and subsequent struggles to interpret missing data.

Table 1. Strategies for optimizing patient compliance with patient-reported outcome (PRO) questionnaire completion rates in clinical trials

Study component	Strategies
PRO questionnaire	Should be brief (no more than 40–50 items if infrequently administered; no more than 10–20 questions if frequently administered). Questions should be salient to study population.
Method of PRO questionnaire administration	Should preferably be electronic and simple to use without complex passwords, hardware, or software. Should offer options to participants with tactile, vision, or hearing impairments (eg, choice of web, handheld, or automated telephone system).
Study site staff	Should be emphasized to site staff that PROs are an essential aspect of the study, and that PRO completion is essential (eg, at startup, training, and in ongoing interactions). Staff should be contacted, engaged, and be accountable when a participant at their site is not compliant with a PRO questionnaire.
Participant engagement	Should be emphasized to participants (and their caregivers) that PRO completion is an essential component of the trial (eg, at enrollment, during PRO system teaching, and at follow-up study visits).
Automated reminders	Patients should receive a prompt to report on their scheduled day, and subsequent follow-up reminders if they do not self-report as scheduled (eg, when scheduled to report on a given day, they will receive an automated email, phone recording, or text message on that day, and if they don't report then again on the subsequent 2 days to complete the PRO).
Compliance monitoring and backup data collection	Compliance with scheduled PRO questionnaire completion should be monitored in real time. If a participant does not self-report even after they receive automated reminders, a human should contact the participant to administer the PRO questions. This can be done by local site staff, or by a central study coordinator. This approach can boost PRO compliance rates by 10–15% in some populations. A wide enough window for backup data collection should be allowed to optimize completeness.
Missing data and proxy reporting	If backup data collection is unable to recover the PRO information and it is truly missing, proxy completion can be considered by a caregiver or provider. This may be particularly helpful if the patient is too ill to complete the questions. The reason for missingness should also be collected on a form. This information will all be useful for sensitivity analyses.

The article by Roydhouse et al. (4) contains additional gems about the use of PROs in oncology trials. Among the total of 169 trials submitted to the FDA in the last decade, 96 (57%) contained PROs. This reflects progress and, as noted elsewhere, an increasing number of trials submitted to the FDA across diseases contain PROs (6). Nonetheless, we can and should do better. Arguably, information about how patients feel and function during therapy is essential to understanding risks, benefits, and value—and there is no substitute for collecting this information directly from patients (2). As an oncologist, the first question I am asked by most patients when discussing a treatment is how prior patients felt. Without PRO data, we are left without this information. Similarly, accurate assessments of tolerability and benefits by regulatory authorities and payers are incomplete without understanding treatment impact on the patient experience. In the United States, this sensibility is encoded in 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.

The FDA authors also find that PROs are substantially less commonly included in open-label controlled trials (about 25% less frequently), which may reflect a bias among investigators that patients' self-reports may be compromised when they are aware of study arm allocation (eg, a belief by investigators that patients might report more symptom improvement simply because they know they are on an investigational arm, and vice versa). However, there is no evidence to support this assertion; in fact, prior analyses suggest no meaningful impact of study arm knowledge on patients' PRO reports (8). Therefore, drug developers should be encouraged to include PROs in open-label oncology trials.

Similarly, Roydhouse et al. (4) find PROs are less commonly used in single-arm trials (more than 40% less frequently). This may reflect a bias among investigators that information about the patient experience is only valuable when between-arm comparisons can be made. Yet in this context, patient-reported information about symptomatic adverse events is valuable, and should be collected, for example using the NCI's Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). The PRO-CTCAE is publically available without fees from the NCI at https://healthcaredelivery.cancer.gov/pro-ctcae.

Reassuringly, the FDA authors found that rates of including PROs do not differ for trials depending on breakthrough status or priority review. There are limitations in their analysis, most notably that some trials did not have sufficient information to quantify completeness of PRO data collection. The authors are currently analyzing those trials to manually quantify this information, and I would suggest requiring sponsors to provide quantitative information about completeness of PRO data in their submissions to the FDA.

In conclusion, I applaud the authors (4) and the FDA's Office of Hematology and Oncology Products, as well as the FDA's new Oncology Center of Excellence for their recent exemplary efforts analyzing internal data and convening stakeholders to advance science and promote standardization for PRO data collection in oncology drug development. Their work has been enormously effective in advancing this field and forming consensus. Moving forward, for the vision of patient-centered cancer drug

development to come to fruition, industry sponsors will need to enlist experts on PRO design and communicate with regulators early in programs to assure that rigorous and meaningful patient-reported endpoints are included in trials, with strategies to assure data completeness. Such proactive and thoughtful approaches to PROs in trials will generate the information we need to fully understand the value of oncology drug products to patients and society.

Notes

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References

1. Kluetz PG, O'Connor DJ, Soltys K. Incorporating the patient experience into regulatory decision making in the USA, Europe, and Canada. *Lancet Oncol*. 2018;19(5):e267–e274.
2. Basch E. Toward patient-centered drug development in oncology. *N Engl J Med*. 2013;369(5):397–400.
3. Inserro A. MEDCAC panel mostly endorses PROs for CAR T therapies. *Am J Manag Care*. Newsroom, August 22, 2018. https://www.ajmc.com/newsroom/medcac-panel-mostly-endorses-pros-for-car-t-therapies. Accessed on October 11, 2018.
4. Roydhouse JK, King-Kallimanis BL, Howie LJ, Singh H, Kluetz PG. Blinding and patient-reported outcome completion rates in US Food and Drug Administration cancer trial submissions, 2007–2017. *J Natl Cancer Inst*. 2019;111(5):459–464.
5. U.S. Department of Health and Human Services, Food and Drug Administration. *Guidance for Industry: Patient-Reported Outcomes Measures: Use in Medical Product Development to Support Labeling Claims*. 2009. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf. Accessed on October 11, 2018.
6. DeMuro C, Clark M, Doward L, Evans E, Mordin M, Gnanasakthy A. Assessment of PRO label claims granted by the FDA as compared to the EMA (2006-2010). *Value Health*. 2013;16(8):1150–1155.
7. 21st Century Cures Act. 2016. https://www.congress.gov/bill/114th-congress/house-bill/34/. Accessed on October 11, 2018.
8. Atkinson TM, Wagner JS, Basch E. Trustworthiness of patient-reported outcomes in unblinded cancer clinical trials. *JAMA Oncol*. 2017;3(6):738–739.