Patient-Reported Outcomes for Tolerability Assessment in Phase I Cancer Clinical Trials

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Patient-reported outcomes (PROs) have historically been used in clinical trials to assess symptoms or quality of life in pivotal (late phase) or postmarketing trials. More recently, interest has risen to use PROs to elicit information about symptomatic adverse events directly from patients, for example, nausea or peripheral sensory neuropathy associated with investigational treatments (1).

Indeed, there is evidence that the current standard approach to symptomatic adverse event reporting in clinical trials, which depends on clinical investigator reporting rather than patient reporting, has substantial limitations. Clinician reporting of patients' symptomatic adverse events has been found to have low inter-rater reliability (2), whereas direct patient reporting of this information is highly reliable (3). Moreover, clinicians have been found to miss up to one-half of patients' symptoms (4,5).

A recent white paper by regulatory, industry, and academic authors recommended that the currently held concept of tolerability be expanded to encompass the patient experience as directly reported by patients (6). Specifically, the report notes that "The tolerability of a medical product is 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. A complete understanding of tolerability should include direct measurement from the patient on how they are feeling and functioning while on treatment."

Towards this goal, there has been substantial progress to date. The National Cancer Institute contracted development of the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) (7). PRO-CTCAE is an item library of questions patients can answer about their symptomatic adverse events. There are 78 discrete adverse events represented in PRO-CTCAE, and these can be elicited individually as warranted in a trial. Each item was individually assessed for measurement properties in prior validation research (4). PRO-CTCAE is now widely used in oncology drug development programs and is freely available for use in research (https://healthcaredelivery.cancer.gov/pro-ctcae). The US Food and Drug Administration has embraced use of PRO-CTCAE in cancer trials (2) and created an online repository for visualizing these data (https://www.fda.gov/about-fda/project-patient-voice/aura3), with ongoing work to standardize reporting of PRO-CTCAE in drug labels.

Although there is now substantial experience embedding PRO-CTCAE in later-phase trials, use has been limited in early-phase research (8,9). It is not yet clear how PRO-CTCAE or similar tools can optimally be used in phase I. Initiatives at Princess Margaret Hospital Cancer Center have led the way in this area. Previously, Princess Margaret investigators demonstrated the feasibility of eliciting the complete PRO-CTCAE library of items from patients in phase I trials, with 96% patient adherence (10). This group now provides an important study in this issue of the Journal, demonstrating underreporting of symptomatic adverse events by investigators in phase I trials compared with patients (11).

In this study, Veitch and colleagues (11) administered the entire library of PRO-CTCAE items to 243 patients in phase I trials. As with prior work, they found high levels of patient adherence with self-reporting (completion rate = 98.7%). The authors reported low interrater agreement between patient and clinician reporting of adverse events, with clinicians missing many adverse events noted by patients. There were 19 adverse events reported 1% or less by clinicians that were reported 10% or more by patients, and 9 adverse events had 50-fold or greater underreporting by clinicians. These findings are consistent with studies outside phase I, where clinicians similarly underreported patients' symptomatic adverse events (5,6).

The implications of these findings are substantial. If investigators miss adverse events, there will be underestimation of toxicity of treatments, leading to inaccuracies when balancing risk and benefit and when establishing tolerable doses. This may result in costly delays or failures in the drug development pathway. Underdetection of adverse events also leads to missed opportunities to intervene clinically or develop supportive measures.

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Veitch and colleagues (11) note 50 symptomatic adverse event items that are particularly common in phase I that could be considered as part of a "core" set of PRO-CTCAE items for standard administration in early-phase trials. Previously, an industry group suggested selecting PRO-CTCAE items based on mechanism and prior experience (12). In early-phase trials, it is reasonable to consider eliciting a wide number of symptomatic adverse events when a product has limited experience in humans. An additional strategy is including a free text option for patients to enter additional symptom experiences (13).

The study by Veitch and colleagues (11) compared the incidence of adverse events between patients and investigators but did not compare the magnitude of reported symptoms. Prior work has shown that discordance is even greater when magnitude is considered, with investigators systematically downgrading severity compared with patients (6).

This study is a meaningful contribution to our understanding of using PROs in early-phase trials. It is now clear that patients are willing and able to self-report in this setting and can provide unique information that investigators otherwise miss. There is therefore a call for wider use of patient reporting in this setting. However, it remains unclear how the patient-reported information should ideally be used for decision making in early-phase trials. This is the needed next step towards standards and adoption. For example, should patient-reported information be conveyed to site clinicians or investigators in real time to inform their adverse event reporting, or should the patient-reported information be reviewed only by the central study team periodically for decisions? Should the patient-reported information be filtered or interpreted by investigators, or used unfiltered for decision criteria (clinician-graded CTCAE are often recorded every week)? How often should patient-reported information be collected in phase I trials? How should patient-reported information be incorporated to influence dose escalation or deescalation decisions in dose-finding trials and in determination of maximum tolerated dose and recommended phase 2 dose? How should trial designs and statistical analysis methods be extended to incorporate PROs? Future research should focus on these questions.

To achieve patient-centered drug development, methods are needed for integrating PROs into early-phase trials. Substantial strides have been made in this direction. Patients are the ultimate recipients of drugs, so their perspectives are essential to determining tolerability.

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