Patient-reported outcomes in drug safety evaluation

The current standard method for adverse symptom monitoring in clinical trials is staff reporting [1, 2]. This is generally conducted via a complex process of data transfer, during which clinicians interview patients and then document impressions in medical charts ad hoc; study personnel abstract these charts and convert reported symptoms to a standard lexicon such as the Common Terminology Criteria for Adverse Events (CTCAE) or MedDRA (Medical Dictionary for Regulatory Activities); and then terms are entered manually into a database.

Rife with opportunities for data entry errors, omissions, and misinterpretation, the current model is also unable to distinguish whether a nonreported symptom was truly not present (i.e. asymptomatic) or was simply not elicited (i.e. missing data). But what is perhaps most concerning about the current approach is that patients themselves are not directly reporting their adverse symptoms—this information is being filtered and in many cases altered by secondary reporters.

Why should it matter if we, as health professionals, rather than our patients, report adverse symptoms? Aren’t we trained to listen to our patients and understand and accurately communicate their experiences? In fact, it has been repeatedly demonstrated that health professionals underreport the incidence and severity of symptoms compared with patients’ own accounts, both in oncology [3, 4] and nononcology [5–7] settings. The potential end result of this phenomenon is an incomplete representation of drug toxic effects in published trial results and in drug labels.

The underlying causes of these discrepancies may lie in the sequence of data transfer outlined above or more likely in the multifaceted dynamics of patient–clinician communication. Regardless, the empiric observation of this disagreement requires interrogation of its potential ramifications for regulatory reporting, and consideration of alternative, potentially superior approaches.

Direct collection of patient-reported outcomes (PROs) presents one such alternative. PROs are already the accepted standard method for data collection in closely related areas: symptom efficacy evaluation, health-related quality of life, satisfaction with care, and drug compliance [8, 9]. In 2006, the Food and Drug Administration (FDA) issued a draft guidance document establishing PROs as the regulatory gold standard in these areas of evaluation when pertaining to labeling claims, paving the way for PROs also to be considered for evaluation of adverse events beyond labeling claims (e.g. in adverse reactions sections of drug labels) [10]. In fact, there is no regulatory barrier to patients reporting their own adverse events (AEs)—the FDA mandates that sponsors provide safety data during drug development and approval, but the source of primary data is not specified.

Why, then, is patient reporting not already employed in this setting? The answer is largely historical. During the early days of drug development, efficacy, rather than safety, was the focus of measurement [11]. However, due to multiple incidents of serious AEs occurring after approval (some well publicized), it became increasingly apparent that safety monitoring was important both to safeguard the public and to enhance scientific understanding of drug mechanisms.

In 1969, the United States FDA developed the Adverse Event Reporting System, a surveillance database used for the identification of safety problems of marketed drugs. However, this approach was limited because safety concerns were primarily identified from spontaneous reports following drug approval [12–14].

In 1984, the National Cancer Institute (NCI) developed the Common Toxicity Criteria (CTC), a lexicon of discrete items for prospective evaluation of safety in oncology trials [1]. In 2003, the CTC was substantially revised and expanded to improve anatomic site specificity and to expand criteria for surgical effects. At that time, the CTC was relabeled as the CTCAE version 3.0 and included 1059 items [15]. In 2009, version 4.0 was released, reducing the total number of items to 790 and harmonizing the CTCAE’s terminology with MedDRA (the standard AE lexicon used in industry trials beyond oncology).

The CTCAE has been, almost since its inception, a minimum requirement for reporting in NCI-sponsored treatment trials and has also been widely adopted by the pharmaceutical industry. It is the de facto standard for reporting of AEs in the oncology clinical trial literature. Its items were developed empirically by clinical experts and were not on the basis of literature reviews or prospective evaluation in patients, and the measurement properties of items have not been formally tested [1, 2]. The CTCAE therefore remains an impressive feat of logistical success but of unproven clinical validity due to its methodologic origins.

Items in the CTCAE can be divided broadly into three categories: laboratory tests (e.g. white blood cell count), technical measurements (e.g. blood pressure), and symptom evaluation (e.g. level of fatigue). The administrative procedures for processing items in all three categories have remained similar, ultimately depending on staff reporting. The predominant culture, which has evolved around current routines for AE reporting in oncology trials has failed to recognize that the third category may merit a different approach to data collection outside of the current model (i.e. PROs) [2].

The study reported by Cirillo et al. in this month’s Annals Of Oncology provides valuable further evidence of discrepancies between patient and provider adverse symptom reporting [16]. The authors report that physicians and patients poorly agree on the severity of several symptoms, while nurses seem to split the
difference—agreeing more strongly with patients in some cases and with physicians in other cases. On the basis of an underlying presumption that the patient’s report is the gold standard, the authors conclude that due to their relatively better agreement with patents compared with physicians, nurses could ultimately be entrusted to be the sole reporters of CTCAE adverse symptoms (if they received ‘adequate and specific training’).

The authors’ proposed approach would certainly be an improvement over the current paradigm. I would further build on the authors’ conclusions and argue that nursing documentation should not be considered as a replacement for patient direct reporting but rather as a complement to patient direct reporting. Data should be collected from both sources in trials because they are distinct and complementary. Indeed, clinicians’ reports of adverse symptoms have been found to be more highly associated with clinical end points (such as death or hospitalization), while patients’ reports more strongly correlate with day-to-day health status [17]. As such, they add information to each other and together provide a more complete picture of the overall impact of disease and treatment.

Could clinicians’ and patients’ accounts of adverse symptoms both be reported in published trials’ results and drug labels or would discrepancies cause confusion for end users? In fact, there are myriad examples outside of medicine in which professional and nonprofessional ratings are juxtaposed despite disagreements, such as Internet review sites for books, hotels, movies, or consumer electronics. Implicit in these sites is an understanding that professionals and nonprofessionals consider different criteria in their evaluation processes and both perspectives assist subsequent individuals with decisions. By comparison, drug labels—which include only the accounts of professionals—are missing half the picture. If both professional and patient perspectives were incorporated into drug labels, we could provide future prescribers and prescribers with a more complete profile of a drug’s toxicity.

Patient direct reporting of symptoms has been demonstrated as feasible in many published accounts (including the Cirillo et al. study), even in patients with end-stage cancers and high symptom burdens [18, 19]. Methods of data capture have been refined in related areas in which PROs are already standard, including paper, computer, handheld device, and interactive voice response/automated telephone systems.

In 2008, the NCI contracted the development of a patient-reported outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE), including the development of items, a software administration platform, validation work, and feasibility assessment [20]. This initiative includes development work across a consortium of six cancer centers (Memorial Sloan-Kettering; Dana–Farber/Harvard; M.D. Anderson; University of Pennsylvania; Duke; and the Mayo Clinic) and is led by the author. The PRO-CTCAE represents a nascent effort to integrate the patient perspective into oncology safety reporting. Many barriers will exist to implementation and dissemination of such a system, including logistics, cost, and most notably health care culture. But its aspiration is that in the future, when an oncologist sits with a patient to discuss starting a treatment, the impressions not only of the clinician’s colleagues will be available but also the accounts of the patient’s peers.

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