Patient-reported outcomes: an essential component of oncology drug development and regulatory review

When evaluating the risks and benefits of a new cancer drug, an understanding of the ways in which a drug affects how a patient feels and functions is crucial. Without such information, clinicians, patients, researchers, and regulators are left with an incomplete picture of the properties of that product; however, this situation is the norm in drug development programmes. Despite rising interest in patient-focused drug development in the past decade,[1] most drug developers still do not rigorously and comprehensively collect information directly from patients about symptoms or physical functioning in pivotal trials upon which regulatory approval is based.[2]

As a result, when I, as an oncologist, sit with patients to discuss starting new therapies, I am often unable to explain how patients tend to experience that treatment. For example, I am unable to adequately answer how many people had improvement of their cancer-related fatigue or pain. Or how many had symptomatic side-effects, like aches and pains? For how many did the tastes of foods change? How many had nausea, diarrhoea, or sleep disturbances? The list goes on. Indeed, most patients with metastatic cancer have symptoms associated with their disease that affect their physical functioning, and most have multiple bothersome symptoms from treatment.[3] Yet information about these symptoms, systematically collected from patients themselves, is palpably absent in drug development programmes. Moreover, because this information is not captured in clinical trials (or is captured poorly via inappropriate questionnaires or with substantial missing data), it is not available or acceptable to regulatory agencies when balancing risks and benefits of a new product, and is thereby

not available to include in drug labels for the public to consider when selecting treatment.

For more than a decade, regulatory agencies, particularly the US Food and Drug Administration (FDA) and European Medicines Authority (EMA), have championed the value of directly collecting such information from patients via patient-reported outcome (PRO) questionnaires. Indeed, the term PRO was popularised by the FDA in the late 2000s when it published a highly influential PRO methods guidance document,[4] which was reinforced by an equally influential reflections document from the EMA.[5] A new accomplishment since then is a framework for PRO data collection presented and published by the FDA that focuses on three domains: cancer-related symptoms, physical functioning, and symptomatic adverse events.[6] Arguably, the FDA and EMA have been two of the most influential entities to move the field of PROs forward, and have, more broadly, recognised the concept of a patient-centred approach to clinical research. By recognising the key role of the patient voice in drug development and the importance of methodological rigour when collecting PRO data, these agencies brought PROs and patient engagement into public discourse. As such, there have been substantial positive consequences as this ethos percolated into the cultures of many funding agencies, professional societies, and even legislation.[1]

In this issue of *The Lancet Oncology*, representatives of the US, Canadian, and European regulatory authorities describe their current perspectives on PROs in drug development.[7] All authors agree on the importance of PROs in drug development for understanding the impact of treatment on disease-related symptoms and symptomatic adverse events. Canada has the least experience considering these endpoints, but laudably has joined the conversation in this Policy Review, and hopefully will become more engaged with PROs in time, particularly given how progressive Cancer Care Ontario has been in integrating routine collection of PROs across all oncology clinics in that province. The USA and Europe provide candid views of the challenges they face with directly reported patient perspectives.

First, they acknowledge that PROs are still not included in most drug labels, restricting the public's ability to understand the patient experience with drug products. Several key barriers are noted, including missing PRO data in trials, poor rigour of PRO designs in trials, and scepticism about the trustworthiness of PRO data in open-label trials (particularly from the FDA). Indeed, the path to solutions lies in the hands of these regulators.

***Panel:* Simplified framework for drug developers to include PRO measures in oncology drug development**

Guiding principles

- PRO data are informative in all trials in which efficacy or adverse events are considered important, regardless of whether the trial is blinded
- When evaluating the risks and benefits of a new cancer drug, an understanding of what ways the drug affects how a patient feels and functions is essential; without such information, we are left with an incomplete picture of the properties of that product; this information applies to all pivotal trials, including unblinded trials

Cancer-related symptoms

- Before starting a pivotal trial, provide evidence on what cancer-related symptoms are prevalent and meaningful in a given target population; evidence should be based on qualitative interviews and surveys done by the sponsor or using previous documentation
- In a pivotal trial, PRO data should be collected systematically at baseline and during treatment to assess for improvements or worsening of these symptoms, or both, with a justified frequency of assessment

Physical functioning

- At baseline and during treatment, systematically collect PRO data to assess improvements or worsening of physical functioning, with a justified frequency of assessment

Symptomatic adverse events

- Before starting a pivotal trial, provide evidence on what symptomatic adverse events are likely to be associated with the drugs in all study groups
- Systematically collect PRO data for these adverse events at baseline and frequently (eg, every 2 weeks) during active therapy, and every 6 months following treatment for 2 years

General methods

- PRO questionnaires should have reasonable evidence that patients understand the terminology in each question item; this evidence should be based on qualitative interviews in a previous patient population that is not necessarily the same as the target population in the trial
- PRO questionnaires should have reasonable quantitative measurement properties that have been tested in a previous patient population that is not necessarily the same as the target population in the trial, including construct validity and reliability
- Translations (ie, linguistic adaptations) should have evidence that patients understand the terminology in each question item; this evidence should be based on qualitative interviews in a previous patient population that is not necessarily the same as the target population in the trial
- Absent PRO data should be minimised at key timepoints (as defined by each study) by a comprehensive data-collection plan, such as continuous PRO adherence monitoring and backup data collection (eg, telephone calls to capture data from non-reporting patients)
- An a priori analysis plan for PROs should be included in the study's protocol

PRO=patient-reported outcome.

Pharmaceutical sponsors that develop drugs are opportunistic by necessity. They jump through multiple hoops to bring their drugs to market, which in the oncology field can be highly lucrative. Therefore, vast infrastructure and resources are in place to navigate the regulatory landscape. In situations in which regulatory authorities have clear expectations about a process, companies will comply. However, these agencies have not clearly articulated whether the rigorous inclusion of the patient experience with drug products should be an expectation. Instead, the message of the Policy Review has focused on how agencies would like to see PRO information if it is included in a trial or package. The agencies have done substantial work on what PRO endpoint designs should look like, which has perhaps impaired the industry working out these designs for themselves. Some investigators have felt that the FDA's guidance and implementation in reviewing PRO endpoints in trials has been overly prescriptive and focused on non-substantive minutia[8] rather than on providing a broader framework that emphasises key concerns like missing data and choice of PRO questionnaire—which the authors now bemoan.

Now that these agencies have developed familiarity with PRO methods, they could clarify that PRO data collection is an expectation from drug developers, without which an application is considered incomplete because the patient experience is unknown. To provide assistance to sponsors, a simplified list of methodological considerations would be useful—as outlined in the panel—to balance the necessary level of rigour needed with pragmatism. Examples of PRO collection in pivotal trials exist with tiny amounts of missing data and reasonable design, although perhaps not perfectly aligned with FDA guidance criteria.[9]

As far as the FDA's concern that PROs are not trustworthy in open-label trials because patients' reports of symptoms might be biased by knowing their treatment allocation, no empirical evidence exists to support this conclusion, and it has not been supported by previous psychobehavioural research. In fact, evidence exists that describes the contrary effect.[10] By harbouring this belief, the FDA is presenting an additional barrier to the patient voice being included in drug development, since an increasing number of pivotal trials in oncology are unblinded.

In summary, I believe that the future behaviour of drug developers for including rigorous PRO assessments in trials lies in the hands of the authors' respective regulatory agencies. If a clear message is sent at multiple touchpoints of communication that rigorous assessments of the patient experience are expected in both the pre-marketing and post-marketing settings, drug developers will enlist internal and external experts to meet these expectations with reasonable designs and minimal missing data. The substantial and ongoing efforts of these agencies to develop standards and standardisation is highly laudable and productive; however, without articulating the essential nature of PRO information in the review process, the quantity and quality of PRO data in cancer drug development will continue to be restricted.

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I declare no competing interests.

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