

Learning from Patients: Reflections on Use of Patient-Reported Outcomes in Lung Cancer Trials

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As patient-focused drug development matures, significant interest exists among therapeutic drug developers, regulatory agencies, and payer bodies to increase the rigor and utility of patient-reported outcome (PRO) data. PROs relating to symptoms, function, and overall health-related quality of life have long been incorporated in cancer clinical trials. Item redundancy and relevance are two important issues for trial participants, whereas the inclusion of PRO measures that are sensitive and relevant to the primary objective of the clinical trial is important to trial sponsors. Balance between sponsor and patient preferences to create a more parsimonious PRO strategy can only be achieved by re-evaluating current PRO measures developed during the 1990s. With technological advances helping fuel progress in this area and heightened interest in these data, we have an opportunity to enhance current PRO efforts.

Using lung cancer as a case study in defining best approaches for incorporating patient reported information into the oncology drug development and approval process, LUNgevity Foundation (LUNgevity) launched a PRO-focused initiative for its Scientific and Clinical Roundtable. LUNgevity convened two meetings to advance understanding of the current landscape and opportunities to enhance future PRO collection. The first meeting, held March 23, 2018, was an interactive roundtable designed to elicit key stakeholders' perspectives. Efforts were considered for leveraging opportunities and addressing challenges associated with measuring and using data from PRO assessments and other clinical outcome measures from lung cancer clinical studies. Participants included senior representatives of U.S. Food and Drug Administration (FDA), National Institutes of Health, National Cancer Institute, United Kingdom National Institute for Healthcare Excellence, Medicines and Healthcare Products Regulatory Agency

UK, pharmaceutical industry, patient advocacy, and the clinical and academic community. The agenda focused on evaluating what outcomes to measure and how to measure them. Key takeaways included the following: (1) Participating stakeholders recognize the potential utility of PROs in clinical trials; (2) PRO experts within industry seek clear guidance from regulators to make the case with company leadership that PROs be gathered; (3) Continued efforts are needed to coordinate and harmonize expectations and requirements among global regulators; (4) There is a need to develop a core set of concepts as a standard expectation for trials investigating the safety and efficacy of cancer therapies; (5) A core set of concepts was proposed for lung cancer, including symptomatic adverse events (AEs), overall effect bother/impact, physical function, and disease symptoms; (6) PRO measures need to capture concepts that address patient needs, but also reflect the needs of clinicians, sponsors, regulators and health technology assessment officials; and (7) Further discussion is needed on how to communicate PRO data from trials to patients and clinicians.¹

The second meeting, the subject of the remainder of this commentary, was a follow-up roundtable discussion involving 17 lung cancer patients and leaders from the FDA. The discussion, designed as a listening session,

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elicited feedback regarding core elements of PROs that the FDA has previously proposed, including disease symptoms, symptomatic side effects, the overall impact/burden from side effects, and physical function.^{2,3} Patients reiterated their primary interest in survival and reinforced the importance of the quality of their extended lives, including impact of treatment side effects and related limitations on normal activities.

In addition to feedback regarding the proposed core PRO outcomes, patients raised an important point regarding their understanding of how PROs were used in clinical trials. Many patients thought their PRO responses were evaluated by their physician and the trial sponsor in real time, and therefore would be used in ongoing decisions about their care. In short, the informed consent form had failed to educate some of the patients at the roundtable that answers they provided to PRO questions were meant to inform regulatory and payment decisions to benefit future patients and their clinicians — not their care while on trial.

Some patients commented that they might under-report their side effects, symptoms, or functional limitations, due to fear of being removed from the trial. Thus, PRO data from these patients may not be an accurate reflection of their experience. One patient said, “I would want to emphasize that it would be very important to have that disclaimer right up front that gets checked off that by reporting accurately what we’re asking you about, you do not risk being kicked out of the trial.” As healthcare providers in trials rely on patients to inform them of symptomatic toxicity during clinic visits, this patient’s tendency to under-report harm also applies to standard clinician-assessed AEs that generate labeled safety information. The discussion highlighted that there is a knowledge gap; FDA representatives assumed patients were aware of how their PRO data were used and some patients at this roundtable believed their PRO data were reviewed by healthcare providers in real time.

We acknowledge that the roundtable included a sample of 17 highly engaged lung cancer patient advocates; a unique subset of all lung cancer patients and their views. However, our interaction illuminated an important potential gap in current patient education about safety reporting and the use of PROs in clinical trials that warrants further research. It is possible that with less engaged patients and/or patients from different countries and cultures, this gap may be even larger. This informal engagement activity served only as a first step in advancing the thoughtful collection of PRO data. Furthermore, formal qualitative studies to prospectively characterize the extent of this issue and identify ways to improve patient understanding are needed.

To our knowledge, no studies have addressed the issue of patients under-reporting treatment side effects. Studies investigating agreement between patient- (PRO) and clinician- (Common Terminology Criteria for Adverse Events safety) reporting of symptoms have mostly focused on clinician under-reporting. These studies found that patients reported higher frequency and severity of AEs compared to the clinician-recorded safety data.^{4,5} Both studies were specifically designed to assess the comparability of patient and clinician reporting and did not address the comparability of reports of AEs between clinicians and patients in commercial clinical trials. Patients at our roundtable who were speaking of their experience on commercial clinical trials noted that the most common reason for under-reporting was fear of being dose-reduced or discontinued from their cancer therapy.

Some trials may come to use PRO data to improve symptom control in real time, and many others will not review the PRO data during trial conduct. In instances where PRO data are used real-time to guide care, the intention is to direct early supportive care — a strategy that has been reported to reduce hospitalizations.⁶ In fact, early supportive care may help prolong the time a patient can remain on cancer treatment, the opposite of the concerns patients who attended the roundtable expressed (i.e., using PRO data to take patients off trial). The use of PROs for symptom monitoring is not currently standard in commercial cancer trials and not required by FDA or institutional review boards.⁷ Regardless of how PRO data are used, the issue raised during this roundtable is that there appears to be a need to better educate patients on the importance of accurately reporting symptoms.

There are advantages and disadvantages to the current approach of keeping patient-reported symptoms separate from clinical care in commercial trials. One advantage is that patients who are aware that their information will not be shared may more accurately report. The clear disadvantage is that patients lose the potential to communicate symptoms earlier than scheduled clinical visits to initiate timely supportive care. Regardless, informing the patient about whether their PRO data will be shared or not should occur at each assessment and patients should always be informed to contact their healthcare provider directly for any concerning symptoms to ensure patient safety.

Recent roundtable discussions by LUNGeity note that multiple international stakeholders are recognizing the utility and growing interest in measuring symptoms and function in cancer trials. Patient-reported outcomes are one source of this important data, but patients must be educated regarding the objective of collecting this information. It may not be clear to patients that accurate

and timely symptom information can lead to supportive care to relieve suffering and maximize the ability to remain on their investigational cancer therapy. Withholding symptom information either directly from treating physicians during face-to-face encounters in clinic, or indirectly through completion of PRO assessments, may result in the outcome patients are most concerned about — dose reductions or discontinuation due to severe AEs that may have been avoided with earlier supportive care. Informed patients are empowered patients, and by understanding the reasons behind symptom monitoring and PRO assessments, trial patients can benefit from timely supportive care, and future patients can make standard treatment choices based on accurate safety data and complementary PRO data obtained from clinical trials.

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