Trends Driving the Use of ePRO in Oncology Trials

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Patient-reported outcomes are becoming more critical to regulators’ decision-making in oncology.

Not so long ago, oncology treatment options were limited to cytotoxic chemotherapies, radiation, and surgery. Today, however, the pharmaceutical industry’s understanding of how cancer develops is such that there are now targeted therapies available for many cancer types. And more are on the way. According to PhRMA, there are more than 800 medicines and vaccines for cancer either in clinical trials or awaiting approval by the FDA.

So, at this point, regulators can raise the bar as they evaluate oncologic treatments. Increasingly, they’re requesting that sponsors demonstrate more than an investigational oncology product’s efficacy, as evidenced by survival and toxicity tests; they would like to see evidence of the product’s treatment benefit in terms of symptom relief and holistic patient impact. Efficacy measures such as survival fall short of providing all the needed information on a product’s therapeutic benefit because they lack information on the patients’ symptoms, adverse events, pain and rescue medication, experience while undergoing treatment, the quality of their survival, and the social and personal impacts of the disease/disease burden.

At the same time, the nature of a cancer diagnosis has changed for many tumor types. Some cancers can now be considered a chronic disease rather than a fatal illness, and those with the disease can be thought of as “people living with cancer” rather than “cancer patients.” In fact, many become cancer survivors—a surprising 4% of the U.S. population are cancer survivors, as reported by the American Cancer Society. Consequently, regulators, physicians, and patients entering treatment have a keen interest in knowing what the symptomatic burden of a treatment is likely to be, as well as adverse event profiles in the near and long term and what impact cancer therapeutics may have on other organ systems and co-morbid conditions. Patients will need to consider this information as they make treatment decisions.

Patient-reported outcomes (PROs)—which include measures of symptoms, health-related quality of life (HRQL), health status, and treatment adherence and satisfaction—are a recognized means both of satisfying regulators and providing information of interest to physicians, patients, and caregivers. PROs, in combination with relevant clinical markers, can provide a complete picture of health status and changes in health status that is both patient-centric and applicable across disease populations, enabling finer tuning of total drug impacts on efficacy, safety, and co-morbid conditions.

FDA’s growing interest in PRO

The first signs of the FDA forming a new position on PRO in oncology trials can be traced to a specific decision the agency made in May 2014 on a new drug application (NDA) for a breakthrough melanoma treatment. The agency denied the application in part because, while the trial design measured lesion response, it did not include assessments of patient symptomatology specific to the disease. Nor did it require enrollment of patients with significant pain symptoms.

Then, in April 2015, the FDA issued draft guidance on non-small cell lung cancer (NSCLC), stat-
ing, “While overall survival remains the standard endpoint of clinical benefit, PRO measures of tumor-related symptoms and functioning can represent direct measures of treatment benefit if demonstrated to be well-defined and reliable.” The NSCLC guidance also made clear that PRO data ideally should include information on the use of rescue medication as a secondary outcome measure. This disease-specific guidance is not directly applicable to other cancers, but is an indication of the agency’s mindset and may signal that there is more to come on this topic.

**Specificity from the European Medicines Agency**

The European Medicines Agency (EMA) has issued more straightforward and far-reaching guidance on PRO than the FDA in its “Reflection Paper on the use of patient reported outcome measures in oncology studies,” published in June 2014. The paper states that PRO data are “welcomed from a licensure perspective,” provided that they are “derived from instruments capturing the consequences of adverse reaction on patient wellbeing, in an unbiased way,” clarifying that the measures “must have acceptable responsiveness, reliability and validity, and may include reference to symptoms, functional status, treatment adherence or satisfaction with care.” The EMA considers symptomatology “particularly significant in the palliative or maintenance setting.”

More recently, the EMA released an appendix to the original oncology guidance, entitled, “The use of patient-reported outcome (PRO) measures in oncology studies.” This guidance states, “The importance of the patient’s point of view on their health status is fully acknowledged, and such information may be used in drawing regulatory conclusions regarding treatment effects, in the benefit-risk balance assessment or as specific therapeutic claims.” The EMA emphasizes that characterizing the time to deterioration of tumor-related symptoms is complementary to the determination of progression-free survival and, thus, may be important in establishing a treatment benefit.

**A shift toward more proximal measures**

Simultaneously, regulators are now recommending more salient PRO measures than what the industry has historically used. Traditionally, exploratory endpoints have been measured via instruments that collect data on health-related quality of life. These, in the words of the EMA Reflection Paper, measure “a patient’s subjective perception of the impact of his disease and its treatment(s) on his daily life, physical, psychological and social functioning and well-being. The notion of multidimensionality is a key component of the definition of HRQL.”

Quality-of-life-based instruments typically are administered at nodes in time and often are not disease-specific. It has become evident that the patient’s characterization is the optimal methodology for understanding changes in health status specific to disease progression or its attenuation. Therefore, it is critical to gather, in patients’ own words, what their exact experience is, what it feels like, and how they describe their symptoms. The reliability and sensitivity of the information that is gained can be maximized through the development and validation of instruments that align the patient experience with the disease. Further, because symptoms are frequently impacted daily, it is equally important to use instruments that detect and record changes at frequent intervals. Thus, only collecting a QoL measure, for example, on a monthly basis provides a mere snapshot of a patient’s health status and can be clouded by factors such as recall bias, recency effects, or an extreme event.

According to Paul G. Kluetz, MD, a clinical reviewer in the FDA’s Office of Hematology and Oncology Products, regulators are starting to consider HRQL measures as insufficient, and they are “favoring assessments of proximal symptoms and functional outcomes that are more directly related to the effect of the drug.” Indeed, this was borne out in the FDA decision on the break-through melanoma product mentioned above, as that package used HRQOL data.

Efforts have been underway to develop and validate novel tools that are more sensitive and reliable, such as the PRO version of the Common Terminology Criteria for Adverse Events (CTCAE), which has converted clinical terminology into patient-facing terminology. The National Cancer Institute (NCI) developed the CTCAE in order to incorporate the patient perspective into assessments of adverse events. The work identified 80 cancer-related adverse events suitable for self-reporting by patients.

**Supporting a patient-centered approach**

Within the broad context of making clinical trials more patient-centered, PRO measures are important to clinical research. In fact, studies show that patients can better and more accurately report on adverse events associated with cancer such as nausea, fatigue, appetite loss, constipation, diarrhea, neuropathy, and dyspnea than the clinicians who historically have collected these profiles. And they do so sooner and more frequently. Clinicians are trained to watch for benchmark events in the status of disease and systematically may miss patients’ adverse symptoms, including at baseline, in trials. In contrast, patients can reliably report on their disease-related symptoms, and by doing so on a daily or regular basis, they can significantly reduce or eliminate the impact of reporting gaps.

To be captured accurately, most symptoms generally need to be recorded on the day they occur. The event’s frequency, severity, and duration are key factors in determining how often a symptom should be captured. Frequent symptom reporting also helps to eliminate recency errors (in which a recent event may be weighted more heavily than those in the past) and errors in reporting, such as a patient trying to average a symptom over the course of days or weeks.

Sharing patient-reported data with clinicians helps to direct their care. In a study of nearly 3,000 cancer patients reported in the *Journal of Clinical Oncology*, 79% of participants agreed that the clinical team took their symptom scores into account when deciding treatment.

Some sponsors express concerns as to the feasibility of using
PRO with oncology patients—particularly via electronic tools—fearing that the process may be a burden to subjects or that it may be hindered by their health status or age. However, studies have repeatedly demonstrated that compliance among oncology patients in completing electronic PRO (ePRO) instruments is high and stable (see Figure 1). Other research has found no difference in compliance rates in oncology studies versus other indications. Overall, ERT has recorded 95% to 100% completion rates of tablet questionnaires given to patients during site visits and 83% to 95% completion rates with handheld diaries over the course of clinical trials—statistics that hold true in oncology clinical studies.

**Methods for easing patients' burden and improving compliance**

**Simplify questionnaires**

Even so, it makes sense to make the process as easy as possible for patients. Many traditional HRQL instruments include over 30 questions, and typically patients require approximately 10–12 minutes to complete 35 items. In order to collect reliable symptom information frequently, the number of items in the questionnaire can often be on the order of three to eight items that measure symptoms proximal to the treatment, bringing the completion time down to two to four minutes. For each symptom, questions typically focus on the presence or absence of a symptom and its frequency, severity, and/or duration.

Using a specific and simple instrument completed by the patient is far preferable to turning to caregivers for survey completion; caregivers are one step removed from the source and should only report what they observe, rather than what they perceive as the patient’s experience. What’s more, their ratings may be influenced by their own stress levels. The EMA Reflection paper points out, “There is generally discordance between ‘patient’ reported PRO and ‘proxy’ reported PRO. The evaluation of PRO by [care-

**Rely on electronic capture**

The question has been raised as to whether cancer patients’ age or lack of familiarity with technology affects their participation in ePRO, but these concerns have been determined to be unfounded. Research has actually shown advantages to electronic reporting within cancer trials via tablets during site visits or via handheld devices at home. In particular, there is ample evidence that ePRO tools yield:

- **Higher patient acceptability.** In an equivalence test between electronic handheld devices and paper questionnaires with NSCLC patients, 60% preferred electronic capture, vs. 12% for paper. In a study of metastatic breast cancer patients, 98% of subjects reported that it was easy to respond to questions using e-Tablets, and 94% of subjects would recommend the e-Tablet to other patients.

- **Improved data quality.** In a study of various cancers using both electronic and paper-based reporting, there were no missed responses in the electronic version compared to 397 missing/multiple/changed responses and 725 scanner-related errors in the paper version. The paper entries had to be checked and verified manually at significant time and cost.

- **Better communication with clinicians.** In one study of 660 cancer patients across diagnoses and stages, one group of patients reported their symptoms electronically prior to their clinician visit while the control group did not. The visits among the reporting group generated 29% more discussion of symptoms and HRQL factors than among the control group.

**Provide education**

The EMA, both in its original position paper and its appendix, stresses the importance of comprehensive education programs in gaining compliance. These programs should be directed to study participants as well as to investigators and the entire clinical research team. The training should go beyond the mechanics of how to complete the PRO, to explain the importance of doing so. Specifically, the EMA recommends, “Comprehensive education and training of research staff, including investigators and the whole clinical research team, in order to ensure they understand the importance of PRO assessment and will be able to motivate their patients to complete the PRO instruments.”

The agency further emphasizes the importance of ‘education and training of patients before completion of the questionnaire,
including that there is no incorrect answer and explaining the purpose of the assessment.”

Best practices in collecting PRO in oncology trials

• Incorporate PRO endpoints into the protocol that map specifically to the symptoms experienced by patients in the specified indication.
• Collect data from patients frequently and “in the moment” rather than infrequently at designated points in time (such as during site visits). The frequency should be determined based on the symptom’s frequency, severity, and duration.
• Collect data directly from the patient whenever possible.
• Keep it short. PRO can be reduced to questions directly related to symptoms (between 3-8 questions) that will take the patient 2-4 minutes to complete electronically.
• Use electronic data capture technologies whenever possible to satisfy patient preferences, improve data quality, and strengthen communication between patients and physicians.
• Educate sites and patients not only on how to complete PRO instrument, but on why it is important. The EMA considers education on using PRO as a methodology for improving compliance, motivation, and engagement.

Regulators in the US and EU are not only accepting of PRO data in oncology trials—they are asking for it. But, they are not necessarily interested in traditional HRQL measures which are distal to the symptoms that patients experience. Rather, they are showing a preference for proximal measures that relate directly to patients’ symptomatology. The myths that many hold about the feasibility of using ePRO in cancer trials are unfounded; cancer patients are compliant with ePRO surveys, comfortable with the tools, and see the practice as a positive factor in their treatment.

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References
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3. “Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics: Guidance for Industry,” FDA, April 2015

Figure 2. Methods for easing patients’ burden and improving compliance.