Regulatory guidance for PRO strategy in oncology trials

Kelly Dumais, PhD, Principal Scientific Advisor

Jowita Marszewska, PhD, Scientific Advisor

CLARIO.

The regulatory landscape in oncology trials has been evolving fast. Oncology drug approvals are now based on more than just survival and tumor response.

Regulators expect Sponsors to incorporate the patient voice and collect more symptomatic data to understand a drug's full impact on patients' functioning, well-being and quality of life. Failure to do so may lead to denial of getting patient-reported data on drug labels and ultimately make it harder to differentiate an oncology drug in a highly competitive market.

The most recent regulatory developments that impact your PRO strategy include:

June 2021 – FDA's Core PROs in Cancer Clinical Trials Guidance for Industry

1. Here the FDA provides detailed guidance on what to measure with PROs, considerations for PRO selection, and how often to collect them.

June 2022 - FDA COA in Oncology Trials Industry Workshop

1. The 7th annual workshop brought industry leaders together, including regulators, experts and patient advocates, to discuss emerging themes relating to the use of PROs in oncology trials.

In the following guide, Kelly Dumais, Principal Scientific Advisor and Jowita Marszewska, Scientific Advisor at Clario eCOA, set out in more detail how these regulatory developments impact PRO Strategy.

Kelly Dumais,
PhD, Principal Scientific Advisor

Jowita Marszewska,
PhD, Scientific Advisor

FDA Guidance – Patient-Centered Oncology Research

Another Step Forward: FDA's Core Patient-Reported Outcomes in Cancer Clinical Trials Draft Guidance for Industry

The evolving regulatory landscape of oncology clinical trials has just added another guidance to its docket. This month, the FDA released a draft guidance for industry on "Core Patient-Reported Outcomes in Cancer Clinical Trials"[1], issued by the Oncology Center of Excellence (OCE), Center for Biologics Evaluation and Research (CBER), and Center for Drug Evaluation and Research (CDER).

This is a big step forward in the acknowledgement of the importance of patient-centered research within the oncology field. There have been many initiatives coming out of FDA's OCE, whose mission is to "achieve patient-centered regulatory decision-making." Annual public workshops on clinical outcome assessments (COAs) in cancer clinical trials, patient-focused programs such as Project Patient Voice and Project Community, are a few of these initiatives that have provided best practices on collecting and disseminating oncology patient-reported outcome (PRO) data.

Now, in this new draft guidance, the FDA has provided recommendations on how to best incorporate PRO measurements into oncology clinical trials in efforts to correct the historical "heterogeneity in PRO assessment strategies [that] has lessened the regulatory utility of PRO data from cancer trials".[1] It provides guidance on PRO strategy, trial design considerations, and labeling considerations, including recommended procedures when seeking PRO-based labeling.

In line with recommendations for a core set of PROs described previously in the literature[2], the new FDA Guidance recommends collecting PROs that map to these core concepts:

1. Disease-related symptoms
2. Symptomatic adverse events
3. Overall side effect impact summary measure
4. Physical function
5. Role function

The guidance includes examples of PROs for all categories, and states that additional PROs outside of these core categories may be beneficial (e.g., measuring cognitive function in neuro-oncology). Importantly however, the FDA acknowledges the need to minimize patient burden as much as possible, by "focusing on the most meaningful and measurable outcomes," and selecting only "the most important and/or high frequency AEs to reduce question burden."[1] The guidance also states that the use of electronic PROs (ePROs) may be a useful method for reducing patient burden by allowing for at-home completion.

Frequency of PRO administration was another important topic, which aligns with recommendations discussed at last year's 5th annual FDA-ASCO Public Workshop on COAs in cancer clinical trials. The frequency of PRO assessments should be thoughtfully considered to be sure that the patient symptomatology is being adequately captured and represented. For example, assessment frequency should take into account the administration schedule of the drug and the administration type (e.g., intravenous or oral), as these will have a significant impact on when symptomatic AEs may occur. Importantly, while recommending to have more frequent assessments within the first few treatment cycles, the FDA keeps with their theme of considering patient burden by suggesting that, when appropriate, different assessment frequencies can be selected for each PRO in order to reduce response burden.

With more people living with cancer now than ever before, it is imperative to truly listen to the patient voice and measure what is most important to patients as we seek to deliver new treatment options. By providing guidance on what core PRO categories to include, considerations for instrument selection for each category, trial design considerations, and PRO labeling considerations, this new draft guidance is a significant step forward in our ability to collect consistent PRO concepts in order to better evaluate and compare data across clinical trials.

New opinions and trends in oncology PROs: Learnings from the 2022 FDA COA in cancer trials workshop

The FDA's Oncology Center of Excellence (OCE) conducts annual public workshops on clinical outcome assessments (COAs) in cancer clinical trials. These workshops bring top leaders (and importantly, patient advocates) together for interactive conversations that seek to answer our most critical questions related to the use of patient reported outcomes (PROs) in oncology trials and to ignite innovative thinking. This year in June, the 7th Annual Clinical Outcome Assessment in Cancer Clinical Trials Workshop discussed the topic of using PROs in open label trials. We learned about overcoming barriers to incorporating PROs in open-label trials, and so much more.

Here are some key takeaways from this year's workshop:

- **Patient-reported data should be the gold standard in understanding patient symptoms and experiences.** Patients know their bodies best, and therefore, it is crucial to capture reports of their experiences with the drug using PROs. The importance of including PROs in clinical trials cannot be stressed enough considering the fact that ClinROs and ObsROs are subjective and prone to bias, with evidence that clinicians and caregivers underreport patient's symptoms for adult and pediatric patients.[3,4] Additionally, regulators often take a more conservative approach with the drug approval when PRO data is not available to complement clinician's observations.
- **The risk of open-label bias should not prohibit the use of PROs in open label oncology trials.** Most oncology trials use an open label trial design, leading to concern that the patient's perception of their symptoms may be influenced by their knowledge of their treatment (i.e., open label bias). While the concern and need for further research was acknowledged, the collective opinion from the panelists, supported by recent literature[5,6] (Atkinson et al., 2017; Efficace et al., 2022), is that there is little evidence or concern for open label bias in oncology trials and that their use in open label trials are valid and supported. Further, most oncology drug approvals that include PROs in the label were open label trials, supporting that this is an accepted practice by the FDA.

"To me, the message was clear. For Oncology trials, you must use PROs to fully understand the patient experience and to better evaluate tolerability. PROs should be included as early as possible in your drug development program."

Kelly Dumais, PhD, Principal Scientific Advisor at Clario

- **PROs should be a standard practice in every cancer clinical trial, even in early phases.** Omitting PROs in early stages of assessing drug's safety, tolerability and pharmacokinetics can have serious implications: Drug dose can be toxic or poorly tolerated but still would be moved forward to another phase. In addition to clinician reported tolerability and adverse events (AEs), optimal dose finding should include evidence of patient tolerability via PROs. PROs that assess tolerability (e.g., PRO-CTCAE) provide complimentary information to provide a more comprehensive and granular evaluation and should be included in all cancer trials, starting at phase 1.
- **Communicate to sites and patients the value of PROs.** Both experts and patients on the panel emphasized the value of an education and training of sites and patients. Patients participate in clinical trials for altruistic reasons and the more they know what is important and why, the more accurate and complete their reporting will be, leading to higher patient satisfaction and better compliance.

The industry is making significant strides in using PROs to bring the patient back to the forefront of clinical trials and making the patient voice heard. This year's FDA workshop on COA in cancer clinical trials provided another successful display of what can be accomplished when bringing everyone to the table: Regulators, academia, international experts and patient advocates.

References

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