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Commentary

Patient-Reported Outcomes in Early Phase Clinical Trials: An Opportunity to Actively Promote Patient-Centered Care

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Almost 5 decades have passed since patient-reported outcomes (PROs) were first recommended for inclusion in clinical trials by the European Organization for Research and Treatment of Cancer (EORTC) and the Cancer and Leukemia Group B.[1,2] In the time since, validated measures have been developed and implemented as a key component in the assessment of new therapeutic agents, with several phase III trials including PROs or Health-Related Quality of Life (HR-QOL) as secondary or exploratory endpoints. In a general sense, PROs provide insight into patients' perceptions of treatment, possible side effects, and impact on their quality of life. PROs can assess a variety of outcomes not traditionally measured in clinical trials, including pain, emotional symptoms, and psychosocial functioning and well-being. Traditionally, phase III PRO data are published after the release of primary outcomes related to efficacy measures (eg, response and overall survival). Together, such data enable providers to assess treatment benefits and risks and guide shared decision making. In contrast, phase I and I/II trials, in which researchers are establishing the safety and tolerability of a new drug, generally do not include PRO assessments or subsequent publications.[3]

Lai-Kwon et al. evaluated attitudes toward the inclusion of PROs in dose-finding oncology trials (DFOT) among international clinical trialists and the National Cancer Research Institute Consumer Forum in the United Kingdom.[4] A total of 112 participants responded to a survey regarding their previous experience with PROs in clinical trial design, along with preferences and attitudes toward the use of PROs to define tolerable doses. Prior to responding to the survey, participants viewed an educational presentation regarding the use of PROs in DFOT. The authors reported that, in general, participants possessed limited experience with PROs in DFOT. Despite this, they noted such assessments would be valuable and provide useful information on dose-finding and dose escalation. Further, the inclusion of PROs can provide insight into new types of toxicities associated with more recent treatment regimens and their frequency and duration. In addition, PROs can be a more effective way by which to track the impact of lower grade toxicities on patients' HR-QOL, replacing the less nuanced traditional approach of focusing on severe adverse events. Nevertheless, participants also highlighted important barriers, including a lack of guidance regarding the selection of the most appropriate measure, lack of experience or training in collecting this data, and handling missing survey responses.[4] Participants also highlighted that publishing this type of data was more challenging than the more traditional clinical trial outcomes.[4]

Even though this was a survey study among participants predominantly from the United Kingdom and United States, it provides valuable insight into the potential relevance of including PROs in early-phase trials, as well as the barriers that exist to such inclusion. For example, the current measures used to assess PROs or HR-QOL are inadequate and inappropriate for DFOT. In such circumstances, these questionnaires should measure outcomes that are meaningful to patients, including their perspective on benefits and harm in the context of new drugs in early development.[5] These data will help to better determine tolerability, type of toxicity, frequency, and duration. This is especially relevant given the inclusion of novel agents (immunotherapy and target therapies) in first-line therapy that may result in different side-effects and toxicities as compared with the traditional cytotoxic drugs. At present, the PRO-CTCAE is widely considered the most appropriate approach to assessing PROs. This measure is composed of 124 items covering 78 symptomatic toxicities.[6] Guidance for using the measure recommends including a core set of items relevant to expected treatment-related symptoms and anticipated toxicities, as well as a free-text section for unexpected toxicities.[7-9] No consensus has been reached regarding the most appropriate HR-QOL measure to be included in oncology clinical trials, with the EORTC QLQ, FACIT, and EuroQol 5 level measures commonly used.[3,10]

Furthermore, including PROs in early phase trials could possess several benefits. These include the promotion of regulator interest in patient perspectives, complementing traditional data on safety and efficacy, assessing feasibility to enhance future PRO strategies, helping to inform future sample size calculations, and providing preliminary efficacy data based

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on the patient experience.[11] As a result, such efforts represent an opportunity to increase patient engagement in early phase trials and enable them to track the progress of DFOT beyond conventional efficacy measures. These efforts much acknowledge the challenges of assessing HRQOL in early phase studies given the absence of substantial toxicity information in many cases. To achieve this end, it is necessary to develop a standardized approach to the measurement and reporting PROs in oncology clinical trials and to address the noted barriers to the inclusion of PRO findings.[12] Guidelines have been developed that address several of these barriers, including the SPIRIT-PRO Extension, the SISAQOL Consortium, and the CONSORT-PRO. These guidelines promote more comprehensive trial protocols and help to standardize the analysis and reporting of PRO and HR-QOL data.[13-15] Whereas there is not yet data regarding the adoption of these guidelines, one Consortium (PROTEUS) funded by the US Patient-Centered Outcomes Research Institute (PCORI) is promoting the application of these tools to optimize the assessment and reporting of PROs in clinical trials.[16] An optimal study design based on these guidelines can help inform clinical practice and treatment guidelines, promote shared decision-making, and informed consent for treatment. In addition, they can help inform health policy and support drug approval, pricing, and reimbursement decisions.[17] These efforts are important, especially among early phase trials, to promote the collection of patient-centered data that can help guide improvements in future clinical care.

Conflict of Interest

The authors indicated no financial relationships.

Author Contributions

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