EDITORIAL


The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force for Clinical Outcome Assessments (COAs) has presented a clear conceptual foundation for the development of precise clinical trial instruments and end points. This article reinforces the “begin with the end in mind” thought processes for clinical trial development, highlighting the need to match clinical outcomes with the concept of interest (COI) and the context of use (COU) to maximize the potential to demonstrate a meaningful treatment benefit. The value of integrating the clearly thought out conceptual nature of clinical outcomes into clinical trial development is not to be underestimated.

As billions of dollars are spent annually in drug development, the impetus to select the correct outcome for a clinical trial to maximize the likelihood of success is paramount. The ISPOR COA conceptual foundation presents much thoughtful work on the considerations of end point selection from a conceptual basis. In this report, the task force authors clearly review and outline the alphabet soup of acronyms that prevails when describing outcomes: COI, COA, COU, patient-reported outcomes (PROs), clinician-reported outcomes (ClinROs), observer-reported outcomes (ObsROs), and performance outcomes (PerfOs). These concepts are explained by the Food and Drug Administration (FDA) in its qualification guidance [1], but through this report, they have been described and illustrated in the context of outcome (instrument) and end point selection. Clearly thinking about what outcomes are best suited for a clinical trial is as critical to success as the assurance of strong measurement properties to ensure that the clinical outcomes are measured with precision.

Several key points are highlighted in this task force report. First, the definition of treatment benefit as a “favorable effect” on a meaningful aspect of how a patient feels or functions in their life or on their survival is nuanced with patient-centricity by considering a treatment as not beneficial unless its effect is “meaningful” to the patient. A word of caution to the literal interpretation of this definition is warranted because not every beneficial outcome is necessarily deemed “meaningful” to patients. Treatments of asymptomatic conditions such as hypertension and hypercholesterolemia can be quite beneficial to patients, but patients may not necessarily view reduced blood pressure or lipid levels as “meaningful” despite the demonstrated effects of reduced morbidity and mortality. Although the lack of “meaningfulness” to patients is likely seen in nonadherence to such medications, this in no way reflects lack of treatment benefit. In addition, many patients have varying definitions of meaningful, with some being highly unrealistic.

Indeed, it is difficult for patients to abstractly express and quantify a meaningful treatment benefit outside of experiencing the treatment [2]. Research in goal setting of patient expectations has demonstrated that if the patients’ expectations of treatment are realistic, they experience more “meaningful” outcomes [3,4]. Thus, although the definition of treatment benefit proposed by the task force is useful and patient-centric, the need for patient meaningfulness in a pure sense may be a bar set too high for drug development. Perhaps an important nuance to this definition is that treatment benefits need to be relevant to patients’ lives to be deemed beneficial. Engaging patients in the drug development process will help in the selection of patient-relevant and meaningful end points.

Following meaningful change is the discussion on interpretability, the ability to interpret the relationship between the outcome results and the treatment benefit. The task force report presents this as a measurement property; however, there is no specific mention of interpretability as a measurement property within the 2009 FDA guidance on PRO development or the qualification guidance [1,5]. Indeed, a measure without meaningful and relevance is not a measure to be used as an outcome; however, the interpretability of a measure is contingent upon the COU, as noted by the task force. Thus, when selecting a COA, an understanding of how the outcomes are interpreted is essential, but one needs to be careful because the COU may alter the measure’s literal interpretation (e.g., a reduction of one incontinence episode per day for a person with mild incontinence may mean a cure, whereas a reduction of one incontinence episode per day for someone with six or seven episodes per day may not be a “meaningful” benefit). Many times when selecting an end point, the true interpretability of the end point as meaningful to a patient within a specific COU is not known. Consequently, interpretability does not necessarily transfer with each COU, which is a point that has been well illustrated by this article.

Although the task force appropriately acknowledges the discussion of the measurement properties of validity, reliability, and responsiveness to previous references, it is important to recognize that these properties are just as essential to consider when selecting an outcome as interpretability. Without a reliable, valid, and responsive outcome measure, the data are meaningless to interpret. As noted by the task force report, the outcome measure should be related to the COI and well related to the meaningful health aspect (highlighting the need for regulatory semantics in matching the COI name with the COA name to enhance consistency when defining outcome).

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An area of discussion that is missing in this task force report is related to personalized medicine and adaptive testing of COA, which will yield a greater diversity in end points. Given the heterogeneity of some diseases, there is no one unique end point; thus, consideration of “bringing your own” end point or most bothersome symptom as a key end point has emerged in FDA’s recent guidance for acute treatment of migraine [6]. Although this type of end point certainly encapsulates the essence of “meaningfulness” to patient aspect, it leads to a quagmire of conceptual and statistical issues that need to be considered and merit further investigation and discussion.

In conclusion, we applaud the ISPOR task force’s work in producing this report that clarifies and links key terms for the development and selection of clearly focused, reliable, valid, and responsive COAs capable of demonstrating meaningful treatment benefits in drug and medical device clinical trials. The future value of this guide should be confirmed in improved end point precision; interpreting the importance of a statistically significant change over time will continue to require careful insight on the meaningfulness within the COU that incorporates patient input.

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REFERENCES