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Advances in Clinical Outcome Assessments

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Clinical trials may fail for many reasons. The most obvious cause is that the drug does not work for the selected indication. Early phase studies may lead to incorrect dose selection. Entry criteria for the definitive studies may be flawed. We are recognizing the complexity underlying the entities we call ''conditions'' or ''diseases''; underlying heterogeneity without diagnostic targeting at those most likely to benefit may lead to a negative study.

Increasingly, issues related to clinical outcome assessments (COAs) have come to the fore. Clinical trials may fail because of flawed selection, or assessment, of outcomes. Failure to understand what really matters to patients, furthermore, can fail to identify key factors that lead to patient adherence and successful therapeutics. Hence, a special section on clinical outcome assessments is timely indeed.

Welcome to Clinical Outcome Assessments

A COA directly or indirectly measures how patients feel or function and can be used to determine whether a treatment has demonstrated efficacy or effectiveness. COAs can also measure safety outcomes of the intervention itself or relative to another intervention. COAs measure a specific concept (ie, what is being measured by an assessment, such as pain intensity) within a particular context of use. The context of use, which describes important boundaries or criteria under which the COA is relevant, typically includes the following elements: disease, injury, impairment or condition being treated (eg, neuropathic pain); patient population demographics (eg, age, disease severity, language, culture, education); and clinical treatment objectives and plan of care (eg, reduction in pain intensity over 3 months with the experimental treatment administered daily).

Qualification of a COA represents a conclusion that, within the stated context of use, the results of the COA measurement can be relied upon to have a specific interpretation and application, as long as there are no serious study flaws and there are no new and conflicting scientific facts not known at the time the qualification was determined. COAs as traditionally used may still be acceptable in a regulatory setting, even though they have not been qualified; however, the use of such COAs will continue to be reviewed by regulators on a case-by-case basis. For qualified COAs submitted to the US Food and Drug Administration (FDA), sponsors of medical interventions will be able to use the targeted COA of interest in the qualified context for submissions on investigational new drugs, new drug applications, and biologic license application submissions without requesting that the relevant FDA review group reconsider and reconfirm the suitability of the COA.

A COA is different from a biomarker assessment. Examples of biomarker assessments include protein levels in blood measured by standardized methods and an automated quantitative measurement of a pathologic lesion from a magnetic resonance image. Relative to COA, a biomarker assessment is one that is subject to less influence from the patient or other rater on a patient's assessment. There are 4 types of COAs: patient-reported outcomes, clinician-reported outcomes, observer-reported outcomes, and performance outcome assessments. Of the 6 articles in this special issue on advances in COAs, 3 involve electronic and technology advancements, 2 contribute to statistical methodology, and 1 emphasizes conduct and strategic opportunities in oncology trials.

Types of Clinical Outcome Assessments

Of the 4 types of COAs, the first 3 of these depend on the implementation, interpretation, and reporting from a rater on a patient's assessment—a rater being a patient, clinician, or nonclinician observer. The fourth type of a COA—performance outcomes—involves no rater judgment but is still considered a COA (and not a biomarker) because, like the other 3 COAs, it centers on active patient performance of a task (or activity) or on subjective assessments regarding aspects of a patient's health status. Thus, COAs involve volitionally performed tasks or subjective assessments of health status that are patient-focused or patient-centered.

Patient-reported outcome assessments have a patient as rater and rely on patient-provided responses to questions that are directly captured, without any interpretation or judgment on the part of anyone else. An example is a patient's self-report on a

pain scale from 0 (*no pain*) to 10 (*worst possible pain*). Responses can be captured in several ways such as on paper, electronic forms, or by an interviewer (without interviewer's interpretation of responses). For several reasons, the use of electronic data captures is becoming the preferred means of collecting COAs. For example, electronic collection on patient-reported outcomes leverages screen-based technologies (eg, handheld device, tablet computers) and telephone-based systems (eg, interactive voice response).

Clinician-reported outcome assessments have a clinician as rater—a member of the investigator team with appropriate clinical professional training. An example would be a clinician-reported rating scale on severity of a patient's depression (*mild*, *moderate*, *severe*). When a clinical interviewer injects his or her judgment in arriving at a score (eg, regarding the patient's state of depression), then the type of COA is clinician-reported and not patient-reported.

Observer-reported outcomes have as rater someone other than patient or clinician, someone who need not have specialized health care professional training. These measures include COAs that are best made by a companion or a caregiver of the patient, as is frequently the case for the assessment of cognitive function for patients with Alzheimer's disease.

The last kind of COA is **performance outcome assessments**, where the patient is instructed to perform a defined task that is quantified in a specific objective way, such as distance walked in 6 minutes or the number of movements needed to master a task. Here an investigator does not apply judgment to quantifying the performance. Once a clinician applies judgment on the quality of the patient's performance, then this kind of COA is a clinician-reported outcome, not a performance outcome, because the clinician rater's judgment has influenced the recorded rating or score.

New Developments in COAs

The articles that follow in this special issue cover advances in COAs—important recent developments intended to aid in the methodology and measurement of COAs and thereby enrich their appreciation and use. In doing so, these developments provide an opportunity for more valid and reliable assessments on clinical outcomes. Although the articles focus primarily on patient-reported outcomes, their general methodology can apply in principle to at least one of the other 3 types of COAs.

In their article "Bring Your Own Device" (BYOD): The Future of Field-Based Patient-Reported Outcome Data Collection in Clinical Trials?" Gwaltney and coauthors, as representatives of the Electronic Patient-Reported Outcome (ePRO) Consortium of the Critical Path Institute, review operational, privacy/security, and scientific/regulatory considerations regarding the BYOD approach. With this approach, subjects use their own smartphone or Internet-enabled device to complete field-based PRO assessments.

In "Considerations for Requiring Subjects to Provide a Response to Electronic Patient-Reported Outcome Instruments," O'Donohoe and colleagues provide guidance on the appropriate circumstances which allow a subject to opt out of responding to ePRO items. Three main scenarios are discussed: (1) requiring subjects to complete all items in all the instruments in the study; (2) requiring subjects to complete all items used to assess endpoints in the study but allowing the subject to opt out of responding to some, or all, other items (including sensitive items); and (3) allowing subjects to opt out of responding to any or all items in the study.

In "Optimizing Electronic Capture of Clinical Outcome Assessment Data in Clinical Trials: The Case of Patient-reported Endpoints," Fleming and associates describe study site-, subject-, and technology-related factors that may lead to deviations from the planned electronic collection of PRO data (eg, defaulting to paper-based data collection) and provide recommendations aimed at preventing potential problems or quickly resolving problems once they occur.

"Advances in the Evaluation of Longitudinal Construct Validity of Clinical Outcome Assessments," by Williams et al, focuses on methods to evaluate longitudinal construct validity. They describe a sample of these methods and provide considerations and recommendations for designing a thoughtful longitudinal construct validity evaluation of COAs.

An overview of key methodological, statistical, and clinical considerations for implementation of patient diaries with a regulatory perspective in mind is presented by Gater and colleagues in "Unique Challenges in Development, Psychometric Evaluation, and Interpretation of Daily and Event Diaries as Endpoints in Clinical Trials." This article can inform researchers who are developing or implementing patient diaries as clinical trial endpoints to ensure that the nuances of this mode of data collection are considered in the development of endpoints, which can serve well when preparing for regulatory interactions.

In "Overcoming Organizational Challenges of Integrating Patient-reported Outcomes in Oncology Clinical Trials," Gnanasakthy and DeMuro note that drug development in oncology is characterized by a high attrition rate of new compounds, faster development times encouraged by the regulatory process, studies that are often open and single-arm, and emphasis on survival-related endpoints. They state that the challenges to include PRO-related endpoints in oncology research are exacerbated by restricted budgets and resources and also an overly rigorous application of the FDA's PRO guidance. The authors propose that an optimal implementation of a PRO strategy in oncology research can be achieved by applying the PRO guidance to the greatest extent possible, making use of off-the-shelf PRO measures to capture concepts of interest, discussing

plans with the regulatory bodies early in the process, and treating PRO-related endpoints just like any other endpoint.

In summary, COAs have become central outcomes in proportion to the increased emphasis on patient-centered research, and the articles in this special section discuss the electronic, technologic, statistical, and strategic advances in this area. There are 4 types of COAs: patient-reported outcomes, clinician-reported outcomes, observer-reported outcomes, and performance outcome assessments. Of the 6 articles in this special issue on advances in COAs, 3 involve electronic and technologic advancements, 2 contribute to statistical methodology, and 1 emphasizes conduct and strategic opportunities in oncology trials. Although the articles focus primarily on patient-reported outcomes, their general methodology can apply in principle to at least one of the other 3 types of COAs.

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