Clinical event adjudication in cardiovascular device trials: An Food and Drug Administration perspective

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Approval of medical products in the United States is based on the demonstration of a reasonable assurance of safety and effectiveness, and for almost all high-risk devices, regulatory decision making is focused on the results of clinical studies. The accumulation of study data is not an end in itself; raw clinical data need to be translated into clinical events (or nonevents) through an adjudication process, most often performed by a clinical events committee (CEC). A rigorous and independent adjudication process boosts clinical study quality by increasing the likelihood of reliable event assessments leading to greater confidence in the accuracy of event rates.

In this issue of the journal, Seltzer et al[1] present an important review of the rationale and best practices for event adjudication in medical device clinical trials. The concepts presented in this work are well aligned with Food and Drug Administration's (FDA's) expectations for an adjudication process that enhances clinical study quality.

Efforts to minimize bias are particularly important for device studies, which, unlike drug studies, are rarely double blind because the operator is most often aware of the device he/she is using. Sham control trials reduce bias, but are challenging to conduct. In strategy trials such as open surgery vs a percutaneously deployed device, even single blinding of the study subject is not feasible. Furthermore, device studies are less commonly randomized than drug trials, and pivotal single-arm device studies that use historical controls, performance goals, or objective performance criteria are not uncommon. For randomized device trials, although it may not be feasible to blind patients or operators of the treatment assignment, study personnel conducting follow-up subject assessments and CEC members should be masked to the treatment assignment to the greatest degree possible.

Event adjudication by an independent CEC increases a study's scientific rigor. Despite best intentions, there may be bias derived from a lack of clinical equipoise among investigators, pressures from institutional quality assurance programs, and financial implications from up-coding events. Furthermore, reliance on site-reported events can be limited by inconsistent assessments among sites. Clinical events committee application of prespecified definitions of events that reflect the available peer-review literature and consensus among academic physicians, professional societies, and regulators is critical to the consistency, accuracy, and reliability of the reported clinical study outcomes. Prespecified uniform event definitions have been successfully used in multiple trials of percutaneous coronary interventions and transcatheter heart valve devices.[2,3]

High standards for CEC membership ethics are critical to maximize data quality and minimize bias. It is expected that CEC members should be physicians who are not otherwise involved with the trial itself, have no financial or administrative conflicts of interest, and have expertise in the underlying clinical conditions of enrolled study subjects (ie, knowledge of the current standard of care in the targeted patient population).

It can be challenging to ensure appropriate CEC membership for cardiac device trials. Technical skills, operator experience, and learning curves often play a much greater role in device compared with drug trials. For most cardiovascular device trials that involve invasive cardiac procedures, study-specific operator expertise in the procedures being performed and knowledge about the current standard of care are required. In these cases, CEC membership may need to include interventional cardiologists, structural heart disease specialists, electrophysiologists, heart failure specialists, and cardiothoracic or vascular surgeons. For some study endpoints, no adjudication is needed (eg, all-cause death) or evaluation of case report form data or clinical study reports is adequate to identify events without further need for adjudication. However, for other events that may be of particular interest in cardiovascular device trials, such as cardiovascular death, myocardial infarction (MI), stroke, ischemia-driven repeat revascularization, or stent thrombosis, the CEC may be needed to examine source documents including electrocardiograms, cardiac biomarker results (timing of measurements, levels, and laboratory reference standards), and imaging studies.

Coordination between the CEC and groups monitoring a clinical trial improves data quality for the adjudication

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process and increases patient protection. To adjudicate some events in a cardiovascular device study that depend on an assessment of imaging metrics, the CEC may, for example, rely on angiographic and echocardiographic core laboratories to measure baseline and follow-up angiographic percent diameter stenosis, identify definite stent thrombosis based on angiographic evidence of an intraluminal filling defect, confirm that a reintervention occurred at the target lesion site, calculate left ventricular function, determine baseline and follow-up valvular regurgitation and stenosis severity, and assess effective left atrial appendage or intracardiac shunt closure.

Multidisciplinary CEC membership is often needed to provide appropriate adjudication decisions for studies of cardiovascular interventions used to prevent or treat noncardiac conditions (eg, left atrial appendage occlusion in atrial fibrillation patients to prevent ischemic stroke and neurohormonal modulation to treat resistant hypertension). In these cases, broadening CEC membership beyond of cardiovascular medicine is required and may include stroke neurologists, neuroradiologists, hypertension experts, endocrinologists, and nephrologists.

Because event adjudication can be resource-intensive and time-consuming, it may be efficient for a device study CEC to focus its efforts on events that are device-specific. In drug trials and epidemiologic studies, the patient is usually the unit of analysis. For example, in a cardiovascular drug trial, the number of MIs may be more important than the location or types of MI, and the adjudication process may be relatively simple. Misclassification of individual events would not impact the interpretation of the overall study results as long as there is no impact on the hazard ratio. In contrast to drugs, devices are often intended to provide local benefits (and/or are associated with local complications), and their mechanism of action is better understood, which allows for a more complete assessment of factors contributing to adverse events. For some endpoints in cardiovascular device studies, the treated lesion is the unit of analysis. For example, in a coronary stent trial, there would be interest in whether an MI occurred in the distribution of the stented target lesion and whether the pathophysiology of the event was due to stent thrombosis. In this case, the event evaluation process would require not only adjudication of the MI itself but also a review of available electrocardiograms and imaging studies. Assigning causality (ie, the relatedness of an event to the device or procedure) impacts the assessment of a device's safety or effectiveness and often influences regulatory decision making.

In recognition of the high cost of traditional clinical trials and to improve the efficiency of data collection, there is an emerging interest in the use of registries and other sources of "real-world" data (such as electronic medical records). Formal event adjudication by a CEC is not typically included in these types of clinical data repositories. However, there may be a role for targeted event adjudication if the additional rigor provides value to physicians and/or is required by regulators or payors. There have also been discussions on using insurance claims data in place of traditional adjudication to reduce the administrative burdens and costs associated with conducting clinical trials.[4] However, there are concerns that claims may underestimate true event rates,[5] and the information in claims may lack the detail needed to evaluate the relatedness of some events to the study device or procedure.

Timely CEC adjudication of potential adverse events plays an important role in patient protection by assisting the Data Safety Monitoring Committee in its responsibility to recommend that the trial continue as planned, institute more intensive monitoring of a potential safety signal, or terminate a study due to either futility or safety concerns. Clinical events committee–adjudicated endpoint data submitted in periodic study reports also assist FDA in ongoing monitoring of study progress.

Regulatory and clinical decision making are aided by high-quality trials, and the key elements of good clinical study practice include the following: a clearly written and scientifically sound study protocol and a prespecified statistical analysis plan; informed consent; accountability of study subjects that minimizes withdrawals and lost-to-follow-up; minimizing missing information; well-designed case report forms; accurate data collection; audits and monitoring of study data by competent and dedicated research study personnel; and procedures for appropriate data sharing among investigators, industry sponsors, and regulators. These study execution inputs are directly relevant to the quality of the event adjudication process. Administrative features of an efficient CEC includes a written CEC charter that describes membership, quorum requirements, staffing to coordinate data, data review protocols, meeting schedules, and other standard operating procedures such as appropriate interactions (and firewalls) between the CEC and the study sponsor.

The FDA considers the adjudication process, as described by Seltzer et al,[1] to be a critically important component of good clinical study practice. A CEC—with appropriate study-specific expertise, guided by established policies and prespecified event definitions that minimize bias, and supported by an effective administrative infrastructure—strengthens regulatory review of new devices (and new uses for approved devices) and helps assure that approved devices continue to demonstrate a reasonable assurance of safety and effectiveness.

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