Use of endpoint adjudication to improve the quality and validity of endpoint assessment for medical device development and post marketing evaluation: Rationale and best practices. A report from the cardiac safety research consortium

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This white paper provides a summary of presentations, discussions and conclusions of a Thinktank entitled "The Role of Endpoint Adjudication in Medical Device Clinical Trials". The think tank was cosponsored by the Cardiac Safety Research Committee, MDEpiNet and the US Food and Drug Administration (FDA) and was convened at the FDA's White Oak headquarters on March 11, 2016. Attention was focused on tailoring best practices for evaluation of endpoints in medical device clinical trials, practical issues in endpoint adjudication of therapeutic, diagnostic, biomarker and drug-device combinations, and the role of adjudication in regulatory and reimbursement issues throughout the device lifecycle. Attendees included representatives from medical device companies, the FDA, Centers for Medicare and Medicaid Services (CMS), end point adjudication specialist groups, clinical research organizations, and active, academically based adjudicators. The manuscript presents recommendations from the think tank regarding (1) rationale for when adjudication is appropriate, (2) best practices establishment and operation of a medical device adjudication committee and (3) the role of endpoint adjudication for post market evaluation in the emerging era of real world evidence. (Am Heart J 2017;190:76-85.)

During both pre-approval testing and post- approval surveillance, medical devices require evaluation to assess whether they provide safe and effective treatment. There are a number of parameters that can be used to assess the impact of a device on disease progression, but clinical endpoints that measure the effect on morbidity and mortality represent the highest standard for patients, providers, and regulatory authorities. Assessment of these endpoints requires a process that provides high quality data, which are reviewed with appropriate expertise and limited bias. Although study investigators are ultimately responsible for data submission and identifying potential endpoints, there is inherent bias among these individuals that may cause over- or under-reporting of events. Ascertainment of clinical endpoint events may also vary among investigators based on local practice or other factors. Independent and consistent adjudication of events using uniformly applied endpoint definitions and processes for endpoint reporting enhances freedom from bias and the interpretability of study results. This paper reviews the rationale and operational processes of independent clinical events committees (CEC) as a method to improve the quality and validity of endpoint assessment (See Figure).

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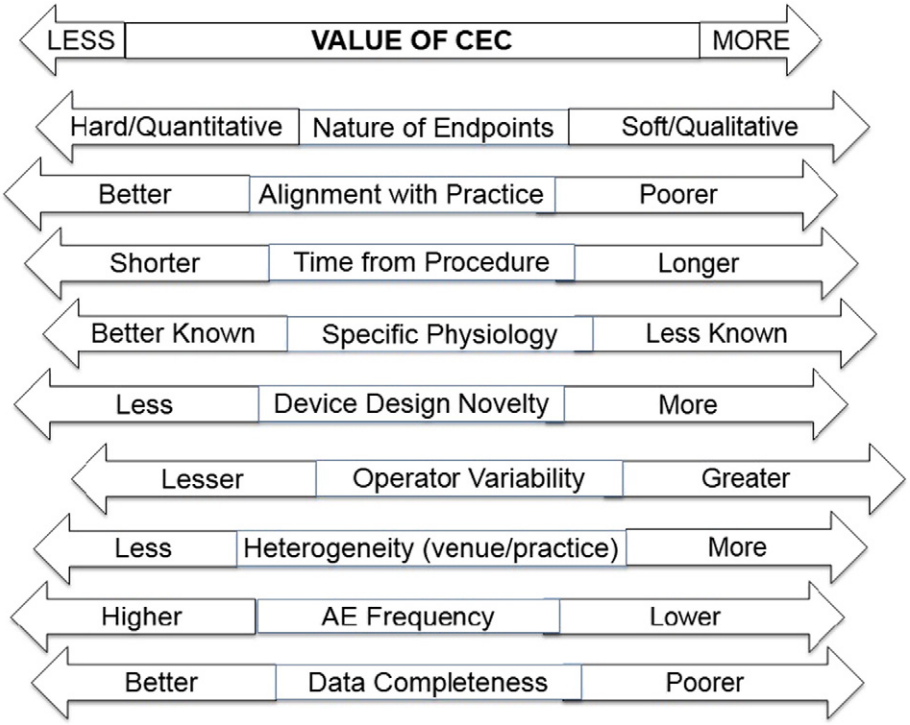
Rationale for adjudication: Why do central adjudication?

Limit bias

The possibility of bias at the investigative site arises from a number of factors. First, particularly in device trials, an investigator that uses the investigational product

Figure



illustrates the value of CEC adjudication as a function of the study elements which should be considered in determining whether a CEC should be utilized in a clinical trial.

may be an enthusiast for the new therapy, and this may influence the interpretation of an event and the relatedness of the event to the device. As a result, sites may underreport events associated with the intervention being studied. The potential for real or apparent bias is exaggerated if the investigator has a financial or scientific relationship with the device manufacturer or a competitor. Second, a site investigator might interpret events erroneously due to their direct involvement in the patient's care, particularly relating to a complication or inadequate care. Third, external factors may inappropriately influence the interpretation or reporting of clinical endpoint events. For example, heart failure might be assigned as a discharge diagnosis even though the findings do not support that diagnosis based on established clinical trial criteria. These coding errors may be influenced by reimbursement incentives or local practice variation and can confound efforts to document bona-fide clinical endpoints.

Standardized definitions

Another issue arises when there are no event definitions pre-specified in the clinical study protocol. This problem is magnified in large multicenter and increasingly global trials, as was observed in the early Studies of Left Ventricular Dysfunction (SOLVD) trials, in which site-reported outcomes used for the interpretation of cause-specific mortality differed from the results of subsequent trials that used central adjudication.[1] An exercise in comparing central adjudication to site evaluation in the assessment of mode of death noted the wide variability in event interpretation among sites from SOLVD.[2] In cardiovascular studies, a general agreement has emerged on endpoints of interest with acceptance of uniform event definitions[3-6] which greatly enhances the ability to assess outcomes within a trial and to compare outcomes across different clinical trials.

Furthermore, it is important that endpoint definitions are relevant to disease progression and are consistently applied. The determination of worsening heart failure as a study endpoint illustrates many of the challenges in adjudication. An event indicating worsening of heart failure should include a reasonable threshold for event severity and primarily focus on the escalation of therapy in response to heart failure signs and symptoms, rather than be limited to a heart failure diagnosis based only on insurance claim coding without adequate supporting documentation (which may occur during a hospitalization for another reason). Alternatively, worsening heart failure noted during a hospitalization for an unrelated procedure or illness may fail to be coded as a discharge