



Centralized adjudication of cardiovascular end points in cardiovascular and noncardiovascular pharmacologic trials: A report from the Cardiac Safety Research Consortium

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This white paper provides a summary of presentations and discussions at a cardiovascular (CV) end point adjudication think tank cosponsored by the Cardiac Safety Research Committee and the US Food and Drug Administration (FDA) that was convened at the FDA's White Oak headquarters on November 6, 2013. Attention was focused on the lack of clarity concerning the need for end point adjudication in both CV and non-CV trials: there is currently an absence of widely accepted academic or industry standards and a definitive regulatory policy on how best to structure and use clinical end point committees (CECs). This meeting therefore provided a forum for leaders in the fields of CV clinical trials and CV safety to develop a foundation of initial best practice recommendations for use in future CEC charters. Attendees included representatives from pharmaceutical companies, regulatory agencies, end point adjudication specialist groups, clinical research organizations, and active, academically based adjudicators.

The manuscript presents recommendations from the think tank regarding when CV end point adjudication should be considered in trials conducted by cardiologists and by noncardiologists as well as detailing key issues in the composition of a CEC and its charter. In addition, it presents several recommended best practices for the establishment and operation of CECs. The science underlying CV event adjudication is evolving, and suggestions for additional areas of research will be needed to continue to advance this science.

This manuscript does not constitute regulatory guidance. (*Am Heart J* 2015;169:197-204.)

In the current clinical trials landscape, independent, blinded, clinical end point committees (CECs) are regularly commissioned to adjudicate potential cardiovascular (CV) end points in CV as well as non-CV trials with CV safety end points. These CECs are thought to enhance the validity of clinical trial CV outcome measures through independent, systematic, and standardized iden-

tification, processing, and review of CV events. Despite a long history of centralized adjudication of CV end point events, the clinical trials community has yet to establish a set of best practices to inform how CECs are to be structured and operated. In addition, little is published that critically and consistently reports on the specifics of CEC establishment and methodology.

Given the limited literature and the absence of widely accepted academic or industry standards and a definitive regulatory policy on how best to conduct CECs, the Cardiac Safety Research Consortium (CSRC) and the US Food and Drug Administration (FDA) convened a think tank on November 6, 2013. This meeting provided a forum for leaders in the fields of CV clinical trials and CV safety to develop a foundation of initial best practice recommendations for use in future CEC charters. Attendees included representatives from pharmaceutical companies, regulatory agencies, end point adjudication specialist groups, clinical research organizations, and active, academically based adjudicators.

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The CSRC is a public-private partnership created to advance scientific knowledge in cardiac and CV safety for new and existing medical products by building a collaborative environment based on the principles of the FDA's Critical Path Initiative and other public health priorities. This collaboration among academicians, industry professionals, and regulators facilitates the development of consensus approaches addressing CV safety issues that can arise in the development and use of medical products.¹ The CSRC views expressed in this manuscript do not represent regulatory policy.

Background

The challenges of CV end point assessments

Clinical investigators with similar training who work at the same institution can genuinely (and legitimately) disagree about the definition of an individual CV end point event. When this scenario is extended to the context of a CV outcome trial (CVOT), where participants must be recruited from several investigational sites encompassing a variety of geographies, cultures, and clinical care standards, it is highly likely that this diversity of interpretation increases. Adjudication of end points by CEC experts is thought to provide uniformity in evaluation of CV end points. However, heterogeneity in the CEC process can threaten the validity of adjudicated CV outcomes. Therefore, a more systematic standard evaluation of clinical end point data by a defined CEC process should improve the reliability of CV end point assessments.²

Frequently, CV end points are composite end points that represent a clinically meaningful outcome. The major adverse cardiovascular events (MACE) end point, comprising any CV death, nonfatal myocardial infarction (MI), and nonfatal stroke, has become the most widely used CV outcome metric in clinical trials. The MACE+ end point comprises MACE plus the presence of ≥ 1 other events such as hospitalization for unstable angina (with or without urgent revascularization) or hospitalization for heart failure. Other major CV end points are also used in some trials depending on the possible mechanism of drug action.

Although CECs have been widely applied, the only current regulatory guidance recommending that adjudication of CV end points be performed by an independent CEC in phase 2 and 3 trials concerns new antidiabetic therapies for type 2 diabetes mellitus.^{3,4}

CEC composition and charter

A CEC is typically composed of clinical experts in CV medicine (eg, cardiologists, stroke/vascular neurologists, and nephrology and hypertension specialists) who evaluate individual patient data and opine as to whether a predefined CV end point has occurred. Exact definitions of CV end points are provided in the CEC charter using objective criteria, often from published clinical expert reviews or other guidelines.⁵ Thus, if a site reports a

particular CV end point but, upon further examination, it is seen that the charter-defined criteria are not fulfilled, the CEC would not classify this as an end point. The process of providing criteria for the classification of end points usually takes into account the expected variability of clinical trial data because of geographic representation, primary investigator specialty, patient population, and the characteristics of the expected events. Although complex, a document released by the Standardized Data Collection for Cardiovascular Trials Initiative, *Standardized Definitions for Cardiovascular and Stroke End Point Events in Clinical Trials*,⁵ can serve as a reference for CECs to develop end point definitions for their charters.

In addition to specification of end point definitions, the CEC charter should also detail the following:

- (a) The standard processes by which the cases to be evaluated will be selected (case ascertainment). For example, will the CEC adjudicate only those cases reported positively, or will they also survey the clinical trial database for potential false negatives?
- (b) The data to be presented to the adjudicators (case dossier) and what key pieces of missing information would typically make a case nonassessable.
- (c) The process of adjudicator decision making and how voting will proceed (voting rules). For example, will there be voting only on primary diagnoses such as fatal stroke or also on secondary diagnoses such as type of stroke (embolic, hemorrhagic, or ischemic/infarction)?
- (d) How CEC decisions are reached (decision rules). Examples include the need for unanimity versus majority and individual independent voting versus discussion followed by consensus opinion.
- (e) Depending upon the various trial factors referenced above, the charter should describe the capabilities and comprehensive expertise required for CEC members to perform the charter-specified adjudication.

CV end point adjudication in trials conducted by cardiologists

Data were presented at the think tank examining whether CEC adjudication decisions in trials with MACE or MACE-like criteria differed from the assessments made by the cardiologist principal investigators. Some data suggested that end point adjudication may more accurately characterize the action of the compound but not change the overall conclusions.⁶ Therefore, although end point adjudication may better classify participants within the appropriate end point, the overall study conclusions would remain the same.^{7,8} For instance, adjudication of CV events might more accurately characterize the event (eg, type of MI) but not change the overall hazard ratio (eg, treatment A has fewer overall CV events than treatment B). In general, the think tank participants felt

that there was no convincing body of evidence to support the contention that end point adjudication of MACE end points in blinded trials conducted by cardiologists adds significant value or alters the precision of treatment arm efficacy or safety assessments. This view is shared by the participants from the FDA Division of Cardiovascular and Renal Products.

Despite the consensus that CV end point adjudication in blinded trials conducted by cardiologists is unnecessary for primary MACE end points, CV end point adjudication in trials conducted by cardiologists may be considered in other situations such as the following:

- (a) Evaluation of subcategorization of MACE events, for example, agreement on the exact mechanism of CV death, subtypes of MI, or specific characterization of stroke;
- (b) Evaluation of MACE+ end points. There is a lack of data regarding whether CEC and investigative site cardiologists agree (or disagree) on the definitions of diagnoses such as hospitalization for heart failure and unstable angina;
- (c) Evaluation of end points in trials in which the pharmacologic treatment is unblinded or in which treatment characteristics functionally unblind the cardiologist investigator. In such cases, a CEC would be useful to mitigate potential investigational site bias.

CV end point adjudication in trials conducted by noncardiologists

Because CV safety concerns are prevalent among many classes of investigative and marketed non-CV products, adjudication of CV safety end points has become increasingly commonplace in clinical development trials in which a putative CV safety concern has been identified, in trials when an unexpected CV safety signal is identified, and in dedicated CV safety trials. The clinical trials for these programs are conducted by expert non-CV clinical investigators from the respective therapeutic areas (eg, rheumatologists, internists, gastroenterologists, endocrinologists). However, because of the CV safety concerns, these investigators are placed in the position of being asked to report and assess CV safety end points in addition to the primary end point measures with which they are very familiar.

There is a paucity of published data examining CV end point agreement by expert CECs versus investigator-reported events when the investigators are noncardiologists. Because of the diversity of investigators and reporting of CV events in such trials, and the general lack of CV disease-specific training, adjudication of CV end points in trials conducted by noncardiologists is recommended to ensure a uniform assessment and classification of CV events to yield a more robust interpretation of the CV risk associated with a given drug.

Table I. Utility of CV end point adjudication

1. Not recommended in blinded trials conducted by CV physicians
2. Recommended in trials that are conducted by non-CV physicians
3. May be recommended in trials conducted by CV physicians when:
 - o Trial is unblinded or there is suspicion of unblinding,
 - o Evaluation of subcategories of MACE end points,
 - o Evaluation of MACE+ end points

MACE+ comprises MACE plus the presence of ≥ 1 other events such as hospitalization for unstable angina (with or without urgent revascularization) or hospitalization for heart failure. Note: Because, in many instances, noncardiologists who are vascular medicine experts (or thrombosis experts) are CEC members, we would broaden the term to CV physicians.

Think tank members who have served as active adjudicators noted that they have reclassified significant numbers of CV events reported by noncardiologists, noting high rates of discordance between investigators and CECs with regard to event classification. (Admittedly, because of the lack of publications in this area, the evidence of high rates of discordance is anecdotal. Recent data from a large, global noncardiologist trial [on file at ACI Clinical, a clinical research organization specializing in CECs] show a site discordance rate of almost 50% in attribution of cause of death to CV or non-CV causes.) In general, there was an agreement that, although noncardiologist investigators have basic training in CV medicine that may be sufficient to make a clinical diagnosis, the evidence they use to make the diagnosis may not be of sufficient consistency to support the more rigorous definitions used by a CEC or to ensure similar diagnoses across a wide range of sites, clinical practices, and geographic regions.

Suggestions for adjudication best practices. Although it became clear that there is an absence of standard adjudication processes, there was agreement that consensus and harmonization of best adjudication practices is an important goal. Summaries of major points are provided in [Tables I, II, and III](#), and more detail is provided in the following text.

Harmonization of best practices could provide regulators and physicians with a standard that would allow aggregation of similarly defined events in a drug development program (a process sometimes used to assess MACE events in antidiabetic development programs) and across programs/populations for event rate comparisons. Despite relatively few published data regarding best adjudication practices, there is a convergence of opinion and experience that allowed recommendation of best practices in the following 8 areas:

1. Prospective adjudication: Prospective adjudication is strongly recommended when there is an intent or need to assess CV safety. This refers to the practice of

Table II. Recommendations for cardiovascular end point committees best practices

1. Prospective approach to adjudication;
2. Independent voting processes;
3. Comprehensive search strategy for potential CV events (eg, MedDRA searches);
4. Standardized event definition CRFs (optional);
5. Adjudication of CV events when an unanticipated safety signal arises in a clinical development program;
6. At least 3 CEC members with knowledge of the geographic variations of care represented in the trial;
7. CEC independence from sponsor;
8. Consideration of risk-based or adaptive adjudication models

Abbreviation: *MedDRA*, Medical Dictionary for Regulatory Activities.

Table III. Future strategies for adjudication processes

1. Studying the utility of standard CRF fields which may ultimately allow optimization of data collection;
2. Development of the proper quality control metric(s) to communicate that adjudication was accomplished in a rigorous fashion;
3. Application of artificial intelligence to EHR data to see if automated adjudication might be possible for certain events (eg, MI). This would entail computer-generated adjudication of noncomplex or less subjective cases, with the use of a CEC for complex or more subjective cases;
4. Development of additional strategies to limit the resources required for adjudication of low-yield populations;
5. Examining the use of adjudication as a quality control mechanism (eg, to qualify a non-CV investigative site as able to discern events based on consistency with predefined definitions);
6. Develop methodology and measure potential cost effectiveness of risk-based or adaptive adjudication processes

Abbreviation: *EHR*, electronic health record.

identifying and gathering data and adjudicating cases prospectively as they occur during the conduct of the study rather than adjudicating all cases at study closeout or after study completion (retrospective adjudication).

During the adjudication process, it is common for the CEC to request additional information from a site. In the case of retrospective adjudication, performed months or years after study completion, it can be much harder or impossible to recover that information. Such information recovery efforts may delay the ultimate trial analysis. The additional resource commitment needed for prospective adjudication is far outweighed by the costs of a potential delay in study closure or an increase in nonevaluable results.

Another advantage of prospective adjudication is the possibility of performing adaptive adjudication, whereby the necessity for adjudication can be tested concomitantly (see item 8 for further discussion).

2. Independent voting: Each member of the CEC should independently review and classify each CV event to which they are assigned. This approach is in contrast to that taken by some CECs, in which all members meet to review/discuss each case nonindependently and reach a conclusion regarding the event. Independent voting diminishes the possibility that a dominating personality or other group dynamics will defeat the idea of reaching a mutually independent conclusion. For those cases in which the individual opinions of the CEC members differ,

the case is often decided by majority voting. A CEC discussion can be used to reach a final decision when a majority vote is not possible (eg, 3 different conclusions: for instance, 1 vote could be 1 positive for a MACE event, 1 negative for a MACE event, and 1 for not enough information) or the charter calls for consensus in the case of a disagreement among voters (eg, a charter may call for unanimous decision, not majority for certain end points). In addition, because many CVOTs have become global in nature and the CEC may include adjudicators from different regions of the world, independent voting is more practical and affords more real-time adjudication.

3. Comprehensive search strategy for potential CV events: To ensure all potential CV events that are reported in a trial undergo adjudication (rather than only those that the site determines are potential CV events), it is recommended that prespecified adverse event trigger terms, need for medications, and specified laboratory results are used to identify potential CV events. In addition, depending on the nature of the end point, having qualified clinical personnel review selected reports such as hospitalizations, imaging, and other case data for potential CV events should be considered.

This strategy is sometimes referred to as *casting a wide net* to make certain that all potential events have been captured, thereby ensuring that the CEC has reviewed all events that might potentially be classified

as a CV end point. Casting a very wide net may result in identification of several cases that are identified for adjudication but have a low likelihood of being CV events (eg, isolated peripheral edema without any other adverse events compatible with heart failure or a deep vein thrombosis). This can be especially true if cases are based on the Medical Dictionary for Regulatory Activities adverse event terms that have only a tangential relationship to the end point and/or an adverse event term that has a low pretest likelihood of representing an actual event (eg, coronary artery disease, palpitation).

There are several potential strategies for reducing the resource commitment required to adjudicate several low-yield cases. The first is to create an adjudication CV case report form (CRF). If it is designed correctly and incorporates key questions, minimal additional information may allow for elimination or triaging of these cases. For instance, in surveillance for a potential heart failure event, if there is a reported adverse event trigger term of *shortness of breath*, a CV end point CRF might ask if the shortness of breath was accompanied by any diagnostic or therapeutic procedure. In addition, if the trigger term was not applicable (eg, in the above example, the shortness of breath was secondary to an asthma episode), the CRF may allow for the investigators to note that no CV event of interest ultimately occurred. A second suggestion is to use an adaptive or risk-based adjudication strategy (see item 8).

4. Use of standardized event definition CRFs: For the past several years, the CSRC and the FDA have advocated for standardized CV end point definitions to more consistently evaluate the safety and efficacy of new compounds and to compare effects across different compounds within a class. The CSRC subsequently created standardized CV end point CRFs⁹ to capture data in alignment with the CV event definitions. These are intended for use in clinical trials and can be used early in drug development. Because the level of detail required and/or the data available for end point adjudication may differ significantly from these standard definitions, definitions for specific end point adjudication programs must be individualized. Therefore, the think tank does not suggest the use of these forms for end point adjudication in all trials but recognizes that they may be a useful resource that can be individualized to the needs or requirements of a given study.

A potential use of standardized event definition CRFs is to prospectively collect data for CV adverse events of interest for a non-CV therapeutic agent in the event that an imbalance is later identified (ie, at trial completion or when pooling safety data for a submission). The information collected, although not as comprehensive as data collection in a CV outcomes trial, would be adequate to enable adjudication at a later date if needed. Just because the standard end point definitions CRFs are

not used does not imply that other standard CRFs or standard processes should not be used in the clinical trial. For instance, it may make sense to use a standard CRF page that asks if any of the key end points has occurred every time a patient is contacted. Another approach would be to have CRFs that are triggered by Medical Dictionary for Regulatory Activities terms used to report CV events of interest. The forms would be prompted to the investigator after the reported adverse event or severe adverse event, thus avoiding the introduction of bias or undue concern (eg, a patient repeatedly asked about any recent chest pain or MI may become reluctant to participate in a trial of a compound that otherwise has no cardiac signal).

5. Adjudication of CV events when an unanticipated safety signal arises: This occurrence refers to a situation in which an unanticipated imbalance of CV events is observed in a trial or development program for a non-CV therapy (ie, events reported by a noncardiologist) and preclinical and/or previous clinical trial experience had not shown evidence of a CV safety signal. The question of interest becomes: Is adjudication of these events by an independent CEC now warranted, and does this provide further insight into the interpretability of the findings? It is likely that the number of events will be small, and because unanticipated, data collection surrounding the events will probably be suboptimal. The routine use of standard CV CRFs, hence capturing additional data regarding the adverse event, may help to improve data collection and thus the adjudication process. When such signals are detected, adjudication may be recommended in the following cases:
 - (a) There is concern that there might be a safety signal that is meaningful either to study participants and/or, when generalized, to the public health;
 - (b) There is a biologically plausible mechanism for the CV events;
 - (c) The nature of the reported events is significantly heterogeneous (eg, reports of heart failure in a global study when there are known differences in the diagnosis among reporting locations) such that adjudication could provide clarity as to the presence or absence of the event. If the reported event rate in the trial is equal to or below the known background study population rate, adjudication is not necessary and would not yield any confident inferences.
6. Structural aspects of the CEC: There are many variations in structure and membership of CECs. Some CECs include only cardiologists; others may have vascular neurologists to handle suspected stroke events or perhaps hematologists to evaluate potential thrombosis/bleeding events. Membership on CECs spans a wide spectrum from cardiology fellows through retired physicians.

For best practices, it is recommended that a CEC have at least 3 members. In addition, to ensure CEC awareness of variations in CV care, it is recommended that, for global studies with known regional variations in diagnostics and clinical care, the membership is familiar with these regional variations. This does not imply that the CEC itself needs to have representative membership from the regions themselves, but the membership should have appropriate global experience to provide knowledge of regional variations in care. The CEC members should be blinded to treatment assignment (except for open-label studies where this is not possible).

Regarding the credentials of an adjudicator, no recommendations are made at this time, other than to suggest that committee members have experience, preferably for several years, with the disease entities of interest, and are able to fully understand and follow the CEC charter-defined processes. As the conclusions of end point adjudication are weakened proportionally to the number of nonevaluable cases, an important qualification for an adjudicator is the ability to make a decision, even when only charter-defined minimal data are provided.

7. Independence of the CEC: For any trial later than mid-phase 2, an external CEC is recommended. External CECs are also recommended for unblinded, open-label trials (as the CEC should be blinded in open-label trials, the case dossier for these trials needs to be cleared of any identifying information that may be used to unblind the treatment group). It is not unusual for sponsors to have input into decisions about events to be reviewed, event definitions, and processes for adjudication. However, once the CEC charter is signed and cases are being reviewed, the physicians reviewing cases and the organization that is commissioned to process the operations of the CEC need to be completely independent of the sponsor. It is not unreasonable to have an internal sponsor adjudication process for early stage trials (phase 1-2a, with the exception of phase 2 antidiabetic therapies). That is, a sponsor may use a single physician, such as a cardiologist, to perform adjudication or create an internal assessment committee composed of internal members that are independent of the study team or development project during the early development process.

For external CECs, members should not have any unmanageable financial and/or intellectual conflicts of interest. Examples would be board membership or significant financial holdings, participation in or intimate knowledge of the clinical trial, or anticipation of using publication of CEC activities for personal gain. In addition, it is important that CEC members serve no other significant roles, such as serving on the Data Safety Monitoring Board (DSMB) or representing the sponsor in regulatory proceedings (except to detail CEC operations) concerning the product.

8. Risk-based or adaptive adjudication models: Risk-based or adaptive adjudication processes are potential means to increase the cost-effectiveness of end point adjudication. In these adjudication models, cases are selected and adjudicated according to differential measures of their complexity and the potential that the investigative site may have provided an erroneous result. For instance, in a population with low likelihood of true underlying CV disease, an adaptive approach might fully adjudicate all cases with the trigger term of *cardiac chest pain* but only a sampling of cases with the trigger term of *fatigue*. The potential benefit of this approach is to focus the CEC on more complex cases and cases where adjudication may affect the reported event rate. A by-product of a risk-based approach can be a reduction in resources necessary for end point adjudication. In addition, in this capacity, the CEC serves as an additional quality control mechanism that validates the veracity of site evaluations. In effect, a risk-based system triages the potential events according to their need for review by a CEC. This area warrants further research.

Potential support for the conceptualization of a risk-based adjudication model can be found in recent literature¹⁰ on risk-based monitoring and in recent guidance documents by both the European Medicines Agency¹¹ and the FDA.¹²

The adjudication process can also be adaptive by continually measuring whether the underlying assumptions for the triage scheme remain relevant throughout the clinical trial. An example of this system might be in the evaluation of MI through the following triage mechanism:

- (a) Algorithmic adjudication: when the investigative site reports an MI and there is evidence of symptoms and biomarker criteria in the clinical database that meet prespecified criteria for MI, these cases would be “automatically” adjudicated.
- (b) Traditional adjudication: when the investigative site reports an MI and evidence is limited to only symptoms or evidence of biomarker criteria, these cases would go to the CEC for adjudication.
- (c) When the investigative site does not report an MI but there is evidence of symptoms or biomarker criteria in the clinical database, there is an adaptive sampling approach designed whereby a prospective sampling methodology provides confidence that any true events are detected (eg, perhaps the first 50 cases might be reviewed, and depending on the results, only 10% of the remaining cases would be adjudicated).

An alternative use for a CEC is to provide quality control of investigative sites' end point decisions on a prospective basis. For example, potential events at sites could be

randomly sampled (or sampled according to an enrichment algorithm such as oversampling sites that enrolled a higher number of at-risk patients) at points during the clinical trial. These cases would be sent to the CEC to adjudicate the performance of sites regarding study end point evaluations. Depending on protocol compliance as assessed by the CEC, individual sites may require differential levels of CEC oversight. Again, this example relates to quality control purposes and should not be confused with the approach that a CEC should have for scientific oversight of a major CVOT.

Concluding comments and future directions. Because end point adjudication involves a significant investment in time and resources, it is imperative that CECs operate in an optimal fashion. For practical reasons, the adjudication community should adopt a standard lexicon, allowing clear communication of its activities. Communicating that a given trial has a CEC is not sufficient: its specific processes and quality control measures should also be communicated both to study participants and in subsequent publications. As a first step toward optimization, the CSRC encourages adoption of the CEC best practice recommendations in this manuscript. These provide a framework on which future developments may build.

Recent regulatory efforts have focused on improving clinical trial efficiency through quality- and risk-based applications of clinical trials processes. This focus encourages the clinical trial community to prioritize its efforts in areas that truly make a difference. Consistent with this model, the think tank consensus is that end point adjudication, if applied and practiced properly, can increase the precision of clinical trial results and improve overarching clinical trial quality that might significantly affect regulatory and clinical decision making.

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