WHITE PAPER PRESENTED BY PREMIER RESEARCH

Clinical Endpoint Committees: Ensuring the Quality, Validity, and Integrity of Clinical Trial Results

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ABSTRACT

The use of Clinical Endpoint Committees for centralized adjudication of efficacy and/or safety endpoints can help to standardize outcomes and optimize the quality of clinical trial data, driving study success.

MEDICAL DEVICE

Introduction

Some compounds and many devices face the challenge of defining efficacy or safety endpoints so that they are scientifically measurable, objective, and valid. Often, clinical trials are driven by clinical events, which may lack standard definitions or are subject to interpretation. In these scenarios, sponsors need a reliable method for reducing the impact of variability on conclusions drawn from analyses of outcomes data. Independent endpoint assessment/adjudication committees, otherwise known as Clinical Endpoint Committees, can play a significant role in reviewing and classifying suspected efficacy and/or safety endpoints to provide standardized endpoint outcomes for statistical analysis. Enabling this centralized adjudication process enhances the quality, validity, and integrity of study results, which can improve the likelihood of clinical trial success.

In this white paper, we discuss the value of Clinical Endpoint Committees in drug development or medical device evaluation programs and explore the process of organizing, managing, and implementing a centralized adjudication process for standardizing study endpoints.

Background

A Clinical Endpoint Committee (CEC) is an independent group of clinical and/or diagnostic experts charged with:

+ Centrally reviewing and classifying suspected efficacy and/or safety endpoints in a blinded, unbiased, confidential, and consensus-based manner
+ Determining whether the endpoints being adjudicated meet protocol definitions/endpoint criteria

Sponsors need a reliable method for reducing the impact of variability on conclusions drawn from analyses of outcomes data

- Providing standardized endpoint outcomes for statistical analysis
- Classifying events as related to a study device and/or procedure (in medical device studies)

CECs review overall subject data, as well as endpoint-specific data, applying complex and systematic medical definitions and pre-defined criteria of data or clinical reports to arrive at their adjudicated outcomes. Their review of overall subject data includes all serious adverse events (SAEs), reports of death, and adverse events (AEs) that have the potential to be clinical study endpoints. For medical devices, this review would also include all serious adverse device effects (SADEs), unanticipated adverse device effects (UADEs), and device deficiencies.

According to the FDA Guidance for Clinical Trial Sponsors on Establishment and Operation of Clinical Trial Data Monitoring Committees, CECs should be blinded to treatment when performing centralized adjudication whenever possible, even if the trial in question is not blinded.[1] In addition, the adjudication process should be carefully designed to both preserve the independence of the CEC and to prevent any undue bias that could impact its decision-making.[2]

Typically, CECs are called upon when a protocol contains clinical events that will be assessed as efficacy or safety endpoints. Centralized adjudication is also helpful when:

- Endpoints are complex and/or subjective
- Studies cannot be blinded
- Studies are expected to have a high enrollment or long duration
- Global or cultural differences are expected across study sites
- Endpoints of interest fall outside the therapeutic specialty of the investigator
- Data is needed to support Data Monitoring Committee (DMC) or Data Safety Monitoring Board (DSMB) functions and subsequent interim analyses or adaptive study designs

CEC-adjudicated outcomes typically validate, negate, or otherwise modify initial classifications (e.g., those assigned by sponsors or investigators) of suspected endpoints. In medical device trials, CECs also adjudicate on the relationship of an event to the device and/or procedure under investigation. In some cases, CEC members may identify new, previously unreported, suspected endpoints for investigation and follow-up. Of note, CEC-adjudicated outcomes are not provided to study investigators, as these outcomes have the potential to unduly bias investigator reporting of suspected endpoints.

Need for centralized adjudication

The classification of study endpoints is, in part, a subjective process performed based on applying a set of medical endpoint criteria to an often complex clinical event. As such, investigator classifications are subject to variability due to differences in individual medical training and clinical judgment or regional differences in event identification, diagnosis, and reporting. Implementing centralized adjudication helps to mitigate this variability by:

- Limiting the number of individuals providing classifications of study endpoints
- Assisting in assuring systematic application of the protocol definitions of suspected endpoints
- Employing experts to provide these classifications, leading to greater precision and standardization in the final classifications of study endpoints

In addition, regulatory authorities, including the FDA, derive confidence in the validity of results when central adjudication is performed.[3]

Use of adjudicated endpoints in decision-making

CEC-adjudicated endpoints may be used in critical decision-making processes, including power estimations, periodic safety reviews by DMCs or DSMBs, sample size re-estimation and other interim analyses, and overall efficacy and safety analyses. Consequently, CEC-adjudicated outcomes need to be finalized and made available on an ongoing basis throughout the lifespan of a trial. By enabling more timely identification of efficacy signals or safety risks, central adjudication may facilitate go/no-go decisions and potentially reduce trial costs; therefore, CECs play an integral role in adaptive clinical trial designs.

Regulatory environment

With increasing regulatory emphasis on benefit-risk balance, sponsors are under pressure to minimize variability in endpoint outcomes.

For example:

+ In December 2008, the FDA released guidance on evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes. The guidance noted that sponsors should establish 'an independent cardiovascular endpoints committee to prospectively adjudicate, in a blinded fashion, cardiovascular events during all Phase II and Phase III trials.' These events should include cardiovascular mortality, myocardial infarction, and stroke and may include hospitalization for acute coronary syndrome, urgent revascularization procedures, and possibly other endpoints.[4]
+ In January 2010, the European Medicines Agency (EMA) released a similar draft guideline addressing cardiovascular safety in the clinical investigation of medicinal products in the treatment of diabetes, which was finalized in November 2012. This guideline calls for a consistent central adjudication system for blinded assessment of all predefined cardiovascular and other adverse events of interest during the Phase II-III program.[5]
+ The 2011 revision of ISO 14155[6] also provides guidance on the use of DMCs in medical device studies.

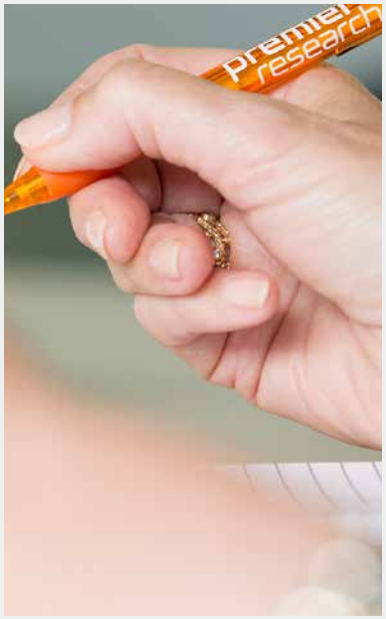
As the use of CECs increases across therapeutic areas and indications, there is a need for additional regulatory guidance on the establishment and operation of these independent panels to standardize an approach to CEC implementation and to help sponsors achieve maximal benefit of centralized adjudication at the protocol – or even the drug development program – level.

Establishing and operating a CEC

The process of managing a CEC can be difficult due to the logistical challenges of coordinating CEC members and disseminating a large quantity of information in a timely manner to facilitate efficient and rapid adjudication of potential events as they occur during the conduct of a clinical trial. In addition, endpoint process flows are inherently complex and dynamic, involving many contributors and stakeholders, including:

+ Investigators, who are responsible for the identification and reporting of suspected endpoints [or, adverse clinical events defined in the Clinical Investigation Plan (CIP)] and for addressing queries related to reported and potential new suspected endpoints or adverse clinical events
+ Data coordinators, who are responsible for the process of endpoint case management
+ CEC members
+ Members of the clinical study team, including monitors, site staff, data managers, pharmacovigilance, and biostatisticians

By enabling more timely identification of efficacy signals or safety risks, central adjudication may facilitate go/no-go decisions and potentially reduce trial costs



As a result, successful implementation of a CEC requires cross-functional planning as early as possible in the course of development.

Sponsors who are considering the use of a CEC should keep the following in mind to support successful central adjudication:[2]

1. The study protocol should include a well-defined data capture strategy that addresses details regarding the handling of suspected endpoint and adjudicated outcome data, which should be defined in a CEC charter.
2. The study protocol should also include a clearly-delineated tactical plan for effective endpoint case management.
3. The CEC adjudication workflow must be structured to deliver consistent, reliable, and accurate results.

Developing an endpoint data-capture strategy

The first step in developing an endpoint data-capture strategy is to define and standardize the endpoints of interest as precisely as possible and to define the required criteria for endpoints requiring adjudication and/or reports needed for the adjudication process at the outset of the development program.[7] Given differences in terminology and standard of care across the world, it is important to map those endpoints to all potentially used event terms across all study sites and to detail them in the CIP. Investigator and site training on the identification and reporting requirements for suspected endpoints will also help support complete and accurate data capture.

When developing an endpoint data-capture strategy for a study that will utilize centralized adjudication, sponsors must consider:[2]

1. What methods will be used to support accurate detection and reporting of all potential suspected endpoints?

Investigator reporting is usually the cornerstone of suspected endpoint detection and reporting, as the investigator has direct contact with the subject. When a suspected endpoint is identified, the investigator is responsible for completing a designated Endpoint Reporting CRF. The data-capture strategy should include a standard triggering process for investigator referral of endpoints for CEC adjudication, as well as a standard query or coding system to ensure no endpoints are missed.[8]

In some cases, the sponsor may rely on the support of an internal safety officer or safety team for collecting blinded anonymized source data and reports from clinical study sites necessary for the preparation of CEC files.

In addition to the primary method of investigator reporting, sponsors should consider supplementing with secondary (e.g., monitoring) and tertiary (e.g., edit checks and reconciliations) endpoint detection methods. If a potential suspected endpoint is identified through secondary or tertiary methods, it is presented to the investigator, who will evaluate it and determine whether it should be reported as a suspected endpoint. However, the sponsor can still elect to submit the suspected endpoint to the CEC for adjudication.

Controls should also be put into place to prevent any clinical trial team member – including the sponsor – from deleting or restricting review of suspected endpoints.

2. How will the suspected endpoint and adjudicated outcome data be handled within the overall study data-capture plan?

Best practice dictates that sponsors should implement a designated Endpoint Adjudication Form, which CEC members use to document their adjudicated outcomes. The overall study data-capture plan should include a procedure to achieve a one-to-one match between Endpoint Reporting CRFs and Adjudication Forms. This creates a data link that is critical for reconciling all known suspected endpoints with final adjudicated outcomes.

3. What methods will be used to ensure that final adjudicated outcomes are complete and current?

Since centralized adjudication occurs on an ongoing basis throughout the lifespan of a trial, CEC members are making adjudication decisions based on study data that have been extracted at a particular point in time. As data continues to accumulate, CRF data that directly impacts CEC decision-making may be updated or additional source documentation entered into a subject chart post-adjudication. As a result, sponsors need to implement a process for accommodating relevant data changes that will require re-adjudication.

Developing an endpoint case-management plan

An endpoint case-management plan should clearly outline endpoint process workflows (e.g., collection of documentation, compilation of endpoint dossiers, procedures for handling requests for additional documentation, etc.), as well as any forms to be used.

It may be wise for sponsors to centralize the endpoint case-management function under a specialized functional group such as Data Coordinating Center (DCC) or with a contract research organization (CRO).

Figure 1. DCC Responsibilities

- Overall management and coordination of the centralized adjudication process
- Tracking all known suspected endpoints
- Collecting all source documentation required for adjudication and obtaining translation, if required
- Performing endpoint document processing and endpoint case processing
- Submitting endpoint dossiers to the CEC for adjudication
- Handling any CEC requests for additional documentation
- Handing any CEC-identified potential new suspected endpoints
- Participating in endpoint-related reconciliation activities

Utilizing a DCC helps to standardize collection of endpoint source documentation and submission of high-quality endpoint dossiers, further limiting potential variability in endpoint outcomes.[2]

Structuring a CEC adjudication model

The two most common adjudication models are the parallel review model and the consensus model, each of which has pros and cons relative to cycle time, cost, and potential impact on quality and consistency of outcomes.[2]

Selecting CEC members

In a landscape in which clinical evidence may be subject to evolving scientific definition including regional and/or cultural variation, selection of the right experts is critical to the success of any CEC.

Thus, the selection process should be guided by a set of documented procedures for identifying, qualifying, and contracting with CEC members.

At a minimum, each CEC member should have extensive therapeutic-area experience and expertise regarding the adjudicated endpoints, as well as the ability to accurately review records, make individual decisions, and understand the independent role of the CEC in the context of the regulatory approval process. Generally, the CEC Chairman should have previous experience as a CEC member, as well as the leadership skills required to facilitate discussion, arbitrate differences of opinion, and make decisions.

Figure 2. Parallel Adjudication Model

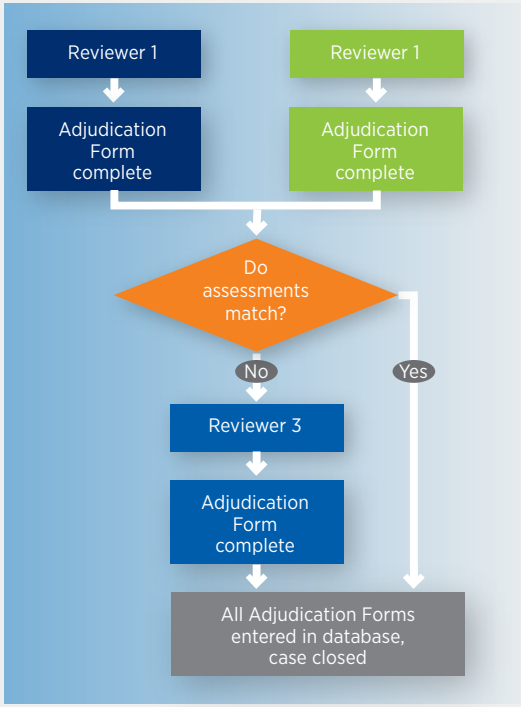
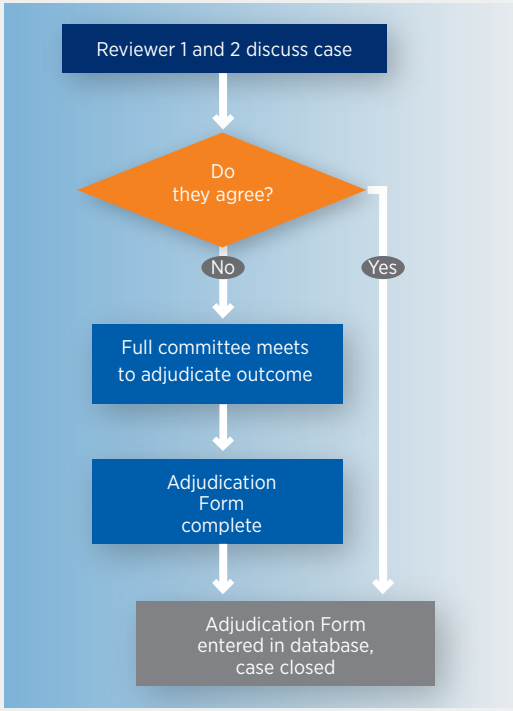


Figure 3. Consensus Adjudication Model



Sponsors should ensure that CEC members are free of serious conflicts of interest, whether financial, intellectual, or personal. It is also important for sponsors to secure a commitment from each CEC member to perform the required adjudication tasks in a timely fashion on an ongoing basis for the duration of the trial.

If the study involves a mix of endpoint categories from different therapeutic areas, it may be necessary to either:[2]

1. Create CEC sub-committees that are organized by specialty, or
2. Implement an adjudication workflow within a single CEC that takes into account the cross-functional nature of the committee with respect to decision-making

When staffing the CEC, sponsors should also consider the anticipated caseload for adjudication. If the caseload is expected to be high, it may be wise to allow for some degree of redundancy in the membership so that cases can be reviewed and adjudicated on a continual basis regardless of spikes in case volume or member unavailability.

Developing a CEC charter

The CEC Charter is a document describing the Standard Operating Procedures for the adjudication process of a specific clinical trial, as well as the expectations and anticipated goals of the CEC. Currently, U.S. regulations do not require the FDA to approve the CEC charter, but regulators should be informed of the charter's definitions and procedures so it can be amended if the FDA deems it to be inadequate. The CEC Charter is generally approved by both the Steering Committee and the DSMB prior to initiation of the trial.

Figure 4. Sample CEC Charter[2,3]

- Study abstract – adjudication rationale
- Adjudication roles, responsibilities, and confidentiality requirements
- Procedures for training CEC members in the systematic assessment of data
- Definitions and identification criteria for endpoints, including an overview of the endpoint data-capture strategy
- Endpoint source documentation, endpoint dossier composition (e.g., documents, key data, imaging, etc.), and endpoint dossier handling, including an overview of the endpoint management plan
- Overview of adjudication workflow, including:
  - + The adjudication model used
  - + Timelines
  - + The process for adjudication form completion
  - + The process for requesting additional information
  - + The process of handling lack of consensus in CEC members' assessments
  - + The process for reporting potential new suspected endpoints
  - + The process for re-adjudication
- Quality control and quality assurance procedures for the handling of all data in any form

Ensuring effective communication

The adjudication process involves a significant quantity of data, which can change before file closure, and the time required to confirm an event as a study endpoint may be a key factor to study success. Consequently, effective communication between sponsors, CEC members, Clinical Safety, Data Management, and study investigators is critical for the CEC to review and arrive at critical endpoints for study decisions.

Integrating centralized adjudication into the overall clinical trial

In order to successfully integrate the centralized adjudication process into the overall clinical trial process, sponsors must consider how the data exchanges required for the endpoint process impact every aspect of study planning, from protocol design and site training, to the monitoring plan and study timeline. Given the added coordination and communication involved in operating a CEC, proactive planning for centralized adjudication should be initiated early in the development process.

Conclusions

Ultimately, the goal of employing a CEC is to standardize key efficacy and safety variables for a clinical trial, resulting in a higher quality study and greater assurance in the consistency of reported endpoints. Although centralized endpoint adjudication requires significant time and energy during planning and implementation, it can have significant downstream benefits in terms of data consistency and quality, patient safety, cost, and clinical trial success. Working with a CRO partner who has experience in organizing and managing CECs can help sponsors maximize the benefit of employing an independent panel of experts to adjudicate outcomes in a manner that is efficient and appropriate for the nuances of their clinical trial.

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With over 20 years of clinical research industry experience, Joanne has a keen focus on operational design and delivery. She began her career in academia within transplant and then cardiovascular research. She joined the CRO space in 1995 and was engaged as a CRA, LCRA, and Project Manager on trials in CNS, Oncology, Respiratory, Cardiovascular Device, and several diagnostic programs. Joanne then moved into oversight and leadership specializing in Clinical and Project Management Delivery, spending time at PRA before joining Premier Research in early 2011. Since then, Joanne has overseen the operational delivery structures and planning for both clinical and project management. She has focused on the key needs and standards within therapeutic areas and medical device and ensuring core process designations for staffing and oversight. Joanne chaired the ACRP Poster Committee in 2006 and the Annual ACRP meeting in 2007. She also assisted with development and implementation of the Post Graduate Clinical Research Program at Humber College in Toronto.

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