Clinical events classification (CEC) in clinical trials: Report on the current landscape and future directions — proceedings from the CEC Summit 2018

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ABSTRACT

Importance Clinical events adjudication is pivotal for generating consistent and comparable evidence in clinical trials. The methodology of event adjudication is evolving, but research is needed to develop best practices and spur innovation.

Observations A meeting of stakeholders from regulatory agencies, academic and contract research organizations, pharmaceutical and device companies, and clinical trialists convened in Chicago, IL, for Clinical Events Classification (CEC) Summit 2018 to discuss key topics and future directions. Formal studies are lacking on strategies to optimize CEC conduct, improve efficiency, minimize cost, and generally increase the speed and accuracy of the event adjudication process. Major challenges to CEC discussed included ensuring rigorous quality of the process, identifying safety events, standardizing event definitions, using uniform strategies for missing information, facilitating interactions between CEC members and other trial leadership, and determining the CEC’s role in pragmatic trials or trials using real-world data. Consensus recommendations from the meeting include the following: [1] ensure an adequate adjudication infrastructure; [2] use negatively adjudicated events to identify important safety events reported only outside the scope of the primary endpoint; [3] conduct further research in the use of artificial intelligence and digital/mobile technologies to streamline adjudication processes; and [4] emphasize the importance of standardizing event definitions and quality metrics of CEC programs.

Conclusions and Relevance As novel strategies for clinical trials emerge to generate evidence for regulatory approval and to guide clinical practice, a greater understanding of the role of the CEC process will be critical to optimize trial conduct and increase confidence in the data generated. (Am Heart J 2022;246:93–105.)

Background

The use of clinical events classification (CEC) programs to adjudicate clinical events is common in clinical trials. Given that definitions for nonfatal events and specific causes of death are generally heterogeneous and often subjective, one reason for a central process of event adjudication is to ensure a systematic application of end-
point definitions in the trial and to reduce variability.\(^1\)
This approach is particularly important for open-label trials, where differential identification of events may occur based on conscious or unconscious biases of investigators and participants about whether the experimental treatment is superior or inferior to the control treatment. The academic and clinical communities that rely on the results of trials to guide clinical practice generally have an expectation that clinical events have undergone consistent classification. Regulatory authorities such as the European Medicines Agency and the U.S. Food and Drug Administration (FDA) may have greater confidence in a trial’s findings when independent blinded adjudication of clinical events has been performed.

Traditionally, clinical events were not adjudicated using a standardized definition, creating significant issues when interpreting randomized controlled trial results\(^2\) because of uncertainty regarding whether the events, and subsequently the treatment effect of the therapy or intervention, were accurately identified. Notably, heart failure events were recently defined in a consensus report.\(^3\) Improving classification of clinical events may prevent misidentification of outcomes that are similar. One example is bleeding events with varying severity, for which the use of a consistent grading tool may benefit discrimination in superiority and non-inferiority trials.

To evaluate the state of the art for CEC, a summit was held on September 26-27, 2018, in Chicago, IL, with clinical trial investigators and operations staff and representatives from regulatory agencies, academic and contract research organizations, and pharmaceutical and medical device companies. This article summarizes the proceedings of the summit and aims to describe (1) the current landscape of CEC program operations, (2) challenges in contemporary CEC, and (3) future directions for CEC programs.

**Role of CEC program operations**

The typical CEC program involves a complex interaction of personnel from every level of the trial’s operation, including site investigators and study coordinators, coordinating centers, technology partners, adjudicators, sponsors, and regulatory agencies. Proper operation of the CEC program requires a systematic approach to defining the program’s structure, function, and utility.

The CEC charter

The charter should detail the events that will be adjudicated, definitions for these events, and the process flow; describe the basis of reviewer selection and the specialties that will be represented on the CEC, including a list of each operation and clinician roles and responsibilities; indicate programmed “triggers” (ie, the specific clinical information that will be required to identify potential outcome events) and queries that will be in place for event capture; specify the source documents that will be required of trial sites; and delineate the quality control process, including the percentage of events that will undergo quality control and how quality control findings will be resolved (Table I).

Large, multinational studies typically are associated with a proportion of incomplete source documents required for adjudication. To increase adjudication consistency, each CEC charter should prespecify contingencies to be followed in adjudicating events with insufficient data. The charter should consider detailing how disagreements among reviewers will be managed. To ensure the thoroughness and quality of event capture, regulatory agencies generally want to prospectively review the trial’s planned electronic case report form (eCRF) for event reporting, the CEC forms, the list of source documents to be reviewed for each event, and the trigger terms and standardized Medical Dictionary for Regulatory Activities (MedDRA) queries being programmed into the electronic data capture. The regulatory agencies’ role in examining CEC forms is to see not only what data will ideally be available, but what the contingencies are for missing data for a given event report. For instance, if a CEC reviewer checks *unable to adjudicate* on the CEC form, a checklist of reasons for inadequacy (eg, unknown event date and time; incomplete description of signs, symptoms, physical findings, or clinical test results; lack of cardiac or other biomarker results and reference limits) should be offered so that the rationale for event non-adjudication is provided. Importantly, given that absence of complete data should not be construed as absence of an otherwise apparent event, worst-case scenarios and standard approaches to missing data are encouraged.\(^4\)

The CEC adjudication form may also consider instructing reviewers to rate the CEC dossier—which refers to the set of documents given to a reviewer to complete the adjudication—as either complete, incomplete but adequate for adjudication, or inadequate; if the dossier is deemed inadequate, the form should prompt the reviewer to specify what information is missing. Regulatory agencies generally expect the CEC form to document the nature of effort required for each case (ie, whether the reviewers agreed after discussion, or required a third party or larger committee to resolve the adjudication result). Deaths adjudicated as “undetermined causes” by CEC Committees are frequent in cardio-metabolic trials.\(^5\) Critically, for any death adjudicated as having an undetermined cause, the CEC form should indicate whether the reason is lack of information that is expected to be available or whether the cause of death remains undetermined after collection and review of all data as planned. Implications for the overall quality of data collected are different in each case.

The CEC physician review process

Different CEC programs tend to follow the same core workflow for the CEC process. Generally, physicians ad-
judicate each suspected event (also known as an event trigger) identified by either sites, programmed queries, core laboratories, or manual trigger procedures using prespecified endpoint criteria. A suspected event is usually allocated to two physicians acting independently. If one reviewer requests and receives additional information, this information is also distributed to the other reviewer. In a situation where the two reviewers agree in their adjudication of a suspected event, the endpoint classification is deemed complete. Otherwise, the event is usually referred to an adjudication committee (Figure 1). Three or more physicians may be required for the secondary review. In this review, the decision is made by consensus. Different review processes may be considered for different types of events. For instance, in the readjudication of the RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes) trial, differential pathways for adjudication were triggered based on the type of events (MI vs stroke) (Figure 2).

Identification of potentially unreported serious adverse events

Protocols provide detailed instructions for submitting potential endpoints and serious adverse events (SAEs) to the CEC team. SAEs and suspected unexpected serious adverse reactions (SUSARs) may be reported only as a potential endpoint event during the adjudication process and are not infrequently obtained while reviewing a hospitalization event.8,9 These CEC-identified clinical events should be communicated to the safety surveillance/pharmacovigilance team. The process for reviewing events that are submitted by sites to the CEC Committee but then not adjudicated as an endpoint event—that is, negatively adjudicated events (NAEs)—is often not spelled out in the trial protocol, even though they may represent a source of SAEs, including SUSARs. All SAEs, including NAEs, reported by sites are to be reviewed by a safety surveillance/pharmacovigilance team, to ensure compliance with reporting requirements.8

In late-phase studies, events that constitute clinical endpoints for adjudication (eg, MI, heart failure, unstable angina, stroke, death) also meet SAE criteria (eg, hospitalization, life threatening, death, important medical event).8 However, events reported as endpoints are typically exempted from reporting as SAEs. When site investigators enter a potential clinical endpoint in the eCRF—or conservatively, enter it twice, in both the endpoint and SAE forms—the burden to clinical trials sites may increase significantly.

Data and definition standards

For the CEC process to succeed, data standards and standardized endpoint definitions must be in place, and the study’s scientific, clinical, regulatory, and industry partners need a common understanding of these standards. CEC standards and definitions are integral to the development of the protocol and the CEC charter; data reporting by participating sites; central collection of source documents; lab sample collection and analysis; event adjudication; and analysis and presentation of CEC results. The initial and largest source of information for defining endpoints is the original research of experienced clinicians and imaging experts, as well as clinical trialists, such as those serving on study-specific steering committees. This experience is augmented by discussions between these individuals and their respective clinical research networks. As data standards and endpoint definitions evolve by use in small networks, they are adopted as standards by networks of academic research organizations; collaborative initiatives among academia, industry, and regulatory agencies; and professional societies.

Several organizations have played key roles in defining endpoints. The Academic Research Consortium (ARC)9,10 is a voluntary collaboration of thought leaders from five academic research organizations with advisory participation by the FDA and nonvoting participants from industry. Since the consortium’s formation in 2006, the ARC has released a steady stream of specialty endpoint definitions, primarily addressing endpoints for cardiovascular (CV) device interventions.11 The Standardized Data Collection for Cardiovascular Trials Initiative (SCTI) and the FDA have also contributed with major

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<td>Description</td>
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<tr>
<td>Specific events requiring adjudication</td>
<td>A prespecified and predefined outcome with specific definition that will be used throughout for adjudication</td>
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<tr>
<td>Defining process flow for adjudication</td>
<td>The strategy and stages whereby clinical events are assessed for meeting the definition of an outcome and the methodology whereby discrepancies are evaluated. In addition, the process for referral of potential serious adverse events to pharmacovigilance committees should be defined.</td>
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<td>Handling of missing or incomplete data</td>
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Sample pathway for the clinical events classification (CEC) process. Reprinted from American Heart Journal, 166(2), Lopes et al., Methodology of a reevaluation of cardiovascular outcomes in the RECORD trial: Study design and conduct, 208-216.e28, 2013, with permission from Elsevier. CRF, case report form; MI, myocardial infarction; QC, quality control.
Figure 2

**MI/Stroke Trigger Process Flow**

- **MI/Stroke Endpoint Form completed**
- **MI/Stroke trigger with Hospitalization Endpoint Form completed**
- **MI/Stroke trigger with SAE form and SAE narrative/summary completed**
- **MI/Stroke trigger with AE Form only (no hospitalization or SAE)**

**MI Triggers: Phase I Review by 2 independent MDs**
- **Stroke Triggers: Neurologist/Phase II Review**
- **MD determines additional documents are required?**
  - **Yes**: Comment entered on Adjudication form indicating required documents
  - **No**: Adjudication form completed
  - **Documents received?**
    - **Yes**: MI Triggers: Phase I Review Complete
    - **No**: Stroke Triggers: Neurologist/Phase II Review Complete

**One Coordinator or MD reviews data present. (10% of Coordinator reviewed triggers will be re-reviewed by MD for QC)**

- **Data indicate a potential MI or Stroke event?**
  - **Yes**: MI Triggers: Phase I Review Complete
  - **No**: Stroke Triggers: Neurologist/Phase II Review Complete
  - **No event**

Adjudication of specific events as demonstrated in the RECORD trial. Reprinted from American Heart Journal, 166(2), Lopes et al., Methodology of a reevaluation of cardiovascular outcomes in the RECORD trial: Study design and conduct, 208-216.e28, 2013, with permission from Elsevier. AE, adverse event; MI, myocardial infarction; QC, quality control; SAE, serious adverse event.
standardization efforts in the CV field. Both collaborations provide overlapping definitions and are largely consistent.

The value of CEC
Clinical trials have increased in complexity and cost over the past few decades. Although the CEC process is usually only a small part of the cost of the overall trial operation, there remains discussion about the need for CEC and whether the process could be simplified to reduce cost. Several studies have suggested that CEC Committee adjudication of events remains similar to investigator-reported events such as death. However, there are strong arguments in favor of the use of CEC in clinical trials, particularly in regard to credibility of study findings, regulatory approval, and SAE identification.

Independent, blinded adjudication of events increases credibility of study results
A prime example of the increase in credibility accruing from independent and blinded event adjudication is the RECORD trial. This randomized, open-label trial compared rosiglitazone-containing combination therapy for type 2 diabetes with the dual oral combination of metformin and a sulfonylurea. When the results of this trial were reviewed and discussed by an Advisory Committee of the FDA (July 2010), an additional requirement was placed on the sponsor of the RECORD trial (GlaxoSmithKline) for a further comprehensive reevaluation of the cause of deaths and of two nonfatal CV events (MI and stroke) in the trial. The Duke Clinical Research Institute (DCRI) was selected to conduct the adjudication of the results and identified only a modest number of additional person-years of follow-up in the reevaluation. Furthermore, the hazard ratios and confidence intervals using the original RECORD endpoint definitions compared to the Advisory Committee’s recommendation for endpoint definitions showed similar treatment effects of rosiglitazone. This example highlights the importance of standardized, independent blinded adjudication to increase confidence in the results of a trial.

Adjudication and regulatory requirements for new drug approval in certain therapeutic classes
Following the identification of a possible increased risk of MI associated with use of rosiglitazone, in 2008 the FDA released guidance to sponsors surrounding the conduct of trials of anti-hyperglycemic medications. This guidance included the recommendation that sponsors should establish an independent CV endpoints committee to prospectively adjudicate, in a blinded fashion, CV events during all phase 2 and phase 3 trials of therapies for diabetes. These events included CV mortality, MI, and stroke, and could include hospitalization for acute coronary syndrome, urgent revascularization procedures, and possibly other endpoints. The importance of independent, blinded CEC was necessary for sponsors to ensure appropriate evaluation of their product by the FDA. Whether certain trials seeking regulatory labeling may not require formal adjudication requires further exploration.

Standardized data collection and definitions of key outcome events
CEC can alter the interpretation of a trial’s results, one example is the CHAMPION-PHENIX (Clinical Trial Comparing Cangrelor to Clopidogrel Standard of Care Therapy in Subjects Who Require Percutaneous Coronary Intervention) study, for which bleeding events were not adjudicated. Initially, there were no apparent differences between the cangrelor and clopidogrel groups with regard to bleeding, as defined by both GUSTO (Global Use of Strategies to Open Occluded Coronary Arteries) and TIMI (Thrombolysis In Myocardial Infarction) classifications. However, when the FDA requested a post hoc review with adjudication of all bleeding events based on standardized definitions, there was a significant difference in incidence of mild bleeding per GUSTO (cangrelor vs clopidogrel, 14.9% vs 10.5%; OR, 1.49; 95% CI, 1.33-1.67; P < .001) and per TIMI (0.6% vs 0.2%; OR, 3.01; 95% CI, 1.52-5.96). Utilizing standardized event definitions and adjudication processes identified potential safety events that otherwise would not have been identified by a simple dichotomous classification without applying standardized definitions of severity.

Challenges for CEC programs
Numerous issues may arise during the conduct of CEC (Figure 3). Failure to address FDA recommendations and questions may result in regulatory hurdles upon completion of the trial. Additional issues include mid-study changes in endpoint definitions without adequate rationale, not submitting revised charters to the FDA, and endpoint definitions that overlap and/or conflict within the same charter. Particularly with CV endpoints, missed events in a submission—such as failure to present all cardiac biomarkers related to a given case alongside the dates and times of their collection, failure to recognize that fatigue or back or epigastric pain in an elderly woman should have been reviewed for MI, or failure to recognize ischemia in patients with bundle branch blocks or with pacemakers—are likely to raise concern from regulatory agencies.

Quality in CEC
Preparation for a regulatory audit should be built into all aspects of study planning, including CEC. Early interaction with the FDA by the CEC group as well as with the
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Current challenges and solutions to issues surrounding clinical events classification (CEC).

Sponsor remains critical to ensure appropriate preparation for a regulatory audit. Securing the FDA’s agreement on the outcome definitions and the CEC charter well in advance of the study is as critical as having the agency’s approval of the final protocol and related documents.

Members of the CEC Committee must be independent of the sponsor and have no conflicts of interest that could be seen as having an impact on the study result. An independent CEC Committee member is a person who does not represent a pharmaceutical industry sponsor, is not involved with carrying out the study, and does not have possible financial implications depending on the study outcome. Ideally, committee members should have expertise in the disease or condition and treatments studied, full understanding of the protocol, and careful training in the adjudication process, and the committee chair should have previous CEC experience. Processes must be in place to govern the collection and circulation of case information and maintain blinding; ensure confidentiality, uniformity, and timeliness in the adjudication of each case; deal uniformly with case disagreements; and establish rules for the conduct and documentation of committee meetings. Generally, regulatory agencies request submission of CEC Committee meeting minutes for new drug applications.

Event definitions
Adjudication of certain CV events, such as MI, is becoming increasingly challenging. As per the new Fourth Universal Definition of MI (2018), adjudication cannot just state that there was or was not an MI. If a rise and fall of troponin was not accompanied by acute ischemia, the event must be assessed for acute myocardial injury (eg, acute heart failure or myocarditis). For events such as heart failure, defining when an event has occurred remains challenging given the heterogeneity of
the disease presentation across disease states. For heart failure patients, troponin may be consistently elevated, and repeated troponin sampling may be required. Consistent and disease-specific event definitions that align with presentation in clinical practice remains a strategy to ensure that such events are defined in a way that enables adjudicators to potentially identify when an event has occurred. Future studies aimed at standardizing and minimizing the number of criteria needed to define events are needed.

If a new standard endpoint definition is validated and adopted as a trial is underway, discussion with regulatory agencies should occur; however, there is generally not an expectation that the endpoints gathered in ongoing research will be rejudicated by the new standard. Any changes to endpoint definitions or to the CEC charter and the rationale for such changes should be submitted to the FDA in real time and not at the end of study. Quick and rapid review of any issues raised by regulatory agencies is needed, and the CEC Committee should be proactively checking with the sponsor(s) to learn what the committee could address.

Interaction between CEC and data monitoring committees

Quick and effective interaction between the CEC Committee and the Data Monitoring Committee (DMC) or Data and Safety Monitoring Board (DSMB) is necessary to respond promptly to the safety signals picked up by adjudication. However, such interactions should be carefully managed, as there must be a firewall between the CEC Committee, whose members are blinded, and the DMC/DSMB, who are unblinded. If a CEC Committee is not getting quality data from certain sites, the DMC should be informed. If there is a need for interaction between the CEC Committee leadership and the DSMB, it should occur only when the latter is in an open session where no unblinded data are discussed. The CEC Committee should not participate in any session in which the DSMB asks to be completely unblinded, and the CEC Committee should not compile unblinded data for the DSMB.

Interaction between the CEC and steering committees

Similar concerns about sharing of unblinded data apply to interactions between the CEC Committee, the CEC Committee chair, and the steering committee. Because of regulatory concern that CEC Committee members could be exposed to unblinded data, agencies have required CEC charters to state that reviewers will not see unblinded data. Another concern is that CEC data may be carried over into the steering committee’s communications with sites and possibly unintentionally send a message that certain types of events tend to be negatively adjudicated, in which case the sites may curtail their reporting of events. This may occur in trials where blindness is challenging, such as device trials.

Clinical ascertainment using real-world data

Pragmatic clinical trials (PCTs), including registry-based trials, are widely perceived as being cheaper and faster than randomized controlled trials, but several caveats must be considered. PCTs are often best suited to answer questions about real-world effectiveness. PCTs can be a supplement to but not necessarily a replacement for traditional, highly regulated randomized clinical trials; the appropriate study design depends on the question and the inference desired. For purposes of CEC, real-world data (RWD) comprise electronic medical record (EMR) and public and private health insurance claims data—that is, data resulting from a patient health encounter. In a true pragmatic trial, the “investigator” is a clinician, often a general practitioner, whose focus is usually on the patient encounter and not on gathering data. This approach has an impact on how much priority is given to patient recruitment or ensuring adequate data for subsequent event ascertainment. Furthermore, it is unclear whether pragmatic studies are truly less expensive. Analyzing RWD requires specialist resources and cost shifting, and one healthcare informatics expert can be far more expensive than multiple data management workers. Still, if a PCT is planned carefully, the lessons learned from RWD can be used to improve the quality and efficiency of all clinical trial conduct. A pragmatic approach can be useful for safety studies or studies with simplified outcomes such as “all-cause mortality,” but stakeholders will have to consider whether the tradeoffs in event ascertainment are acceptable. Given practicality considerations, there has to be a threshold for saying an RWD study is the only choice in a situation where it is possible to conduct a randomized controlled trial.

The DCRI-led ADAPTABLE (Aspirin Dosing: A Patient-Centric Trial Assessing Benefits and Long-Term Effectiveness) study is an example of a PCT with broad, multimodal recruitment methods. ADAPTABLE was the first study initiated by the National Patient-Centered Clinical Research Network (PCORnet) and was designed to compare outcomes of adults with CV disease taking either high- or low-dose daily aspirin. A total of 15,076 patients with a primary CV indication for aspirin have enrolled via a secure patient portal, with or without the direct support of health care providers. They were followed for 26.2 months. The primary endpoint was the composite of all-cause mortality, hospitalization for nonfatal MI, or hospitalization for nonfatal stroke; the primary safety endpoint was hospitalization for major bleeding with an associated blood product transfusion. The study attempted to mimic the real-world patient experience of a patient with heart disease, while maintaining
the scientific rigor of a randomized controlled trial with a robust primary endpoint. Once enrolled, participants were randomized to follow-up every 3 months or every 6 months. Via the secure portal, participants could complete the entire study via internet portal. If they preferred or they did not complete the internet portal visits, they were contacted by the trial call center. Endpoint ascertainment occurred via multiple methods including compilation of electronic health records using the PCORnet Common Data Model, linkage to health insurance claims data from the Centers for Medicare & Medicaid Services (CMS), and 3 private health insurance providers (Aetna, Anthem, Humana). Each data source arrived at the coordinating center via a different mechanism, but all will contribute to the eventual study database. Algorithm-based decisions were in place to resolve discrepancies among data sources and for ascertainment of events. Overall, there was substantial switching to the low-dose aspirin from the high-dose aspirin with no difference in the primary outcomes seen in the intention-to-treat analysis.23

With this approach and different sources of data contributing to endpoint ascertainment, ADAPTABLE will be able to provide unique insights into event ascertainment in the context of pragmatic studies. For instance, data may vary by site depending on differences in CMS or health plan coverage, may vary by patient if fields are inaccurate or missing, and may further vary because some participants may have an EMR but not be in the CMS system, while others may have data from multiple systems.

Furthermore, while information latency is inherent in ADAPTABLE, this is not unique to PCTs; there can often be significant delays in traditional clinical trials in order to get clean query results for adjudication. Although patient self-reported data are available to the coordinating center instantly (optimistically), data from patients’ EMRs, CMS, and the National Death Index may lag.

The ADAPTABLE trial raises several key questions regarding ascertainment of events. The results will provide insights into whether a multifaceted, pragmatic data capture of outcomes can be complete and accurate enough to allow validation and reconciliation of major adverse cardiac events and major bleeding events. Furthermore, ADAPTABLE will enable a greater understanding of how a pragmatic approach to endpoint collection can be leveraged in clinical trials.

Future directions and recommendations

CEC independence definition

Successful clinical trial operations require efficient setup and execution of activities, which is best achieved by precise description of procedures in the CEC charter before start of activities, and by aiming for operational excellence. Furthermore, predefined channels for feedback from an independent CEC process to the coordinating center, steering committee, or DSMB (eg, for incomplete adjudication dossiers, late adjudications) need to be in place. At the same time there should be a firewall between the CEC and other parties that could be influenced by the information held by the CEC or vice versa. Defining CEC independence is a priority of the industry, and efforts are needed to standardize this definition.

The consensus of the CEC Summit attendees was that the CEC Committee must maintain independence, in the context of both double-blinded and open-label trials, but have the appropriate channels to raise issues with those overseeing the execution of the study.

The need to consider a broad range of events

To ensure optimal conduct of CEC, collaboration between various clinical trial operations is critical. An example is provided by the PRECISION (Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen or Naproxen) trial, an FDA-mandated CV safety study of the COX-2 inhibitor celecoxib.24 PRECISION comprised 24,081 evaluable participants who required medication to manage their osteo- or rheumatoid arthritis pain. To assess the CV effects of standard doses of celecoxib, ibuprofen, and naproxen, the primary objective was to compare time to first occurrence of the Antiplatelet Trialists’ Collaboration composite endpoint (first event of CV death, nonfatal MI, or nonfatal stroke); comparative incidence of major adverse cardiac event was one of the secondary objectives, and standard definitions were available for the CV endpoint events. However, given that adverse effects are expected beyond the CV system when a patient is administered a nonsteroidal anti-inflammatory drug or COX-2 inhibitor, PRECISION was also designed to look at comparative incidence of effects on renal function and blood pressure, as well as arthritis efficacy (pain scale, global improvement, function). Considering what events may occur based on a predefined understanding of the safety profile prior to initiation of the trial is necessary to develop standardized definitions and to allow valid adjudication of extra-cardiac events.

Ensuring adequate infrastructure

Proactive development of the infrastructure necessary to support the CEC program for the duration of the trial and potential harmonization across an entire program of trials for a specific drug or device should also be undertaken. This can help ensure accurate, consistent identification of events that may not be identified by individual trials within a program. For example, the clinical development program for TAK-87525,26 involved the first G-protein-coupled receptor 40 (GPR40) agonist studied in humans. All trials in the entire phase 2 program of TAK-875 used the same CEC, DSMB, and steering committees, and a pattern of liver effects was observed across the trials—a small increase in incidence of mild-to-moderate
transaminitis. As a result, the CEC Committee decided to add a liver safety specialist. Multiple phase 3 studies were planned to look at TAK-875 alone or in combination with other drugs and in a variety of populations with type 2 diabetes, including patients for whom diet and exercise changes were unsuccessful, those who did not respond to metformin or to dipeptidyl peptidase-4 inhibitors, and patients with high CV risks. However, in a global, placebo-controlled phase 3 trial of TAK-875 in 3207 adults with type 2 diabetes and CV disease or risk factors, increases in transaminases similar to those in phase 2 were noted: during daily oral treatment, 1.4% to 2.1% of patients receiving TAK-875 had new elevations in aspartate transaminase/alanine aminotransferase ≥ 3× the upper limit of normal versus 0.3% to 0.4% for the placebo group.26 The difference in incidence between treatment groups was still apparent when considering all final visits regardless of individual subjects’ duration of treatment. The sponsor voluntarily terminated all phase 3 studies, and given the potential exposures avoided across the planned phase 3 program, there was a huge benefit to having a carefully structured and proactive CEC program.

Ability to adjudicate events electronically

Working electronically provides several advantages to the CEC Committee: the ability to perform accurate and concurrent review of events, transparency in workflow status, data analytics that are immediately accessible, and the capability to integrate CEC data collection with electronic data capture systems so that sites do not have to enter data twice. Electronic CEC systems allow real-time reports showing, for example, where any disagreements are occurring, so that the committee can decide whether to bring in intercessors to help with the final decision.

Identification of adverse events in negatively adjudicated events

As previously highlighted, SAEs may be missed because NAEs do not undergo further scrutiny. Some strategies are being developed to address this issue. Safety surveillance and CEC groups should further categorize an NAE as having either the same pathophysiologic pathway as the site-reported endpoint or an alternate pathway, based on the idea that a symptom such as chest pain can be related to the gall bladder or angina. Events related to the underlying disease generally will not represent SUSARs and do not require further review. By contrast, in a case where a site reports a heart failure hospitalization but the CEC Committee determines that the true etiology of the event was pneumonia, this represents an alternative pathophysiologic process. These “alternate causal pathway” events represent situations where a potential SAE may be the cause of the NAE. If the CEC Committee determines an NAE is an alternate causal pathway event, referral to safety surveillance should be triggered. A safety surveillance group should cross-check the SAE database for any previously reported event related to the NAE. If a related SAE has already been reported, no further action is taken. However, if an SAE has not been reported, CEC source documents should be reviewed once more for potential SAEs. Such strategies can be utilized to ensure that SAEs and SUSARs are not being missed.

Utilizing artificial intelligence and mobile devices to streamline CEC processes

New strategies and technologies such as artificial intelligence and digital health are increasingly being used in clinical and research settings and can facilitate and streamline the CEC process.27,28 One critical issue in the conduct of adjudication is that past hospitalizations may be missed during clinical trial event reporting. Patient recall of hospitalizations is poor, especially among elderly patients.29 Utilizing the geolocation technologies on mobile phones can facilitate identification of hospitalizations.29 A pilot study by the DCRI to leverage geolocation technology to trigger hospitalization events was conducted in the US, France, and Canada. Of 150 hospital encounters by healthy volunteers, a specificity of 98.7% and sensitivity of 100% to identify a hospitalization were demonstrated. Voice-based technologies are now being tested to determine if they can collect medical grade information.30 If conducted using a strategy that protects privacy, real-time identification of hospital visits and patient centric outcomes through mobile phones or voice-based technologies may allow for more rapid identification of events and therefore can enhance the adjudication process to increase confidence that all potential hospitalization events are being identified.

Further standardization of event definitions

Several event categories require further standardization. Adjudication of death, and specifically the subcategorization of CV death adjudication, is still a challenge.3 Further work is needed to reach consensus on the definition of periprocedural MI. Full harmonization of MI may be required for widespread adoption of the Fourth Universal definition of MI, and it may take time to grow comfortable with its 10 categories.12 Given the growing number of aortic valve-related studies, specific endpoints need further development. The SCTI and ARC definitions of coronary revascularization also require further alignment. Efforts to define and potentially simplify the definition of worsening heart failure should be embraced by the CEC community, and general classifications of heart failure specifically for research are needed across disease classes. Finally, detailed instructions on how to implement these definitions in the context of missing or limited data would aid in the practical use by adjudicators.
Quality control and audit readiness

Ensuring quality of the CEC process remains paramount to provide reassurances of trial validity to sponsors, trial investigators, regulators, payors, and most importantly patients. In establishing guiding principles for CEC, the following issues should be considered:

1. Proportion of all suspected events triggered as planned.
2. Ensuring all events processed per charter procedures.
3. Ensuring all adjudication results were databased accurately.
5. Identified issues documented along with how the issues were addressed.
6. Documentation of any major ethical or regulatory violations (Health Insurance Portability and Accountability Act, institutional review board, or Good Clinical Practice).
7. Ensuring the CEC Committee received all information pertinent for event adjudication that was available to the investigator.
8. Defining the independence of the CEC.

Furthermore, the CEC team should be reviewing the protocol in collaboration with the multi-functional project team and in particular must confirm that the plan for endpoint collection and ascertainment will reinforce the currency of the protocol's endpoint driven target. The CEC charter should list in detail the source documents to be collected and the specific information each source document type is expected to provide. The CEC group should also have input into and review/approval of the configuration of the cCRE the triggers programmed to fire from the event detail page, and the edit checks and data validation checks. In addition, the CEC team must be ready for an audit of the adjudication process by regulatory agencies, which is often required. Inadequate readiness for audits will result in challenges to the trial's integrity.

Global collaboration for CEC

Expert consortia have made great advances in defining various clinical endpoints. Further global collaboration among research organizations may identify known gaps and differences in CEC operations, gain consensus for uniform adjudication practices, identify areas requiring process change, implement the needed changes, share best practices, and perform continuous evaluation of process improvement.

Conclusion

CEC Committees play a pivotal role in the conduct of contemporary clinical trials. Adjudication by a CEC Committee provides reassurance to regulators, investigators, and treating physicians, ultimately benefiting the patients. Urgent need exists for studies on ways to improve efficiency and reduce barriers to the conduct of adjudication across clinical trials and specialties. Furthermore, adjudication is crucial to the accurate identification of safety events, which is vital for patient safety. Emerging evidence suggests that artificial intelligence and digital health may help streamline the adjudication process and reduce costs; however, more research is needed before these technologies can be routinely implemented in adjudication processes. As novel strategies for clinical trials emerge and are used to generate evidence for regulatory approval and to guide clinical practice, a greater understanding of the role of the CEC process will be critical.

Funding

Funding provided by ACI Clinical, AG Mednet, AstraZeneca, Language Scientific, Amgen, Janssen, CSL Behring, Baim Institute for Clinical Research, Cisys LifeSciences, and the Cardiovascular Research Foundation.

Declaration of competing interest


Disclaimer

This publication reflects the views of the authors and should not be construed to represent FDA’s views or policies.
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