Demonstrate that the upper bound of the two-sided 95 percent confidence interval for the estimated increase in CV risk across all Phase II and III studies has a hazard ratio (HR) less than 1.8. If the HR upper bound is less than 1.3, a post-marketing trial of CV risk may not be necessary.

There is no doubt that meeting these requirements is a costly proposition. CV outcomes are relatively rare, and accruing enough events to fulfill regulatory expectations and statistical analysis criteria is likely to require larger and longer trials that include a diverse set of patients representative of the drug’s target population.11 However, clients face potentially greater challenges in developing, validating and integrating efficient processes to manage these large studies and datasets. Given the critical importance of end point assessment in CV outcomes studies, clients designing such studies need to proactively establish carefully planned and comprehensive end point adjudication procedures to ensure the quality and reliability of their data.

This paper reviews the integral components of an effective adjudication strategy, including committee selection, relevant end point definitions, data capture and management, and investigator site and study team training for prompt review of potential CV events.

CHOOSING AN ADJUDICATION COMMITTEE

In an effort to reduce data variability and minimize bias, FDA recommends utilizing external end point assessment committees (EACs) – also called clinical event committees – to blindly review all pertinent clinical and diagnostic source documentation and independently adjudicate CV outcomes. The membership of a EAC is at the discretion of the client or assigned designee (e.g., contract research organization [CRO] or academic research organization [ARO]) and usually includes physicians with therapeutic and medical expertise relevant...
Choosing the common catch-all term of major adverse cardiac events (MACE) may not be sufficient, because this term presently does not have a globally accepted standard definition. Historically MACE has included CV-related death, non-fatal MI and non-fatal stroke, but pharmaceutical/biotechnology companies and adjudication committees have, at times, expanded the definition to include hospitalization for heart failure, arrhythmias, cardiac revascularization, peripheral vascular disease interventions and unstable angina.13

Selection of event end points is a delicate balance between rigor and practicality. While it may be tempting to take a conservative approach and use the broadest possible definition, such a choice may significantly raise operational costs due to the additional time involved in collecting and reviewing the increased quantity of ultimately irrelevant data. Conversely, using a definition that is too narrow may exclude relevant events and compromise the integrity of the analysis. The choice of end points will dictate the sample size and trial duration needed to accumulate the minimum number of outcomes mandated in the SAP.

A working group called the Standardized Data Collection for Cardiovascular Trials Initiative is a collaboration between academicians, professional societies, the Clinical Data Interchange Standards Consortium (CDISC), Health Level 7, the Clinical Trials Transformation Initiative (CTTI), industry and FDA.14 The group aims to “provide a framework of definitions for cardiovascular end points in clinical trials” based on “clinical and research expertise, published guidelines and definitions, and [the group’s] current understanding of the specific laboratory tests, diagnostic tests, and imaging techniques used in clinical practice.”15 The most recent (November 2012) version of these definitions is currently undergoing testing,16 and clients and designees planning clinical trials with CV end points are encouraged to review this document thoroughly before finalizing the protocol and SAP.
MANAGING DATA FOR PROMPT END POINT ADJUDICATION

Successful adjudication depends heavily on two additional factors:

- Compiling accurate, complete dossiers of medical records and documents for each potential event. Missing or incorrect information could cause the EAC to come to an inconclusive or erroneous decision.
- Timely collection, submission and review of the dossiers to meet regulatory expectations ultimately alleviates delays in the statistical analysis of the data.

Clearly, compiling the relevant data is the most time-consuming component of the adjudication process. Multinational studies often pose additional challenges because of differences in language, privacy laws, and the time frame and procedures for obtaining documents. In particular, it can be difficult to access source data from a medical institution that treated a patient for a CV event but is not part of the study.\(^{18}\)

Overcoming these challenges requires a multipronged approach.

- First, the ability to access documentation on potential events should be considered when choosing sites to participate in the clinical trial. The advantages of fast enrollment at a particular site may be reduced if information needed to adjudicate an event is inaccessible or delayed.
- Second, prior to the start of the study, the EAC should agree on which documents are required for adjudication and under which circumstances alternative sources of information are acceptable. For example, U.S. privacy laws make it increasingly difficult to obtain autopsy reports, so the committee may choose to accept death certificates or death sum-

RELIABLY CAPTURING RELEVANT END POINTS

Once the end points and included events are rigorously defined, the client must decide how the data is to be collected. Capturing all potential events for adjudication is essential, as the total number of confirmed events usually is quite small and missed events can prolong the ultimate trial duration and, therefore, increase study costs. There are three main ways to achieve this goal:

1. **Adjudication of all reported serious adverse events.**
   While this approach ensures that no event will be missed, it is time consuming and costly for site personnel, clinical trial management staff and the EAC. Most adjudicated events will not be CV in nature and will not provide any relevant value during the statistical analysis.

2. **Submission of potential events by the principal investigator (PI).** This method depends entirely on the PI’s accurate assessment and identification of potential events. Success requires the PI to have a solid working knowledge of what truly comprises a potential event for adjudication as well as a thorough understanding of the EAC adjudication criteria. While this approach may help contain costs, the potential for missed end points can be quite significant.

3. **Use of MedDRA preferred terms to identify events.**
   This technique, which is gaining popularity in the industry, searches the investigators’ verbatim diagnosis of any adverse event for predetermined terms relating to CV events.\(^{17}\) All events that match any of the terms are submitted to the EAC for adjudication. This systematic approach is efficient and cost effective because it identifies only meaningful events that may have true value for analysis while also ensuring that all potentially relevant events are captured.
Adjudication Strategies in Cardiovascular Outcomes Research

pre-specified MedDRA terms that may indicate a CV event.

- Real-time notification of PPD’s pharmacovigilance (PVG) and clinical operation teams when a new event is identified, triggering personnel to contact the site and begin collecting source documentation within 24 hours of event identification.

- Electronic repository for all dossier content, including lab reports and digital images, following translation (if needed) and review by the PVG team to ensure redactions are in place for patient confidentiality protection.

- Simultaneous review by multiple EAC members once the dossier is complete. All comments are entered into the system, providing an audit trail and giving physicians the freedom to complete reviews on their own schedules.

- Real-time tracking, so the status of an event is instantly available to any team member at any time. Aging reports identify bottlenecks and keep the process moving forward on schedule.

- Integrated metrics that can be used to evaluate events and timelines at a region, country or site level and determine overall trends or identify specific training needs.

Traditionally, the adjudication process has used paper-based case report forms, source documents and/or diagnostic films. This approach requires EAC members to review the information sequentially instead of concurrently and, perhaps more importantly, does not provide an adequate audit trail for regulatory authorities. Electronic adjudication systems (EAS) can address these issues as well as automate event reporting, expedite document collection, allow EAC members to individually review events in a timely, concurrent fashion, and eliminate the delay imposed by the need for EAC face-to-face meetings.

At PPD, use of our EAS in conjunction with our effective dossier compilation strategies has shortened average dossier submission and adjudication timelines by 30 – 45 days or more (Table 1) while maintaining high standards of quality. Key features of the system include:

- Automated daily import of all newly reported adverse events from the clinical database to EAS, allowing a nearly real-time comparison of the data to a list of pre-specified MedDRA terms that may indicate a CV event.

Table 1: Average adjudication cycle times with paper-based vs. electronic processes

<table>
<thead>
<tr>
<th>ACTIVITY</th>
<th>Paper Process</th>
<th>Electronic Process</th>
</tr>
</thead>
<tbody>
<tr>
<td>Notification of event</td>
<td>Day 0</td>
<td>Day 0</td>
</tr>
<tr>
<td>Completion of dossier</td>
<td>45 – 60 days</td>
<td>45 – 60 days</td>
</tr>
<tr>
<td>Distribution of dossier</td>
<td>2 – 5 days</td>
<td>0 days</td>
</tr>
<tr>
<td>Committee review</td>
<td>17 – 42 days</td>
<td>1 – 14 days</td>
</tr>
<tr>
<td>Committee results to data management/biostatistics</td>
<td>2 – 5 days</td>
<td>0 days</td>
</tr>
<tr>
<td>Data entry into clinical database</td>
<td>3 days</td>
<td>0 days</td>
</tr>
<tr>
<td>TOTAL</td>
<td>69 – 115 DAYS</td>
<td>46 – 74 DAYS</td>
</tr>
</tbody>
</table>

Third, studies with EAC-adjudicated end points may benefit from proactively identifying ways to track patients who withdraw from the study or who are lost to follow-up. Use of global locator services or more region-specific procedures require prior written authorization, and appropriate language should be included in the informed consent documents to ensure the patient’s pre-approval.

Finally, consider the benefits of using an electronic adjudication system to accelerate data collection, review and final adjudication.

At PPD, use of our EAS in conjunction with our effective dossier compilation strategies has shortened average dossier submission and adjudication timelines by 30 – 45 days or more (Table 1) while maintaining high standards of quality.
TRAINING SITE PERSONNEL AND THE STUDY TEAM

Successful adjudication of CV events begins with specialized training for site personnel as well as the study team (clinical research associates [CRA], operations, biostatistics, PVG, etc.) Investigators need a thorough understanding of the:

- Study protocol
- Events to be adjudicated, and how to identify and report these events
- Signs and symptoms associated with CV events, including more subtle manifestations such as shortness of breath, back pain or dizziness
- Documentation required by the EAC (and the associated timelines)

To meet these needs, PPD suggests providing specific adjudication training at the investigator meeting. It is also important to consider analyzing completed dossiers at the site or country/region level to help identify local and/or regional areas for improvement in quality and/or timeliness and create tailored follow-up training to boost performance and enhance interest in the study. PPD also recommends providing each site with a hard copy resource guide containing: a specific list of the required source documents, by event type; written expectations regarding event reporting, source document quality and submission timelines; and contact information in the case of questions.

Any member of the study team involved in collecting, reviewing or analyzing CV outcomes also needs an in-depth knowledge of the protocol, end points and event dossier requirements. CRAs should be well-versed in identifying potential CV events from case report forms and source documentation. When a potential event is identified, well-trained CRAs can guide the site through the process of gathering and submitting information and help ensure that timelines are met. CRAs can provide additional value by becoming familiar with the local laws and procedures for the release of medical information at each site they monitor.

SUMMARY

Meeting current regulatory expectations regarding the independent assessment of CV outcomes in clinical trials of CV and non-CV therapies requires a comprehensive, carefully planned end point adjudication process to ensure the quality and timeliness of event reporting. Adjudication committee members should be chosen judiciously and charged with establishing clear guidelines outlining the required dossier contents, the methodology used to review data and the defining criteria used to make a decision about an event. The compound development team is responsible for identifying which primary and/or secondary end points in a given study require adjudication and providing specific definitions of the outcomes included in each end point. This task is complicated by the variable interpretations of the term MACE. However, recent efforts toward global standardization may lessen the impact of this issue in the near future. It should be noted that adjudication is best focused on events that are ambiguous in nature and require confirmation by a panel of experts.

The clinical study team must proactively decide on a method for capturing the events, setting standards and timelines for the submission of information, and providing appropriate training for CRAs, investigators, site study personnel, clinical and data managers, biostatisticians, and other team members involved in collecting, reviewing or analyzing CV events. Given the complexity of these tasks and a push by regulatory authorities to ensure that all events are reported in a timely manner, electronic adjudication systems have become a valuable tool to accelerate the process without compromising quality. PPD’s end point management system automates event reporting, expedites document collection, allows for simultaneous review by multiple EAC members, creates an audit trail, and offers real-time status tracking and metric reporting. When compared with the previous paper-based process, our electronic approach shortened average dossier submission and adjudication timelines by approximately 35 percent, reflecting improved efficiencies and potentially reduced costs.
REFERENCES


15. Ibid.


