Executive Summary

This White Paper outlines the role and purpose of Clinical Endpoint Committees (CEC) and provides key considerations regarding the establishment and implementation of centralized endpoint adjudication procedures. In particular, it discusses best practice for CEC composition, endpoint data capture, endpoint management, CEC charter development, and integration of centralized adjudication within the overall study design.
Introduction

Clinical endpoints are events of interest which have been selected as statistical points of measure for the purposes of demonstrating either efficacy or safety within a drug’s clinical development program, or in post-marketing settings. When efficacy is the focus, the questions of interest are: Are there fewer valid clinical endpoints in the treatment group(s) than in the comparator group(s), and is the lower event rate in the treatment group(s) statistically significant when compared with the standard, un-treated event rate observed in the corresponding subject population? If so, there is evidence of efficacy. When safety is the focus, the questions of interest can be framed as follows: Is the number of clinical endpoints in the treatment group(s) greater than the number in the comparator group(s), and is the higher event rate in the treatment group(s) statistically significant when compared to the standard, un-treated event rate observed in the corresponding subject population? If so, there is evidence of a potential safety concern, and potentially evidence of unacceptable safety risk.

For a number of reasons, there can be a considerable degree of variability in clinical endpoint classification practices performed by investigators. To answer efficacy and safety questions of interest with the accuracy needed requires a reliable method to reduce the impact of this variability on the conclusions drawn from analysis of endpoint outcome data. As a result, it is increasingly expected (and in some cases now newly required) by regulatory agencies that certain events, whether they are to be assessed as formal clinical endpoints (i.e., outcomes utilized in statistical analyses) or whether they are to be assessed as events of special interest (i.e., outcomes utilized in safety risk assessments), undergo centralized adjudication by a Clinical Endpoint Committee (CEC). For the purposes of this paper, the term “endpoint” is used broadly, to encompass both of these scenarios.

A CEC is a panel of independent experts charged with centrally reviewing and classifying suspected efficacy and/or safety endpoints in a blinded and unbiased manner, ascertaining whether they meet protocol definitions (endpoint criteria), and providing endpoint outcomes for critical decision-making that are as standardized as possible. Through the acquisition of optimal quality endpoint data and robust adjudicated outcomes, the centralized adjudication process significantly enhances the consistency, and therefore the validity and integrity, of a study’s clinical endpoint outcomes.

Regulatory requirements for centralized adjudication are on the rise. For example, guidance documents specifically addressing the assessment of cardiovascular safety for new anti-diabetic drugs for type 2 diabetes mellitus (T2DM) have recently been released in the United States and Europe, as discussed in earlier white papers in this series. Moreover, while similar regulatory guidance for drugs in other therapeutic areas is not yet released at the time of writing this paper, it is certainly possible that centralized adjudication will be required in other areas, too: indeed, Sponsors are already widely employing this methodology in drug development for other indications.

It was noted in the first of the papers in this series that operational considerations needed to be discussed separately, and this white paper accomplishes this task. It discusses in detail the procedures necessary for successful implementation of centralized adjudication processes, providing best practice for the establishment and operation of CECs across the biopharmaceutical industry, regardless of therapeutic indication or study phase.
Clinical Endpoint Committee Role and Purpose
Clinical Endpoint Committees (CECs) review overall subject data, as well as endpoint-specific data, applying complex medical definitions to provide standardized adjudicated outcomes. CECs should be blinded to treatment when performing centralized adjudication, regardless of whether the trial is conducted in a blinded manner. Also, the centralized adjudication process should be designed to both preserve the independence of the CEC and prevent any undue bias that could impact its decision-making processes.

When is centralized adjudication by a CEC needed? CECs are employed when a protocol contains clinical events that will be assessed as key efficacy or safety endpoints. CECs are also employed when there are events of special interest which require assessment (e.g., events of special interest which are not formal, protocol-defined endpoints but which are utilized to perform a safety risk assessment, such as the assessment of cardiovascular safety). For the purposes of this paper, the term “endpoint” is used to encompass both of these scenarios.

Since classification of such clinical events as study endpoints is a partially subjective process which is performed based on application of a complex set of medical endpoint criteria to an often complex clinical event, investigator classifications can vary considerably due to differences in individual medical training and application of clinical judgment. The dual purpose behind implementation of centralized adjudication by a CEC is to limit the number of individuals providing classifications of study endpoints to control for this variability, and to employ experts to provide these classifications to achieve greater precision in the final classifications of study endpoints.

CEC-adjudicated outcomes typically either validate, negate, upgrade, downgrade, or otherwise modify initial classifications of the suspected endpoints (i.e., those assigned by investigators). Therefore, the occurrence of differences between initial classifications and final CEC-adjudicated outcomes is the expected result of any centralized adjudication process. In addition, for validated endpoints, the CEC may provide further endpoint sub-classifications. CEC adjudicators can also identify new, previously un-reported suspected endpoints for investigation and follow-up. Final CEC-adjudicated outcomes are not provided to investigators, as they have the potential to unduly bias investigator reporting of suspected endpoints, and their intended use is for the purposes of performing uniform analysis of key clinical efficacy and safety variables. CEC-adjudicated outcomes are not intended or suited for medical treatment decisions. Final CEC-adjudicated outcomes do not replace or overwrite initial classifications; however, it is the CEC-adjudicated outcomes that are used to assess key efficacy and safety variables in primary and secondary endpoint analyses, rather than the initial classifications.

The use of CECs to adjudicate suspected endpoints has increased considerably over the past 10 years. CEC-adjudicated endpoint outcomes can figure prominently in a number of key clinical trial decision-making processes. Therefore, CEC-adjudicated outcomes need to be finalized and made available on a rolling basis throughout the lifespan of a trial. The approach to managing the outputs of the endpoint process flow within the larger study design plan is a careful balance. Some critical operational considerations are discussed in detail in the next sections of this paper.
The Case for a CEC Guidance: Standardizing the Standardization Process

With an increasing focus on pro-active management of product benefit-risk balance and the prominence with which endpoint data factor into this equation, it is more critical now than ever for Sponsors to use every means possible to minimize any impact of process-driven variability on adjudicated endpoint outcomes. However, many Sponsors face a significant challenge. Even though there are now regulatory guidances requiring cardiovascular adjudication in cardiovascular outcomes studies conducted during the development of new anti-diabetic drugs for T2DM (as noted earlier in this paper), and even though centralized adjudication has been – and continues to be – implemented on a widespread basis beyond this requirement, no accompanying guidance has been issued regarding the establishment and operation of CECs. As a result, many different CEC models have been, and continue to be, implemented with prolific variety across the biopharmaceutical industry.

For a process that is ultimately intended to achieve standardization of key clinical efficacy and safety variables, the implementation of centralized adjudication is remarkably non-standard and un-regulated. Certainly, some variability is to be expected and supported, as different models meet distinct needs in certain settings. Nonetheless, it is important to note that there are inherent advantages and disadvantages to certain components of the models commonly used. It is equally important to note that the overall effectiveness of centralized adjudication in achieving its three primary objectives can either be enhanced or diminished by the manner in which these process components are assembled into a whole.

Planning for CEC Implementation

Endpoint process flows are dynamic and interactive, with multiple steps and dataflows, contributors and stakeholders. As a result, implementation of a CEC requires cross-functional planning with respect to study timelines, budget, and quality management. The design of any study with centralized adjudication should include the following: a well-defined integrated data capture strategy to ensure complete and accurate capture of all suspected endpoints for adjudication; a clearly-defined tactical plan for effective endpoint case management; and a CEC adjudication process that is structured to deliver consistent, reliable, and accurate results.

The Need for an Industry Guidance Document on CEC Establishment and Operations

The implementation of centralized adjudication is remarkably non-standard and un-regulated. A CEC guidance document, similar to the one issued for the establishment and operation of Clinical Trial Data Monitoring Committees, is needed.

A guidance document on the establishment and operation of CECs would shape overall understanding of the primary objectives of centralized adjudication across the industry, and it would outline the advantages and disadvantages of common approaches and models in use, providing Sponsors with the necessary context and background to make informed decisions regarding endpoint project design. Such a guidance would enable Sponsors to achieve maximal benefit of centralized adjudication at the protocol or program level. In addition, the guidance would drive an industry-wide standardized approach to CEC implementation, enabling Sponsors to work from a set of clearly outlined, robust processes that govern the most critical components related to the establishment and operation of a CEC: CEC composition, endpoint data capture, endpoint management, CEC charter development, and integration of the centralized adjudication process within the overall trial. Towards this end, a discussion of current and best practice in these areas follows.
CEC Composition

The selection of qualified and effective CEC members is extremely important, as CEC members make critical, complex judgments. Their decisions result in outcomes that are used in a wide number of contexts for decision-making on efficacy and subject safety at various levels, ranging from impacts that are protocol or program-specific to impacts on next steps in compound development and/or approval.

A CEC should be comprised of members who are able to commit to the workload, duration, and timelines of their CEC duties, operate with medically-relevant adjudication competence, and work with the appropriate level of independence so that the adjudicated outcomes they provide are both clinically sound and not subject to bias.

Establishing CEC Membership

At the outset of planning for CEC implementation, Sponsors need to answer some key questions that will drive decisions in the CEC establishment process:

> **Who will identify, screen, qualify, select, and contract with the CEC members?**
> **What will be the composition of the CEC (e.g., specialties, level of experience, number of members)?**
> **What CEC organizational structure will be utilized?**

With regard to qualifications for the individual members of the CEC, considerations include clinical expertise, experience in clinical trials, prior CEC experience, and absence of serious conflicts of interest of an intellectual, financial, or personal nature.

With regard to the choice of the CEC Chairperson, prior CEC experience is typically a more important requirement than for the other CEC members. The Chairperson's committee leadership skills are also important to assess, including ability to organize the administrative aspects of the committee functions, facilitate discussion, arbitrate differences of opinion and move towards consensus, and make decisions as necessary.

The Sponsor should also ensure that CEC members do not also serve as investigators or as DMC members on the same trial for which they carry CEC responsibilities.
The Sponsor is typically the party who is ultimately responsible for approving the final membership of a CEC. In some cases, the Sponsor works with the trial steering committee to appoint CEC members, or the Sponsor may appoint the CEC Chairperson and ask that individual to appoint the members. In other cases, the Sponsor delegates some or all of the activities associated with establishing the CEC membership to a third party, such as a Contract Research Organization (CRO) or Academic Research Organization (ARO). Regardless of which party is responsible for establishing the CEC membership, this process should be based on documented procedures that specify the means to identify, screen, qualify, select, and contract with the CEC Chairperson and its members. A thorough overview of the considerations related to committee composition can be found in Section 4.1, “Committee Composition,” of the existing FDA guidance on the Establishment and Operation of Clinical Trial Data Monitoring Committees. Although not CEC-specific, this guidance contains a number of practices that can be applied to the composition of a CEC.

Although there are significant commonalities in the composition of DMCs and CECs, there are certain aspects of committee composition that are unique to CECs. One of the most prominent distinctions between the two committees is that DMCs typically make decisions by a full-committee voting process, whereas the majority of CECs make individual decisions (with arbitration of any disagreements between two adjudicators) or paired decisions (via discursive review and consensus). Keeping this in mind, the Sponsor should determine the mix of CEC members needed to establish the CEC, and how this mix factors into selection of the adjudication workflow that will be specified in the CEC Charter.

Optimal Mix of CEC Members

Sponsors should consider the range of endpoint categories requiring adjudication and which specialties are needed within the CEC membership to adjudicate them with the requisite expertise. If all endpoint categories requiring adjudication fall into the same therapeutic area, the CEC membership can be comprised of a set of individuals from the same specialty, who are qualified and experienced to adjudicate that category of endpoints. If a mix of endpoint categories from different therapeutic areas require adjudication, it is important to take one of two approaches: Create CEC sub-committees that are organized by specialty; or compile a single CEC consisting of members with multiple specialties and implement an adjudication workflow which takes the cross-functional nature of the CEC into consideration with respect to decision-making.

As an example: For CECs charged with adjudicating MACE on T2DM trials, cross-functional CEC membership is optimal, including individuals who specialize in cardiac, cerebrovascular, and peripheral vascular events. This approach equips the CEC to fully address the different components of the MACE composite endpoint at the individual case level, and it enhances the CEC’s collective ability to classify complex events and clusters of events occurring in a population that may have multiple disease conditions.
A further consideration specific to the establishment of a CEC is its organizational structure. The two most common committee structures are compiled CECs and co-located CECs. A compiled CEC is typically established for the purpose of working on a particular protocol or program and is most often comprised of individuals who have been selected separately to serve together in this capacity. A co-located CEC is typically a standing CEC whose members operate within the same organization and/or whose members work together across a large body of adjudication work. The typical advantages and disadvantages of compiled vs. co-located CECs are summarized in Table 1.

Table 1: Typical Advantages and Disadvantages of Compiled vs. Co-located CECs

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Compiled CEC</strong></td>
<td><strong>Co-located CEC</strong></td>
</tr>
<tr>
<td>&gt; CEC Chairperson and members can be selected separately for their individual strengths</td>
<td>&gt; CEC may be highly specialized and therefore the bandwidth to adjudicate multiple therapeutic areas may be limited</td>
</tr>
<tr>
<td>&gt; CEC composition is fit-for-purpose with respect to specialties and experience</td>
<td>&gt; Established CEC procedures may not be flexible enough to accommodate the specific needs of a given trial</td>
</tr>
<tr>
<td>&gt; This type of CEC does not typically have overhead costs and is therefore often more cost effective</td>
<td>&gt; Costs are typically higher than a compiled CEC</td>
</tr>
</tbody>
</table>

A further consideration specific to the establishment of a CEC is a tactical one, i.e., workload, which differs significantly from that of a DMC. Whereas DMC members must typically commit to periodic review of accumulating trial data at scheduled meetings, it is often necessary for CEC members to review and adjudicate batches of endpoint cases on a continual basis (monthly, weekly, or daily), sometimes at a high volume. It is therefore critical to staff the CEC with enough members to manage the anticipated caseload for adjudication, allowing for some degree of redundancy in the membership, which will provide flexibility in reviewer assignments and account for any spikes in endpoint volumes, as well as any adjudicator outages due to vacation and holidays. It is also critical to ensure that the selected members will be able to make the appropriate time commitment to perform the adjudication work within the necessary timelines. These parameters should be clearly captured in the CEC Charter, along with the approach to CEC composition and establishment, and a number of additional CEC operational details (see the CEC Charter section of this paper).
Endpoint Data Capture Plan

Some of the core questions Sponsors need to answer during the endpoint study design decision-making process, for inclusion in such a plan, are as follows:

> What methods will be utilized to ensure complete and accurate identification of all suspected endpoints requiring adjudication?
> How will information regarding suspected endpoints be captured?
> How will the suspected endpoint and adjudicated outcome data be handled within the overall study data capture plan (e.g., with respect to reported adverse events [AEs] and SAEs)?
> What methods will be utilized to ensure the completeness and currency of final adjudicated outcomes?

Endpoint Data Capture

Sponsors implementing studies with centralized adjudication should be equipped to clearly understand key similarities and differences with respect to the handling of events as serious adverse events (SAEs) versus as endpoints. In addition, Sponsors should develop an endpoint data capture plan that addresses details regarding the handling of suspected endpoint and adjudicated outcome data.

Handling of Events as SAEs versus Endpoints: Some Important Distinctions

Some key conceptual differences exist between SAEs and endpoints, and these distinctions carry operational implications. The first and most important of these is that different parameters are used to define and classify SAEs versus endpoints. Whereas the decisions regarding SAEs center around assessments of seriousness, expectedness, relatedness, and reportability, the decisions regarding suspected endpoints are based on complex, partially subjective, clinical judgments of whether a set of medical endpoint criteria have been met.

The first operational implication associated with this distinction is that overlap between reported SAEs and reported endpoints is not always 100 percent. By definition, not every endpoint qualifies as an SAE and vice versa. As such, even if the same event is reported as both an SAE and a suspected endpoint, it must be handled and classified separately within each of these two event categories, according to the distinct SAE or endpoint definitions and workflows. In addition, while case information and key updates should be shared between events which are both an SAE and an endpoint, changes in overall SAE classification should not impact endpoint classification, and vice versa. For example, the deletion of the event as an SAE should not automatically result in the reciprocal deletion of the suspected endpoint as an endpoint, and vice versa.

The second operational implication is that the supporting documentation needed for SAE versus suspected endpoints differs in type and level of detail, and the case completion and case closure strategies and cycle times differ as well (as discussed in more detail in the next section). The third operational implication is that it is important to consider putting additional measures in place to detect potential un-reported suspected endpoints in certain settings, a practice not implemented in an SAE workflow, so it is unique to endpoint workflows. A primary reason for the need to perform supplementary endpoint detection is that, while SAEs are classified based on attributes which are mostly clinically overt (typically requiring clinical intervention or change in clinical treatment), endpoints are classified based on attributes that are not always clinically overt. Consider, for example, a “silent” myocardial infarction (MI) that may meet endpoint criteria but does not result in the subject presenting with overt symptoms of an MI. In this kind of scenario, the subject may be unaware that he/she experienced an event, and it may also be difficult for the investigator to recognize that an event occurred that is reportable as a suspected endpoint. Therefore, a suspected endpoint that could potentially be confirmed through adjudication as a valid study endpoint is at risk of being missed.
Another primary reason to perform supplementary endpoint detection is that SAE definitions are
fairly straightforward assessments, whereas endpoint classifications are medically complex and
require clinical judgment to assess a multi-faceted set of medical criteria. It is widely recognized that
investigator endpoint classifications are more subject to variability than investigator SAE
classifications, due to this difference in how endpoints and SAEs are defined. As a result, while
investigator reporting is a critical method for the identification of suspected endpoints, it is subject
to both over-reporting and under reporting due to this variability. The risk of investigator over-
reporting is a manageable one, because it is mitigated by the CEC adjudication process itself, in that
CEC adjudicators have the ability to downgrade or negate investigator-reported suspected endpoints.
However, the risk of investigator under-reporting must be addressed with a comprehensive endpoint
detection strategy. This important point is discussed further in the next section.

The second distinction is that SAE and endpoint decision-making is attributed to different parties.
First and foremost, it is imperative that the Sponsor implement robust study processes that
support the reporting and detection of all potential suspected endpoints, including supplementary
endpoint detection methods as appropriate, and it is critical that the Sponsor ensure that no study
processes result in restriction of the suspected endpoints submitted to the CEC for adjudication.
This imperative requires a different paradigm to be applied to decision-making as it pertains to the
handling of endpoints versus the handling of SAEs. Whereas SAEs are ultimately classified by the
Sponsor, it is the remit of the CEC, and the CEC alone, to classify suspected endpoints.

Operationally, this means that when the Sponsor is processing endpoints, the Sponsor
should refrain from applying practices that are common in SAE processing to endpoint processing
(e.g., pursuit of downgrades or upgrades, roll-up of related events, and/or pursuit of deletions for
events that in the Sponsor’s judgment do not meet event criteria). The Sponsor should make it a
practice to submit 100 percent of all known, suspected endpoints to the CEC for review and
adjudication, regardless of whether it is the judgment of the Sponsor that the suspected endpoints
meet endpoint criteria. This approach allows all of the known suspected endpoints for a given trial
to reach the CEC experts in an unabridged, unfiltered, and unbiased manner, thereby promoting
the robustness and consistency of the CEC decision-making process and ensuring the scientific
integrity of the CEC-adjudicated outcomes.

A number of undesirable risks result when Sponsors elect to implement processes that do not
route all of the known suspected endpoints for adjudication by the CEC. Consider, for example,
some models used in the industry that include endpoint screening processes, by which certain
suspected endpoints are routed into a “not for adjudication” workflow. Consider also that there
are some models used in which programmatic methods are employed to “auto-adjudicate” certain
suspected endpoints, rather than routing them to the CEC for adjudication. In both cases there are
a number of resulting concerns:

> There is an artificial delineation within the accumulating trial data regarding which suspected
   endpoints are and are not reaching the CEC for adjudication, and this can create an imbalance in
   the CEC decision-making process, reducing the overall effectiveness of the central adjudication
   process, as the CEC is only exposed to and is only addressing part of the whole through their review.
> These models carry the risk of bias and variability within the final endpoint outcome dataset, as the
   endpoint outcomes it contains do not have the same source across the trial.
> In by-passing the CEC, these workflows are essentially performing CEC decision-making processes,
   but without the benefit of the CEC members’ professional expertise.
Ultimately, these models appear to be implemented without recognition of the basic fact that CECs have the remit to either validate, negate, upgrade, downgrade, or otherwise modify initial endpoint classifications. Through careful review of the circumstances surrounding a suspected endpoint, CEC adjudicators analyze and weigh supporting contextual information from a subject’s chart, which provides increased clarity about the suspected endpoint and which can significantly change its disposition from a CEC classification standpoint. This kind of close case-level CEC review process results in increased specificity and accuracy in the classification of suspected endpoints. When suspected endpoints by-pass the CEC, this opportunity is lost, and the end result could be that valid endpoints are not confirmed, or that endpoints which would have been negated, upgraded, or downgraded are confirmed “as is.”

The third distinction is that different methodologies are used to categorize SAEs versus endpoints. Whereas SAEs are reported with verbatim terms that are subsequently rolled up to coded terms, endpoints are reported under a specific set of pre-determined categories and therefore do not require the use of verbatim terms or subsequent coding. Endpoints are essentially “coded” up front via the manner in which they are reported. The associated operational implication relates to the means by which endpoints are reported by investigators. Sponsors should implement a designated Endpoint Reporting Case Report Form (CRF), which investigators utilize to report suspected endpoints as discrete endpoint events (discussed in more detail in the next section). Some models in place across the industry involve detection of suspected endpoints through review of reported SAEs. However, this is not a recommended practice if it is the sole method through which endpoints will be identified for adjudication. Since the definitions for SAEs versus endpoints are different, one concern associated with this approach is that it could either lead to missed endpoints that would go un-reported if they did not meet SAE criteria (but could potentially meet endpoint criteria), or it could lead to inflated SAE reporting (reporting of suspected endpoints as SAEs, even though they do not meet SAE criteria). There is also a practical concern with this approach, which is the complexity and questionable feasibility of performing a human or programmatic review of all verbatim or coded SAE terms, on an iterative basis as event data are updated, with the necessary sensitivity to detect 100 percent of the suspected endpoints indicated by this kind of dataset. In addition, a significant concern (discussed more fully in the next section) is that this approach by-passes the investigator’s role in the reporting of suspected endpoints. This approach, therefore, is likely to result in diminished ability to capture all reportable suspected endpoints.

Methods to Ensure Complete and Accurate Identification of Suspected Endpoints

The scientific imperative Sponsors work under for any trial with centralized adjudication is to ensure the complete and accurate identification of all potential suspected endpoints within the established endpoint categories requiring adjudication. The scientific integrity of a trial can be significantly compromised if the methods employed to identify and detect suspected endpoints are not comprehensive, and if these methods are not implemented consistently across the trial.

There are various methods employed to identify suspected endpoints, beginning with the primary method which is investigator reporting, and extending to secondary and tertiary endpoint detection methods which are designed to supplement the investigator’s identification of potential un-reported suspected endpoints. Secondary methods typically include monitoring, Sponsor medical review, and CEC identification. Tertiary methods typically include edit checks, reconciliations, and triggering. Best practice to ensure complete and accurate identification of all suspected endpoints requiring adjudication is to employ an approach that includes a protocol-appropriate mix of primary, secondary, and tertiary methods.
As with SAE reporting, it is the primary responsibility of the investigator to identify and report suspected endpoints experienced by subjects enrolled in trials operating under his/her oversight. Because the investigator is able to directly interface with enrolled subjects, he/she is on the front lines with regards to event identification. As part of his/her responsibilities, the investigator engages in a discussion with the subject to elicit whether the subject has experienced events that are reportable as SAEs and/or suspected endpoints.

This method to elicit subject-reported events is often the only way awareness of an event is achieved, especially since subjects may be treated for their events at facilities other than the investigative site, or by physicians other than the investigator. As such, investigator reporting of suspected endpoints is a critical component of the process for the identification of suspected endpoints, and should be employed as a basic component of any endpoint data capture plan. To ensure that investigator reporting component is as effective as possible, the following practices, at a minimum, should be in place:

- **Clear endpoint definitions** (i.e., detailed in the protocol).
- **Investigator training on the identification and reporting requirements for suspected endpoints** (i.e., at the investigator meeting and refreshers during site initiation and monitoring visits).

As discussed earlier, the paradigm for identification of suspected endpoints differs from that for SAEs. Due to the fact that the attributes of reportable suspected endpoints are not always clinically overt, and the variability that exists across investigator reporting according to endpoint criteria, there are limitations associated with investigator reporting. It is therefore necessary for Sponsors to implement supplementary means to identify suspected endpoints, i.e., secondary and tertiary endpoint detection methods.

The value of secondary endpoint detection methods (monitoring, Sponsor medical review, CEC identification) is that another party performs review of available reported SAE and suspected endpoint data, as well as subjects’ chart documentation, to ascertain whether there are clinical indicators (i.e., clinically overt signs and symptoms that could meet endpoint criteria) of potential under-reporting of suspected endpoints by the investigator. The most commonly employed secondary method is monitoring. The monitoring plan used for a trial with centralized adjudication should include 100 percent source document verification (SDV) of all reported SAEs and suspected endpoints, regardless of whether the trial employs a targeted or full monitoring strategy. In addition, the monitoring plan should include 100 percent chart review of enrolled subjects to identify potential un-reported suspected endpoints.

The value of tertiary endpoint detection methods (edit checks, reconciliations, triggering) is that programmatic methods are employed across the available accumulating trial data to ascertain whether the endpoint-related data recorded by the investigator are consistent, and to ascertain whether there are data indicators (e.g., AE or SAE terms, lab data patterns) of potential under-reporting of suspected endpoints by the investigator. The most commonly employed tertiary methods are endpoint edit checks and reconciliations, which should be included in the Data Management plan for any trial with centralized adjudication.

Endpoint trigger programs are not used on all trials with centralized adjudication: the Sponsor should determine whether an endpoint trigger program is needed, based on whether the risk of investigator under-reporting of certain types of suspected endpoints is considered to warrant this level of endpoint detection as a mitigation strategy. Endpoint trigger programs are most commonly applied on trials that include MI and bleeding as established endpoint categories requiring adjudication, particularly when the parameters of the endpoint criteria for MI and bleeding allow for CEC validation of “silent” (non clinically-overt) events.
The limitation of secondary and tertiary methods to detect suspected endpoints is that these reviews are performed without the benefit of the investigator’s clinical judgment, which is based on the broader clinical context available to the investigator. Therefore, if a potential un-reported suspected endpoint is identified through secondary or tertiary methods, it is important for the Sponsor to present it to the investigator with a request that the investigator evaluate it and consider whether it should be reported as a suspected endpoint. If the investigator decides that the event in question should not be reported as a suspected endpoint, the Sponsor should collect and evaluate the investigator’s rationale for this decision.

This approach is aligned with the approach taken in any clinical data cleaning effort; the Sponsor can inquire about the disposition of data and/or certain events, but the investigator must finally decide what should be recorded in the study CRF. It should be noted that if the investigator declines to report the potential suspected endpoint, it is acceptable for the Sponsor to elect to submit it to the CEC for adjudication. In this case, the Sponsor should provide the CEC with relevant supporting documentation of the potential suspected endpoint, including the investigator’s rationale for not reporting the event as a suspected endpoint. The CEC then has the opportunity to provide a final classification that may either agree with the investigator (resulting in a negated suspected endpoint), or the CEC may elect to validate the suspected endpoint (resulting in a standalone CEC-validated endpoint with no matching investigator-reported endpoint).

As discussed, best practice is for Sponsors to implement a protocol-appropriate mix of primary, secondary, and tertiary methods to ensure a comprehensive approach to the identification and detection of suspected endpoints. Models based on investigator reporting alone without supplementary endpoint detection methods, and models based on endpoint detection methods alone which by-pass investigator reporting, are imbalanced and carry the risk of missed endpoints. In particular, models that by-pass investigator reporting are significantly sub-optimal, for the following reasons:

- In by-passing the investigator, these models do not benefit from the investigator’s ability to question the subject regarding the occurrence of potential suspected endpoints. Therefore, information about these potential suspected endpoints will be missing from the accumulating trial data and will not be available for endpoint detection.
- These models rely on methods that are once-removed from the clinical relationship that an investigator maintains with subjects enrolled in the trial. Therefore, they eliminate the clinical judgment of the investigator from the process.
- Typically, the endpoint detection methods utilized in these models are both over-sensitive and under-sensitive at the same time.

With respect to over-sensitivity, these methods can detect potential suspected endpoints which are subsequently classified as non-endpoints once the investigator has had the opportunity to review and provide clinical context. With respect to under-sensitivity, these methods are restricted in the range of endpoint detection that can be performed, because they are typically constrained by two factors:

- Scope: the data utilized in these methods have typically been captured for purposes other than the detection of endpoints.
- Timing: the data utilized in these methods are typically a snapshot in time of the accumulating trial data. Therefore, they are in different stages of completeness and cleanliness when utilized for this purpose.

These methods, therefore, operate under some significant limitations.
In summary, the available data and the decision-making employed in secondary and tertiary endpoint detection methods are more narrowly-focused than investigator reporting, but they serve an important purpose. They are best suited to reconcile endpoint-related data already recorded by the investigator and/or to identify indicators of suspected endpoints that are not clinically overt for consideration by the investigator. Endpoint detection methods should not supplant, but rather supplement the investigator’s reporting of suspected endpoints. Implementation of both methodologies together, i.e., investigator reporting combined with endpoint detection methods, is the most effective strategy to meet the scientific imperative of the centralized adjudication process, which is to ensure complete and accurate identification of all potential suspected endpoints within the established endpoint categories requiring adjudication.

Data Capture for Suspected Endpoints
Best practice in the area of data capture for suspected endpoints can be summarized as follows:

> **SAE and endpoint data capture should be handled as two distinct event reporting processes.**

> **For primary endpoint identification purposes, Sponsors should implement a designated Endpoint Reporting CRF, which investigators use to report suspected endpoints.**

> **As with core CRFs, Sponsors should implement a defined set of edit specifications used for data cleaning of the content of completed Endpoint Reporting CRFs.**

> **Ongoing reconciliations between reported SAEs and reported suspected endpoints should be performed to ensure that events are not missed in either event category. To facilitate this reconciliation, it is recommended that the data capture for SAEs be set up to indicate relationship to suspected endpoints and vice versa (e.g., it is critical to capture whether reported SAEs are also suspected endpoints, and if so, to capture the relevant endpoint category and specific endpoint onset date with the report of the SAE).**

> **The endpoint data capture plan should address how potential suspected endpoints identified via secondary and tertiary endpoint detection methods will be handled (i.e., how they will be recorded and followed-up with the investigator and/or CEC).**

One of the key challenges in event data capture for SAEs and endpoints is that these data are often captured in different locations at different timepoints, and therefore require transcription of event data by the site. This results in significant reconciliation efforts. Ideally, the near-future practice for data capture of SAEs and endpoints would be to utilize the study AE CRF in eDC databases for centralized event reporting. This would entail implementation of two targeted questions for each reported AE, asking whether the AE is an SAE and/or whether the AE is a suspected endpoint. Based on the investigator’s response, a detailed SAE form and/or a detailed Endpoint Reporting CRF would be generated by the eDC system to capture the additional case details required for processing and classification/adjudication purposes (without the need to record any information more than once).

Data Handling for Suspected Endpoints
Best practice in the area of data handling for suspected endpoints can be summarized as follows:

> **If a suspected endpoint meets SAE criteria, it should be handled separately as both an SAE and an endpoint. This allows the specific requirements for SAE and endpoint processing to be met in parallel, since data handling procedures for SAEs and endpoints differ significantly in focus, timing and workflow (as discussed in subsequent sections of this paper).**
Sponsors should not implement processes that restrict the CEC’s review of suspected endpoints. Even if a Sponsor makes the judgment that certain suspected endpoints would not meet endpoint criteria, these suspected endpoints should not by-pass CEC review, as the CEC is the final decision-maker with respect to the classification and adjudication of suspected endpoints. Therefore, all suspected endpoints identified within the established endpoint categories for a given trial should be routed into CEC adjudication.

Sponsors should implement processes that ensure complete and accurate identification of all potential suspected endpoints for adjudication. These processes should include a protocol-appropriate mix of primary, secondary, and tertiary methods, including investigator reporting and supplementary endpoint detection.

If a potential un-reported suspected endpoint is identified through secondary or tertiary endpoint detection methods, the Sponsor should not direct the investigator to report the event as a suspected endpoint. Instead, it is critical for Sponsors to present potential un-reported suspected endpoints to the investigator for evaluation and consideration as a reportable suspected endpoint. This is both consistent with GCP and also allows for the investigator to add perspective and context to the disposition of the event.

There are two common scenarios in which the Sponsor must not delete suspected endpoints. The first is one in which the Sponsor’s judgment is that the suspected endpoint does not meet endpoint criteria. In this case, the suspected endpoint should not be deleted but rather submitted to the CEC, which will make the determination of whether endpoint criteria are met. The second is one in which a related SAE is being deleted. Here, the suspected endpoint should not be deleted simply due the SAE deletion. Since separate definitions are in place for SAEs versus endpoints, it is possible that the event could meet endpoint criteria even if it does not meet SAE criteria.

With regard to the deletion of suspected endpoints from the reported endpoint dataset, it is current common practice to handle the deletion process differently according to whether deletion is under consideration pre-adjudication or post-adjudication. Typically, if there is a valid rationale to delete a suspected endpoint pre-adjudication (whether it is a “spontaneous” deletion requested by the investigator or due to another reason), this rationale is documented, investigator authorization is obtained in writing, and the suspected endpoint is deleted. If deletion is under consideration post-adjudication, the CEC negated the suspected endpoint, the deletion request and rationale are provided to the CEC and its permission sought to delete the corresponding Adjudication CRF. However, if deletion is under consideration post-adjudication and the CEC had validated the suspected endpoint, the deletion request and rationale are provided to the CEC, and the CEC is asked to decide whether they agree with the rationale and the Adjudication CRF can be deleted, or whether they disagree with the rationale and elect to retain the Adjudication CRF as a standalone adjudicated outcome with no matching reported suspected endpoint. Moving forward, it is recommended that best practice involve submission of all deletion requests for suspected endpoints, including those which are under consideration pre-adjudication, to the CEC for evaluation. This would allow the CEC the option of providing a standalone CEC-validated endpoint outcome for any suspected endpoints undergoing deletion and not just those undergoing deletion post-adjudication.

Data Handling for Adjudicated Outcomes

Best practice in the area of data handling for adjudicated outcomes can be summarized as follows:

- **Sponsors should implement a designated Adjudication CRF, which CEC members use to capture their adjudicated outcomes.**
- **As with core CRFs and Endpoint Reporting CRFs, Sponsors should implement a defined set of edit specifications that are used for data cleaning of the content of completed Adjudication CRFs.**
CEC adjudicators can validate, negate, upgrade, downgrade, or otherwise modify the initial classification of a suspected endpoint. Therefore, Adjudication CRFs should be designed to support these options. CEC adjudicators can also identify potential un-reported suspected endpoints, and Adjudication CRFs should also be designed to support this option.

Sponsors should set up the Endpoint Data Capture Plan to achieve a one-to-one match between investigator-reported endpoints (Endpoint Reporting CRFs) and adjudicated outcomes (CEC Adjudication CRFs). To facilitate this one-to-one match, it is recommended that the Adjudication CRF header be set up such that it contains the event identifiers from the initial classification of the suspected endpoint (i.e., the endpoint type and onset date provided by the investigator), and that it captures the CEC-assigned event identifiers along with the CEC-adjudicated outcome in the body of the Adjudication CRF. This practice creates a critical data link between the initial classification of a suspected endpoint and its final CEC-adjudicated outcome. Since adjudicated outcomes for suspected endpoints may differ in endpoint type and/or endpoint onset date from their initial classifications, this link is critical for reconciliations targeted to ensure that all known suspected endpoints have final adjudicated outcomes.

There is an exception to this one-to-one match, i.e., where standalone CEC-adjudicated, validated outcomes exist (e.g., for potential un-reported suspected endpoints that the investigator does not agree to report but which are validated by the CEC, and for suspected endpoints that have undergone deletion in the endpoint reporting dataset but the CEC has validated the suspected endpoint and does not agree with the deletion).

Adjudication CRFs may be housed in the clinical database along with other study CRF data. Important considerations with respect to this practice are as follows: Sponsors may have access to adjudicated outcomes; since the CEC operates in a blinded fashion, CEC-adjudicated outcomes cannot un-blind the Sponsor to how the data in the trial are trending. Investigators, on the other hand, should not be able to access the completed Adjudication CRFs, because knowledge of adjudicated outcomes for the suspected endpoints he/she has reported has the potential to unduly bias the investigator's reporting of suspected endpoints going forward, which carries the risk of increased under-reporting by the investigator. As a result, if the need for re-training an investigator(s) on the reporting requirements for suspected endpoints is noted, this should be approached as a general training with general case examples, rather than as a targeted training based on specific cases reported by the investigator.

For suspected endpoints which are negated by the CEC as non-endpoints, it is important for the CEC to document the reason for the negation, as well as the alternate disposition of the event, since it was adjudicated as a non-endpoint. The Adjudication CRF should be designed to capture this contextual information.

It is not recommended to allow the CEC the option of adjudicating suspected endpoints as unclassifiable; the Adjudication CRF should not contain this kind of outcome. The endpoint criteria and the adjudication conventions in the CEC Charter should address this prospectively.

It is also not recommended to allow the CEC the option of negating suspected endpoints due to the lack of sufficient information. This kind of decision should only be reached as a final resort if efforts to obtain supporting documentation have been documented as exhaustive and there is not enough information to confirm the endpoint criteria were met. Otherwise, if an adjudicator(s) does not have sufficient information to adjudicate a suspected endpoint, the adjudicator(s) should follow an established process for requesting additional documentation until the need for additional documentation has been satisfied, or until it has been documented that no further additional documentation is available, along with the rationale for this result.
Methods to Ensure Completeness and Currency of Adjudicated Outcomes

A key challenge with centralized adjudication is that CECs must adjudicate suspected endpoints on an ongoing basis throughout the lifespan of a trial, because CEC-adjudicated outcomes are needed for different purposes at different timepoints in the trial (e.g., DMC reviews, interim analyses). If CEC members are receiving CRF data as a component of the data submitted for adjudication, and particularly if the CRF data directly impact their decision-making for the adjudication of suspected endpoints (i.e., CEC critical fields), CEC adjudicators are making decisions based on accumulating study data extracted as a snapshot in time. Since CRF data in an open clinical database become increasingly more complete and more accurate over time, CEC critical fields may be updated post-adjudication. Also, additional source documentation may be entered into the subject chart post-adjudication which provides important additional context regarding a suspected endpoint. Both of these factors require implementation of a re-adjudication process and may result in potential updates to CEC-adjudicated outcomes.

Best practice in the area of ensuring completeness and currency of adjudicated outcomes for suspected endpoints can be summarized as follows:

> It is critical for Sponsors to define whether any CEC critical fields exist in the documentation submitted for adjudication, and if so, to implement a process to detect post-adjudication data changes and to submit them to the CEC to capture updated adjudicated outcomes. A recommended practice to effectively detect post-adjudication changes to CEC critical fields in the CRF is to provide the CRF data via a programmed output, so that the data provided for adjudication are fixed within a historical dataset. Moving forward, the data for these same fields can be programmatically compared to the original data to determine if the content of any fields changed.

> It is equally critical for Sponsors to submit any new or updated source documentation that is received post-adjudication to the CEC to capture updated adjudicated outcomes. A recommended practice is to track the date of receipt of source documents versus the date of CEC submission for suspected endpoints, so that source documents received post-adjudication can be easily identified.

> Operationally, it is optimal to coordinate the re-adjudication workflow such that it is managed in conjunction with relevant trial milestones. That is, it is most efficient to collect post-adjudication changes and perform a round of re-adjudications prior to milestones such as DMC reviews, interim analyses, and finally prior to database lock.

> Since the types of post-adjudication data changes warranting re-adjudication should be defined prospectively in the CEC Charter, the Sponsor should not make case-by-case decisions regarding which suspected endpoints require re-adjudication. Methods should be established to identify the relevant data changes which require re-adjudication, and all cases with these kinds of changes should be submitted for re-adjudication without exception.

> When performing re-adjudication, the CEC should document whether the contents of the Adjudication CRF were or were not updated as a result of the new data reviewed post-adjudication.
Endpoint Management

In addition to an endpoint data capture plan, it is critical for Sponsors to develop a tactical endpoint management plan that addresses the logistics of endpoint data collection.

At a minimum, the tactical endpoint management plan should be accompanied by the following supporting documents: endpoint process training materials, Endpoint Site Manual, endpoint process workflow(s), Endpoint Data Coordinating Center (EDCC) procedures, and any forms and CRFs utilized in the endpoint process. A discussion of current and best practice in these areas follows.

Stakeholders and Contributors in the Endpoint Process

Endpoint workflows are dynamic and interactive, with multiple steps, dataflows, contributors, and stakeholders. Parties typically playing a role in the central adjudication process include the investigator and site personnel, an EDCC, a translation vendor, the CEC adjudicators, and a number of members of the clinical project team (e.g., monitors, safety and medical personnel, data managers, biostatisticians, and project managers). A summary of the key roles and responsibilities typically carried by these parties follows.

The investigator is responsible for the identification and reporting of suspected endpoints and for resolving queries related to reported as well as potential un-reported suspected endpoints. Site personnel are responsible for providing supporting documentation of the suspected endpoints.

An EDCC is typically directly responsible for endpoint management. This includes:

> Overall management and coordination of the centralized adjudication process through a project management function, and execution of discrete tactical activities within the endpoint case management workflow.
> Tracking all known suspected endpoints.
> Collecting the documentation required for adjudication.
> Performing endpoint document processing and endpoint case processing.
> Obtaining translation of any non-English documentation.
> Submitting endpoint dossiers to the CEC for adjudication.
> Coordinating implementation of the CEC-adjudication workflow steps to achieve final adjudicated outcomes.
> Handling any CEC requests for additional documentation.
> Actioning any CEC-identified potential un-reported suspected endpoints
> Participating in endpoint-related reconciliation activities.

A best practice is for EDCCs to employ the services of a translation vendor to provide medically certified translation of any non-English source documentation received for CEC adjudication. Some models used in the industry rely on site personnel or monitors to provide translation of the source documentation needed for adjudication purposes. The issues associated with this approach are:

> The parties providing translation in these models are not certified translators, and they are not qualified to perform medical translation. As a result, the translations provided through these models could contain errant information. Since the CEC adjudicators typically rely on the translated document for decision-making purposes, this errant information could diminish the accuracy of the CEC-adjudicated outcomes.
The parties providing translation in these models have other roles and responsibilities and may not be able to provide translated documents in a timely manner. Use of this model can therefore unnecessarily lengthen the cycle time for endpoint case closure.

**CEC adjudicators** are responsible for the following:

- Closely reviewing each suspected endpoint submitted for adjudication and completing Adjudication CRFs to capture their adjudicated outcomes.
- Requesting additional documentation of suspected endpoints as necessary.
- Identifying potential un-reported suspected endpoints as appropriate.
- Participating in the steps of the adjudication workflow as outlined in the CEC Charter.
- Resolving any adjudication-related queries.
- Performing re-adjudication as needed.

**Monitors** are responsible for performing SDV of reported suspected endpoints and performing secondary endpoint detection for all subjects enrolled in a given trial. Since monitors are ultimately responsible for ensuring that their assigned sites are compliant with deliverables and completion of trial-related action items, monitors are also responsible for assisting the EDCC with the closure of outstanding endpoint-related items (e.g., document requests, queries, reconciliation activities).

**Safety and medical personnel** may be involved in secondary and tertiary endpoint detection activities, including endpoint reconciliation activities. In addition, these parties may be consulted by the investigator regarding the reporting of suspected endpoints.

**Data managers** are typically responsible for implementing some tertiary endpoint detection activities such as endpoint-related edit checks and reconciliations, participating in data cleaning activities for Endpoint Reporting and Adjudication CRFs, and providing data transfers of reported and adjudicated endpoint data.

**Biostatisticians** are typically responsible for performing the analyses of endpoint-related data. This can include providing investigator-reported classifications and CEC-adjudicated outcomes to DMCs for periodic review, performing interim analyses, and performing final study analyses of endpoint data. Biostatisticians may also program outputs from the clinical database for inclusion in endpoint dossiers.

**Project managers:** Since the basic endpoint process map includes a number of touchpoints and data exchanges with other functions, the project management role is key to the success of any centralized adjudication process. Project managers (PMs) execute various roles and responsibilities, including:

- Establishing the scope, timelines, budget, and deliverables associated with conduct of the central adjudication process.
- Providing oversight of the conduct of the endpoint process.
- Monitoring endpoint-related study progress and performance.
- Management of the communications associated with the endpoint process.
- Cross-functional coordination of the workflow steps, handoffs, and data exchanges within the endpoint process flow.
These responsibilities are typically performed by the EDCC PM, who may work with an overall study PM on some or all of these activities. Figure 1 depicts these interfaces.

**Figure 1: Coordinating Function of the Endpoint Data Coordinating Center Project Manager**

**Information Provided to the CEC for Adjudication**

The endpoint case management process is essentially a synthesis activity, its primary objective being the extraction and compilation of supporting data (i.e., an endpoint dossier) for CEC adjudication of suspected endpoints. To determine whether each suspected endpoint reviewed meets endpoint criteria, the CEC typically requires a mix of data and documents, including overall contextual information about the subject and detailed event-specific information. The processes and requirements that define endpoint dossier compilation activities, therefore, warrant strategic and tactical planning to ensure that the information used in the CEC decision-making process is accurate, focused, and complete.

The primary component of any endpoint dossier should be supporting source documentation from the subject’s chart that provides context and descriptive information regarding the suspected endpoint.

Some models are based on adjudication of CRF data alone, which is not a recommended practice. In addition, some models include an endpoint narrative in endpoint dossiers, which is either written by the site or by a third party (e.g., the EDCC or Safety personnel): this practice is also not recommended. See Table 2 for additional detail.

**Endpoint Dossiers**

Source documentation collected for inclusion in endpoint dossiers may include the following documents: (1) Admission history and physical exam; (2) Discharge summary; (3) Progress notes; (4) Medication administration records; (5) Procedure reports, lab reports, and radiology reports; (6) Consultation notes; (7) Medical imaging data (e.g., chest X-rays, angiograms, echocardiograms, ultrasounds, and MRIs); (8) Data from external devices (e.g., pacemakers); (9) Autopsy reports; and (10) Supplementary information, such as CRF data (which may need to be query-clean prior to adjudication), SAE reports, and central and core lab analyses.
Table 2: Considerations Regarding Selection of Dossier Components

<table>
<thead>
<tr>
<th>Priority Level &amp; Value Added</th>
<th>Source Documentation</th>
<th>Case Report Form Data</th>
<th>Endpoint Narrative</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Priority, High Value</td>
<td>Data and documents collected from subject’s chart</td>
<td>Subset of CRF data pertaining to subject/event context and event details</td>
<td>Site event narrative or third party event narrative</td>
</tr>
<tr>
<td>Low Priority, Moderate Value</td>
<td>Review of a specific subset of CRF data can enable the CEC to receive concentrated/summarized data that are typically more diffusely spread throughout the subject’s chart. Since CRF data contain information that is already documented in the subject’s chart, it is possible for the CEC to adjudicate endpoints, based on source documentation, only. It is not recommended for the CEC to adjudicate based on CRF data, only. CRF data lack the necessary level of clinical detail and context the CEC requires, and CRF data are one step removed from the source data. CRF data alone do not enable independent CEC decisions; CRF data should be accompanied by supporting source documentation.</td>
<td>Provision of an endpoint narrative is often thought to have the benefit of expediting CEC review time, by focusing the reviewer’s adjudication on summary-level information regarding the endpoint. However, in order to perform a full adjudication of the endpoint, the reviewer needs to understand event context and confirm that the endpoint criteria were met - both assessments which are done at the detail level, and most optimally determined from direct review of the raw source documentation which was available to the site. Therefore, even if a narrative is included for CEC review, it should be accompanied by supporting source documentation.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Logical Considerations</th>
<th>RECOMMENDED AS PRIMARY DATA TYPE</th>
<th>RECOMMENDED FOR SPECIFIC ENDPOINT TYPES</th>
<th>NOT CRITICAL TO CEC DECISION-MAKING</th>
</tr>
</thead>
<tbody>
<tr>
<td>✓ Meets specific need for independent, unbiased CEC adjudication</td>
<td>x Adds costs and time for additional data processes</td>
<td>x Site narrative viewed as extra work for site</td>
<td></td>
</tr>
<tr>
<td>✓ Infrastructure and expertise needed to implement scalable data coordinating center process</td>
<td>x CRF collection and cleaning processes must be expedited</td>
<td>x Either narrative type adds time for writing/review</td>
<td></td>
</tr>
<tr>
<td>✓ Medically certified translation needed for non-English documentation</td>
<td>x CRF data with endpoint critical fields must be query-clean</td>
<td>x Increases labor costs</td>
<td></td>
</tr>
<tr>
<td>✓ Requires source document verification for accuracy</td>
<td>x Requires source document verification for accuracy</td>
<td>x Site narrative quality varies</td>
<td></td>
</tr>
<tr>
<td>✓ Post-adjudication CRF changes require re-adjudication</td>
<td>x Post-adjudication CRF changes require re-adjudication</td>
<td>x Potential introduction of bias</td>
<td></td>
</tr>
<tr>
<td>✓ Potential inconsistencies between narrative, source documents and CRF data</td>
<td></td>
<td>x Potential inconsistencies between narrative, source documents and CRF data</td>
<td></td>
</tr>
</tbody>
</table>
For models that include CRF data in endpoint dossiers, it is important for Sponsors to do the following:

> Determine which CRF data will be provided, and whether these data contain any CEC critical fields which directly impact CEC decision-making regarding the classification of suspected endpoints.

> If CEC critical fields are included in the CRF data provided within endpoint dossiers, implement processes to reach a query-clean status for these CEC critical fields, prior to submitting a suspected endpoint to the CEC for adjudication. Even though this query-clean status will be a snapshot in time, this approach helps ensure that key information provided to the CEC is as complete and accurate as possible, and it helps reduce the percentage of cases requiring re-adjudication due to post-adjudication data changes.

> For trials which include a query-clean requirement for CEC critical fields in the CRF, implement expedited CRF data collection and cleaning processes that will support the achievement of endpoint case closure cycle time targets.

> For trials which include a query-clean requirement for CEC critical fields in the CRF, also implement processes to identify post-adjudication data changes to these CEC critical fields.

> If post-adjudication data changes are identified, implement a re-adjudication process based on the most up-to-date CEC critical fields in the CRF. This will ensure that the final CEC-adjudicated outcomes are as complete and current as possible.

In summary, it is through review of overview data regarding the subject and detailed descriptive event-related source documentation that CEC adjudicators are able to independently and critically assess the circumstances surrounding the suspected endpoint, thus enabling them to produce a medically precise adjudicated outcome. Where feasible, it is recommended that the documentation provided for CEC adjudication is based primarily on source documentation from the subject chart, and that the role that CRF data and other secondary documentation plays is minimal/supplementary to the source documentation. There are a number of reasons to take this approach in the design of an endpoint process:

> The source documentation from the subject chart contains the raw, descriptive, supporting information that the CEC adjudicators need to review to perform an independent assessment of the suspected endpoint. In many cases, this information alone is completely adequate for CEC adjudication.

> A source-document-driven approach significantly simplifies and streamlines the overall endpoint process, which is otherwise quite complex, as discussed throughout this paper. The simplifications include:

  > Removal of the need to achieve query-clean data prior to endpoint dossier submission.
  > Removal of the requirement to identify post-adjudication data changes to CEC critical fields in the CRF.
  > Removal of the requirement to re-adjudicate suspected endpoints due to changes in CRF data – which significantly reduces the percentage of cases requiring re-adjudication, as the rate at which new or updated source documentation is identified post-adjudication is significantly lower than the rate at which CRF data are updated.

In addition, a source-document-driven approach reduces the cycle time needed to prepare and submit suspected endpoints to the CEC for adjudication since this approach eliminates the segment of time necessary to complete the iterative cleaning process for CRF data from the overall endpoint cycle time.
Endpoint Case Management
In the models currently in practice today, there are a number of different parties who perform the endpoint case management function. It can be performed by the Sponsor, or the Sponsor can elect to assign the responsibility to a third party such as a CRO or an ARO. Additionally, there is a great deal of variability with respect to which roles are responsible for this function within different organizations. Historically, for example, endpoint case management has been performed by safety personnel, medical personnel, data managers, and monitors.

There are advantages to centralizing the endpoint process under a specialized functional group which specializes in endpoint case management, i.e., an EDCC. The key advantages of this approach include:

> Deployment of a dedicated resource pool of staff who are focused on endpoint case management and whose priorities are not split with other activities.
> Ability to implement established, proven endpoint case management practices and benefit from infrastructure developed to specifically facilitate centralized adjudication (including endpoint-specific systems).
> Ability to benefit from accumulated lessons learned by staff performing this highly specialized activity in a concentrated manner.

The risks associated with not centralizing the endpoint process under an EDCC include:

> Potential delay in endpoint case closure due to divided focus and competing priorities experience by staff who hold other roles in parallel to this responsibility.
> Potentially inefficient process implementation, deviance from best practice and/or sub-optimal use of systems by staff who are not fully versed in endpoint case management.
> Potential variability in the content, structure, and quality of endpoint dossiers submitted to the CEC (particularly if this task is completed by a large number of individuals).

The most effective practices implemented by an expert EDCC include the following:

**Standardized collection of endpoint source documentation.** This is achieved by establishing a set of specific source documents, per endpoint type, that the site should collect and submit for each suspected endpoint.

---

**Standardized Collection of Endpoint Source Documentation**

A standard list of specific source documents, per endpoint type, is typically specified on a checklist that the site uses to guide their source document collection efforts, and the checklist is also typically used as a cover sheet to accompany the site’s endpoint packet submitted to the EDCC. Since the source document generation practices differ from facility to facility, and since suspected endpoints may have unique components that are captured in non-standard documents, it is possible that it will be necessary for the EDCC to collect additional documents above and beyond the ones listed on the checklist. Nonetheless, using a checklist method to guide the sites in the provision of basic source documentation for review by the EDCC has proven to be effective as a first step in the source document collection process.
Compilation of high quality dossier contents. To ensure high quality dossier content is compiled for adjudication, it is critical to perform a number of quality control steps, including:

> A series of consistency checks on the individual contents of the endpoint packet submitted by the site and resolution of any discrepant information prior to submission of these materials to the CEC. These checks include, but are not limited to: confirmation that all documents are for the correct subject, that they are complete (no missing pages), that they are all relevant to the timepoint of the suspected endpoint, that they do not contain conflicting information about the suspected endpoint, and that subject identifiers have been redacted as appropriate.

> A content review process for source documentation to verify that endpoint criteria are sufficiently addressed and that there is enough clinical and contextual information on the suspected endpoint for the CEC to provide an adjudication. This means that an effective EDCC does not simply perform document management. Rather, EDCC staff apply their expert understanding of what the CEC needs for decision-making purposes and use analytical problem-solving skills, working with the site to ensure that the collected source documentation regarding the circumstances surrounding the suspected endpoint is as complete and clear as possible, including the identification and collection of case-specific, non-standard documents as necessary.

> A centralized QC process of the final compiled dossier, to ensure global consistency in format, content and quality of the information it contains, prior to CEC submission.

Electronic endpoint management. A number of established EDCCs have developed electronic systems which facilitate paperless endpoint processing and online adjudication, to different degrees of functionality (see the next section for additional details).

Mature business procedures to support timely endpoint case closure. This is achieved through a number of means, including:

> Working closely with the site, through training, provision of documented process requirements (e.g., in an Endpoint Site Manual), and direct communications to ensure that expectations are clear regarding the suspected endpoint reporting process and the endpoint packet submission process. This information outlines what is needed at the overall and case-specific level, within specified timelines, to complete endpoint dossiers in a timely fashion.

> Provision of regular status reports to the clinical team indicating reported suspected endpoints, their status with respect to readiness for submission to the CEC, and itemization of any outstanding action items that need to be addressed for endpoint case closure.

> Implementation of effective escalation plans by the EDCC as needed.

Regardless of which party is responsible for endpoint case management, there are some known process limitations and challenges inherent within the endpoint dossier compilation process which bear consideration, as they drive endpoint case closure timelines (i.e., endpoint cycle times). A discussion of the most common limitations and challenges follows.

Challenges and Limitations in the Endpoint Dossier Compilation Process

As noted previously, the data handling procedures for SAEs versus endpoints differ significantly in focus, timing, and workflow. Specifically, the fairly straightforward nature of SAE definitions and the SAE regulatory reporting timelines both drive the SAE case processing flow, which focuses on rapid finalization of initial SAE classifications that can be assigned based on the collection of a limited
amount of supporting data that are available within either a 7 or 15 day reporting period. SAE case closure is then typically targeted for completion within the next 90 days, as additional necessary SAE information and clarifications are requested and become available.

The timing of the endpoint case processing flow is in some ways similar and in other ways significantly different. It is understandably longer than that of an SAE, given the discussion of specific process limitations that follows. Most importantly, to put longer endpoint cycle times in perspective, it is important to note an underlying principle: since there is no regulatory reporting timeline for suspected endpoints, an expedited initial classification process like the one required for SAEs is not needed for suspected endpoints. In fact, since endpoints are also processed in parallel as SAEs (if they meet SAE criteria), any important safety-related aspects associated with a suspected endpoint are handled through its expedited treatment as an SAE. Therefore, the length of the cycle to achieve endpoint case closure does not have a direct impact on subject safety. For this reason, endpoint case closure cycle times should be managed to meet the primary objectives of centralized adjudication, which is a process that strongly favors accuracy and completeness of information over speed.

Due to the medically complex nature of endpoint definitions, the documentation that must be collected to support CEC decision-making on suspected endpoints is extensive and far exceeds the sum total of documentation collected for SAE purposes. It is the challenges and the timing associated with the collection of this documentation which present the majority of limitations in the endpoint case processing workflow, and which drive the longer cycle times observed for endpoint case closure. Some of these key challenges and limitations can be summarized as follows:

> Many facilities require a minimum of 4 weeks to generate and finalize source documents. Moreover, if the subject experiences a long hospital stay in relation to a suspected endpoint, key documents such as the hospital discharge summary will not be available until after the subject has been discharged and the document generation process has been completed by the hospital. This means that the hospital discharge summary and other documents needed for an endpoint dossier could be pending collection for many months. In this case, if a long delay is expected or observed, it is necessary for the party responsible for endpoint case processing to decide whether the suspected endpoint can be adjudicated based on best available data, or whether the dossier should be placed on hold until further source documentation is available.

> Subjects may be treated at another facility other than that of the investigative site. In such cases, the site must work with the other facility to collect the necessary source documentation. In addition to the typical source document generation timelines discussed previously, additional time can elapse in these scenarios due to the steps of the document request process between facilities. In this case, it is important for the site to actively follow-up with the other facility to obtain the necessary documentation. It is also recommended that sites obtain a signed, general medical records release permission form from all enrolled subjects so that if documents need to be obtained from another facility, this permission for the site to do so is already on file at the site.

> There are some country-specific limitations regarding the collection of source documentation, including, for example, scenarios in which there is a prohibition regarding the release of certain kinds of documents (e.g., death certificates, autopsy reports) and scenarios in which subject’s records are retained by the subject rather than the facility. Both of these scenarios can contribute to longer cycle times for endpoint case closure. In these cases, the EDCC works with the site to identify the documents that can be collected and which will contain the information needed by the CEC to classify the suspected endpoint.
There are some facilities that do not typically produce the types of source documents indicated as standard on the study checklist for inclusion in the site’s endpoint packet. In this case, extra time and effort is needed for the EDCC to work with the site to identify and collect appropriate alternate documents that contain the information needed by the CEC to classify the suspected endpoint.

Some suspected endpoints occur outside a facility (e.g., subject’s death at home, some “silent” events). In these cases, the source documents indicated as standard on the study checklist for inclusion in the site’s endpoint packet will likely not exist. Therefore, extra time and effort is needed for the EDCC to work with the site to determine how any documentation of the circumstances surrounding the subject’s suspected endpoint can be obtained (i.e., a note to file documenting information provided by the subject, a family member, or a caregiver may be the only potentially available information, and it can prove challenging to obtain this kind of information for some cases).

There are numerous recommended solutions to address these challenges and limitations, and some of the main ones have been discussed. In summary, it is critical that Sponsors are equipped to understand the unique nature of the endpoint process, and it is important for Sponsors to establish study parameters and performance measures for central adjudication that are based on realistic, achievable expectations that allow for the necessary longer cycle times associated with endpoint case processing.

The risk of imposing expedited or unrealistic timelines on the endpoint case processing workflow is that the completeness of supporting endpoint documentation will be sacrificed for speed, with undesirable results such as the following:

> If endpoint dossiers are submitted prematurely to the CEC (i.e., dossiers where the contents are known to be incomplete and collection of necessary documentation is pending), this does not necessarily lead to more rapid CEC decision-making. In fact, the CEC should submit a request for additional documentation if the information for the suspected endpoint is incomplete, and hence this would be an expected result of submitting endpoints dossiers that are known to be incomplete. Therefore, it is more efficient for the EDCC to hold an incomplete dossier and only submit it once the most complete information possible has been collected.

> If endpoint dossiers are submitted prematurely to the CEC, and the CEC does provide an adjudicated outcome in return, the quality and integrity of this CEC-adjudicated outcome is diminished since it is not based on the full information necessary, and may be lacking the appropriate clinical context for robust CEC decision-making. Therefore, CEC-adjudicated outcomes provided under these circumstances could be inaccurate, and this inaccuracy could adversely influence the decision-making by other parties (e.g., DMC members, biostatisticians performing interim analyses) who include CEC-adjudicated outcomes in their data review and analysis processes.

> If endpoint dossiers are submitted prematurely to the CEC, and the CEC does provide an adjudicated outcome in return, there is also an operational issue that arises, which is that a higher rate of re-adjudication will be needed, to obtain up-to-date adjudicated outcomes, once the necessary documentation has been collected.
As in most things, it is important to strike a balance in the endpoint case closure cycle times achieved within the central adjudication process. While the endpoint case processing workflow should not be unduly pressed into unrealistically expedited cycle times for the reasons just discussed, there are certain scenarios in which it is appropriate to expedite dossier compilation and adjudication. In particular, it is important for Sponsors to ensure that CEC-adjudicated outcomes are finalized and made available on a rolling basis throughout the lifespan of a trial if certain inter-dependencies exist, for example:

- If a DMC will review CEC-adjudicated outcomes as part of their periodic safety review process.
- If the protocol calls for an interim analysis of event rates as evidenced by CEC-validated suspected endpoints.
- And/or if the protocol is event-driven and a targeted number of CEC-validated suspected endpoints must be reached in order to stop the trial.

To ensure an endpoint process is designed to meet the primary objectives of centralized adjudication and also aligned to project-specific objectives, it is best practice for the Sponsor to establish a set of mutually agreed targets and milestones to monitor endpoint process performance.

**Endpoint Process Performance Metrics**

The most common and informative metrics regarding the performance of the endpoint process include the following:

- **Endpoint volume metrics:** the percentage of known suspected endpoints submitted to the CEC. It is recommended that this percentage ramp up to approximately 80 percent by the point at which the project is in steady state, and that there is a clear plan to achieve 100 percent prior to database lock.

- **Adjudication rate:** the percentage of known suspected endpoints with final adjudications provided by the CEC. This rate is typically established to coincide with DMC reviews and/or interim analyses that occur during the course of a trial. While the exact adjudication rate targets should be established to meet specific protocol and study parameters, the key take-away from this practice is that a 100 percent adjudication rate is not necessary for these purposes: DMC review and interim analysis can be performed on a partial dataset of CEC-adjudicated outcomes, in conjunction with a full dataset of initial classifications for suspected endpoints. A suggested benchmark for the adjudication rate threshold to be achieved during the steady state of a trial is 75 percent.

- **Endpoint cycle time metrics:** the duration of each main segment of the overall endpoint process workflow. The following cycles are recommended for consideration as targets, but should be applied with discretion, in consideration of project-specific parameters and case-specific circumstances:
  - From identification to reporting of suspected endpoint by investigator = 48 hours.
  - From reporting of suspected endpoint to initial submission of endpoint packet by site = 6 weeks.
  - From reporting of suspected endpoint to submission of endpoint dossier to CEC = 90 days (without query-clean CRF data) and 160 days (with query-clean CRF data).
  - From receipt of endpoint dossier to final adjudicated outcome = 30 days (without CEC disagreement resolution or CEC requests for additional documentation) and 60 days (with CEC disagreement resolution and/or CEC requests for additional documentation).
Site compliance metrics: captured as the number of follow-ups needed by the EDCC to collect required information, the percentage of cases escalated by the EDCC, and/or the percentage of cases not closed after the projected cycle time for endpoint case closure has elapsed. The following metrics are recommended for consideration as targets but should be applied with discretion, in consideration of project-specific parameters and case-specific circumstances:

- Average number of follow-ups per case = 3.
- Percentage of escalated cases = less than or equal to 25 percent.
- Percentage of cases not closed by projected timeline = less than or equal to 15 percent.

Rate of Adjudicator Requests for Additional Documentation (RAD): the percentage of endpoints submitted to the CEC that resulted in an adjudicator request for additional documentation rather than a CEC-adjudicated outcome. It is recommended to maintain this rate at the lowest feasible percentage. A suggested benchmark is 20 percent or less.

Adjudication confirmation rates: the percentage of suspected endpoints validated by the CEC. This percentage varies by endpoint type and is impacted by a wide number of different factors. On average, CEC confirmation rates of suspected endpoints identified through investigator reporting range from 75-90 percent.

Adjudicator concurrence rates: the rate at which the individual outcomes provided by CEC adjudicators are in agreement with each other (adjudicator consistency). It is recommended to maintain this rate at the highest feasible percentage. A suggested benchmark for consideration is 90 percent or greater.

Assessing the Performance of Central Adjudication

Since a wide number of project- and protocol-specific parameters influence the components of endpoint study design implemented in a central adjudication process, it is not feasible to establish a full set of typical metrics that can be used across the board to measure the performance of central adjudication: For this reason, the metrics for this purpose discussed in this White Paper are expressed in general terms/ranges as suggested benchmarks. Instead, the Sponsor should consider the elements of the project-specific workflow that has been implemented, make projections regarding what the process can reasonably achieve, and establish targets based on this projection exercise. In setting these targets, the Sponsor should ensure that the primary objectives of centralized adjudication, as well as the project-specific objectives of the endpoint process in question, are met. The Sponsor should then measure performance against these projections and targets to identify whether any endpoint-related study processes require adjustment so that its objectives are successfully met.
Implementing the Optimal Endpoint Process Flow

While the centralized adjudication process can be implemented effectively via a manual, paper-based process flow, there are significant advantages to utilizing a paperless, semi-automated electronic workflow. Discussion of the optimal end-to-end endpoint process flow therefore focuses on electronic endpoint management.

In current best practice, electronic endpoint management involves the use of eDC technology that is specially configured to support the specific needs of the centralized adjudication process. This approach involves the use of a single system for all of the following purposes:

- **Investigator Module**
  - Completion of Endpoint Reporting CRFs
  - Electronic submission of supporting source documents for suspected endpoints
  - Resolution of endpoint-related queries

- **EDCC Module**
  - Online endpoint case processing including all typical EDCC activities
  - Paperless dossier compilation
  - Submission of dossiers to CEC adjudicators

- **CEC Module**
  - Online review of dossiers for suspected endpoints
  - Completion of Adjudication CRFs
  - Requests for additional documentation
  - Identification of potential un-reported suspected endpoints
  - CEC disagreement resolution

The value that an electronic endpoint management system brings to the centralized adjudication process is recognized in a number of ways across all components of the endpoint workflow. A fully comprehensive endpoint management system creates significant process efficiencies by incorporating all components of the endpoint reporting, endpoint case processing, and CEC adjudication workflows into a single system environment with a centralized, flexible, and automated electronic workflow, as shown in Figure 2.

Figure 2: Comprehensive Electronic Endpoint Management System
This approach integrates role-based activities performed by all relevant stakeholders and contributors into a collaborative workspace, as shown in Figure 3.

This approach also improves process consistency and quality through the governance that the system brings to the process, elimination of manual handoffs, and reduction of the need for manual data reconciliations. In addition, this approach improves endpoint cycle time by facilitating real-time information exchange and eliminating steps associated with paper-based processes. Accordingly, an approximate reduction by 33 percent in overall endpoint cycle time is possible through use of electronic endpoint management.

Additional benefits include the fact that electronic endpoint management reduces the labor associated with what has traditionally been a labor-intensive effort, by partially automating some of the workflow steps and by reducing the volume of data and statuses that need to be tracked manually. An electronic endpoint management system also lowers project costs by eliminating fax and courier charges, which have traditionally been required to transport paper documents from sites to EDCCs and from EDCCs to CEC adjudicators, and by reducing, and in some cases eliminating, travel costs traditionally required for regular face-to-face CEC adjudication meetings.

For additional information on the value of an electronic endpoint management system, see the article, Electronic Endpoint Adjudication: How an integrated, EDC-based system can optimize the endpoint process.¹

---

**Advantages of Electronic Endpoint Management Systems**

The distinct advantages of an electronic endpoint management system begin with ease of use, integrated processes, collaborative workflows, and flexibility. Significant gains are achieved from shorter cycle times and notable project cost savings. In addition, there is a marked increase in quality by enabling comprehensive review of all necessary documentation for adjudication, enabling early and partially-automated detection and resolution of discrepancies, and contributing significantly to overall process standardization and compliance. The result is a thorough, well-governed centralized adjudication process that operates in real-time, achieving more rapid delivery of robust adjudicated endpoint outcomes for critical project-level and product-level decision-making.
CEC Charter Development

The CEC Charter is a document that serves as the Standard Operating Procedure to describe and govern key activities within the endpoint process, both those conducted by the EDCC and the CEC members. While CEC Charters are typically implemented at the protocol-specific or program level, some co-located CECs work under a central charter with protocol-specific addendums, as needed.

In current practice a number of different parties can take full or partial ownership for writing the CEC charter. The most common contributors to CEC Charter development are a Sponsor representative, a CRO and/or ARO representative, and the CEC Chairperson (or designee). The majority of CEC Charters are developed through collaborative efforts by each of these parties. Regardless of who develops the content of the CEC charter, it is critical to ensure that the document outlines the relevant procedures pertaining to endpoint data capture, endpoint case processing and dossier compilation, and CEC adjudication. It is also critical to ensure that any parties who have direct responsibility within the endpoint process flow described within the CEC Charter have the opportunity to provide review and approval of the document before it is finalized.

Recommended CEC Charter Contents

It is recommended that, at a minimum, Sponsors include the following items in the CEC Charter:

- Roster of CEC Members and Primary Points of Contact for the Endpoint Process
- Summary of the Scope of the CEC Charter
- Overview of the Remit of the CEC (including a protocol synopsis and methods by which CEC independence will be preserved)
- Establishment, Composition, and Training of the CEC (including how changes in membership will be handled)
- Roles and Responsibilities (e.g., the Sponsor, the EDCC, the CEC Chairperson, the CEC members, and other parties participating in the endpoint process flow)
- Endpoint Criteria and Adjudication Conventions
- Overview of Endpoint Data Capture Plan (in particular, this section should cover how suspected endpoints will be identified for adjudication and data handling procedures for adjudicated outcomes)
- Overview of Tactical Endpoint Management Plan (in particular, this section should cover the standard documentation to be included in endpoint dossiers and any associated requirements, as well as the method by which endpoint dossiers will be submitted to the CEC adjudicators)
- Overview of the Adjudication Workflow, including:
  - The workflow steps for the adjudication model which will be implemented
  - CEC administrative logistics, including whether the CEC will adjudicate during or outside of meetings and specific details regarding CEC meeting format and frequency if applicable
  - The process for Adjudication CRF completion and data cleaning
  - The process for CEC adjudicators to request additional documentation
  - The process for CEC adjudicators to report potential un-reported suspected endpoints
  - The process for re-adjudication
- The requirements for CEC data confidentiality and data retention
Common attachments to a CEC Charter include lists of standard dossier contents by event type, specifications for query-clean CRF data if applicable, and relevant workflows, forms, and CRFs. It is not uncommon for a CEC Charter to operate in conjunction with other endpoint-related study documents (e.g., detailed EDCC SOPs, an Endpoint Site Manual, a study-specific Endpoint Data Capture Plan, and a study-specific Tactical Endpoint Management Plan).

Preserving the Independent Nature of the CEC

When defining the operating model for a CEC, Sponsors should ensure that the key principles of CEC independence are met. Just as the independence of a DMC is not pure, CEC independence is not pure for the same reasons: the Sponsor is ultimately responsible for approving CEC members, for giving the CEC its charge and for paying CEC members for their services. However, there are key principles of independence that should be built into the CEC charter to preserve CEC independence in its operations and decision-making process. The recommended best practice in this regard is as follows:

> CEC membership should be comprised of independent individuals who are not Sponsor members or agents of the Sponsor (e.g., CRO and ARO staff).

> Only the CEC members should participate in the adjudication of suspected endpoints. For example, if the CEC holds adjudication meetings, the portion of the meeting during which cases are adjudicated should be an executive session attended only by the CEC members.

> The Sponsor may query CEC-adjudicated outcomes, in accordance with GCP, in the same manner that clinical data provided by investigators are queried, based on established edit checks and/or the identification of potential logical discrepancies.

> Sponsors should refrain from questioning the judgment of the CEC for specific cases, as this practice has the risk of introducing Sponsor bias into the central adjudication process. If the Sponsor has a concern regarding the outcomes provided by the CEC, the Sponsor may engage the CEC in a methodology-focused discussion regarding how aspects of the endpoint criteria and adjudication conventions are applied in certain scenarios to determine whether a concern is valid and what next steps are needed, if any.

> Along these same lines, Sponsors should refrain from requesting re-adjudication of suspected endpoints unless re-adjudication triggers have been prospectively defined (e.g., post-adjudication changes to query-clean CRF data and/or the receipt of new or updated source documentation), or unless there is a systemic need (with robust rationale) to implement a mid-study change in the CEC endpoint criteria (e.g., a protocol amendment, a signification change in industry-wide endpoint criteria which warrants implementation in ongoing projects). If Sponsors request re-adjudication of specific suspected endpoints or sub-sets of suspected endpoints beyond these scenarios, there is the risk that this will be viewed as undue intervention of the Sponsor in the CEC’s decision-making process.
Selecting the Optimal CEC Adjudication Model

Two basic adjudication models are used most commonly: the consensus and the parallel approach. In the parallel approach, two reviewers receive a case at Stage 1 and provide separate adjudicated outcomes. Outcomes are compared by a third party, any disagreements are identified, and the case is routed to an additional reviewer at Stage 2, who provides a third adjudicated outcome. This third adjudicated outcome typically either overrides the initial adjudications from Stage 1 (e.g., if provided by the CEC Chairperson), or it serves as a tie-breaker to determine the final result by majority rule. Figure 4 presents this process.

Figure 4: Parallel Adjudication Model

PARALLEL ADJUDICATION MODEL

Reviewer 1 adjudicates case  
Reviewer 2 adjudicates case
Adjudication CRF completed  
Adjudication CRF completed
Do reviewer 1 and 2 agree?

No (can be 50% of all cases)  
Reviewer 3 adjudicates case  
Adjudication CRF completed

Yes  

Adjudication CRFs entered in clinical database. Case closed.

2-3 adjudication CRFs per endpoint

CEC Adjudication Models

A key factor Sponsors should consider when defining the operating model for a CEC is the adjudication model that will be employed by the CEC members. Just like with practically all other aspects of endpoint project design, there are many adjudication models in place throughout the industry, and there appears to be no limits to the hybridization applied to this aspect of the central adjudication process.
In the consensus approach, presented in Figure 5, two or more reviewers discuss cases and reach mutual agreement. They provide a single adjudicated outcome, indicating consensus on the case. This approach can be implemented with a paired reviewer or multiple reviewer (e.g., full committee) model. In the rare case that consensus cannot be reached in the paired consensus review model, the case is typically reviewed by the full committee to determine the final adjudicated outcome.

Figure 5: Consensus Adjudication Model

CONSENSUS ADJUDICATION MODEL

Stage 1
Reviewers 1 and 2 meet to discuss case

Is there consensus?

Yes

Adjudication CRF completed

No (Rare)

Stage 2
Adjudicated outcome determined by full committee

Adjudication CRFs entered in clinical database. Case closed.

1 adjudication CRF per endpoint
A comparative analysis of the advantages and disadvantages of these two models is presented in Table 3.

Table 3: Comparative Analysis of Consensus vs. Parallel Adjudication Models

<table>
<thead>
<tr>
<th>Consensus Adjudication Model</th>
<th>Parallel Adjudication Model</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Advantages</strong></td>
<td>Theoretical:</td>
</tr>
<tr>
<td>Shorter cycle time:</td>
<td>The level of independence with which each adjudicator makes their decision in this model is thought to lend credibility to the adjudicated outcomes produced (independent agreement between two experts who did not confer with each other).</td>
</tr>
<tr>
<td>&gt; Final result obtained in a single stage</td>
<td>However, in practice, CEC disagreement rates can be as high as 50 percent in projects using parallel adjudication models, which offsets this perceived advantage – adding cycle time and cost to the central adjudication process.</td>
</tr>
<tr>
<td>Lower costs:</td>
<td></td>
</tr>
<tr>
<td>&gt; A single adjudication CRF per case for processing (tracking, data entry, queries, reconciliation, statistical analysis)</td>
<td></td>
</tr>
<tr>
<td>&gt; Even though adjudicators discuss cases, it is not necessary for them to do this via a face-to-face meeting</td>
<td></td>
</tr>
<tr>
<td>&gt; Payment required to 2 adjudicators per case, only</td>
<td></td>
</tr>
<tr>
<td>Promotes high quality and consistency of outcomes:</td>
<td></td>
</tr>
<tr>
<td>&gt; Disagreements are resolved through true arbitration; root cause for initial disagreement identified through discursive review and resolved by mutual agreement.</td>
<td></td>
</tr>
<tr>
<td>&gt; Results are more refined, as this model naturally routes complex cases into a closer review process</td>
<td></td>
</tr>
<tr>
<td>&gt; Allows for synthesis decisions</td>
<td></td>
</tr>
<tr>
<td>&gt; Promotes adjudicator consistency</td>
<td></td>
</tr>
<tr>
<td><strong>Theoretical:</strong></td>
<td></td>
</tr>
<tr>
<td>A perceived risk of this approach is that one adjudicator will unduly influence and override valid opinions offered by the other adjudicator(s).</td>
<td></td>
</tr>
<tr>
<td>Although this risk is low, it is possible to put measures in place to manage impact. For example, utilizing qualified CEC members lowers the risk that they will not stand by their clinical judgments. In addition, adjudicators can document their initial assessments (including minority opinions and reason for any change, post discussion), so that the steps of the individual and then consensus decision process are captured.</td>
<td></td>
</tr>
</tbody>
</table>

| Disadvantages                |                             |
| Longer cycle time:          |                             |
| > Model includes multiple steps to obtain final result |                             |
| Higher costs:               |                             |
| > 2-3 adjudication CRFs are produced per case for processing (requiring tracking, data entry, queries, reconciliation, statistical analysis) |                             |
| > Labor to compare adjudication CRFs and identify disagreements is required |                             |
| > Payment to third adjudicator is necessary for a percentage of cases (i.e. CEC disagreement cases) |                             |
| Potential impact on quality and consistency of outcomes: |                             |
| > Adjudicators work in isolation and do not benefit from surmounting learning curve through discursive case review |                             |
| > CEC disagreements are resolved through a false arbitration process; therefore, it is possible that the root cause for the initial CEC disagreement will not be determined (with risk of repetition), and that the tie-breaking decision may not yield the most accurate classification as it may not take the differing perspectives that led to CEC disagreement into account |                             |
Along with the above considerations regarding whether a consensus or parallel adjudication model will be utilized, Sponsors should also ensure that the adjudication decision-making process flow is aligned with the composition of the CEC and vice versa. For example, if the CEC is comprised of individuals with different backgrounds, the decision-making process will be most effective when these individuals contribute cross-functionally to a composite decision which is formulated based on merging their different perspectives. As a result, the adjudication decision-making process flow best suited to this kind of CEC composition is either paired consensus or full committee review of suspected endpoints. Specifically, the adjudication decision-making process involved in the parallel adjudication model would not be suited to this type of CEC composition, due to the fact that a high adjudication disagreement rate and/or a low adjudication concurrence rate is likely to result when individuals with different backgrounds classify a suspected endpoint without being able to discuss the case together.

As another example, if the CEC is comprised of individuals (or groups of individuals) with homogeneous backgrounds, the decision-making process will be effective when these individuals contribute to either a composite decision, or to a convergent decision which is formulated based on achieving the same perspective between two or more members. Therefore, this kind of CEC composition is suited to any adjudication model: parallel, paired consensus, and full committee.

Integration of the Centralized Adjudication Process within the Overall Trial

Successful integration of central adjudication into the overall clinical trial process map entails adjustment of almost every aspect of the typical clinical trial process to accommodate the endpoint process: protocol design and content, CRF design, project systems implemented, site training, the data management plan, the project safety plan, the monitoring plan, the project communication plan, the event reconciliation plan, the statistical analysis plan, study status reporting, study team priorities, and study timeline planning. Consider then that CECs are one of the many different kinds of oversight groups that can operate on a given trial, and that when multiple oversight groups are in place on the same trial, there are added project design considerations which must be accommodated. As a result, it is important for Sponsors to be equipped to understand the distinct remit of each oversight group, the important data exchanges which must take place across the study to support their individual needs, and the boundaries which must also be maintained between them.

The primary dependencies between oversight groups and other functional groups that impact, or are impacted by, the centralized adjudication process performed by a CEC can be summarized as follows:

> It may be necessary to collect core laboratory assessments for inclusion in endpoint dossiers; therefore, the Sponsor should consider implementing a means to prioritize analysis of certain subjects’ data within the core laboratory so that these assessments are available when the endpoint dossiers are ready for CEC submission.

> It may be necessary for the EDCC to escalate source document collection action items to achieve case closure, a measure that typically impacts the Clinical team.

> It may be necessary to include query-clean data in the endpoint dossiers, and if this is the case, the Sponsor should implement expedited CRF collection and cleaning targets to endpoint case closure targets, a prioritization effort that impacts Clinical and Data Management.
As part of the DMC remit, DMC data reports may include both initial endpoint classifications and adjudicated outcomes. It is best practice to establish mutually agreed targets for the adjudication rate to be achieved prior to each data cut-off for the DMC data reports. These targets should be agreed by the Sponsor, CEC, DMC, EDCC, data manager, and biostatistician. The DMC may request case-specific information for suspected endpoints and/or specific core lab data for closer review.

Figure 6 presents a depiction of these relationships.

Figure 6: Inter-dependencies & Key Data Exchanges Between Oversight Groups

The primary boundaries needing to be drawn between oversight groups center around access to un-blinded information, confidentiality, and independence. Related best practice can be summarized as follows:

- **Individuals in a DMC role should not also serve as member of any other oversight group on the same trial.**
- **Whereas DMCs can become fully un-blinded to treatment at the study level on a blinded trial, the Sponsor and all other oversight groups should remain blinded to treatment. Therefore, while communication with the DMC members is supported and valuable, these communications must be handled so that individuals who must remain blinded in their role(s) do not become un-blinded through information shared by the DMC.**
- **As discussed previously, to maintain the independence of the CEC and DMC, Sponsor staff should not serve as members of either committee, and Sponsor staff should not participate in CEC or DMC operations or decision-making.**

In summary, studies with multiple oversight groups require a considerable amount of added planning, oversight, coordination, and communication. It is important for Sponsors to ensure that a project is designed so that the individual requirements for each separate oversight group process can be met, and also to ensure that the study-wide objectives can be met through achievement of a set of clearly established, inter-dependent, cross-functional deliverables.
Conclusions
There is a long-standing practice across the biopharmaceutical industry of employing CECs to assess clinical efficacy and safety endpoints. In addition, the use of CECs to assess special events of interest is on the rise. In fact, centralized adjudication is now required, via regulatory guidances in both the United States and Europe, to assess for unacceptable cardiovascular risk of new anti-diabetic drugs for T2DM. In addition, there has been an increase in the number of long-term cardiovascular outcomes trials that regulators have required as a condition of approval for marketed products targeting noncardiovascular indications. As a result, it is likely prudent to expect a continued increase in the employment of centralized adjudication processes to examine important clinical endpoints, including cardiovascular events, in efficacy and safety investigations of new and marketed drugs. It is also likely that additional guidances will be issued in the future, requiring centralized adjudication in additional areas of focus.

Given the shifts in the regulatory landscape which have resulted in an increased use of CECs, Sponsors implementing centralized adjudication are in need of an operational guidance which clearly outlines processes and sets standards in this critical area. This white paper has discussed overall best practice with respect to the establishment and operation of CECs. It is hoped that these discussions will prove helpful to Sponsors across the biopharmaceutical industry who are planning and executing centralized adjudication processes.
About the Authors

Catherine A. Tyner, MA, MFA, ABD
Senior Director and Global Unit Head
Clinical Safety and Oversight Group Solutions
Lifecycle Safety

Tyner holds a bachelor’s degree from Wake Forest University and two master’s degrees from Bowling Green State University. Her primary remit since joining Quintiles in 1997 has been within Oversight Group Management. In addition, she has gained extensive operational business process knowledge and experience in other functional areas including Clinical, Project Management, Data Management, and Safety and Pharmacovigilance. Cathy’s most recent interests and responsibilities extend into the Lifecycle Safety division of Quintiles Clinical Development – with an emphasis on Safety Risk Profiling and Risk Management.

In 1998, Tyner founded the global Clinical Event Validation & Adjudication Service (CEVA) department, a division of Quintiles Lifecycle Safety which delivers management, coordination, and integration of oversight group processes for Clinical Endpoint Committees, Core Laboratories, Data Monitoring Committees, Advisory Groups such as Trial Steering Committees, and Medical Decision Committees. CEVA staff have successfully provided oversight group management services for more than 250 trials, involving over 120 Clinical Endpoint Committees and over 150 Data Monitoring Committees, spanning numerous therapeutic areas and all study phases.

Tyner’s specific focus with respect to professional development activities is centered around promoting oversight group management best practice and standardization initiatives. In November 2008, she initiated and chaired the first-ever conference focusing on endpoint best practice. In June 2009, she presented a poster at the 45th Annual DIA Meeting entitled “Optimizing the Value of Clinical Endpoint Committees: Strategies to Enhance the Structure and Performance of Clinical Endpoint Committees for Optimal Impact on Trial Timelines, Budget and Quality.” In October 2009, she chaired the first-ever conference focusing on Clinical Oversight Group best practice. And in March 2010, she co-authored an article which was published in Applied Clinical Trials, entitled: “Electronic Endpoint Adjudication: How an Integrated, EDC-Based System Can Optimize the Endpoint Process.”
Ransi Somaratne, MD, MBA, FACC
Director, Medical and Scientific Services

Dr. Ransi Somaratne is board certified in cardiology, nuclear cardiology and internal medicine. He completed his residency at Santa Barbara Cottage Hospital in Santa Barbara, CA and a cardiology fellowship at Kaiser Permanente Medical Center in Los Angeles, CA.

Dr. Somaratne was in clinical practice for nine years as an invasive cardiologist with significant interests in cardiac imaging (including cardiac CT), critical care and heart failure. He founded his area's first outpatient program dedicated to the management of congestive heart failure. He also served as Chief of Operations for a mid-sized cardiology practice from 2002 through 2007.

Dr. Somaratne has been involved with clinical research as a medical advisor since 2007 and has experience with trials in phases I-IV, including cardiac devices, acute coronary syndromes, congestive heart failure, hypertension, rheumatoid arthritis and weight management. He has also provided consultative services to clients regarding protocol design via Quintiles Consulting. He regularly assists Quintiles Capital with due diligence activities, and also holds an MBA from the University of North Carolina at Chapel Hill.

Christopher H. Cabell, MD, MHS, FACC
Senior Vice President and Global Head, Therapeutic Delivery

Prior to joining Quintiles, Dr. Cabell was on faculty at Duke University School of Medicine and the Duke Clinical Research Institute in Durham, NC, where he was Director of the Echocardiography Core Lab, Associate Director of the ECG Core Laboratory, Co-Chair of the Cardiac Safety Research Consortium and Director of the International Collaboration on Endocarditis.

Dr. Cabell is an honors graduate of The Pennsylvania State University and the Duke University School of Medicine. He completed his Internship and Residency in Internal Medicine at Duke as well as a Chief Residency Year. He completed a Fellowship in Cardiology at Duke and completed a Masters in Health Sciences. He is Board Certified in both Internal Medicine and Cardiovascular Diseases.

Dr. Cabell has over 75 original articles, reviews, editorials, book chapters and electronic publications. His research has been published in several prestigious journals including NEJM, JAMA, Annals of Internal Medicine, Circulation, American Heart Journal, Archives of Internal Medicine, American Journal of Medicine, American Journal of Cardiology and Clinical Infectious Diseases. He has received numerous awards and recognition including induction into AOA, the Greenfield Scholar in Cardiology Award, the Four School Physician/Scientist Training Program, and he was a Howard Hughes Medical Student Research Training Fellow. In addition, Dr. Cabell helped to found the Cardiac Safety Research Consortium, which is a public-private partnership between academia, FDA, and the industry expressly designed to answer pragmatic questions regarding cardiac safety and therapeutic drug development.
J. Rick Turner, PhD, PGCE, MTOPRA
Senior Scientific Director, Cardiac Safety Services

Dr. Turner is an experimental research scientist and clinical trialist who first worked in the field of Cardiovascular Behavioral Medicine, where his innovative behavioral genetic research investigated genetic and environmental influences in cardiovascular responses to psychological stressors. He moved into the pharmaceutical industry 14 years ago, and has held positions as a clinical submissions scientist at GlaxoSmithKline, Chairman of a Department of Clinical Research at a school of pharmacy, and President and Chief Scientific Officer at Turner Medical Communications LLC. He has published four books on drug development and drug safety, including Integrated Cardiac Safety: Assessment Methodologies for Noncardiac Drugs in Discovery, Development, and Postmarketing Surveillance (2009), and New Drug Development: An Introduction to Clinical Trials, 2nd Edition (2010).

Dr. Turner has spoken before two FDA advisory committees on cardiovascular safety issues, given numerous presentations at international conferences and written many articles on topics within the field of integrated cardiac safety. He has published 60 peer-reviewed papers, and is a Senior Fellow, Center for Medicine in the Public Interest, and an Affiliate Clinical Associate Professor at the University of Florida College of Pharmacy.
References


