

---

# Transform Your Drug and Device Safety Data & Adjudication Processes with Technology

---

## Table of Contents

---

Transform your Drug and Device Safety Data & Adjudication Processes with Technology	3
The Rise of Clinical Endpoints Committees	3
A Brief History	4
The Perils of Paper	5
Process Makes Perfect	5
The Digital Solution	6
References	9

## Transform your Drug and Device Safety Data & Adjudication Processes with Technology

How do you decide when a patient in a clinical trial has suffered an internal bleed or in another situation a heart attack? The answer to this question has historically been surprisingly elusive.<sup>1</sup>

Research shows that clinical site investigators often differ significantly in their interpretation of even the most common of clinical events.<sup>2</sup> This is especially the case when clinical endpoints are subjective, image-based, or complex to assess. Examples of such endpoints include: cardiovascular events; pain, fatigue and depression; neurological scans; genetic information; incidence of infection or disease; disease severity and progression; and determination of cause of death.<sup>3</sup> A number of studies have documented that disagreement between investigators in the interpretation of endpoint data can run as high as 10%.<sup>4</sup>

The ramifications can be serious: the larger the variation in clinical event data, the more difficult it is to identify treatment effects<sup>5</sup>. Inconsistent event data can jeopardize drug and device safety evaluations and significantly delay or even imperil regulatory approval of new drugs and medical devices.<sup>6</sup> Delays are costly—each additional month on a trial can cost hundreds of thousands of dollars.<sup>7</sup> And keeping clinical trial costs in check is a top priority for most sponsors at a time when political pressure is growing to make healthcare and medicines more affordable and accessible.<sup>8</sup>

**Integrated, flexible cloud platforms can streamline your clinical endpoint adjudication process, cutting costs, improving data quality, smoothing regulatory approval and speeding time to market.**

## The Rise of Clinical Endpoints Committees

One major hurdle to consistency of endpoint interpretation is a shortage of standard clinical endpoint definitions due to differences in medical training, geographical variation in disease management and the availability of diagnostic tests. Bias can also derail assessments, as the head investigator on a clinical trial is often the treating physician, and may have preconceived ideas about the patient's health and care.<sup>9</sup> Large multi-country and multi-center studies present the greatest risk, as the highest numbers of medical opinions come into play.

To remedy this problem and deliver consistent, reliable results to regulators, clinical research organizations, including Contract Research Organizations, Pharmaceutical Sponsors and Medical Device companies, are increasingly relying on Clinical Endpoints Committees (CEC), also known as Endpoint Adjudication Committees (EAC) or Data Monitoring Committees (DMC). These teams of expert clinicians are tasked with providing independent, blinded evaluation of suspected clinical events reported by site investigators.

Today, certain therapeutic categories actually require<sup>10</sup> the use of CECs to secure U.S. Food and Drug Administration (FDA) or European Medicines Agency (EMA) approval for drugs and devices, including cardiovascular, nephrology, endocrinology, gastroenterology, infectious diseases, oncology, pediatrics, and respiratory medicine. Where CECs are not mandated, they are often recommended for smoother regulatory approval: the use of CECs has been included in guidance from FDA, the Pharmaceuticals and Medical Devices Agency (PMDA), and the EMA, in the interests of greater risk-benefit balance and reduced variability in endpoint outcomes.<sup>11,12</sup>

But managing CECs can present cost and resource burdens as well as compliance challenges for drug and device makers and research organizations. Some small and mid-sized research organizations still rely on outmoded, laborious methods such as paper, Excel and fax to collect and redact patient documents for privacy, route these documents to the right physician experts for adjudication, collect their decisions and make the requisite adjustments to their clinical trials. But most large research groups now use technology to help streamline this process, which is far more efficient and cost effective. At the cutting edge, cloud-based platforms that are integrated with electronic data capture (EDC) systems, such as Medidata Adjudicate, offer single sign-on, flexible workflows, self-configuration and real-time data management.

## A Brief History

Clinical Endpoint Committees first came into regular use in randomized clinical trials in the 1990s.<sup>13</sup> They were conceived by former FDA commissioner, cardiologist and Duke University professor of cardiology, Robert Califf, M.D. together with Kenneth Mahaffey, M.D., a former member of Duke's faculty in the division of cardiology and currently Vice Chair of Clinical Research in the Department of Medicine at Stanford University. Califf and Mahaffey conceived CEC as a way to verify the accuracy of clinical outcomes reported in randomized clinical trials.

The FDA Center for Drug Evaluation and Research now defines endpoint adjudication as a process of interpretation of clinical source data to reach a qualitative or quantitative conclusion. FDA admits in its manual of policies and procedures that many types of clinical source data require little or no interpretation after collection, but other clinical source data types demand detailed interpretation by expert clinicians in order to reach reliable endpoint values.<sup>14</sup>

In the early years, a CEC was conducted exclusively on paper and focused on cardiovascular trials. Device and biopharma sponsors relied on site investigators to inform them about events. One of the first studies to use CEC was the Valsartan in Acute Myocardial Infarction Trial (VALIANT) trial, which recorded a total of 1,700 myocardial infarctions (MI) in 14,703 high-risk patients,<sup>15</sup> events that were recorded entirely on paper.

By the 2000s, CECs were beginning to incorporate electronic medical records into adjudication in addition to paper processes, and the number of therapeutic categories using CEC began to expand beyond cardiovascular trials. CEC committees also began to examine and adjudicate not just investigator-identified events, but ancillary data as well, including laboratory results, symptoms, and medical procedures. In some cases, regulators would request retrospective adjudication, though these could be time consuming and cumbersome to complete. Medical experts also began to create standard event definitions, which continue to evolve.<sup>16</sup>

For example, until recently, there were several sets of definitions available just for “bleeding.” To account for this, some studies would include several bleeding definitions that could be applied to an endpoint. But an international expert group, the Bleeding Academic Research Consortium (BARC), recently developed the BARC standardized bleeding criteria, which are now widely accepted. The definition of myocardial infarction (MI) has also been updated several times by the Universal Definitions expert group and an expert committee led by the FDA, who recently jointly published a suggestion on endpoint definitions for the most important cardiovascular events, which is now becoming a standard.<sup>17</sup>

Over the past two decades, the work of adjudication has also increasingly become automated via technology platforms<sup>18</sup> with an emphasis on data security and integrity. Pharmaceutical and device clinical research organizations, CROs, and technology providers have also begun to design more efficient methodologies for the electronic triggering of endpoints in order to reduce noise and redundancy in the data.<sup>19</sup>

## The Perils of Paper

Today, some smaller pharmaceutical and device companies, continue to use a paper-based approach to CEC, but this carries significant time, cost, and resource burdens and raises the risk of errors and regulatory issues.

Medidata operational advisor, Lauren Price, who used to work as a CEC coordinator with the Duke Clinical Research Institute, the largest CEC organization in the world, recalls that when research organizations began migrating to an electronic adjudication platform, this translated into a massive savings of time for CECs. In the days when paper was the principal method of adjudication, she would physically carry her adjudication folders up in the elevator to the offices of the assigned physicians, put them on their desks with post-it notes and then retrieve the paper forms when they were done. She would then manually enter all of the information from these documents. When the process moved online to an electronic platform, this whole ordeal—which could take hours per endpoint—was automated. No more elevators. No more post-it notes. No more manual data entry.

But just upgrading from hand delivery of data to mail or email presents its own set of problems. Email is not a secure means of transferring sensitive protected health information (PHI), nor does it allow you to track the full chain of custody. Documents can also get lost or misplaced when they are delivered by mail, causing extra work for sites. A secure cloud-based platform that is integrated with an EDC and provides redaction tools is the most secure approach.

## Process Makes Perfect

Clinical endpoint adjudication is a labor-intensive, multi-step process. [See Figure 1] The first step is to receive and validate all the endpoint data that need to be adjudicated. The average number of endpoints in a typical Phase III protocol jumped from 7 to 13 between 2005 and 2015, while the total data points collected per trial doubled to almost one million.<sup>20</sup> Adjudicating a single endpoint typically entails evaluating several pieces of data, for instance, a neurology scan, an echocardiogram, and a genetic test. The best ways to facilitate collection of all of this data include electronic data capture systems and automated data checks routed to a centralized portal.

The second step, usually conducted by a CEC coordinator, is to assemble a dossier of data on each patient and distribute these dossiers, either as paper copies or electronically, to individual expert physicians or to a CEC. The specialist physicians then review the dossiers, complete their assessment, and return that assessment to the coordinating center. When more than one committee member reviews each subject’s data, these reviews are compared. If the reviews do not match, a third reviewer or committee chairman makes a tiebreaker assessment. The committee may also meet in person or via teleconference to discuss and adjudicate each case together. Once a final call has been made on a trial subject’s status, the adjudicated endpoint is incorporated into the database.<sup>21</sup>

Common oversights in the data collection process include inconsistent, erroneous or missing exam dates, missing signatures, illegible data and missing source data.<sup>22</sup> Un-redacted or partially redacted PHI on images is also a particular challenge, given the complexity of these data objects and the flexibility of Digital Imaging and Communications in Medicine (DICOM) standards. But the sharing of images that still contain PHI can result in costly and time-consuming queries that delay a trial and leave a clinical research organization liable for noncompliance with privacy regulations.

**Figure 1: Common Adjudication Process Flow**



## The Digital Solution

It is widely believed by the clinical trials industry that electronic processing is the most efficient and reliable way to manage the adjudication process. In 2016, a joint industry-regulator body known The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), recommended that clinical research partners turn to digital solutions to streamline and safeguard adjudication processes. The 2016 ICH-E6 Addendum Guidelines (Section 5.0 on Quality), which outline good industry practices, specifically supports the use of an eAdjudication platform rather than traditional models, especially when evaluating, controlling, communicating, reviewing, and reporting risk in endpoint adjudication project management.<sup>23</sup>

Two key features of digital platforms significantly drive efficiency and data quality improvements: cloud-based access and integration with electronic data capture (EDC) with a single sign-on. A cloud-based platform allows adjudication committee members anywhere around the world to securely and efficiently review clinical event dossiers, in real time, without the need to download or install software to view documents and images. All they need is Internet access. This reduces the time to complete event reviews and mitigates the risk of delays.<sup>24</sup>

Integration with EDC also reduces errors related to data entry, eliminates the need for reconciliation between sets of documents, and enables process controls and early warnings.<sup>25</sup> When data collection, de-identification, dossier aggregation, adjudicator assessments and CEC management all happen in one place, sponsors and regulators can easily evaluate site performance, run QC on the adjudication process, and compare individual adjudicators to their peer group within and across protocols.<sup>26</sup> Individuals managing the CEC process and Adjudicators also benefit from integrated display of source documents and images, automated committee worklists, the ability to generate queries within the system directly to trial sites and proactive reminders and alerts. These features can save a trial weeks or, for trials with thousands of endpoints, up to months.

## Benefits of Integrating Adjudication Management with EDC

Reduces errors related to data entry	Eliminates the need for reconciliation between sets of documents
Enables process controls and early warnings	Provides easier evaluation of site performance
Active QC on the adjudication process	Provides comparison between individual adjudicators to their peer group within and across protocols
Displays source documents and images	Automates committee worklist
Generates queries within the system directly to trial sites and	Provides proactive reminders and alerts

Features such as self-configuration, flexible workflows, built-in quality control and real-time visibility also drive significant time and cost savings and data quality improvements. Self-configuration gives organizations the ability to adjust and optimize timelines, data collection and quality control processes, the organization of documents and images, as well as the formats in which data is presented to the CEC for each clinical trial.

Flexible workflows accommodate sets of data and adjudication processes, which differ from one trial to the next. One study may use a definition of a myocardial infarction that requires an EKG, cardiac enzymes data and a discharge summary. Its adjudication process may require the evaluation of two individual independent reviewers, with a third called in to make the final call if they disagree. An oncology trial, meanwhile, may require the evaluation of five weeks of tumor scans by a committee of four experienced oncologists who need to reach a consensus. Each workflow will look different based on the documents that need to be collected and the physicians to whom they need to be routed.

To further reduce errors and speed regulatory approval, integrated platforms should provide built-in quality control systems that can facilitate audits of communications between physicians and trial managers, with notes tracking every query and step of the decision-making process.<sup>27</sup> Real-time visibility features give biopharmaceutical and device companies and CROs a timeline that maps each clinical endpoint's journey through the adjudication process, preventing delays and missed events, which can generate compliance concerns. The real-time model also allows sponsors to terminate a trial as soon as they have sufficient endpoints adjudicated to analyze their trial for efficacy, potentially saving weeks of time and associated costs.

Ultimately, the best adjudication platform is also user-friendly and intuitive for all key stakeholders, including sites that are uploading data as well as the event committee members performing the assessments. A web-based pdf editor may facilitate the creation of dossiers, including easy PHI masking, labeling, bookmark creation and organization of dossier elements.

As with many other areas of clinical research, innovative new technologies, including Medidata Adjudicate—when combined with scientific and medical expertise—can vastly improve the quality and cost-effectiveness of medicines and medical devices that patients need most.

## About Medidata Adjudicate

Medidata Adjudicate is a cloud-based end-to-end platform, designed to support investigator sites, CROs, data managers, the Clinical Event Committee (CEC) and sponsors who collect, manage, organize, adjudicate and submit clinical endpoint data. Easily configurable modules enable quick set up to manage all endpoint adjudication with a built-in web-based pdf editor to create dossiers, including easy PHI masking, labeling, bookmark creation and organization of dossier elements. Self service configuration puts the control in your hands for quicker study implementation. Medidata Adjudicate is part of the Medidata Unified Platform Solution making Medidata your one-stop solution for all your clinical trial technology needs.

Learn more about Medidata Adjudicate on our website:

<https://www.medidata.com/en/clinical-trial-products/clinical-operations/clinical-adjudication>



## References

1. Claes Held, "When do we need clinical endpoint adjudication in clinical trials?" Ups J Med Sci. 2019 Jan; 124(1): 42–45
2. Michael O’Riordan, "Site Investigators Missed Clinical Events in GLOBAL LEADERS Getting accurate event adjudication is a problem for pragmatic trials; investigators for the GLASSY substudy have suggestions," tctmd, Feb. 12, 2021: <https://www.tctmd.com/news/site-investigators-missed-clinical-events-global-leaders>
3. Tracy L. Nolen, "A web-based endpoint adjudication system (WebEAS) for interim analyses in clinical trials," Clin Trials. 2009 Feb; 6(1): 60–66.
4. Nolen T, Dimmick B, Ostrosky-Zeichner L, et al. "A web-based endpoint adjudication system (WebEAS) for interim analyses in clinical trials." Clin Trials. 2009;6(1):60–6.; Mahaffey K, Harrington R, Akkerhuis M, et al. "Disagreements between central clinical events committee and site investigator assessments of myocardial infarction end-points in an international clinical trial: review of the PURSUIT study." Curr Control Trials Cardiovasc Med. 2001;2:187–94.
5. Scott R. Evans, "Fundamentals of Clinical Trial Design," J Exp Stroke Transl Med. 2010 Jan 1; 3(1): 19–27.
6. "Which clinical trials need a Clinical Endpoint Adjudication Committee," George Clinical, Jan. 8, 2017: <https://www.georgeclinical.com/resources/research/clinical-trials-need-clinical-endpoint-adjudication-committee>
7. "Clinical trials and their patients: The rising costs and how to stem the loss," Pharmafile, march 11, 2016: <http://www.pharmafile.com/news/511225/clinical-trials-and-their-patients-rising-costs-and-how-stem-loss>
8. "Meeting the demand for lower drug prices in Medicare," National Committee to Preserve Social security and Medicare, June 2021: <https://www.ncpssm.org/documents/medicare-policy-papers/meeting-demand-for-lower-drug-prices-in-medicare/>
9. Pardeep Jhund, "Adjudication in Clinical Trials: A primer," Journal for Clinical Studies, Mar4, 2019, Vol. 11, Issue 1.
10. Pardeep Jhund, "Adjudication in Clinical Trials: A primer," Journal for Clinical Studies, Mar4, 2019, Vol. 11, Issue 1.
11. "CECs: What Are They and Why Does Your Trial Need One?," Premier Research, June 27, 2017. <https://premier-research.com/perspectives-clinical-endpoint-committees-trial-needs-one/>
12. "CECs: What Are They and Why Does Your Trial Need One?," Premier Research, June 27, 2017. <https://premier-research.com/perspectives-clinical-endpoint-committees-trial-needs-one/>
13. Renato D. Lopes and Matt Wilson, "Clinical Events Classification Past Present and Future," Clinical Leader, June 5, 2018: <https://www.clinicalleader.com/doc/clinical-events-classification-past-present-and-future-0001>

14. "The use of clinical source data in the review of marketing applications," Center for Drug Evaluation and Research, 2010 Manual of policies and procedures: <https://www.fda.gov/files/about%20fda/published/The-Use-of-Clinical-Source-Data-in-the-Review-of-Marketing-Applications.pdf>
15. Renato D. Lopes and Matt Wilson, "Clinical Events Classification Past Present and Future," Clinical Leader, June 5, 2018: <https://www.clinicalleader.com/doc/clinical-events-classification-past-present-and-future-0001>
16. Renato D. Lopes and Matt Wilson, "Clinical Events Classification Past Present and Future," Clinical Leader, June 5, 2018: <https://www.clinicalleader.com/doc/clinical-events-classification-past-present-and-future-0001>
17. Claes Held, "When do we need clinical endpoint adjudication in clinical trials?" Ups J Med Sci. 2019 Jan; 124(1): 42–45.
18. Jane Aziz, "Experience from creating electronic systems with generic endpoint review and adjudication flows," Trials volume 16, Article number: 061 (2015).
19. Renato D. Lopes and Matt Wilson, "Clinical Events Classification Past Present and Future," Clinical Leader, June 5, 2018: <https://www.clinicalleader.com/doc/clinical-events-classification-past-present-and-future-0001>
20. Ken Getz, "Industry Practices that Benefit/Will Benefit by Patient Engagement," Tufts Center for the Study of Drug Development, October 2017: <https://www.fda.gov/media/108077/download>
21. Tracy L. Nolen, "A web-based endpoint adjudication system (WebEAS) for interim analyses in clinical trials," Clin Trials. 2009 Feb; 6(1): 60–66.
22. Elizabeth Tolmie, "Clinical Trials: Minimising source data queries to streamline endpoint adjudication in a large multi-national trial," May 6, 2011, Trials volume 12, Article number: 112 (2011)
23. Moe Alsumidaie, "Endpoint Adjudication and the ICH E6," Applied Clinical Trials, May 24, 2017: <https://www.appliedclinicaltrials.com/view/endpoint-adjudication-and-ich-e6> ; "E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) Guidance for Industry," U.S. Department of Health and Human Services Food and Drug Administration, Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER), Mar. 2018 procedural.
24. Dan Gebow, "Transforming Clinical Trial Adjudication in the Era of COVID-19," Applied Clinical Trials, May 6, 2021: <https://www.appliedclinicaltrials.com/view/transforming-clinical-event-adjudication-in-the-era-of-covid-19>
25. Dan Gebow, "Transforming Clinical Trial Adjudication in the Era of COVID-19," Applied Clinical Trials, May 6, 2021: <https://www.appliedclinicaltrials.com/view/transforming-clinical-event-adjudication-in-the-era-of-covid-19>
26. Pardeep Jhund, "Adjudication in Clinical Trials: A primer," Journal for Clinical Studies, Mar4, 2019, Vol. 11, Issue 1.
27. Pardeep Jhund, "Adjudication in Clinical Trials: A primer," Journal for Clinical Studies, Mar4, 2019, Vol. 11, Issue 1.