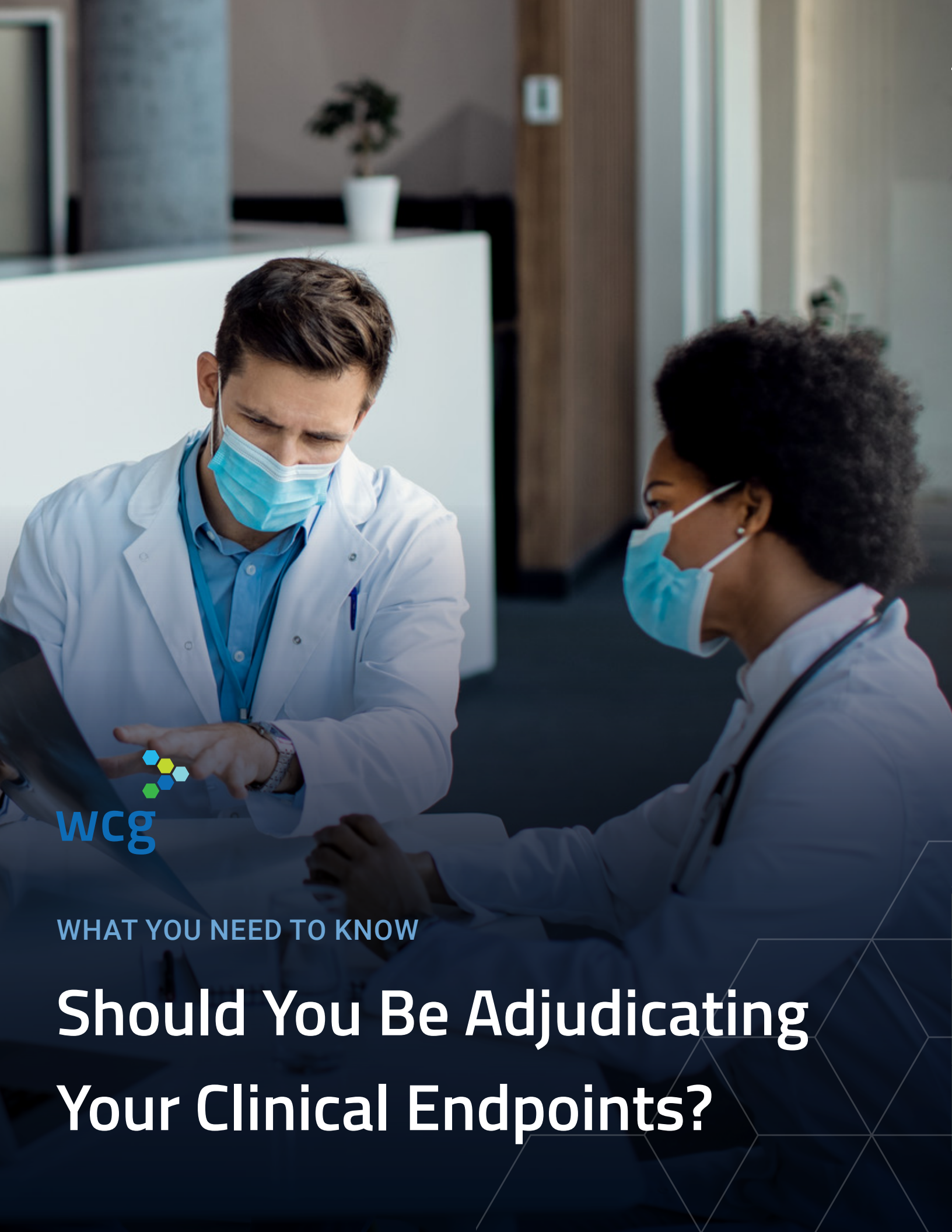

WHAT YOU NEED TO KNOW

Should You Be Adjudicating Your Clinical Endpoints?

Clinical endpoint adjudication plays a critical role in many large clinical trials, supporting the consistency and accuracy of study results. As science advances, we must navigate new indications, new diseases, new conditions and new medicines, leaving us with endpoints that are often imprecise.

But when are clinical Endpoint Adjudication Committees (EACs) most beneficial in a clinical trial?

Know When to Deploy an EAC

Subjective endpoints, such as "asthma exacerbation," most certainly demand the rigorous classification offered through adjudication. The risk of variation is too high and too costly. These costs can include, at a minimum, additional site and statistical resources needed to mitigate this unexpected variability. At worst, too much variability in the endpoint can threaten or even invalidate an entire clinical trial.

Other examples include studies...

- with complex endpoints;
- where the endpoint is syndromic;
- that cannot be blinded (e.g., medical device trials)
- with high enrollment or long duration;
- being conducted in different locales with varying clinical practices;
- in which the endpoints of interest fall outside the investigator's expertise.

In such circumstances, adjudication can ensure precision and give the scientific community some certainty about what's being reported.

More Regulatory Certainty

Sponsors can leverage endpoint adjudication to establish greater regulatory certainty. Deployed correctly, endpoint adjudication bolsters regulatory strategy prior to submission, which can streamline the process and lower cost-to-market.

Sometimes, Endpoint Adjudication Committees must be set up quickly. Such was the case with a mid-tier biopharma client.

Our client received an FDA request that required rapid adjudication results, so they turned to WCG. The project required urgent review of available materials, convening a panel of drug-induced liver injury (DILI) experts and creating a DILI adjudication database. It also involved developing a charter that would cover three protocols in three unique situations: the ongoing study, locked retrospective studies, and a group of patients who had already been adjudicated by previous experts (under no charter), with the ability to incorporate those results in the new process.

WCG accomplished all of this before deadline. It set up the committee and achieved all the deliverables within 11 days. Within a few weeks, the committee adjudicated 400 endpoints.

Retrospective Adjudication on Tight Deadline

We're seeing a trend toward greater use of adjudication in post-marketing evaluation. In this example, WCG helped a client with retrospective adjudication in support of a drug targeting menopausal vasomotor symptoms.

A few months before its NDA submission, our client received guidance to adjudicate endpoints in order to satisfy regulatory requirements. The sponsor turned to WCG to expand adjudication to include all cardiovascular, neurological and thrombotic events of interest while maintaining the original submission timelines. That left less than four months to adjudicate all events.

WCG rapidly devised a rigorous adjudication plan that included a triage system allowing for both the swift processing of low probability cases and a full endpoint adjudication process for others. The two separate committees were contracted, trained, and voting within two weeks, and the client stayed on schedule.

Black Box Removed: Post-Approval Adjudication

In another retrospective analysis, we helped our client obtain a labeling change that made a tremendous difference in revenue—far more than the cost of external review.

With a black box warning, our biopharma

client risked losing its massive investment in an important new therapy. Its therapy was similar to others in its class, but its safety profile showed a significantly greater incidence of adverse cardio events compared to some competitors. For this reason, the FDA required a black-box warning. The client needed to understand what was going on with the safety data, and turned to WCG.

The therapeutic had been acquired several times. WCG determined that each time a new company bought the drug, the FDA changed the reporting requirements for adverse cardiovascular events. The challenge: Identify what really constituted a cardiovascular event during the study.

The WCG-convened adjudication committee did just that. It discovered that the incidence of cardiovascular events was much lower than originally reported. Upon reviewing the data, the FDA granted a label change, removing the black box.

A Fluid Landscape

These examples help illustrate that sometimes, establishing an Endpoint Adjudication

Committee is not merely cost efficient, but essential. We're seeing a move toward fewer events across a much broader range of therapeutic areas, such as rare disease and oncology trials. We perform adjudication across dozens of therapeutic areas, and that list will continue to expand.[1]

Another issue is of particular concern to CNS trials. *Any* trial medication that crosses the blood-brain barrier is at risk for abuse. That applies to an array of novel therapeutics in the pipeline—not just opioids. Endpoint Adjudication Committees need to be able to identify potentially abuse-related events not already classified as an adverse event or drug accountability discrepancy. An FDA guidance from 2017 states, *"All clinical safety and efficacy studies should be evaluated for CNS-related AEs that may suggest the test drug produces effects that will be sought out for abuse purposes."*

The landscape continues to shift, and new AI-based approaches using registry data may soon change how sponsors and regulators approach adjudication.[2] So the answer to the question, "When is implementing an EAC cost effective?" continues to change as well.

But determining *when* an EAC is needed is only the beginning.

Best Practices

Sponsors sometimes fail to realize just what's involved in creating EACs—building the technology, crafting an effective charter, defining criteria for the endpoints in question, finding the experts, and more.

It's a heavy lift, and requires the right people, processes and technology to do this effectively. Why not take it inhouse or leave it to the CRO? Because aside from the operational challenges, there's the potential for bias or merely the perception of bias. Having an independent specialty provider manage adjudication mitigates bias and reduces the perception of bias. Sponsors need an arms-length relationship with committees and committee members.

Another important question to answer: "How will EAC members be chosen, compensated and trained?"

Creating the charter—which helps ensure the most efficient and highest quality reporting of trial outcomes—is another crucial part of EACs. Here are just a few of the elements that must be included:

- descriptions and definitions of the endpoints to be adjudicated;
- methods for the identification of events to be adjudicated;
- quality assurance methods; and
- committee member qualifications.[3]

And then there's managing the data, which requires the right technology platform. What type of data do your adjudicators need? Will they have direct EHR access? If not, how will

they access the patient case data?

It's a major undertaking, and most sponsors will need a trusted partner.

Moving Forward with Confidence

Successful endpoint adjudication demands expertise—the right people, the processes and technology.

Our global worldwide network of over 950 medical, statistical, safety and research professionals possess the subject-matter expertise and the EAC experience to independently assess and advise on trial endpoints. They are subject-matter experts who fully understand an EAC's operational processes. That means we don't waste valuable time bringing them up to speed.

We also have the technology. In fact, we created it. Our AIMS® (Adjudication Information Management System) web-based platform allows committee members to review packaged clinical trial event data and provide their assessment seamlessly through a single interface. Our MADDERS® (Misuse, Abuse, and Diversion Drug Event Reporting System) fills the need for standardized approaches to quantifying potential abuse in clinical trials.

By leveraging our global network of experts, internal expertise and proprietary technology, sponsors have access to robust endpoint adjudication solutions, spanning all therapeutic areas, indications and modalities.

Does your study need endpoint adjudication? We can help you make the determination. If you decide to move forward, we can help ensure your success.

To speak with your experts about an Endpoint Adjudication Committee for your trial, fill out this form and someone will be in touch.

FILL OUT THE FORM

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3. Seltzer JH, et al. "Use of endpoint adjudication to improve the quality and validity of endpoint assessment for medical device development and post marketing evaluation: Rationale and best practices. A report from the cardiac safety research consortium." Am Heart J. 2017 Aug; 190:76-85.