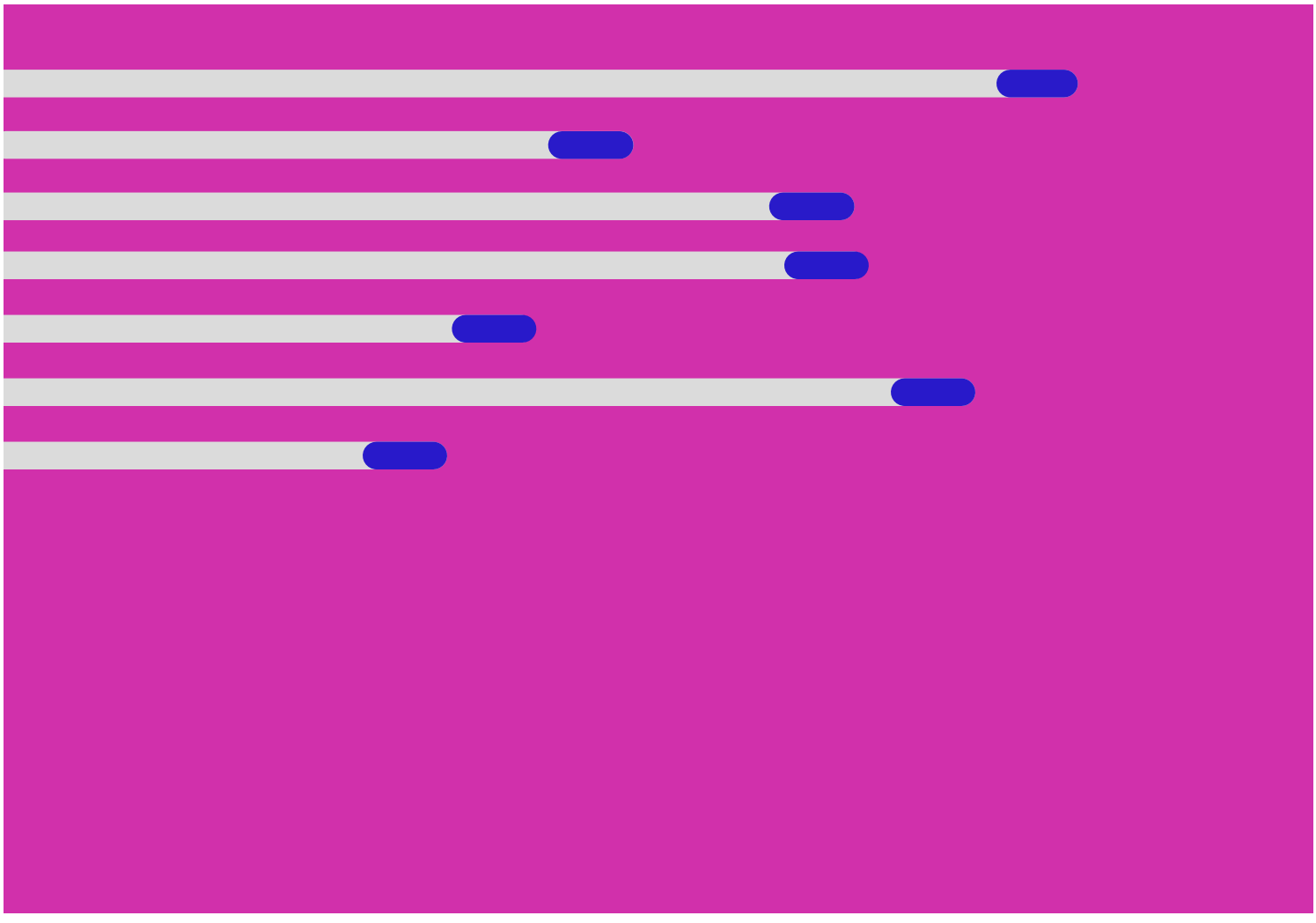
The Expanding Need for End-Point Adjudication



Endpoint adjudication is nothing new. Sponsors often turn to endpoint adjudication committees (EACs) for large, complex studies, but they aren't limited to large trials anymore. Many other factors need to be considered when determining the need for an adjudication committee.

In recent years, we've seen a growing trend to leverage EACs in new ways. The goal, however, remains the same: to reduce bias and increase accuracy of clinical trials.

One of the best arguments for an EAC is that clinical trials are growing more complex. Consider the following findings from Tufts CSDD Impact Report[1]:

- The number of endpoints for Phase II and Phase III protocols grew 27% since 2009.
- Phase III trials collect, on average, three times more data than in 2009.
- The mean number of distinct Phase II and Phase III protocol procedures increased 44% since 2009.

POST-MARKETING ADJUDICATION

While EACs typically focus on prospective review of clinical trial data, thoughtful retrospective adjudication during the postmarketing phase gives sponsors valuable insights and provides regulatory certainty.

- **Retrospective adjudication to ensure accurate characterizations:** According to our internal data, up to 30% of cases show discordance between site investigators and adjudicators. Sponsors, therefore, would be wise to take a second look. In one instance, retrospective adjudication helped one of our clients obtain a post-marketing labeling change by more accurately identifying what constituted a cardiovascular event during the study. The EAC discovered that the incidence of cardiovascular events was much lower than originally reported. The FDA reviewed the data and granted a label change.
- **Adjudicating real-world data:** Sponsors, with the encouragement of regulatory bodies, are increasingly supplementing trial data with real world-data. This yields important new insights, but it also poses challenges. Real world findings use completely different data sources than clinical trials and, hence, may give different results. Applying endpoint adjudication to real world studies enhances the rigor of their findings and provides diagnostic clarity. In fact, we believe it will be essential to

understanding the long-term safety and efficacy of therapeutics, especially those that have been authorized quickly.

ENSURING CV SAFETY IN ONCOLOGY DRUG DEVELOPMENT

In recent years, it's become clear that some emerging cancer therapies may have a deleterious impact on cardiovascular health, leading to cardiac AEs [2, 3]. At the same time, because cancer mortality rates have plunged, the survivor population is aging, which itself increases cardiovascular risk.

So how do you determine if cardiovascular events are secondary to an aging, at-risk, population or directly related to the cancer therapy, many of which have known potential cardiotoxicities? It's essential to identify the actual cardiotoxicity – something many trials still fail to do adequately. Regulatory bodies have encouraged endpoint adjudication in in similar circumstances[4]. We need more precision about cardiovascular events for patients in oncology trials, and dedicated adjudication of cardiovascular events can provide that precision.

MORE CLARITY AROUND INFECTIOUS DISEASE

Given the current confusion between clinical cure and the various diagnostic modalities, endpoint adjudication can be quite helpful in providing clarity. For instance, infectious disease practitioners may use clinical cure and others may use PCR evidence to define "cure." In trials where similar PCR modalities may not be available, criteria for "clinical cure" may be a reasonable target for adjudication.

BEYOND ENDPOINTS: ELIGIBILITY ADJUDICATION

Adjudication is increasingly important in therapeutic areas with complex inclusion/exclusion criteria. Eligibility is often based on factors that require medical expertise, such as disease progression, comorbidities, symptoms, severity, etc.

An eligibility adjudication committee would adjudicate specific inclusion or exclusion criteria during the screening process, drawing on available medical history, lab results, and information from the investigator. Perhaps even more than other types of adjudication, eligibility adjudication requires timely turnaround to avoid delays in enrollment.

Eligibility adjudication committees can be particularly useful in rare disease trials precisely because the disease is rare: There's a lack of data from which standardized decisions can be made. Adjudication is a useful tool when such standards do not exist.

CNS: ACCOUNTING FOR ABUSE POTENTIAL

EACs can also be deployed to identify potential abuse-related events—something the FDA requires. According to 2017 FDA guidance, "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."

Any trial medication – not just opioids — that crosses the blood-brain barrier is at risk for abuse. It's therefore crucial to determine whether events are attributable to non-medical use of study medication or are merely falsepositive signals.

BETTER STRATEGY THROUGH ADJUDICATION

Deployed correctly, endpoint adjudication can bolster regulatory and commercial strategy prior to submission, which can streamline the process and lower the cost-to-market.

WCG specializes in endpoint adjudication committees, leveraging our global network of 1,000+ experts, internal process expertise and proprietary technology to provide the strategic guidance sponsors need.

And no, not every study requires independent endpoint adjudication, but many do—more than most sponsors realize.

To speak with one of our experts to help determine if your trial needs endpoint adjudication, complete this form and someone will be in touch.

REFERENCES

1. Tufts CSDD Impact Report; volume 23 Number 1 • January/February 2021
2. iBarac, A., Murtagh, G., et al. S. (2015). "Cardiovascular Health of Patients with Cancer and Cancer Survivors: A Roadmap to the Next Level." Journal of the American College of Cardiology, 65(25), 2739–2746. doi:10.1016/j.jacc.2015.04.059
3. Pettit, S.D., & Kirch, R.A. (2018). "Do current approaches to assessing therapy related adverse events align with the needs of long-term cancer patients and survivors?" Cardio-Oncology, 4, 1-16.
4. Seltzer JH, Gintant G, Amiri-Kordestani L, et al. Assessing cardiac safety in oncology drug development. American Heart Journal. 2019;214:125-133. doi:10.1016/j.ahj.2019.04.010

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