Advances in Oncology Extend Lives, but Lead to New Safety Considerations for Sponsors and Investigators

Jonathan Seltzer, MD, MBA, MA, FACC, Chief Scientific Officer, WCG ACI Clinical
James A. Bannon, PharmD, President Scientific & Regulatory Review Division
Angela K. Pitwood, MBA, Vice President, WCG Vigilare
Steven Beales, Senior Vice President, Safety Solutions, Scientific and Regulatory Review, WCG

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From cardiovascular adverse events to complex dosing regimens, oncology trials present unique safety-related considerations. Left unaddressed, they could undermine a trial or put patient safety at risk. In this paper, we discuss some of those issues and how sponsors can best address them.

Does the data suggest a causal relationship between the drug and an adverse event (AE)? This is never an easy question in any trial, but with oncology—and especially in terms of immuno-oncology therapies—it presents a unique set of challenges.

Here are just a handful of the considerations that come in to play:

Sicker patients: Perhaps the most obvious starting place is the patient. Generally, it's the sickest cancer patients who participate in trials—patients who have few alternatives and are hoping for the next big breakthrough.

Polypharmacy and comorbidities: These patients likely have multiple comorbidities and could be on an array of medications for those conditions. Also, chances are, they're already on chemotherapy. Now, you're adding a new drug to the mix. All of this makes it harder to discern which safety issues are attributable to the investigational therapy and which are related to other medications, other conditions—or to the cancer progression itself.

Dosing: Sometimes, the investigational medication is given in cycles. Sometimes it's a pill, other times multiple injections. Compounding that, there are often several drugs within the actual protocol you're trying to study. The simple tasks of recording and collecting information on dosing can become complex.

Underlying all of this is the potential toxicity of the investigational treatments themselves. Research has extended the lives of patients. But as potential treatments enter the pipeline and the number of survivors grows, new safety concerns are emerging.

Focus on CV events

In recent years, it's become clear that some emerging cancer therapies may have a deleterious impact on cardiovascular (CV) health, leading to cardiac AEs. [i,ii] Rates of CV adverse events have reportedly topped 30%, and heart disease and other CV issues are leading causes of morbidity and mortality in cancer survivors. [iii, iv, v, vi] Moreover, because cancer mortality rates have plunged, the survivor population is aging, which itself increases cardiovascular risk.

A 2019 paper[vii] from the private/public Cardiac Safety

Research Consortium discusses emerging cardio-oncology considerations and the latest thinking on ways to manage risks. It makes the case for including the cardiology perspective from the beginning to ensure signals of cardiotoxicity are promptly detected, evaluated and shared with clinicians and regulatory authorities. It also calls for including it in the adjudication of cardiovascular events:

> **"the cardiology community should have a central role in developing standardized criteria and definitions for adjudication. Cardiac SAEs in particular should be adjudicated as to whether they are likely to have been primary events that might be attributable to the drug or … to the patient's underlying state of health."**

The role of committees

The complexity of oncology trials makes protocol development especially challenging. Moreover, protocols offer little guidance about serious adverse event reporting. It's probably one of the smaller sections in the protocol—sometimes only a couple of paragraphs. Data monitoring committees (DMCs), also called Data Safety Monitoring Boards (DSMBs), can help assure patient safety and are increasingly standard in oncology trials. DMCs typically include key opinion leaders who focus on aggregate data and trends.

We're also seeing more clients opt for endpoint adjudication committees (EACs) to enhance the quality of key clinical trial endpoints. As noted above, it's not always easy to tell if a cardiovascular or other adverse event is native to the patient due to a different cause. Having an EAC that includes pulmonology, cardiovascular and/or other relevant experts can help distinguish the true cause of the adverse event.

Regardless of what's in that toolbox, you need a plan for how you will use the tools.

It starts with a plan

However, neither a DMC nor an EAC is an oversight committee. They don't do the work of the sponsor and its medical director. That's why a comprehensive, detailed safety management plan is essential for any trial, and especially for oncology.

One thing we've come to realize is that many sponsors

are focused on the product itself and may not understand just how granular the plan needs to be. It must delineate the respective roles, responsibilities, processes and timelines for all safety activities. This is a practical, operational document, not a strategic one. It's particularly important when smaller sponsors outsource activities to multiple CROs and other vendors. Each may manage safety in a different way. With three or four parties involved, the same event could be coded three or four different ways, making it impossible to get a complete, aggregate view of safety data.

All of this requires astute management of adverse event monitoring, analysis and reporting.

But reporting creates its own set of safety challenges.

Overwhelmed and underinformed

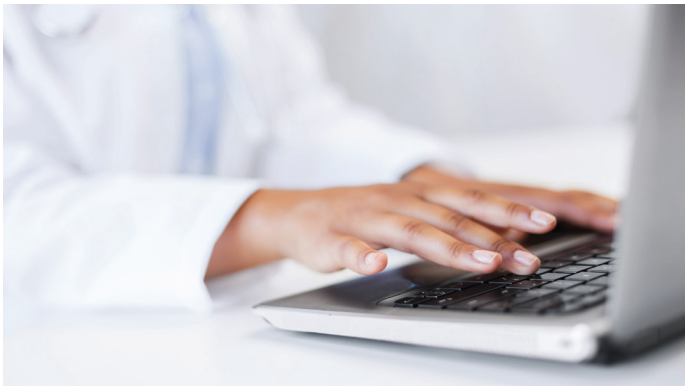
Sponsors and CROs tend to bombard sites with safety notifications, many of which are unnecessary.

Consider this: A patient in an oncology trial experiences angina after receiving an investigational therapeutic and ends up in the ICU. A SUSAR letter must go out. But it's never just one patient: For a large pharmaceutical company or CRO, the scale is enormous—with tens of thousands of notifications distributed each day to dozens of countries. One investigator working on several trials may receive the same notification multiple times.

Compounding this is the lack of global harmonization—perhaps the biggest problem in safety reporting. There are more than 40 different regulatory frameworks for safety reporting worldwide. Many sponsors—especially small and midsized ones— lack the access to the regulatory intelligence needed to be able to follow each country's rules. So being overly cautious, they overdistribute.

Bombarding sites with safety alerts may give the appearance of adhering to the letter of current regulations, but it most certainly violates the intention—which is to keep sites informed of new information that's relevant to the product's safety.

That's not happening.



It's difficult enough to follow a complicated oncology protocol, but then to have unnecessary work on top of it—that's unsustainable. The IRBs, site staff and the investigator should be evaluating these reports to determine the need for protocol revision, informed consent modifications—even whether the trial should continue at all. But overdistribution makes it more difficult. The goal is to alert them to something new and different that's happening. But if the investigators aren't reading the reports and the IRBs aren't reading them, it's as though the alerts were never sent.

When sites receive only the relevant notifications, they can address the safety issues with patients. That's much less likely to happen when the site is bombarded.

Dealing with safety reporting issues has become fragmented, and that's risky for everyone involved.

The need for context

Perhaps more than any other area, oncology needs an integrated approach to safety.

The success of pharmacovigilance efforts—especially in oncology—hinges on the ability to spot risks early, manage them effectively and comply with increasingly complex regulations. But all of that requires context.

Investigators need to understand what the reports mean at the compound level, in context, across protocols. Investigators aren't getting that perspective until the new investigator brochure (IB) arrives—which means the IB raises more questions than it answers. What changed? How do the changes affect the investigator and the site? How should they influence patient selection?

It's incumbent on sponsors and CROs to provide that context by ensuring investigators and site staffs have the tools, insights and data they need. Only then can they ensure that safety is being handled in a controlled, integrated, consistent way.

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