IRB ADVISOR

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Newest Oncology Studies Raise Ethical, Other Questions for IRBs

IRBs must stay on top of study design changes, experts say

By Melinda Young, Author

Clinical research — especially involving oncology trials — is evolving with the introduction of new therapies and therapeutic mechanisms. These raise new and sometimes challenging questions for IRBs reviewing the study protocols.

For instance, some Phase I studies no longer look solely at safety. The new model for some Phase I studies also evaluates efficacy for first-in-human trials, says **Lindsay McNair**, MD, MPH, MSB, WIRB-Copernicus Group chief medical officer in Princeton, NJ.

"It's changing the paradigm, and studies are not just phase one, two, three anymore," she explains. "It's changing the whole process of how we think about drug development."

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Another change is in the characteristics of people recruited for these early-stage cancer trials. The traditional participant was someone who had cancer and who had exhausted their options for available therapies.

"Now, we have therapies that are so promising they're not tested in people who have exhausted all other therapies, and they might be first-line therapy," McNair says. "When do we think we have enough evidence about an investigational product to be comfortable having somebody forgo or delay an approved therapy to take an investigational therapy?"

This is a question each IRB confronting such a study proposal will need to answer — and it's not an easy one from an ethical standpoint.

"There's just a wider variety of early-stage oncology studies happening now, and IRBs have to examine long-held assumptions and [let go of] 'this is the way we have always done it,'" McNair adds.

The clinical trial industry is shifting toward studies that advance personalized medicine. They have new study designs like the basket protocol, in which people with the same genetic mutation in their tumor — regardless of where the tumor is in their body — are placed in the same study arm, she explains.

The study could include people with breast cancer, colon cancer, and prostate cancer. "It's called a basket protocol

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because everyone with the same mutation goes in one basket," McNair says.

"It's not a treatment based on the location of cancer in the body, anymore," she adds.

When presented with these new era protocols to review, IRB members might have a number of questions to consider, including:

- When is there enough scientific evidence to be comfortable going forward with a therapeutic purpose in a Phase I trial?
- When is it appropriate for a cancer patient, who has not received any oncology treatment, to receive an investigational therapy instead of a standard chemotherapy regimen?
- How do IRBs assess risks for patients receiving their first "treatment" in the form of an investigational drug trial?
- How do they assess the weight of science to determine potential benefits of these new study designs?

IRBs that review protocols with new study designs need to make certain they have relevant expertise on their board.

"IRBs need to have people on the board who are comfortable doing that review and comfortable understanding what standard of care is," she says. "They need someone who can help determine the risks of doing something different than standard of care."

WCG has dedicated oncology panels, as well as specialist consultants who can provide assistance when protocols involve rare situations or unusual cancers. WCG also has an advisory board of experts.

"We meet with them, along with IRB chairs, a couple of times a year to talk about what is at the forefront of cancer research," McNair says.

"We talk about what's in discovery now and how research designs are changing," she adds. "We find out what's happening at other institutions, so we can make sure our boards are as prepared as possible for the new research coming through. We've had this board in place for more than three years."

Another issue IRBs might note involves informed consent with studies using new therapies and mechanisms.

"How do we ensure that someone's decision to participate in research is informed when we know that the animal models may not be predictive of risks in humans?" McNair asks. "We don't know very much about long-term risks because some of the mechanisms are so new that we don't know what might happen in 10 to 15 years from now."

Cancer treatments and cures have evolved, and IRBs should think of long-term effects, she notes.

The problem is that answers to study participants' questions about these new cancer trials mostly are unknown. "How do we make sure when people are thinking about participating in a study that they understand how much is unknown, before they make their decision?" she says.

With previous Phase I oncology studies with patients who had exhausted all other options, the chance of their responding to the study drug was pretty low. For people in the first group of a new drug's trial, the study drug dose they'd receive was too low to have therapeutic value, as the goal was to test the drug's safety, McNair explains.

Informed consent could explain this to people before they choose to participate in the study. The saying in the research community was that no one gets better in a Phase I study, and there is no potential personal benefit to participants.

Now, it's difficult to give people an idea of what to expect. There might be little hope of response to a new drug, or it could be a life-extending therapy.

"Now we have these therapies and different kinds of study designs, and we see responses that are better than what's available with some of the approved standard therapies," McNair says. "For example, the response rate in some melanoma studies was better than what was available with approved treatment."

For example, Merck's pembrolizumab (KEYTRUDA) received an FDA breakthrough therapy designation for advanced melanoma. The overall response rate in a Phase 1b trial, of 2mg/kg dose among 89 patients, was 24%, according to a 2014 media release from Merck. The drug was available to patients before Phase II and III trials began.

The success of novel studies like these can be confusing to people, and it's up to IRBs to ensure the informed consent process provides some clarity about the purpose of research and what to expect.

"We have a long way to go in terms of the general public understanding — and, sometimes, our researchers understanding — that clinical research is designed to develop generalizable data to move forward to new therapies," McNair says. "It's not designed to find optimal treatment for individuals in a study." ■