Proposed centralization of trial oversight stirs mixed reaction

Over the last two decades, scientists have increasingly followed the mantra that "bigger is better" when planning drug trials. Large, multisite trials have become staples of clinical investigation, enabling wider enrollment and more statistically meaningful research results.

But, as the number of participating sites per study has grown, so has the administrative red tape. And, nowadays, dozens of local ethics committees—known as institutional review boards (IRBs)—are commonly involved in approving multisite studies, routinely suggesting changes to protocols and consent forms that then need to be reapproved by all the other parties involved. As a result, trials can take months to launch, delaying progress, and meaning that study participants don't benefit from the oversight of one central committee with ultimate responsibility for the research.

The current system "is time consuming and slows research," says Kathy Hudson, deputy director for science, outreach and policy at the US National Institutes of Health (NIH) in Bethesda, Maryland. "It also may introduce vulnerability for subjects, because if there are many, many IRBs involved, does any single IRB feel like they have the real responsibility to examine the risks and benefits to research participants in exquisite detail?"

To remedy the situation, on 22 July the NIH's parent agency, the Department of Health and Human Services (HHS), proposed that multisite studies conducted in the US should each be overseen by a single IRB for that study. Under the proposal—made as part of a sweeping overhaul to the Common Rule, the 1991 regulation that governs human research funded by 17 federal agencies, including HHS—this centralized IRB would approve protocols on behalf of all institutions involved and oversee midcourse corrections in the study in response to any unexpected adverse events.

The proposed change, which is currently open for public comment, "would make a lot less work for all the individual IRBs and allow them to focus on the studies they should be focusing on: the homegrown studies that haven't been reviewed by anybody else," says Richard Galbraith, director of the University of Vermont Center for Clinical and Translational Science in Burlington, who has studied the issue for the Federation of American Societies for Experimental Biology (FASEB).

Moving to a single IRB for multisite trials "is basically a very good idea," says Robert Levine, who teaches at the Yale University School of Medicine in New Haven, Connecticut and chaired the Yale–New Haven Hospital's IRB for 31 years. But he's concerned that the proposed rule does not specify the location or quality of a central IRB. "I wish they could strengthen the requirement to say that they are talking about a highly qualified, prestigious collection of people," he says.

Without such clear guidelines, the HHS proposal could conceivably lead trial investigators to outsource their study oversight to freestanding, commercial IRBs—although Levine is not convinced this scenario will be borne out. "I don't think it would increase the business of the for-profit IRB appreciably," he says.

Instead, Levine expects IRBs similar to the ones set up over the last decade at two federal agencies to have a greater role. One, at the US Department of Veterans Affairs (VA), has been in place since 2008 and is now mandated for all the multisite studies funded by the agency. Similarly, the US National Cancer Institute (NCI) created its own central IRB in 2001 and a corresponding pediatric IRB in 2004—both of which are available on a voluntary basis to organizers of NCI-funded oncology trials.

Faster, cheaper—better?

Both boards "are working very well," says Jacquelyn Goldberg, who heads the NCI's central IRB initiative. According to a study published last year by Goldberg and her colleagues, sites affiliated with the NCI's central IRB reviewed trial protocols on average 34 calendar days faster than unaffiliated sites that used their local IRB, at a savings of around $700 in staff wages for each initial review (*J. Clin. Oncol.* **28**, 662–666, 2010). "Review by the NCI's IRB was also associated with faster and less variable review times," Goldberg notes. Other studies have also found that local IRBs often make consent forms longer and more complicated, sometimes even introducing errors in the description of the study and its attendant risks (*Clin. Infect. Dis.* **49**, 328–335, 2009).

Other NIH institutes are taking notice of the NCI's and VA's initiatives. The agency's National Heart, Lung and Blood Institute, for example, held a workshop in June examining the use of central IRBs, with an eye to endorsing their use for its grantees. "We have many studies with a large number of sites and no evidence that requiring 70 to 140 separate IRB reviews, annual reviews and reporting improves the protection of the participants or contributes to the quality of the science," says Susan Shurin, the institute's acting director. She notes that most EU countries now have single national IRBs for multicenter trials, too.

Up for review: Centralized oversight proposed.

Nonetheless, some institutions remain reluctant to join a central IRB, "either because of wanting to keep the control at the local level or because of perceived liability concerns," says Goldberg.

As noted in a letter dated 27 July from FASEB president Joseph LaManna, under the current system, institutions can be punished by the government for lapses by IRBs, even if the at-fault IRB was not located at the institution. LaManna's letter, to a government task force that is looking at how to reduce the regulatory burden on educational institutions, asks it to "hold IRBs, not institutions, accountable" in these situations.

Others are concerned about the loss of local IRB autonomy if central IRBs are mandated for multisite trials. "There's an argument that all IRBs in a multisite study should be able to review and weigh in on the protocol, consent form and other documents," says Karen Maschke, a bioethicist at the Hastings Center in Garrison, New York, who edits the journal *IRB: Ethics & Human Research* and sits on the review board at Vassar Brothers Medical Center, a community medical center in Poughkeepsie, New York.

"IRBs get consent forms all the time for NIH- and industry-funded multisite studies, and they don't like the consent form; they think it's not worded properly," she says. "Sometimes they think the risks aren't clearly identified, and they change it. Some IRBs might be unwilling to cede this role to another IRB."

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