Trial Design and Patient Safety — The Debate Continues

Robert Steinbrook, M.D.

On July 3, 2003, nearly a year after it first became involved, the Office for Human Research Protections (OHRP) of the Department of Health and Human Services released its decision about two disputed multicenter clinical trials of treatment for the acute respiratory distress syndrome (ARDS).1,2 In a 15-page letter, the office seems to substantiate the ethical appropriateness and research design of both trials and to refute concern that participants were subjected to unnecessary risks. The OHRP does this by referring to the opinions of outside consultants whom it retained, without taking a position on the controversy itself. However, the OHRP, which regulates institutions and other entities that conduct or oversee studies involving human subjects, faults the many institutional review boards (IRBs) that reviewed the two studies for failing to obtain sufficient information to make the determinations they were required to make about the risks to subjects before approving the research. The OHRP also criticizes the IRBs for approving informed-consent documents that inadequately described the purpose of the research, the nature of the experimental design, and the risks — most notably, death.

According to Dr. Bernard A. Schwetz, the acting director of the OHRP, the office has to “straddle a fine line” by making a “positive effort to protect human subjects without standing in the way of important clinical research.” In an interview, he said, “This is not a black-and-white area. These studies are not frivolous. They are designed to generate information that will help people. If we are too conservative and shut down studies all over the place, we will become powerless, and that is not a stance we will be taking. On the other hand, if we blow off our responsibilities, that is not responsible either.”

The first trial was a study of mechanical ventilation that was hailed, when it was stopped early in 1999, as demonstrating that a lower tidal volume than had traditionally been used would improve the care of patients and save thousands of lives each year.3 The second trial was a comparison of different approaches to the use of intravenous fluids and catheters; at the request of the OHRP, the National Heart, Lung, and Blood Institute (NHLBI) suspended the study in the summer of 2002, after 418 of a projected 1000 patients had been enrolled. Both trials are part of the ARDS Network, which comprises 20 academic medical centers in the United States and Canada and is funded by the NHLBI.

The OHRP did not require any changes in the design of the suspended trial, known as the Fluid and Catheters Treatment Trial. Before enrollment can resume at any site, however, the IRB must review additional information, reapprove the research, and approve a revised informed-consent document that addresses the OHRP’s concerns. Although the trial is expected to resume at most, if not all, sites, the outcome will not be known for several months. Before the end of August, each of the ARDS Network institutions must also reassess its overall procedures for ensuring that it receives sufficient information about the research it reviews and for approving an informed-consent process that satisfies all the requirements of federal regulations, and must report back to the OHRP.

Federal regulations that set criteria for the approval of research by IRBs require that the risks to research subjects be minimized “by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk.”4 The ARDS Network studies were criticized for choosing comparison groups that reflected two extremes of practice rather than more common practice, which may be safer. The investigators responded by noting that many aspects of the care of patients with the syndrome, including the aspects being studied, have been so highly variable that there really has been no standard of care, which is why their studies were needed in the first place.

To help review a 74-page letter from the ARDS Network investigators and hundreds of pages of documents and data that it had requested, the OHRP retained eight consultants with expertise in issues concerning the protection of human subjects, bioethics, critical care and pulmonary medicine, and biostatistics. The names of the consultants and their actual recommendations have not been made public. In its July 3 letter, the OHRP stated that “almost all of the consultants . . . opined that risks to sub-

---

4. Federal regulations that set criteria for the approval of research by IRBs require that the risks to research subjects be minimized “by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk.”
jects (participating in the two trials) were minimized and reasonable in relation to anticipated benefits to the subjects and the importance of the knowledge that was expected to result.” However, the office also encouraged further discussions within the scientific and bioethics communities “about issues regarding appropriate research design in the absence of a standard of care” that were raised about the ARDS Network trials.

Some of the key participants in the controversy were encouraged by the OHRP’s decision, but for different reasons. According to Dr. Gordon R. Bernard of Vanderbilt University, the chair of the ARDS Network steering committee, the decision is “very good news [because] the OHRP decided the study was designed in a way that minimized the risk to subjects. That was the crucial question.” Bernard said that the ARDS Network “has never had any objections to discussions about informed consent and how it could be made better.” Dr. James Kiley, the director of the Division of Lung Diseases at the NHLBI, said the decision “sends a strong message that what we are doing [to evaluate and monitor studies] is appropriate.” Dr. Peter Q. Eichacker of the National Institutes of Health Clinical Center, one of two physicians whose concerns triggered the investigation, said that the issues “are coming back full circle, in going back to the IRBs. The OHRP is requesting that the boards take into account what routine care is, and consider the extent to which proposed experimental treatments may differ from it. That is positive.”

One lesson from the ARDS Network investigations is that the OHRP expects IRBs to continue to upgrade their professionalism and the rigor of their review process. Another is that the OHRP expects IRBs to be responsible not only for traditional concerns about ethics and patient safety that arise during the conduct of a trial but also for concerns that derive from the scientific design of the research or from a comparison of the potential risks to subjects with those in “concurrent routine clinical practice.” Although the OHRP sees all these responsibilities as inherent in the federal regulations, many members of the research community believe that the National Institutes of Health and other research bodies are best qualified to assess safety issues related to trial design. The OHRP’s decision is “very, very troubling as a precedent,” said Dr. David Korn of the Association of American Medical Colleges. “Does this mean that the OHRP can come into any clinical research study because it believes that something in the design may not be optimal and force the whole program to be redone to meet its concerns?”

According to Schwetz of the OHRP, “IRBs are not charged with second-guessing the scientific basis for conducting a study. However, they are responsible for determining whether the design of a study creates unnecessary risks to the subjects.” It should soon be clear how the ARDS Network institutions respond to the OHRP’s direction. The question that remains unanswered, however, is how the office and individual IRBs will respond if other research is challenged because of concerns about trial design and patient safety.