Rules and ethics betrayed

Numerous safeguards exist to protect subjects enrolled in medical research studies, but are they enough?

BY CULLEN T. VOGELSON

Medical research oversight has increased steadily over the course of the past 30 years, but so have the number of clinical trials conducted and the total number of participants. The United States maintains the world's most stringent set of rules and regulations meant to guarantee both scientific validity and patient safety in human research. Those regulations, among other things, require that

- new drugs be proven both safe and effective;
- research protocols be reviewed and approved by local independent review boards (technically known as Investigational Review Boards, or IRBs);
- patients be told in advance of all treatments, procedures, potential risks, and benefits associated with study participation; and
- the right to refuse or withdraw consent be extended without prejudice to all subjects.

Given these requirements, it would seem that patients are protected adequately during studies and that only ethically sound trials could occur within the United States. Unfortunately, in just the past four years, serious incidents have forced the temporary suspension by regulators of medical research at universities in Massachusetts, North Carolina, Oklahoma, and Alabama; additionally, after the death of a teenage participant, the University of Pennsylvania voluntarily discontinued all genetic research on human subjects.

Last year, Johns Hopkins University (JHU), one of the most prestigious research centers in the country and the institution that receives the largest percentage of federal research dollars, was investigated for not one, but three serious instances of alleged misconduct. One of these incidents resulted in the death of a volunteer and the subsequent, albeit temporary, suspension of the school's clinical trials program. How could this happen at an institution known as much for its teachings in the field of medical ethics as for its medical expertise? A review of the three publicized cases from last summer at JHU serves to answer that question and to illustrate the arrogance, carelessness, and ethically questionable practices that can occur in research programs. Further, these examples help to suggest ways of strengthening existing regulations in order to improve the whole of clinical research practice. However, if an institution of Johns Hopkins's repute is capable of conducting misguided research, it is chilling to think what an independent investigator with slighter credentials and a much lower profile might attempt.

ILLUSTRATION: ERIC DROOKER

Death of a volunteer

On June 2, 2001, a normal, healthy, 24-year-old volunteer participating in an asthma study at JHU died as a direct result of the medications given to her during the trial. The research program, which was part of a $1.55 million grant from the National Heart, Lung, and Blood Institute, paid healthy participants a maximum compensation of $365 to inhale a drug, methacholine, which induces mild coughing, shortness of breath, and tightness in the chest. After a period of five such exposures, subjects were given the methacholine in combination with either a placebo or the drug hexamethonium. Physicians monitored the patients during each of their visits, and the effects of the drug were expected to last no more than 3–4 h.

Hexamethonium itself is not an unknown compound: It was prescribed in the 1950s for hypertension and to minimize bleeding during surgery. In the 1970s, however, when more potent medications were introduced, it was discontinued and voluntarily removed from the market by its manufacturer; the modern regulations associated with drug safety, efficacy, and approval were just being put into effect as the drug was being withdrawn. Some research evidence reported in the 1950s, however, indicated that high doses of the drug, when taken over long periods of time, could result in fatal human lung changes.

In reviewing the death associated with the JHU study, federal regulators identified several significant flaws in the trial's conduct, including the following:

- The study's principal investigator failed to gain federal permission to use the drug, hexamethonium, in an investigational manner (never mind failure to comply with regulatory requirements

meant to control the uses of experimental therapies).

- Participants were unable to give proper consent because JHU failed to notify them that inhalation of hexamethonium was experimental (regulations require that patients be fully briefed on the nature of all therapies included in each study).
- The principal investigator did not disclose to the IRB that he was deviating from the approved protocol in the administration of hexamethonium—he mixed it with sodium bicarbonate (IRBs must, by law, approve all protocol changes including the reformulation of test materials).
- The investigator failed to notify the IRB when one of the patients developed a severe cough that lasted nine days, beginning just two days after inhaling the experimental drug (regulations require that events be disclosed regardless of suspected causation).

JHU addressed these concerns by first stating that hexamethonium was once marketed and, in any case, was not being studied for its therapeutic value. The unreported adverse event was not considered to be life-threatening and was, in fact, believed by researchers to be the lingering effects of a cold. In addition, the scientists said that the sodium bicarbonate was included only to improve the patients' comfort and that the informed consent form used properly met JHU's requirements.

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The FDA, however, found JHU's responses insufficient and, citing "systemic problems" in JHU's review process, temporarily suspended the university's permission to recruit new patients into any of its nearly 3000 ongoing trials. (Research was finally allowed to restart five days later, but only after the FDA mandated a re-review of almost all JHU research protocols.)

JHU's response to the suspension was swift. The school denounced the action as "unwarranted, unnecessary, paralyzing, and precipitous." Further, JHU said, it represented "an extreme example of regulatory excess." Eventually, however, JHU conceded that the minutes of many of its IRB meetings were not recorded, that some meetings were not properly convened, that some board members had conflicts of interest in studies they oversaw, and that many programs were considered collectively rather than individually.

Troubles in India

In July 2001, JHU launched an internal investigation following a complaint filed by a cancer center radiologist who charged that a JHU investigator was using a toxic substance, banned in the United States, for human experimentation in his clinic in India. Further, the radiologist, V. N. Bhattathiri, claimed that patients were neither informed of the associated risks nor told of the availability of other, approved treatments. The researcher at JHU, however, after admitting that the experimental compound was a known toxin, argued that the drug was entirely safe to use in the specific formulation being administered.

Because the FDA does not have the authority to police trials conducted in foreign countries—although it can refuse to consider foreign data used to support approval requests in the United States—this case merely raised new questions in the media about the ethics of U.S. researchers who conduct studies abroad.

Induced lead poisoning

Beginning in the mid-1990s, a Kennedy Krieger Institute study—overseen by JHU and funded through a $200,000 grant from the U.S. Environmental Protection Agency—sought to identify easy and cost-effective methods to clean up lead-contaminated homes. The study asked poor families with young, healthy children to move into lead-contaminated houses in a Baltimore, MD, neighborhood. Landlords were given incentives to recruit subjects, who then were placed randomly into homes that received varying levels of lead abatement or contained no lead contamination whatsoever. The subject families signed JHU-approved consent forms that allegedly failed to disclose the study's inherent risks, and were then given T-shirts, food stamps, and payments of $5–$15 for their "participation". Researchers subsequently tested the children's blood lead levels over time and thus assessed the various cleanup technologies.

Two parents, whose children's lead levels increased over the course of the study from normal limits to those that the U.S. Centers for Disease Control and Prevention considers high enough to reduce IQ and possibly cause mental retardation, later sued Kennedy Krieger for damages. The Baltimore courts ultimately dismissed the suits without conducting hearings.

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On August 21, 2001, the Maryland Court of Appeals overturned the lower court dismissals and ordered trials in the lawsuits. In the appeal court's ruling, Judge Dale R. Cathell wrote that "the researchers intended that the children be the canaries in the mines but never told the parents." In his opinion, he went on to criticize the JHU review board for not properly reviewing the study or its consent form. He further criticized the researchers for withholding test results that demonstrated that one of the two children involved in the suit suffered from lead poisoning contracted during the study. Judge Cathell also found that test results showing low lead contamination levels were given to families, whereas test results indicating higher levels were not. "Otherwise healthy children," he wrote, "should not be enticed into living in, or remaining in, potentially lead-tainted housing."

Corrective actions

The Department of Health and Human Services and the FDA vigilantly pursued complaints against JHU. However, although the current regulatory environment properly allows for a significant degree of research monitoring, there is not sufficient

supervision to guarantee the protection of all study participants.

A presidential commission recently found that most IRBs are overwhelmed in their oversight duties and lack crucial technical knowledge. As a result, the commission recommended that IRBs obtain federal registration permits that would necessitate their increased vigilance in monitoring and approving clinical trials. The commission also suggested that existing conflict of interest disclosure requirements be stiffened and board memberships be expanded.

Other improvements to the system have been suggested. For example, many patient advocacy groups have called for increased scrutiny by regulators of the payments made to researchers for conducting their studies. The National Bioethics Advisory Commission has also recommended the establishment of both a national database to log adverse events associated with human experimentation and a fund designed to compensate injured participants. In addition, the Department of Health and Human Services has begun investigating ways to tighten the restrictions on studies conducted overseas by U.S. researchers. Finally, numerous medical ethics groups have called for increases in the FDA's funding for the monitoring of research trials.

So what if you happen to be considering participation in a clinical trial? Should you be concerned? The answer must certainly be yes, but with some strong reservations: Medical research conducted in the United States is largely safe (at least as safe as the testing of any experimental compound could be) and within the restrictions imposed by the FDA. Overall, there is a low instance of fraud and malpractice. But before entering a study, every patient should carefully weigh the potential risks and benefits of participation, establish a comfortable relationship with the researchers, treat each new physician with a healthy degree of skepticism, ask detailed questions, and never hesitate to report incidents of concern to the sponsoring agencies, local IRB, and FDA.

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