

[Current Table of Contents](#)[Past Issues](#)[Search](#)[Index](#)[Prev.](#) [Full Text Item](#) [Next](#)[■ Annals Services](#) [■ Site Guide](#) [Classifieds](#) [Pharmaceutical In-Site Corner](#)[Evaluate This Article](#)[Search PubMed](#)[Page Top](#)**CURRENTS****Research on Humans Faces Scrutiny: New Policies Adopted**

Paul T. Kefalides, MD

Pages 513-516

Ann Intern Med. 2000;132:513-516.

Structural changes in the field of biomedical research have in turn changed the climate for research involving humans. Both Institutional Review Board (IRB) administrators and investigators are feeling new pressures. Although they are stirred by a steady increase in research projects, especially those sponsored by industry, they are challenged by new public advocacy for the protection of human participants and aggressive, punitive enforcement by government regulators. Several reforms are being drafted and may be put into place by the end of the year, intended to modernize the system of research oversight and regain the public's trust.

**Obligations of Institutional Review Boards**

Institutional review boards are charged with the responsibility of reviewing and approving all research projects that involve human participants. In addition to approving new projects, IRBs are responsible for continuing reviews, a form of oversight on ongoing research. Most research institutes divide IRB duties between a small administrative staff and a committee or committees that are composed primarily of faculty members, supplemented by ethicists, attorneys, and community representatives. Most institutional IRBs meet monthly or biweekly to discuss new applications.

In its review process, an IRB must refine investigators' proposals and preempt any potential harm to the participants by synthesizing ethical principles of human subject research with clinical practice guidelines, federal regulations, and local laws. The institution's investigators are permitted to experiment with humans within the limits imposed by a federal contract known as the multiple project assurance. Institutional compliance with the provisions of the multiple project assurance is a prerequisite for access to federal research funds.

**The Market Economy for Research**

An increasing budget for the National Institutes of Health (NIH), a booming biotechnology sector, and the proliferation and prosperity of independent IRBs (see sidebar) are all markers for the continuing growth of clinical research. The expansion has put pressure on the IRBs of nonprofit research institutions that are now widely recognized as understaffed and inadequately funded. "Institutions have been focused on getting new researchers and labs and have not paid attention to monitoring the research," observed Gary Chadwick, PharmD, director of the research subjects review board at the University of Rochester, Rochester, New York.

According to administrators, a graph of the number of research proposals submitted per year would show a constant upward-sloping line. "It's a steady increase at 4% to 5% a year," commented Sharon Friend, director of the research subjects protections committee at the University of California at San Francisco. "We probably have at least

700 new biomedical studies each year," she stated. At the University of Rochester, volume has increased an estimated 25% over the past 4 years. In response to that growth, Chadwick says, administrators subcontracted a portion of their research reviews to Western IRB in Olympia, Washington.

The trend toward multicenter trials has complicated the review and reporting duties of IRBs. In addition, because research is increasingly sponsored by commercial organizations, there are financial incentives to acquiring accelerated IRB approval. Industry-supported study offers valuable overhead revenue to institutions whose clinical medicine incomes are shrinking; in fact, for many health systems, increasing revenue streams today are attributable exclusively to growth in clinical research. However, industry support also presents new challenges to a review process that has historically been marked by university bureaucracy. "The faster an IRB reviews and approves [projects], the more an institution stands to gain," observed Moira Keane, director of the research subjects protection programs at University of Minnesota Medical School in Twin Cities, Minneapolis. "There is tremendous pressure to do things faster," she stated.

According to Friend, industry-supported research now constitutes 50% of her institution's studies on humans. "It's a lot more difficult to work with industry than with the federal government," she asserted. "Every drug company study is different...they have different staff and lots and lots of lawyers. It's a lot more labor-intensive [to work with companies]; we estimate three times as much."

## **Punitive Actions of the Government**

The influx of research proposals for human study coincides with more rigorous enforcement of the government regulations that apply to research on humans. In the past 14 months, federally funded research has been restricted or suspended at several research institutions and more institutions have received federal inquiries. Although NIH officials stress that the rules for protection of human participants have not changed, it is clear that enforcement of these rules has become increasingly strict. "Prior to this year, we had not taken such global action," stated Michael Carome, MD, chief of the Compliance Branch, Division of Human Subjects Protection (DHSP), Office for Protection from Research Risks (OPRR), National Institutes of Health.

"I don't think OPRR should have been very surprised," commented Erica Heath, president of Independent Review Consulting (IRC) in San Francisco, California. "For 30 years, nobody asked the question, 'What's going on?' They relied on the collegiality and integrity of academics. Then in 1 year with a great deal of fanfare, there was this change in enforcement."

At institutions where research was suspended, thousands of projects were shelved immediately. Most could not resume until they were reviewed again or until specific problems cited by the government were fixed. According to David C. Clark, PhD, director of research affairs at Rush-Presbyterian-St. Luke's Medical Center in Chicago, Illinois, the full effects of his institution's suspension are difficult to quantify. "We probably lost huge amounts of revenue from clinical trials and studies that just picked up and moved. It probably set some researchers back a couple of years," he stated.

Duke University Medical Center in Durham, North Carolina, received a 4-day suspension. "The negative effect on morale was tremendous," asserted John M. Falletta, professor of pediatrics and chairman of the IRB. "Since then, we have been under close scrutiny by OPRR."

According to many ethicists and IRB officials, OPRR's new vigilance directly followed the 1998 publication of a report by the Office of the Inspector General (OIG) of the Department of Health and Human Services. The report sharply criticized OPRR's oversight of human subject research and asserted that IRBs "review too much, too quickly, and with too little expertise." The report also cited institutional and individual conflicts of interest that hinder the ability of IRBs to protect human participants. It concluded that reviews of continuing research were inadequate and that IRB staff members were insufficiently trained.

## **Public Outcry**

The national media also helped create the new probing environment for human subjects research. According to several experts, renewed publicity about government-run

experiments on the effects of radiation, along with accounts in the lay press that portrayed specific researchers as reckless, stimulated public awareness of human subjects research. Arthur Caplan, PhD, director of the Center for Bioethics at the University of Pennsylvania in Philadelphia, cited a cascade of events that included the radiation reports, the OIG report, and a series of improprieties involving research on children and mentally handicapped persons. "I think people still have a positive attitude towards medical research, but there is a growing distrust of medicine that has been fueled by managed care... The really driving force has been the scandals," declared Caplan. "These incidents have led people to believe that OPRR is not doing its job."

The new concern is reflected in the quantity of letters that OPRR receives. According to the NIH's Carome, the number of complaints logged against researchers and received by OPRR is almost 50% higher than 1 year ago. "There is heightened public attention on human subject research," agreed the University of Minnesota's Keane. "[New publicity about] the Tuskegee and radiation experiments have had a profound effect on suspicion. We have changed the culture. It [IRB oversight] is no longer a quiet little ethical endeavor."

The new sensitivity has culminated in government inquiries and more challenges to IRB administrators. Friend noted that on her staff, she needs one person whose only job is responding to the government. She commented that OPRR now sends her office so many requests for detailed information on human subjects research — most with unrealistic deadlines — that her first response is usually to request an extension.

## **The Most Common Institutional Review Board Mistakes**

According to Carome, when the OPRR investigates an institution's IRB, they find problems that fall into three categories: insufficient IRB staffing, inadequate training and education of IRB members and staff, and (analogous to charges against clinicians) failure to maintain proper documentation. At Duke University, for example, OPRR auditors concluded that the minutes of the IRB meetings were incomplete. At Rush-Presbyterian-St. Luke's Medical Center, audiotapes of IRB proceedings were not accepted as substitutes for written documentation. Other institutions have enrolled more patients in a study than originally planned and have failed to use informed consent.

Carome offered an example of violations that apply to individual researchers. He stated that many investigators perform human subjects research without realizing that it should be classified as such. "If you do a survey of patients, and you ask name and address and obtain identifiable private information, that is human subject research," he clarified.

From the perspective of a private IRB, the misunderstandings on the part of investigators are fundamental. Independent Review Consulting's Heath complained that many of the research proposals submitted by clinical researchers demonstrate ignorance of the elementary vocabulary of science. "There are more and more clinical investigators, and they don't even know what they're doing... they don't know the elements of informed consent. These problems are pretty basic," she commented. Some of IRC's clients are private practitioners capitalizing on the new opportunities offered by partnerships with the pharmaceutical industry and by participation in clinical trials. "Research used to be a quest for discovery. Now it is a business," Heath lamented.

## **The Scope of Institutional Review Board Authority**

In an effort to make the quality of research more consistent and minimize the number of ineffective and inappropriate studies, some scientists advocate a broadening of IRB duties to include assessment of investigators' research design and their review of the literature. Ideally, this would require all IRBs to evaluate proposals within the context of related published literature using statistical methods to ensure sound methodology. "If you put a subject into a study to answer a question that cannot be answered, is that ethical?" asked James Hinson Jr. MD, Research Compliance Officer, University of Missouri — Columbia School of Medicine in Columbia, Missouri.

Such an expansion of IRB responsibility referenced by Hinson was outlined in a 1996 article (Savulescu J, Chalmers I, Blunt J. *BMJ* 1996;313: 1390-3). The authors cited specific examples of misconduct where patients were enrolled in clinical trials that conferred risk in order to test hypotheses that had been proven and summarized previously in systematic reviews. They also criticized researchers for burying undesirable

results of clinical trials. The authors argued that research ethics committees should be responsible for preventing redundant or irrelevant research and ensuring that all results — good and bad — are reported to colleagues in the scientific community.

While some such as Caplan agree that it would be desirable to use the IRB mechanism to police more aggressively the quality of research, most experts in the field concede that an official broadening of IRB powers is currently not on the table — and that existing guidelines will have to serve for now. "IRBs are not intended nor constituted to be scientific review committees," explained Chadwick, "although some IRBs have made scientific review a part of their process."

Chadwick identified other differences in the European model for research review where the review committee has much broader powers to assess scientific merit and to investigate financial conflicts of interest. For example, in the United States, where many sponsors make small payments to investigators to cover the costs of recruiting patients for trials, Chadwick thought determining certain types of financial conflicts would be challenging. "You have to dig deep to determine what is conflict of interest.... This would turn an IRB into an accounting function. We [in the United States] have tried to focus on the interface between subject and investigator rather than investigator and sponsor."

"This is not a specific concern that we have raised," added OPRR's Carome in response to the idea to broaden the scope of IRB authority. "[But] IRBs have authority to require anything they feel is necessary to protect human rights." He added that assuring that research is meaningful is implicit in current guidelines. To determine the merit of a proposal, an IRB must involve other scientists with adequate expertise to make a judgment or else seek outside consultants.

Duke's Falletta thought the issue of research design could be approached under current rules through consideration of the risk and benefit of the study. "If the principal investigator is not asking an answerable question, does not have the means to answer the question, or is asking a question that has already been definitively answered, then no benefit will likely be detectable from the research. If that research is risky, which most research is, then the risk vs. benefit assessment of the research is unfavorable, all risk and no benefit, and the research must not go forward."

Hinson admits that researchers will probably have an unfavorable opinion of any new policies that create the expectation that review boards judge scientific merit. "A lot of people will say that that is out of bounds; submitters get upset when you challenge their design."

## Strategies for Reform

Currently, prospective reforms focus on ways to improve education and training of IRB professionals, educate and certify individual researchers, and establish an accreditation process for institutions that perform research on humans. The possibility of centralizing certain IRB functions is being debated, and in the distant future, a professional organization might offer board certification in the supervision and performance of research.

The University of Rochester's Chadwick is also past president of the Applied Research Ethics National Association (ARENA), a national organization of IRBs. He reports that a certification examination for IRB professionals has been adopted and will be introduced at ARENA's annual meeting in the fall of 2000. The examination will include a history of research, a review of the principles of bioethics, and descriptions of international codes and standards. It will also describe the features of good experimental design.

Chadwick was among the first to introduce a formal education program for researchers. All investigators whose proposals are thought to confer at least moderate risk to participants must complete a self-study manual and pass an examination before IRB approval is given. Other institutions are expected to develop similar investigator-training programs.

Education and training of investigators and IRB staff has also become the top priority at Rush-Presbyterian-St. Luke's Medical Center. According to Clark, the IRB now has a full-time training and education director. "We instituted mandatory workshops for investigators to educate them on the history of medical research abuses, bioethics, and conflict of interest. Rush scientists will not be allowed to have studies approved or reapproved until they complete the workshops," Clark stated. A formal examination for

investigators is also in the pipeline.

Public Responsibility in Medicine and Research (PRIMR), a nonprofit organization with 35 years of experience in educating scientists and policymakers about research ethics, is drafting a voluntary accreditation program for institutions that experiment on humans. The OPRR has already endorsed the program. According to PRIMR executive director Joan Rachlin, JD, MPH, "We are in the process of developing performance standards for a self-assessment instrument, and this would be followed by a site visit team." Institutions will be able to apply for accreditation as early as the fall of 2000.

Some ethicists, such as Caplan, have suggested creating a centralized review board, although others, who seek to maintain local standards in research review, oppose the idea. It has been suggested that a national review board would be a particularly important means of expediting multicenter trials of new therapies for cancer. Caplan sees further gains of centralization. He believes that IRBs are ill equipped to monitor negative aspects of trials, such as adverse events, because they are frequently the last to be informed of them. In his view, it would be helpful to have a national IRB for high-risk experiments. Caplan argued that the recent death associated with a gene therapy experiment at the University of Pennsylvania was a case study in three ways: "One, the ability to collect adverse event information was limited; the IRB didn't know. Two, there was no connection between the data safety and monitoring committee and the IRB. And three, once the IRB approved the study, they were uninvolved."

Independent IRBs, such as Heath's IRC, are also looking to the future and anticipate that they will have to adapt to the new regulations. The proposed reforms emphasize knowledge about ongoing research projects rather than such issues as initial informed consent. Firms like IRC will need to subcontract with monitoring companies to meet the need for on-site auditing.

Chadwick agreed that investigators should anticipate more ongoing inspection of their work and should understand that protection of human participants does not begin and end with the informed-consent document. "The biggest issue that investigators run afoul of is in the consenting process. Informed consent is not just a document; it is a process," he explained. In 1976, the Belmont Report of the National Commission for the Protection of Human Subjects identified the three key elements of the consent process: information, comprehension, and voluntariness. Friend considers the Belmont Report required reading for any clinical investigator who wants the work to go smoothly. "This is not something that will go away," she stated. "Research standards change, and investigators need to work with their IRB office."

## Private Institutional Review Boards

Not all institutional review boards (IRBs) are affiliated with research institutions. Privately organized IRBs now review clinical projects and compete with traditional IRBs by offering faster research reviews and approvals. Indeed, in today's research environment, the for-profit IRB market is rapidly expanding. The oldest and largest of such enterprises is Western IRB (WIRB) in Olympia, Washington. Its president, Angela Bowen, MD, says that business is going "straight up."

Thirty years ago, Bowen founded the panel that would become WIRB when she relocated from a large research center to a private practice in Olympia. She asked a nonprofit organization to create a group of reviewers to read and offer suggestions on her own clinical studies. "I felt I needed somebody to test my judgment against," she recalled. Fortuitously, the group that she helped organize contained all of the personnel that federal regulations would later mandate.

By the 1980s, WIRB was serving small and medium-sized hospitals. In recent years, it has added several universities to its list of clients. As the largest private IRB, WIRB employs 157 people and maintains 40 alternates for its 9 board members. Western Institutional Review Board charges \$550 to review a protocol and expects to review 1400 proposals this year; it is a subcontractor for 4 universities and 15 hospitals. In 1999, WIRB was selected to perform a comprehensive audit of all of the research projects at the University of Colorado in Boulder, Colorado. The audit is a prerequisite for the removal of the university's research suspension, which was imposed by the Food and Drug Administration.

According to Bowen, speed is a key factor the success of her business. "We usually have a board meeting every day, sometimes twice a day," she explained. She noted that

WIRB usually reads, analyzes, and gives an opinion on a research proposal in 10 working days. At a nonprofit IRB, the average turnaround time is approximately 1 month.

### Useful Web Sites

<http://www.aamc.org/research/primr/>

[http://www.mco.edu/research/fed\\_regs.html#anchor180315](http://www.mco.edu/research/fed_regs.html#anchor180315)

[http://grants.nih.gov/grants/oprr/library\\_human.htm](http://grants.nih.gov/grants/oprr/library_human.htm)

<http://www.fda.gov/oc/oha/IRB/toc10.html#AppendixE>

---

Copyright ©2000 American College of Physicians – American Society of Internal Medicine