

Department of Health and Human Services

**OFFICE OF
INSPECTOR GENERAL**

Protecting Human Research Subjects

Status of Recommendations



**JUNE GIBBS BROWN
Inspector General**

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EXECUTIVE SUMMARY

PURPOSE

To provide an update of National Institutes of Health (NIH) and Food and Drug Administration (FDA) responses to recommendations we directed to them in a June 1998 report entitled, *Institutional Review Boards: A Time for Reform*.

BACKGROUND

Our June 1998 Report on Institutional Review Boards

Institutional review boards (IRBs) play a central role in providing human-subject protections. In our June 1998 report, we warned that the effectiveness of these boards was in jeopardy and presented numerous recommendations to NIH, its Office for Protection from Research Risks (OPRR), and FDA. In our call for widespread reform, we conveyed a sense of urgency, one that was reinforced by one of our prior inquiries. In that inquiry we discovered disturbing inadequacies in IRB oversight of clinical trials involving investigational medical devices.

Subsequent Actions

Since the issuance of our report, human subject protections have received considerable attention within the Department and at the national level. Congress has held two hearings addressing how the effectiveness of IRBs can be improved. The National Bioethics Advisory Commission (NBAC) has continued its deliberations on what reforms should be undertaken. The Secretary of Health and Human Services (HHS) has decided to relocate OPRR to the Office of the Secretary and to establish an advisory committee to provide scientific and ethical guidance to OPRR. Both NIH and FDA have been engaged in multiple efforts to address how human subject protections can be enhanced. With the death of a teenager participating in a gene transfer clinical trial funded by NIH, they have given particular attention to ways of improving the oversight of such trials.

This Follow-up Report

In this report, we provide an accounting of how fully our prior recommendations have been enacted. We do that because they have attracted substantial attention and because we believe they remain timely. In providing this update, we draw on information obtained over the past two years from HHS officials and from pertinent HHS documents. This report is deliberately limited in scope. It does not represent a further examination of the adequacy of the Federal oversight of human subject protections or of the protections themselves. It accepts as a starting point our prior recommendations and seeks to provide an accounting of how fully they have been carried out.

UPDATE

Since June 1998, there has been a substantial increase in the enforcement of Federal human-subject protection requirements.

Investigations. Between April 1997 and May 1998, NIH/OPRR had conducted an on-site investigation at only 1 institution. Between June 1998 and March 2000, it conducted on-site investigations at 10 institutions. FDA's number of routine on-site investigations of IRBs increased from 213 in Fiscal Year 1997, to 253 in FY 1998, and 336 in FY 1999.

Sentinel Effect. OPRR's reviews, which have occurred at major medical centers and have resulted in the suspension of federally funded research at 7 institutions, have been particularly influential in drawing attention of the national research community to the adequacy of IRB oversight and human-subject protections.

Several promising steps have been taken.

NIH and FDA have enacted two of our recommendations. NIH now requires data and safety monitoring boards to share summary information with IRBs and FDA now informs sponsors and IRBs about its findings of clinical investigator misconduct.

In addition, both agencies have ongoing initiatives, particularly in the area of education. NIH and FDA continue to be active in educational outreach and programs, conducting numerous training presentations and seminars. OPRR hired a full-time educational staff person and is in the process of further expanding its educational staff. FDA convened a national meeting addressing current issues in human subject protections and has had numerous workgroups examining specific issues. NIH, also, has constructed a website containing bioethics resources.

But overall, few of our recommended reforms have been enacted.

Flexibility and Accountability. Minimal progress had been made in recasting Federal IRB requirements so that they grant IRBs greater flexibility and hold them more accountable for results. Too much IRB attention now focuses on review responsibilities of questionable protective value.

Oversight and Protections. Minimal progress has been made in strengthening continuing protections for human subjects participating in research. Continuing IRB review of research after it has been initially reviewed is a low priority at many IRBs. IRBs know little of what actually occurs during the consent and research processes.

Education. No educational requirements have been enacted for investigators or IRB members. The most important continuing protection for human subjects is the presence of well-trained and sensitized investigators and IRB members.

Conflicts of Interest. There has been no progress in insulating IRBs from conflicts that can compromise their mission in protecting human subjects. The increased commercialization of research and the growing importance of research revenues for institutions heightens the potential for conflicts of interest in clinical research.

Workload. Minimal progress has been made in moderating workload pressures of IRBs. IRBs are inundated with protocols and adverse event reports. With limited personnel and few resources, many IRBs are hard-pressed to give each review sufficient attention.

Federal Oversight. Minimal progress has been made in reengineering the Federal oversight process. Federal oversight of IRBs is not equipped to respond effectively to the changing pressures and needs of the current system of protections.

For a complete accounting of our prior recommendations and any Federal responses to them, see text beginning on page 9 and appendix C.

The Common Rule represents a significant barrier to HHS progress in implementing many of our recommendations.

In 1991, the HHS core regulations concerning IRBs and human-subject protections became the basis of a common Federal policy on human-subject protections. Known as the Common Rule, this policy is adhered to by HHS and 16 other Federal agencies. Any changes to the Rule call for the concurrence of all 17 agencies.

Many of our recommendations call for changes in the Common Rule. NIH has emphasized to us that it cannot make those changes without the consent of the other agencies and that such a process is a long, complex one with uncertain results. We have to recognize that its observation is well-based.

The goal of a common Federal rule is an important one. It can foster a level of consistency in protecting human subjects and make it easier for researchers and sponsors to understand and comply with regulations. Yet, we must acknowledge that the reality of gaining concurrence among 17 Federal agencies inhibits a timely response to many of our recommendations and to the rapidly changing developments in the clinical research environment. In view of this reality, legislative change may well be necessary to achieve a timely implementation of many of our recommendations.

LOOKING AHEAD

Gene Transfer as a Catalyst

The recent national attention given to gene transfer trials has raised the public's awareness of the risks that can be associated with clinical research and has prompted several important initiatives by NIH and FDA. One is a new requirement calling for study

sponsors to submit to FDA monitoring plans for gene transfer trials; another is a series of symposia that will be held on the directions and safety of such trials.

These initiatives may prove to be quite helpful, but they apply only to gene transfer research trials. We urge that these initiatives serve as a catalyst for improving human-subject protections for the broad universe of clinical trials, particularly those in which patients face significant risks.

Our prior inquiry convinced us that often too much is expected of IRBs and that IRBs alone can not provide a sufficient degree of protection. That is why we gave so much attention to Federal actions that could be taken to help educate investigators about human-subject protections. It is why we have called in a subsequent report for the development of stronger guidelines on human-subject recruitment practices. And, it is why we drew attention to the vital roles that, for example, the Data and Safety Monitoring Boards can play particularly for trials that pose significant risks to patients.

New Opportunity for Leadership

Once OPRR is located in the Office of the Secretary and a new advisory committee on protection from research risks is established, as the HHS Secretary has called for, HHS will have a significant new opportunity to exert Federal leadership in protecting human subjects.

We urge that the new office give significant attention to our prior recommendations and to those that will be forthcoming from NBAC. We also urge that it continue the important enforcement efforts undertaken by OPRR over the past 2 years. In increasingly commercialized research environments where IRBs are facing heightened pressures to conduct quicker reviews, the NIH/OPRR efforts have served as a reminder to research institutions, sponsors, individual investigators, and IRBs that the reviews must still be substantive ones that ensure adequate protections for human subjects. They must not only protect subjects from unnecessary physical harm, but must ensure that the informed consent process is one that fosters understanding and voluntary participation.

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INTRODUCTION

PURPOSE

To provide an update of National Institutes of Health (NIH) and Food and Drug Administration (FDA) responses to recommendations we directed to them in a June 1998 report entitled, *Institutional Review Boards: A Time for Reform*.

BACKGROUND

Our June 1998 Report on Institutional Review Boards

Institutional review boards (IRBs) play central roles in protecting human subjects enrolled in clinical research. In a June 1998 report, which was based on more than a year of extensive inquiry, we found that the effectiveness of IRBs was in jeopardy. While we did not claim there were widespread abuses of human research subjects, we did warn that the capacity of IRBs to accomplish all that is expected of them is strained. We conveyed a sense of urgency that was buttressed by earlier findings by a Presidential advisory body, by the General Accounting Office, and by one of our own prior inquiries.¹ In that inquiry we examined clinical trials involving four investigational medical devices and in each case discovered disturbing inadequacies related to IRB oversight.

In our June 1998 report, we presented six sets of recommendations. We directed them jointly to the two entities within the Department of Health and Human Services (HHS) that are responsible for IRB oversight: NIH, through its Office of Protections from Research Risks (OPRR), and the FDA (for a primer on HHS oversight roles, see page 8).

In the formal comments they offered on our recommendations, both NIH and FDA expressed a number of reservations. But overall their reactions were quite positive. NIH responded as follows: “Twenty-four years after the initial promulgation of our Department’s rules for protection of human subjects, your summary of the challenges today facing IRBs, and your recommendations for DHHS oversight, form important additions to the evolving body of analysis of our system of protecting human subjects in research.” Similarly, FDA indicated that the reports “highlight and add support to a number of areas where we believe change may be needed.”

Subsequent Actions

In response to the substantial interest in the report, we have discussed its findings and recommendations in many different settings. We testified at two congressional hearings on IRBs, one held just as the report was issued in June 1998 and the other in December 1999.² We gave a presentation before the committee responsible for the uniform implementation of the common human subject protection regulations across 17 Federal

agencies (including HHS) and gave speeches and participated in panel discussions at the meetings of many professional associations.³

During the period from June 1998 to the present, the topic of protecting research subjects gained considerable prominence within the Department. Of particular note was the July 1999 decision by the HHS Secretary to relocate OPRR from NIH to the Office of the Secretary and to establish a new advisory committee on protection from research risks to provide scientific and ethical guidance to the office. These actions, not yet completed, were taken to strengthen the stature and effectiveness of OPRR in its oversight role.

At the same time, both NIH and FDA have been actively addressing human subject protections. NIH has been giving particular attention to ways of reducing the regulatory burden for IRBs and research institutions. FDA, in March 1999, convened a national meeting addressing current issues in human subject protections and has had numerous workgroups examining specific issues. Both NIH and FDA officials have been participating in private sector efforts intended to develop mechanisms for accrediting human subject protection programs. With the September 1999 death of an 18-year-old participating in a gene transfer trial, both agencies have also been examining ways in which they might improve their oversight of such trials.

This Follow-up Report

In this report, we provide an update on the implementation of the recommendations we offered in our June 1998 report. We do that because 2 years have passed since we first made the recommendations, because they have drawn considerable interest in congressional hearings and many other forums, and because they remain relevant to current, heightened concerns about human subject protections. In appendix C, we list all of the recommendations we made in June 1998 and indicate their state of implementation.

This report is deliberately limited in scope. It does not represent a further examination of the adequacy of the Federal oversight of human subject protections or of the protections themselves. It accepts as a starting point our prior recommendations and seeks to provide an accounting of how fully they have been carried out. In that context, it does address some related actions that have been taken, but does not purport to be a full accounting of all HHS actions that are relevant to human subject protections. We recognize that our recommendations address complex issues which can take some time to implement. But in this brief report, we seek to simply and clearly address what has and has not changed.

In providing this update, we have drawn on information obtained over the past two years from pertinent HHS documents, from interviews with NIH, FDA, and other HHS officials, and data reported to us by NIH and FDA. We have also drawn on their comments on a prior working draft of this report. We have sought to make our accounting as straightforward, accurate, and nonjudgmental as possible. But we recognize that others may offer different interpretations of the significance of actual actions and of the state of progress in implementing our recommendations.

HHS Oversight Roles and Competencies

Delineation of HHS Authority and Activity

Agency	Purview	Primary Body for Protections	Oversight Conducted
NIH/OPRR	research supported or otherwise subject to regulation by HHS	IRBs	assurance, inspections of IRBs
FDA	research conducted on products subject to FDA approval	IRBs	inspections of investigators, IRBs, and research sponsors

The Office for Protection from Research Risks (OPRR) within the NIH, acts as the primary body for human-subjects research oversight and guidance for the Department. HHS/NIH regulations were established in 1974 and in 1991 became the basis for the Common Rule for 17 Federal Departments and agencies. The FDA established another set of regulations in 1981 which were later harmonized, to the largest extent possible, to conform to the Common Rule in 1991. The two sets of regulations are distinct, but very similar. The most significant distinction between the agencies is their purview.

Delegation of Responsibility

The focus of both regulations is to require the review of human research by an institutional review board. Institutional review boards (IRBs) are committees of scientists and lay people, independent of the research being conducted, who review and approve the research. As part of their review, boards approve the research before it can begin, provide ongoing review of amendments and adverse event reports, and conduct continuing reviews at least annually. IRBs seek to ensure adequate protections are in place and that subjects are given the opportunity for informed consent. For further explanation of the roles and responsibilities of IRBs, see appendix A.

Oversight

Despite the primary role of IRBs, both FDA and OPRR are responsible for subject protections and IRB oversight.

OPRR's primary mechanism of oversight is the assurance process. Institutions wishing to conduct human-subjects research under OPRR jurisdiction must appoint an IRB of record by applying for and receiving an assurance from OPRR. The assurance is a document that states the institution's commitment to uphold human-subject protection regulations and their policies and procedures for meeting the regulations. Institutions must renew their assurance every 5 years, after an initial period of 3 years. OPRR also conducts a limited number of IRB inspections. Their reviews are primarily based on complaints or concerns about compliance. Spontaneous reviews are rare.

FDA conducts inspections of clinical investigators, research sponsors, and IRBs. FDA generally inspects investigators through its bioresearch monitoring program when the investigators' research is associated with a product approval application. FDA also inspects investigators during the conduct of research when a for-cause inspection is warranted.

UPDATE

Since June 1998, there has been a substantial increase in the enforcement of Federal human-subject protection requirements.

Within HHS, the increase in enforcement activity is the most significant action that has been taken to foster human-subject protections since the issuance of our report. The increased enforcement responds to the sense of urgency that we presented in our prior report and more specifically responds to our call for a greater on-site focus addressing the performance of IRBs.

OPRR and FDA have stepped up their on-site presence at research institutions.

► **Between April 1997 and May 1998, OPRR had conducted an on-site investigation at only 1 institution. Between June 1998 and March 2000, it conducted on-site investigations at 10 institutions.**

Since June 1998, OPRR also conducted off-site investigations (document reviews) at more than 140 additional institutions. It found performance problems at a number of institutions it investigated and has required 7 of them to suspend some or all of their federally funded research.

In letters to research institutions where OPRR found weaknesses in the institutions' systems of protections, it cited institutions for substantive, broad-based deficiencies—ones that have direct consequences on the rights and safety of research subjects. For instance, in one case OPRR found that the IRB failed to review a research protocol's recruitment procedures, including a document that discussed how to persuade reluctant potential subjects to enroll in the study. Some of the potential subjects from this study were recontacted so many times after refusing to participate that they filed a complaint, which led to the OPRR investigation

► **FDA's number of routine on-site investigations of IRBs increased from 213 in Fiscal Year 1997, to 253 in FY 1998, and 336 in FY 1999.**

FDA's Center for Devices and Radiological Health, for example, issued eight warning letters to IRBs during FY 1999, compared to zero in FY 1998. The Center for Drug Evaluation and Research took administrative action against eight IRBs during FY 1998 and 1999.

FDA's presence in reviewing IRB practices remains much more direct and extensive than

that of NIH/OPRR. The strong enforcement capability of FDA is especially important as FDA is the primary Federal on-site presence at most research sites outside of academic medical centers, where an increasing proportion of research takes place.

OPRR's oversight activities have been particularly influential in drawing attention to the adequacy of IRB oversight and human-subject protections throughout the research community.

With OPRR's reviews occurring at major medical centers and in 7 cases actually resulting in a temporary suspension of federally funded research those centers, they have had the strongest sentinel effect. Although we can not determine precisely how fully the research community has responded to OPRR's recent actions, the fact that many major medical journals and newspapers gave prominent attention to OPRR's enforcement actions [see box] suggests that these actions are being widely noted.

Some recent professional conferences also reflected a growing sense that Federal enforcement activities are being taken seriously by research institutions, investigators, and IRBs. The 1999 annual meeting of Public Responsibility in Medicine and Research (PRIM&R) drew 1,300 attendees compared with about 900 the year before, and its first panel session included a presentation by the director of research affairs from Rush-Presbyterian Medical Center, an institution

that OPRR had visited. The presentation was entitled: "Learning from Recent Compliance Hot Spots: The Top Ten Compliance Problems and How to Avoid Them." The 1999 annual meeting of the Applied Research Ethics National Association, which immediately preceded the PRIM&R meeting, featured a presentation by an ethicist from Duke entitled, "The Duke University Experience: What Lessons Can IRBs Learn?"

NIH/OPRR Puts the Research Community on Notice

"A virtually unknown federal agency with only 31 employees is sending shock waves through the nation's billion-dollar clinical-research community." *Physician's Weekly*, July 19, 1999

"OPRR has put every federally funded U.S. research institution on notice that its right to conduct clinical research could be summarily yanked." *Science*, May 21, 1999

"But even as business goes back to normal at the prestigious medical center...new questions arose about the safety of human subjects at other institutions around the country." *The Washington Post*, May 5, 1999

"Across the country, university administrators and researchers are worried, even panicked that the same thing could happen at their institutions with millions of dollars of research funds from the National Institutes of Health and pharmaceutical companies at stake." *Chronicle of Higher Education*, February 4, 2000

"OPRR is moving with new aggressiveness to monitor IRB performance." *New York Times*, May 25, 1999

"Recent suspensions indicate to some that NIH/OPRR is more aggressively enforcing the federal protections for human subjects" *American Medical News*, November 1, 1999

Finally, the opening panel of a recent national conference on legal issues affecting academic medical centers, sponsored by the American Health Lawyers Association, was entitled, “Clinical Research: Staying Out of Trouble With the Regulators.”

Several promising steps have been taken. But overall, few of our recommended reforms have been enacted.

In the following text, we provide a brief synopsis of our prior six recommendations and a more detailed description of Federal actions taken, if any, since the release of the report.

Minimal progress in recasting Federal IRB requirements so that they grant IRBs greater flexibility and hold them more accountable for results.

Prior Recommendations:

- ▶ *Eliminate or lessen specific procedural requirements that are of questionable value.* Our aim was to provide overburdened IRBs with greater discretion that would enable them to develop more innovative and strategic approaches to their reviews. There are requirements, for example, that limit what IRBs can accomplish in conducting protocol reviews outside of convened board meetings. In addition, we highlighted requirements that call for IRBs to conduct full, annual reviews of approved protocols and that call for complete reviews of Federal funding applications prior to funding decisions.
- ▶ *Require that IRBs undergo regular performance-focused evaluations that are carried out in accordance with Federal guidelines.* In our review, we were struck by how little attention Federal oversight bodies and IRBs themselves gave to evaluating how successful IRBs were in protecting human subjects. It is time, we concluded, for the Federal government to mandate self-evaluations or, better yet, evaluations conducted by independent, outside parties. We also urged that the results of such evaluations be made public.

Update: While some deliberations have been taking place, there have been few enacted reforms along the lines we recommended. The most tangible action was a November 1998 Federal Register notice issued jointly by FDA and NIH/OPRR that expands the categories of research that may be reviewed by IRBs through an expedited review procedure.⁴ This change, already in process before our report was issued, does help minimize IRB workload, but is only one small step toward that end.

The NIH established the Regulatory Burden Advisory Group to identify burdensome procedural requirements and make recommendations on steps to help streamline the regulatory processes for grantee institutions. Among its recommendations, the group proposed a change to the requirement that IRBs review all protocols before funding decisions are made, an improvement we suggested. NIH indicates this change is about to be implemented. Also, NIH/OPRR has been working with the National Cancer Institute to develop a pilot project to establish a central IRB that for certain trials would take on the review functions previously carried out by separate IRBs and streamline the process.

We identified no significant movement in the Federal sector in response to our call for performance evaluations. The most notable development in this regard is in the private sector, where some momentum has been established in developing a system for accreditation of human research protection programs. PRIM&R, a private group devoted to the ethical conduct of research, is working to develop performance standards and apply them as part of an accreditation process. Both NIH/OPRR and FDA are participating in these discussions. We believe that this movement toward accreditation and certification has significant potential for improving human subject protections and urge both NIH/OPRR and FDA to pay particular attention to how it might best complement their continuing oversight responsibilities.

Minimal progress in strengthening continuing protections for human subjects participating in research.

Prior Recommendations:

- ▶ *Require Data Safety Monitoring Boards (DSMBs) for certain high-risk and multi-site trials.* DSMBs are independent assessment bodies that provide medical, scientific and other expertise that typically is not available on IRBs, thereby serving an invaluable function in protecting human subjects. We recommended that NIH and FDA take the lead in seeing that DSMBs become more firmly established as oversight mechanisms and become more clearly accountable.
- ▶ *Require DSMBs to provide summary information to IRBs.* We urged that DSMBs provide their summary assessments of adverse event reports to IRBs. IRBs are swamped with individual adverse event reports from multi-site trials, but these reports lack the essential context to confer meaning about the relative safety of the trial. DSMBs can provide this context and thereby enhance the IRB's capacity to assess the ongoing safety of a trial.
- ▶ *Alert IRBs to corrective actions taken against investigators under the board's purview.* Although FDA provides information on its website about corrective actions that result from investigator inspections, the Agency does not routinely inform the respective IRBs of such actions. We recommended that FDA inform individual IRBs when it takes corrective action against an investigator who is conducting research reviewed by the IRB.
- ▶ *Require sponsors and investigators to notify IRBs of any prior IRB review of a research plan.* Sometimes sponsors shop around for an IRB that will give their protocol a favorable review. We pointed out that such action can undermine the IRB review process and, accordingly, urged that this requirement be enacted.
- ▶ *Call for increased IRB awareness of on-site research practices involving human subjects.* IRBs are rarely aware of what actually takes place between investigator and subject. We called for IRBs to move beyond their focus on the informed consent document and periodically check for themselves how the actual consent process is working. For particularly sensitive or risky projects, we suggested they might call for the participation of counselors, ombudsmen, or other third parties that could be available to make certain that the consent process functions in the interest of human subjects.

Update: For the most part, little has been done to strengthen continuing protections of clinical research subjects. Neither NIH nor FDA has issued requirements for sponsors to notify IRBs of prior reviews, nor have they issued guidance to IRBs to increase their attention to on-site research practices. FDA has not set forth regulations mandating

DSMBs in trials, beyond those for emergency research, or setting standards for the composition of DSMBs, nor has it required that existing DSMBs provide their assessments to the respective IRBs.⁵ Ongoing concern about continuing protections was recently reinforced by the Chairman of the President's National Bioethics Advisory Commission (NBAC). Upon hearing testimony of NIH and FDA witnesses at a NBAC hearing, he responded, "One problem we have heard again and again is that, once an experiment is approved, there is a failure to follow what's going on with the patients. I think there is a growing consensus that something must be done."⁶

Some promising action has been taken. When FDA finds evidence of misconduct on the part of clinical investigators, as of October 1998, FDA now informs the sponsors and IRBs associated with that investigator. In June 1998, NIH reaffirmed its policy that all NIH-supported or -conducted trials "should have a system for the appropriate oversight and monitoring of the conduct of clinical trials."⁷ For example, phase III trials are required to have DSMBs and most involve site monitoring as part of the quality assurance program of the funding Institute or Center. More directly related to our recommendations, in June 1999, NIH issued a policy stating that all DSMBs associated with NIH trials are expected to forward summary reports of adverse events to IRBs.⁸ This is a significant development because this summary information is key to an IRB's ability to ensure the continued safety of subjects.

In March 2000, FDA and NIH announced an initiative that could have important implications for the continuing review of gene transfer trials.⁹ Among other things, FDA will require sponsors of gene transfer trials to routinely submit their monitoring plans to FDA. FDA will review the plans, seek changes it deems necessary, and will perform surveillance and for-cause inspections of the trials to ensure that proper monitoring is taking place. This is an important response to the concerns that have been raised about the adequacy of the oversight of gene transfer trials. FDA's Center for Devices and Radiological Health also requires sponsors of its trials to routinely submit monitoring plans. But both of these policies do not address a large majority of clinical trials, outside of gene transfer or device trials, in which patients can face significant risk. We continue to urge FDA and NIH take similar initiatives directed at other research areas.

No educational requirements have been enacted for investigators or IRB members.

Prior Recommendations:

- ▶ *Require institutions to establish an education program for investigators in human-subject protections.* Such a requirement exists for research involving animal subjects. We found the case for education requirements no less compelling for research involving humans. The mandatory education we called for could be provided through media such as seminars, individual instruction, videos, or on-line tutorials.
- ▶ *Require investigators receiving funding under the Public Health Service Act for research involving human subjects to provide a written attestation indicating that they will uphold Federal policies concerning human-subject protections.* We recommended such an attestation as a way of heightening investigators' awareness of their responsibilities as investigators and interest in participating in educational programs addressing human-subject protections.
- ▶ *Require IRBs to educate their members about human-subject protections.* In order for IRBs to adequately review research protocols to ensure human-subject protections, each board member must be educated in both applicable Federal regulations and ethical principles. We called for a specific mandate that IRBs and their parent institutions provide initial and continuing education.

Update: These recommendations draw on similar ones made in 1995 by the Commission on Research Integrity and, in part, parallel existing NIH policy for institutional recipients of research training grants.¹⁰ No Federal regulations have been enacted requiring institutions to establish education programs for clinical investigators. Similarly, no Federal requirements have been enacted calling for education for IRB members.

NIH intramural researchers are required to complete a web-based tutorial in order to conduct human-subjects research on campus.¹¹ We urge NIH to consider expanding this policy to all extramural researchers, who conduct the majority of research funded by NIH.

In responses to inspection findings, NIH/OPRR and FDA have called upon institutions to establish education programs for clinical investigators, IRB members, and IRB staff. Implicit in these actions is the recognition that an adequate system of protections requires the sensitivity and understanding of everyone involved in human-subject research. Also noteworthy is that a number of institutions have taken important initiatives of their own to strengthen educational efforts.¹²

Both NIH and FDA have increased their activity in educational outreach, conducting numerous training presentations and seminars for IRBs and professional groups. NIH has constructed a website containing bioethics resources and has launched important new initiatives, through training grants, that seek to involve a wide array of investigators in education on human subjects issues and bioethics.¹³ FDA is in the process of updating its Information Sheets, an important source of IRB guidance. NIH/OPRR hired a full-time educational staff person in January 1999, and is in the process of further expanding this staff.

No progress in insulating IRBs from conflicts that can compromise their mission in protecting human subjects.

Prior Recommendations:

- ▶ *Require more extensive representation on IRBs of nonscientific and noninstitutional members.* At present just one IRB member can wear both of these hats and satisfy the requirement. We found that to be an untenable situation, one that can deprive IRBs of a valuable counterbalance to internal, institutional pressures that can threaten their independence.
- ▶ *Reinforce to IRBs and their parent institutions the importance of IRBs maintaining sufficient independence.* It is particularly important that IRBs not report to a part of an institution responsible for bringing in research funds.
- ▶ *Prohibit equity owners from participating in the IRB review process.* Such a practice does not necessarily inhibit the independence of the review process, but it establishes a situation that can undermine a perception of impartiality. We recommended that it should be disallowed.

Update: We did not identify any significant action in HHS that moves in the directions we called for above. We continue to regard this as a significant area warranting attention. In this increasingly commercialized research environment, the potential for conflicts within research institutions loom larger than ever. The gene transfer trials that have gained so much attention in recent months help reinforce the importance of such attention. In some of these trials, the investigators may also have financial investments in the products they are testing. This makes it ever more important that IRB reviews be sufficiently independent, both in reality and in appearance.

Minimal progress in moderating workload pressures of IRBs.

Prior Recommendations:

- ▶ *Require that IRBs have access to sufficient resources to adequately carry out their duties.* Our recommendation was directed not only to staff and board member resources, but also to space, computers, and other essential elements. We urged OPRR to hold institutions accountable for the resource commitments they made in their assurances and for FDA to modify its site visit protocol so that it could more readily identify situations where resource shortages jeopardize an IRB's ability to oversee research.

Update: OPRR's enforcement efforts have brought attention to IRB resource shortages at individual institutions and have led to additional support for IRB functions at a number of those institutions—and quite likely at others that have taken note of the OPRR efforts. However, no further action has been taken to develop indicators of adequate resource levels or to enable greater investments to support IRB functions. One approach that warrants more attention, and that NIH reports is under consideration, would be to allow an additional increment of grant funds to institutions to be used to provide necessary resources for IRBs. Such an approach could help reinforce to institutions and investigators that a well-supported IRB is a necessary cost of doing business.

Minimal progress in reengineering the Federal oversight process.

Prior Recommendations:

- ▶ *Revamp the NIH/OPRR assurance process.* NIH/OPRR's oversight process has been concentrated on reviewing up-front assurances aimed at obtaining an institution's commitment to adhere to Federal requirements. We found that assurance process to be paperwork-laden with little effect on IRB functioning. We urged that NIH/OPRR reorient the assurance process so that it rests on an institutional attestation to conform to Federal requirements, and then devote more NIH/OPRR resources to periodic performance-based reviews of institutions and their IRBs.
- ▶ *Revamp the FDA on-site inspection process.* We recognized that FDA has a much greater on-site presence than NIH/OPRR, but urged that FDA transform its site visit protocol from a narrow compliance orientation to one that is much more performance-based. Such an approach would pay particular attention to how individuals were actually being approached about participating as human subjects and to how IRBs were making risk-benefit trade-offs.
- ▶ *Require IRBs to register with the Federal government.* We found that one of the major impediments to Federal oversight of human-subjects research is that there is no complete registry of the IRBs reviewing this research. Such a registry would be invaluable for FDA and NIH/OPRR as it would allow them to target their oversight and communicate more effectively with IRBs.

Update: OPRR's and FDA's response, as we have already indicated, has been quite significant in one sense. Since issuing our report, both bodies, have increased their enforcement efforts and in so doing have fostered compliance with Federal regulations.

But neither FDA nor NIH/OPRR have to date enacted any significant revamping of their oversight processes as we have called for—even though they can initiate such reform without the constraints of the Common Rule as explained below. This is unfortunate because stepped up enforcement without a more efficient, performance-oriented enforcement process will still leave us with an oversight system that falls well short of its potential.

While FDA has substantially increased its IRB inspections since the issuance of our report, it has not yet engineered any significant changes in its approach to these inspections. The inspections remain narrow and focused on compliance. We recognize the importance of ensuring compliance, but we continue to believe that FDA is losing a major opportunity by not injecting a more results-oriented focus to its inspections. As we indicated in our June 1998 report, such a focus would involve paying particular attention to how individuals are actually being approached about participating as human subjects and to how IRBs are making continuing assessments of risk-benefit trade-offs. It might also involve some probing on how often potential subjects actually turn down requests to participate in research or on how much time they are given to deliberate about participation.

NIH/OPRR reports that it has been developing plans to streamline the assurance process as we called for in our June 1998 report and in accord with a congressional directive to lessen the regulatory burden associated with extramural scientific research. But no actual

change has taken place to date. When and if such change occurs, we continue to urge NIH/OPRR to heed our recommendation that some of the Federal resources freed up by the reform should be directed to periodic performance-oriented reviews of IRBs

Finally, it is important to note that FDA has formed a working group to establish an IRB registration system. The working group has agreed upon specifications for this registry that reflect many of our suggestions. However, nothing has been implemented yet. We encourage the group to follow through with this effort.

The Common Rule represents a significant barrier to HHS progress in implementing many of our recommendations.

In 1991, the HHS core regulations concerning IRBs and human-subject protections became the basis of a common Federal policy on human-subject protections. The Federal policy, known as the Common Rule, is adhered to by HHS and 16 other Federal agencies. Any changes to the Rule call for the concurrence of all 17 Federal agencies.

Several of our recommendations can be carried out through administrative changes, for example through contract and grant language. Many others are incorporated in the Common Rule. In reacting to our June 1998 report and to an earlier version of this report, NIH emphasized that it cannot unilaterally implement any of those recommendations that concern the Common Rule. It reminded us that a number of the changes we call for—for instance, more extensive representation on IRBs of nonscientific and noninstitutional members or stronger requirements on IRBs having sufficient independence—could not be carried out without the agreement of the other 16 agencies. It also made it clear that this was a long and complex process. NIH's point, we have to recognize, is well-taken.

The intention of having a common Federal policy on human subject protections is an important one. One set of standards fosters a level of consistency in protections of human subjects in many different areas of research and is easier for researchers and sponsors to understand and comply with. At the same time, we must acknowledge that the reality of gaining concurrence among 17 Federal agencies inhibits a timely and effective HHS response to a number of our recommendations. With the clinical research environment changing rapidly, we believe it is essential for the Federal policy and regulatory actions to keep pace. The current cumbersome process associated with changing the Common Rule seems to preclude that. It suggests that legislative change may be necessary to achieve a timely implementation of many of our recommendations.

Looking Ahead

Gene Transfer Research as a Catalyst

The untimely death of the subject in a gene transfer trial has raised the public's awareness of the risks that can be associated with clinical research and has spurred some important initiatives by NIH and FDA. These include: (1) a new requirement calling for study sponsors to submit to FDA monitoring plans for gene transfer trials and (2) a series of gene transfer safety symposia that will bring together, in public forums, leading experts to discuss the conduct and potential of this important research.¹⁴ These initiatives may prove to be quite helpful. But, they apply only to gene transfer trials. It is essential, we believe, for similar attention to be directed to ensuring human-subject protections for a broader universe of clinical trials, particularly those in which patients face significant risks.

The Need for Additional Sources of Expertise

Our June 1998 report focused on IRBs, but concluded with recommendations on a broad range of Federal actions that must be taken to protect human subjects. That is because our inquiry convinced us that IRBs alone can not do the job and that in various subtle ways IRBs are expected to carry too much of the burden. We ought not to allow the reform agenda to focus strictly on what can be done to buttress IRBs. That is why we give so much attention to Federal actions that can help educate investigators, who, while they are in a position to do the most harm to patients, are also in a position to do the most good. It is why we have called in a recent report for developing stronger guidelines on human subject recruitment practices.¹⁵ It is also why we draw attention to the vital role that DSMBs can play, particularly for trials that pose significant risks to patients and multi-site trials.

Our Recommendations as a Reference Point

The recommendations we presented in our June 1998 report offer an important reference point for how the current effort to enhance protections for subjects can be extended. We continue to support the recommendations we made in our earlier report and call for a greater sense of urgency in carrying them out. They offer a balanced and practical set of actions that would strengthen human-subject protections without impeding the clinical research that has much potential for society and perhaps even for the individuals participating in the clinical trials. They reflect a respect for the largely collegial manner in which IRBs operate and seek to nourish the volunteer contributions that have provided the underpinning of IRB reviews. Yet they recognize that verification and accountability must also be important features of a system intended to protect human subjects.

While our recommendations serve as an important framework for reform, we do not intend to suggest that they provide a complete blueprint for action. In the months ahead, we will be conducting further inquiry that more closely examines how HHS oversight can help enhance human subject protections. In that period, the National Bioethics Advisory Commission (NBAC) is also likely to offer further guidance on the kind of changes that need to be made in the Federal regulatory system. Its recommendations will offer valuable perspective and grounding for the reform agenda that we continue to call for with a sense of urgency.

New Opportunity for Leadership

Once OPRR is located in the Office of the Secretary and a new advisory committee on protection from research risks is established, as the HHS Secretary has called for, HHS will have a significant new opportunity to exert Federal leadership in protecting human subjects.

We urge that the new office give significant attention to our prior recommendations and to those that will be forthcoming from NBAC. We also urge that it continue the important enforcement efforts undertaken by OPRR over the past 2 years. In increasingly commercialized research environments where IRBs are facing heightened pressures to conduct quicker reviews, the NIH/OPRR efforts have served as a reminder to research institutions, sponsors, individual investigators, and IRBs that the reviews must still be substantive ones that ensure adequate protections for human subjects. In the important quest to reduce regulatory burdens, it is important not to lose sight of this underlying protection function.

Continued Significance of FDA and NIH Roles

At the same time, we continue to call for stronger FDA and NIH responses to our recommendations. Even with the establishment of the new office, both agencies retain significant statutory and operational responsibilities for protecting human subjects. With FDA conducting about 300 on-site inspections of IRBs each year, it still has the most visible on-site presence and thus is in the best position to identify shortcomings and opportunities for improvement. We recognize that FDA must operate with limited resources, but much could be accomplished through a revamping of its on-site inspection process in the performance-oriented direction we spelled out. FDA can make better use of the opportunities its site visits offer as catalysts for positive change. In addition, we continue to urge FDA to expedite its efforts to require registration of IRBs.

As a major funder of clinical research and as a major link with the research community, NIH retains significant roles in ensuring human-subject protections despite the relocation of OPRR. We urge particular attention to our recommendations calling for Federal requirements to ensure that investigators are adequately educated about and sensitized to human-subject protections. It is vital, we continue to believe, for NIH to exert stronger, more directed leadership in this educational arena.

Institutional Review Boards: The Basics

What Do They Do?

The responsibilities of IRBs fall into two main categories: initial review and continuing review of research involving human subjects.

Initial Review. IRBs review and approve a research plan before the research is carried out. This review encompasses the research protocol, the informed consent document to be signed by subjects, any advertisements to be used in recruiting subjects, and other relevant documents. In carrying out this review, the boards seek to ensure that any risks subjects may incur are warranted in relation to the anticipated benefits, that informed consent documents clearly convey the risks and the true nature of research, that advertisements are not misleading, and that the selection of subjects is equitable and justified. IRBs focus much attention on the informed consent document because it is the vehicle for providing information to potential research subjects.

Continuing Review. The continuing review process is multifaceted and includes required reviews at an interval appropriate to the degree of risk but not less than once per year. In addition to this continuing review, IRBs receive periodically and review amendments and reports of subjects' unexpected adverse experiences. This review seeks to ensure that the risk-benefit ratio of the research remains acceptable.

Why Were They Established?

As public awareness and concern about the treatment of human subjects in research increased, the need for additional review mechanisms was evident. These concerns grew from stories of the abuse of subjects during the World War II trials at Nuremberg, the promotional distribution of thalidomide resulting in numerous children born with birth defects, the administration of cancer cells to chronically ill and senile patients at a hospital in New York, and others. In 1966, Henry Beecher brought prominent attention to human research abuses in medical schools and hospitals, citing 22 cases involving highly questionable ethics. The formal requirements for the establishment of IRBs were outlined in regulations stemming from the National Research Act of 1974 and in FDA regulations issued in 1981.

Where Are They Located?

An estimated 3,000-5,000 IRBs can be found across the country. They are most commonly associated with hospitals and academic centers. Boards also exist in managed care organizations, government agencies (such as the NIH, FDA, the Centers for Disease

Control and Prevention, and State governments), or as independent for-profit entities.

How Are They Organized?

Federal regulations require that boards have at least five members with varying backgrounds. At least one member must have primarily scientific interests, one must have primarily nonscientific interests, and one must be otherwise unaffiliated with the institution in which the IRB resides. A quorum, with at least one member whose interests are primarily nonscientific present, is needed for voting.

How Does the Department of Health and Human Services (HHS) Oversee Them?

Two agencies within HHS share responsibility for IRB oversight: NIH, through its Office for Protection from Research Risks (NIH/OPRR), and the FDA. The NIH/OPRR's main tool for oversight is the assurance document. Any institution that intends to conduct HHS-funded research must have an assurance on file with NIH/OPRR. The assurance is a written statement of an institution's requirements for its IRB and human-subject protections. Institutions consistently conducting multiple HHS-supported studies are eligible for a multiple project assurance which can be renewed every 5 years. Institutions with smaller HHS-funded workloads, however, use a single project assurance for each such project it conducts. The NIH/OPRR also conducts a small number of site visits. The FDA's main mechanism for IRB oversight is the inspection process. FDA becomes aware of IRBs when they are listed by a clinical investigator in a statement that the investigator will comply with all pertinent regulations. The FDA also inspects research sponsors and scientists (also known as research investigators).

FINDINGS

Institutional Review Boards: A Time for Reform (OEI-01-97-00193), June 1998

What follows are the findings taken from the Executive Summary of our June 1998 report, *Institutional Review Boards: A Time For Reform*:

The Effectiveness of IRBs Is in Jeopardy.

They Face Major Changes in the Research Environment. The current framework of IRB practices was shaped in the 1970s in an environment where research typically was carried out by a single investigator working under government funding with a small cohort of human subjects in a university teaching hospital. In recent years, that environment has been changing dramatically as a result of the expansion of managed care, the increased commercialization of research, the proliferation of multi-site trials, new types of research, the increased number of research proposals, and the rise of patient consumerism. Each of these developments has presented major disruptions and challenges for IRBs. “Never before,” concluded one recent review, “has such a pressure-cooker atmosphere prevailed within the IRB system.”

They Review Too Much, Too Quickly, with Too Little Expertise. This is especially apparent in many of the larger institutions. Expanded workloads, resource constraints, and extensive Federal mandates contribute to a rushed atmosphere where sufficient deliberation often is not possible. At the same time, the IRBs frequently are hard-pressed to gain access to the scientific expertise they need to reach informed judgments about the research taking place under their jurisdiction.

They Conduct Minimal Continuing Review of Approved Research. In the environment described above, continuing review often loses out. Even where there is the will, there often is not the time to go beyond the perfunctory obligations. A lack of feedback from other entities that oversee multi-site trials contributes to the problem. The result is that IRBs have all too little information about how the informed consent process really works and about how well the interests of subjects are being protected during the course of research.

They Face Conflicts That Threaten Their Independence. Clinical research provides revenue and prestige to the institutions to which many IRBs belong. The institutions expect IRBs to support these interests at the same time that they protect human subjects. The resulting tension can lessen the IRBs’ focus on their basic mission. The minimal “outside” representation that typically exists on IRBs deprives them of an important counterbalance to the institutional interests. For independent IRBs, the dependence on

revenue from industry sponsors exerts similar possibilities for conflict.

They Provide Little Training for Investigators and Board Members. The IRB system depends heavily on research investigators' commitment to uphold human-subject protections. But as that system now operates, it offers little educational outreach to investigators to help them become informed and sensitized about these protections. Similarly, it provides minimal orientation and continuing education for IRB members—a deficiency that is especially detrimental to nonscientific and noninstitutional members.

Neither IRBs Nor HHS Devote Much Attention to Evaluating IRB Effectiveness. IRBs rarely conduct inquiries to determine how well they are accomplishing their mission; their judgments of effectiveness rely mainly on the number of protection lapses or complaints that are brought to their attention. The HHS agencies conducting oversight seldom go any further. The Office for Protection from Research Risks, in the National Institutes of Health, focuses almost entirely on up-front assurances. The Food and Drug Administration relies on compliance-focused inspections.

Current Status of FDA and NIH/NIH/OPRR Response to Recommendations
Institutional Review Boards: A Time for Reform (OEI-01-97-00193), June 1998

Recommendation		
1. Recast Federal Requirements	1a. Eliminate or lessen some of the procedural requirements	<ul style="list-style-type: none"> ▶ FDA and OPRR issued more expedited review categories (11/98) ▶ OPRR/NCI proposed demonstration project using a central IRB to streamline processes
	1b. Require IRBs undergo regular performance-based evaluations	<ul style="list-style-type: none"> ▶ No action ▶ Private accreditation movement initiated
2. Strengthen Continuing Protections	2a. Require Data Safety Monitoring Boards (DSMBs) for certain trials	
	2b. Require DSMBs to provide summary information to IRBs	
	2c. Alert IRBs to corrective actions taken against investigators under their purview	
	2d. Require sponsors and investigators to notify IRBs of any prior review	
	2e. Call for increased IRB awareness of on-site research practices	
3. Enact Educational Requirements	3a. Require institutions to establish an education program for investigators in human-subj. protections	<ul style="list-style-type: none"> ▶ NIH has launched a number of initiatives and OPRR has required the establishment of education programs as a result of investigations ▶ No action towards a requirement
	3b. Require investigators provide a written attestation to uphold human-subj. protections	<ul style="list-style-type: none"> ▶ No action
	3c. Require IRBs to educate their members about human-subj. protections	<ul style="list-style-type: none"> ▶ No action ▶ FDA and NIH/OPRR have required the establishment of educ. programs as a result of investigations and are active in outreach
4. Help Insulate IRBs from Conflicts That Threaten Their Independence	4a. Require more extensive representation of nonscientific and noninstitutional members	
	4b. Reinforce the importance of IRBs maintaining sufficient independence	
	4c. Prohibit equity owners from participating in the IRB review process	
5. Recognize Workload Pressures	5. Require that IRBs have the resources to adequately carry out their duties	<ul style="list-style-type: none"> ▶ No action
6. Reengineer Federal Oversight Process	6a. Revamp NIH/OPRR assurance process	
	6b. Revamp FDA on-site inspection process	

Endnotes

1. (1) Advisory Committee on Human Radiation Experiments, *Final Report*, (Washington DC: U.S. Government Printing Office, 1995). (2) U.S. General Accounting Office, *Scientific Research: Continued Vigilance Critical to Protecting Human Subjects*, GAO/HEHS-96-72, March 1996. (3) Department of Health and Human Services, Office of Inspector General, *Investigational Devices: Four Case Studies* (OEI-05-94-00100), April 1995.
2. (1) *Institutional Review Boards: A System in Jeopardy?: Before the House Comm. on Government Reform and Oversight*, 105th Cong., June 11, 1998. (2) *Do Current Federal Regulations Adequately Protect People Who Participate in Medical Research?: Before the Subcomm. on Criminal Justice, Drug Policy, and Human Resources of the House Comm. on Government Reform*, 106th Cong., December 9, 1999.
3. These groups include, but are not limited to, Public Responsibility in Medicine and Research, Applied Research Ethics National Association, the Society of Administrative Managers of General Clinical Research Centers, the American Health Lawyers Association, and the Food and Drug Law Institute.
4. 63 Fed. Reg. 60,364-60,367 (November 9, 1998).
5. FDA does require DSMBs for trials in emergency circumstances in which informed consent is waived. (21 C.F.R. 50.24)
6. Phillip Hilts, "Panel Seeks Better Monitoring of Experiments Using People," *New York Times*, March 2, 2000.
7. "NIH Policy for Data and Safety Monitoring," National Institutes of Health, June 10, 1998. [<http://www.nih.gov/grants/guide/notice-files/not98-084.html>, accessed 4/1/99]
8. "Guidance on Reporting Adverse Events to Institutional Review Boards for NIH-supported Multicenter Clinical Trials," National Institutes of Health, June 11, 1999. [<http://grants.nih.gov/grants/guide/notice-files/not99-107.html>, accessed 3/00]
9. "New Initiatives to Protect Participants in Gene Therapy Trials," National Institutes of Health, March 7, 2000. [<http://www.nih.gov/news/pr/mar2000/od-07.htm>, accessed 3/00]
10. The Commission on Research Integrity, *Integrity and Misconduct in Research*, (Washington, DC: U.S. Government Printing Office, November 1995).
11. The web-based tutorial is available on the internet at [<http://helix.nih.gov:8001/ohsr/newcbr/>]
12. Of particular note is the effort at the University of Rochester. After the death of a healthy subject participating in a trial, University administration formed a committee to recommend needed reforms. The Committee recommended, "that all investigators at the University be informed adequately, and on a continuing basis, of the fundamental requirements, responsibilities and ethical issues related to the conduct of human subject research." In addition, it recommended

“that this be accomplished in the setting of a formalized educational program and that a reasonable effort be made to assess the understanding of the information conveyed.” As a result, all investigators must follow a self-study training program and pass a brief exam before their projects will be reviewed by the IRB and, thus, before they may conduct clinical research at the university. (Further information, see [<http://www.urmc.rochester.edu/urmc/rsrb/hspp.htm>, accessed 3/00])

13. The website can be found at [www.nih.gov/sigs/bioethics/]. The training initiatives include a short-term training program in bioethics, for which 15 awards have been given to date, a clinical program in 35 academic health centers which addresses clinical research more generally but also includes bioethics issues, and a mentored scientist award that supports scientists who want to specialize in training in bioethics.

14. “New Initiatives to Protect Participants in Gene Therapy Trials,” National Institutes of Health, March 7, 2000. [<http://www.nih.gov/news/pr/mar2000/od-07.htm>, accessed 3/00]

15. Department of Health and Human Services, Office of Inspector General, *Recruiting Subjects for Industry-Sponsored Clinical Research* (OEI-01-97-00196), in draft.