Part 2: Protecting Future Human Subjects

Overview

The success of the effort to open the historical record will be measured, in part, by whether we avoid repeating the mistakes of the past. ACHRE's review of human radiation experiments raised questions of whether the current system of protection is adequate for all types of human subjects research. The measures described below will strengthen the protection of human subjects and address ACHRE's findings.

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Federal responsibilities for maintaining ethics in human subjects research are dispersed in several agencies and committees in the government. First, each agency is responsible for the ethical administration of its programs, including grants and contracts. Second, the President's Office of Science and Technology Policy has a statutory oversight role, and will continue to monitor and address issues of science and ethics. Third, the Department of Health and Human Services has a convening role among agencies that are bound by the Common Rule—the Federal Policy for the Protection of Human Subjects which, along with Food and Drug Administration (FDA) regulations, governs all federally conducted, funded, or regulated research (56 *Federal Register* 28010, June 18, 1991). Finally, the National Bioethics Advisory Commission (NBAC)—an independent body recently established by the President—is taking up some of the most pressing ethical issues faced by this country. (For a description of NBAC see page 11.)

The National Bioethics Advisory Commission (NBAC) is taking up some of the most pressing ethical issues that we face.

The Human Radiation Interagency Working Group (IAWG) is a temporary collaboration among several Federal agencies. The IAWG has worked to support ACHRE and to respond to its recommendations. The policies in this report seek to ensure appropriate follow-up on ACHRE recommendations by more permanent bodies.

ACHRE Findings and Recommendations on Protecting Human Subjects in the Future

Based on its review of current human subject protections, the Advisory Committee found, among other things, that

> **[H]uman research involving radioisotopes is currently subjected to more safeguards and levels of review than most other areas of research involving human subjects. The Advisory Committee further finds that there are no apparent differences between the treatment of human subjects of radiation research and human subjects of other biomedical research. (Finding 20)**

Responsibility for ethical conduct of research begins with researchers and extends to their institutions, and the Institutional Review Boards (IRBs).

> **[T]oday research involving human subjects sponsored by the government may be classified and conducted in secret, but it must comply with the provisions of the Common Rule. (Finding 21)**

> **[I]n comparison with the practices and policies of the 1940s and 1950s, there have been significant advances in the protection of the rights and interests of human subjects of biomedical research. However, we also find that there is evidence of serious deficiencies in some parts of the current system for the protection of the rights and interests of human subjects. (Finding 22)**

ACHRE Recommendation on the Centrality of Ethics

ACHRE recommended that active efforts on a national scale be made to ensure that human subjects researchers fully understand the ethical implications and responsibilities of their work, and the centrality of ethical decisions. (Recommendation 9)

Response

Responsibility for the ethical conduct of research begins with researchers and extends to their institutions and the Institutional Review Boards (IRBs). The Administration has multiple efforts underway to reach, educate, oversee, and hold accountable each layer of the research system. The Administration is also taking steps to promote understanding of, and consensus about, ethical issues.

National Bioethics Advisory Commission

The National Bioethics Advisory Commission (NBAC), a national deliberative body of private citizens, was established by the President to provide guidance to all Federal agencies on the ethical conduct of human behavioral and clinical research, and the applications of that research. NBAC was established, in part, to respond to ACHRE, and the Administration expects NBAC will choose to address the key issues identified in ACHRE's recommendations. NBAC will not be able to review all issues raised by ACHRE. The Administration has been careful to ensure that issues not taken up by NBAC will be addressed elsewhere.

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As a first priority, NBAC will seek to improve protection of the rights and welfare of human research subjects. The Executive Order establishing NBAC, required each agency to review its current human subjects research in light of the Advisory Committee recommendations and report the results to NBAC. NBAC is currently reviewing these documents. Appendix C details specific activities currently being carried out by the agencies as a result of their reviews.

NBAC's meetings are public and provide a forum for dialogue on ethics issues. NBAC has heard presentations on issues related to genetic research, including cloning, as well as the broader area of human subjects research. Members of Congress, Congressional staff, and representatives from diverse organizations including the Task Force on Radiation and Human Rights, the College of American Pathologists, the Biotechnology Industry Organization, and Citizens for Responsible Care in Psychiatry and Research testified on ethics issues and on NBAC's mission. Further information can be obtained from the NBAC Web Site (www.nih.gov/nbac/nbac.htm).

Education

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ACHRE's report made clear that a key to preventing the repetition of past mistakes is thorough and continuing education about ethics and how they apply to current human subjects research. The Administration is responding to ACHRE's specific recommendations by co-sponsoring educational programs with external groups such as medical schools, universities, and scientific societies. The goals of these educational efforts are to strengthen human subjects protection, to provide a forum for addressing ongoing as well as emerging issues in human subjects research, and to familiarize professionals engaged in non-federally funded human subjects research with relevant ethical considerations.

Part of the ongoing educational process is a reinforcement of the importance of Institutional Review Boards (IRBs) at institutions conducting federally funded research. These IRBs are local groups

whose membership and responsibilities are regulated by the Federal government. They are responsible for reviewing and approving the ethical content of all proposed human subjects research projects. IRBs are a linchpin in the protection of human subjects, and their credibility and effectiveness depend on adequate awareness of basic ethical topics.

Similarly, educational programs are also being targeted at government-regulated research that is not government-funded (e.g., FDA-regulated research sponsored by the pharmaceutical industry). In September of 1996, the FDA sponsored its first nationwide conference on human subjects protection.

Government employees who have responsibility for supporting or overseeing human subjects research are also targeted for educational programs. Thus, Federal agencies are implementing training programs to educate senior level officials on regulations and policies governing this research. For example, NASA is working with international research partners to develop common ethical principles that ensure the protection of human subjects. DOE educational efforts target laboratory staff, field office personnel, and program officials.

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Information Gathering

ACHRE's report highlighted the limited state of knowledge regarding some key issues in human subjects research. Most importantly, NBAC will be reviewing and evaluating the IRB process.

In addition, Departments have pooled resources to sponsor research on the informed consent process. The informed consent process is intended to help each potential research subject decide whether to participate in research by providing advance information about the research. Information includes a description of the nature of the research, the subject's role and potential risks, and the subject's rights and responsibilities. Despite the vigor with which all parties embrace the informed consent process, it is not well understood. Much of the Advisory Committee's commentary on current human subjects research was centered on informed consent. The National Institutes of Health (NIH), VA, and DOE are committed to supporting research that will more fully illuminate the informed consent process. A Request for Applications (RFA) to conduct research on this issue was published in the fall of 1996, and Fiscal Year 1997 monies are earmarked to support this RFA.

ACHRE Recommendation on Institutional Review Boards

ACHRE recommended specific changes to IRBs in five critical areas (Recommendation 10):

(1) mechanisms to ensure a stronger focus on studies that pose more than minimal risk to subjects;
(2) better means of explaining to potential subjects the distinction between research and treatment, the realistic likelihood of medical benefit to the subject from participation, and the potential for discomfort and pain;
(3) ensuring that potential subjects fully understand the sponsors and purposes of the research;
(4) ensuring that potential subjects fully understand the financial implications of participation; and
(5) recognition that the IRBs must decide if the quality of the science justifies the risk to the subjects.

The Administration anticipates specific recommendations from NBAC regarding reform of IRBs, including recommendations that address ACHRE's concerns.

Response

The Administration agrees that there are indications that the IRB system is not always adequate to ensure protection of human subjects. NBAC has undertaken to review the current IRB system and intends to finish that project within a year. The Administration anticipates specific recommendations from NBAC regarding reform of IRBs, including recommendations that address ACHRE's concerns.

In the interim, agencies are informing IRBs of ACHRE's recommendations and are working to improve IRBs.

The Office for Protection from Research Risks (OPRR), part of NIH, is undertaking a national effort to educate the research community about ACHRE's recommendations. OPRR and FDA support an annual public meeting for individuals interested in the governance of human subjects research. In addition, OPRR, in cooperation with FDA and local academic institutions, has held discussions of the recommendations at national workshops in Atlanta, Oklahoma City, Honolulu, Peoria, Houston, and San Diego.

OPRR and the FDA make extensive use of public meetings, forums, hearings, and electronic media to address evolving issues on human subject protection. OPRR and FDA also regularly mail information directly to IRBs and other interested parties. FDA seeks public input through the *Federal Register* and by mailing proposals to the IRB and clinical investigator communities. In October 1995, FDA issued

a major revision of its "Information Sheets for Institutional Review Boards and Clinical Investigators," to take into account the latest thinking and to provide guidance to IRBs. This information is available on the Internet (www.fda.gov/oc/oha/toc.html).

As noted above, ACHRE recommended that IRBs focus the bulk of their time on studies that present more than minimal risk to subjects. To educate the research community about the importance of this recommendation, OPRR sent information to 5,500 addressees worldwide. The information highlighted regulatory provisions for (1) exemption from IRB review of 6 categories of low-risk research, and (2) expedited IRB review of 10 other kinds of research when it is judged by IRBs to be of minimal risk. Proper use of these time-saving mechanisms permits IRBs to devote greater effort to the areas of concern to ACHRE.

ACHRE Recommendation on Maintaining an Open Public Forum

The National Bioethics Advisory Commission (NBAC) will provide an opportunity for public participation in the continuing review and interpretation of ethical rules.

ACHRE recommended the creation of a mechanism to provide for continuing public discussion and interpretation of ethical rules and principles that govern human subjects research. (Recommendation 11)

Response

The Administration agrees that continuing discussion of ethical rules is vital to protection of human subjects in government-sponsored and privately sponsored research. Both the government and private institutions have key roles in ensuring that this debate continues. The National Bioethics Advisory Commission (NBAC) will provide an opportunity for public participation in the continuing review and interpretation of ethical rules.

Private organizations and periodicals also serve an important role in the continuing public discussion of ethical rules.

The Administration also agrees that there is a need for a mechanism to interpret the existing rules that apply to government-sponsored research. The Department of Health and Human Services (HHS), particularly OPRR and FDA, provides information and interpretations of the regulations for protection of human subjects. OPRR also maintains an Information-by-FAX service (301-594-0464) and a World Wide Web site (nih.gov:80/grants/oprr/oprr.htm) to distribute information, and responds to inquiries by mail. FDA provides these functions for FDA-regulated research and OPRR provides them for other federally supported research.

Individual agencies are also promoting public discussion of current ethical issues. For example, DOE's Ethical, Legal, and Social Issues (ELSI) program sponsors a wide variety of educational programs, including meetings and seminars. DOE has recently sponsored two highly acclaimed public television programs on the human genome program. DOE has also sponsored a workshop for trial judges to receive information about, and discuss the use of, DNA evidence in the courtroom. The genome program has also sponsored conferences to discuss genetics in light of religion, discrimination, and other ethical issues.

These projects are good examples of public and private entities working together to promote civil discourse over ethical issues. The Administration will seek additional opportunities to support this kind of effort.

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ACHRE Finding and Recommendation on the Protection of Military Personnel

ACHRE found that it is often difficult, in a military setting, to distinguish requests for volunteers from orders.

> **The military setting, with its strict hierarchical authority structure and pervasive presence in the lives of its members, poses special problems for ensuring the voluntariness of participation in research activities. Thus, although the DOD has adopted and implemented the consent requirements of the Common Rule, additional procedural safeguards and educational activities for officers may be warranted to counteract the generalized deference to authority inherent in military culture. Also, because the opportunity to serve the nation as subjects in defense-oriented research projects is closely akin to the demands placed on members of the military in their routine duties, it is desirable to emphasize the distinction between research and course-of-duty risks both in consent procedures and in officer training programs.**

ACHRE recommended that the military better ensure the protection of rights and interests of military personnel who are involved in human subjects research by reviewing general policies and procedures, educating officers and investigators, implementing policies and practices that make certain participation is genuinely voluntary, and maintaining a registry of volunteers. (Recommendation 12)

Response

The Administration agrees that extraordinary steps are needed to protect military personnel, and DOD is implementing ACHRE's recommendations. Among other steps, DOD is revising directives and Military Department regulations, and incorporating needed training into courses for commanders, senior leadership, and those involved in human subjects research. In the summer of 1997, DOD will publish a revised human subjects protection directive that includes policy changes recommended by the Advisory Committee. For example, to avoid undue command influence, the new policy will preclude officers and noncommissioned officers from playing a role in selecting volunteers for military tests. (See Appendix C for more details).

In the summer of 1997, DOD will publish a revised human subjects protection directive that includes policy changes recommended by the Advisory Committee.

ACHRE Findings and Recommendation on the Federal Oversight of Research

ACHRE found that oversight of human subjects research is limited and is constrained by practical considerations. ACHRE found that the "current mechanisms for oversight . . . do not provide a sufficient basis for ensuring that the current system is working properly."

ACHRE found that sanctions may be inadequate for violations of human subjects research protections. For example failure to obtain consent from subjects (who are not physically injured) is generally punishable only by the withdrawal of research funding.

ACHRE also found that "there is a need to assess the level of research performed outside [the Common Rule] and to consider action to ensure that all subjects are afforded the protections it offers." ACHRE recommended the improvement of three parts of the current Federal system for human research subject protection: oversight of the research process; sanctions for violations of human subjects protections; and protections for subjects of non-federally funded research. (Recommendation 13)

Response

The Administration agrees that there are important gaps in the current system of human subjects protection, and has identified, in testimony before Congress, examples of research that does not fall within the ambit of Federal protection. Congress has proposed the Human Research Subject Protection Act of 1997 (S. 193) to ensure that all human subjects are adequately protected. The Administra-

tion believes that Congress is also the appropriate place to consider whether additional civil or criminal sanctions for the violation of human subject protections are necessary and desirable. (Sanctions, including criminal liability, apply to investigators conducting FDA-regulated research who violate FDA regulations protecting human subjects.) Any legislation would need to protect research subjects and avoid deterring needed research.

In addition to exploring legislation, Federal agencies are undertaking specific activities to strengthen oversight, some of which are described in Appendix C. The Administration expects that NBAC will recommend additional actions to improve oversight of Federal research, and will identify the highest priority steps.

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ACHRE Findings and Recommendation on the Compensation of Subjects in the Future

ACHRE found that the Federal government lacks a "policy or guide for a fair system of compensation of research subjects."

ACHRE recommended that the government resolve the longstanding issue of whether and how all persons injured in the future from federally funded human subjects research should be compensated. ACHRE recommended that the Federal government consider a system of compensation for research subjects who suffer physical injury or dignitary harm as a result of federally funded research. (Recommendation 14)

Response

In the absence of a finding that a significant number of modern research subjects are unfairly denied compensation, the Administration is not prepared to propose a system outside the existing network of Federal and state liability and insurance systems.

The Administration does, however, view the debate over the extent and effectiveness of our current human subject protections to encompass this issue. The Administration would be open to considering any recommendations from NBAC or legislation from Congress that seek to address this issue.

The desire to spread the cost of research injury is a reason to consider a compensation scheme. The current tort system, though imperfect, provides one mechanism to seek compensation for injuries that arise from research. In addition, the tort system

provides a powerful incentive to researchers to observe appropriate standards of care in conducting the research. These standards generally include providing for informed consent and exercising care in the conduct of research.

ACHRE Recommendations Regarding Classified Research

Because of its concerns about past use of secret research, ACHRE recommended that (a) the Administration establish a formal policy prohibiting waiver of informed consent for classified research and requiring that potential subjects of classified research must be told the identity of the sponsoring agency. ACHRE also recommended that (b) for classified research, the Administration establish an independent panel to review scientific merit, risk/benefit balance, consent procedures, and whether subjects need a security clearance to assure fully informed consent. The records of this panel would be permanent. (Recommendation 15)

Response

Federal agencies will jointly propose modifications to the Federal Policy for the Protection of Human Subjects (Common Rule) as it applies to classified research.

ACHRE acknowledged that it is in the nation's interest to continue to allow the government to conduct classified research using human subjects where such research serves important national security interests. The Committee found, however, that classified human subjects research should be a "rare event" and that the "subjects of such research, as well as the interests of the public in openness in science and in government, deserve special protections." ACHRE was concerned about "exceptions to informed consent requirements and the absence of any special review and approval process for human research that is to be classified." ACHRE recommended that all classified research meet the following requirements:

- obtain informed consent from all human subjects;
- inform subjects of the identity of the sponsoring agency;
- inform subjects that the project involves classified research;
- establish permanent records; and
- be approved by an "independent panel of nongovernmental experts and citizen representatives, all with the necessary security clearances."

The Administration agrees with the first four recommendations. The President is issuing a memorandum directing Federal agencies to jointly propose modifications to the Federal Policy for the Protection of Human Subjects (Common Rule) as it applies to classified research in order to implement these changes. Further, subjects will be informed of the sponsoring agency, except in limited, minimal-risk cases. In all secret studies, researchers will obtain informed consent, disclose that the project involves classified research, and keep permanent records.

The Administration also agrees with ACHRE's call for a special review process for classified research and permanent recordkeeping. The Federal agencies will jointly propose (1) amending the common rule to require that IRBs for secret projects include a non-governmental member; (2) establishing an appeals process so that any member of a review board who believes a project should not go forward can appeal the board's decision to the head of the agency and, if necessary, the Assistant to the President for Science and Technology; and (3) requiring the sponsoring agency to keep permanent records of the panel's deliberations and the informed consent process, and to declassify such records as soon as appropriate.

The Administration is taking two additional steps to ensure that classified human subjects research remains rare. The President is directing the heads of Federal agencies to disclose annually the number of secret human research projects undertaken by the agency and the number of human subjects participating in each project.

These steps will preserve the government's ability to conduct any necessary classified research involving human subjects while ensuring adequate protection of research participants. (See Appendix E for the directive from the President regarding classified research.)

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ACHRE Findings and Recommendations Regarding Secret Environmental Releases

The Advisory Committee found that events that raise the same concerns as the intentional environmental releases of radiation in 1948 to 1952, "could still take place in secret under current environmental laws and regulations."

The Advisory Committee further noted that,

> **Today the law provides that environmental reviews may be conducted in part or even in whole in secret, thereby eliminating provision for public notice and comment. In classified programs, the government must still comply with environmental standards, and the Environmental Protection Agency must oversee and review environmental compliance. However, the EPA has not maintained records of environmental releases where the reviews were conducted in whole or in part in secret. (Finding 23)**

The Advisory Committee recommended that (a) there be review by an independent panel of any planned environmental release where any aspect involves secrecy; and that (b) environmental oversight of classified programs, now done by the Environmental Protection Agency (EPA), should include keeping review records permanently and reporting to Congress. (Recommendation 16)

Response

EPA, in conjunction with Federal agencies conducting classified programs, is taking steps to improve environmental oversight and enforcement capability over all classified activities.

The Administration agrees that the framework for oversight and recordkeeping of reviews of secret environmental releases needs to be improved.

EPA, in conjunction with Federal agencies conducting classified programs, is taking steps to improve environmental oversight and enforcement capability over all classified activities. These steps include formal agreements between EPA and other Federal agencies to streamline the process of providing information about environmental compliance related to classified activities. This effort will give environmental enforcement authorities the information they need to appropriately review secret environmental releases. It would be difficult, if not impossible, to create similar enforcement capabilities in a new regulatory entity, such as an independent review panel, that focuses only on these extremely rare occurrences. In addition, a new entity would add to the bureaucratic complexities of ensuring environmental safety and would not necessarily increase public protection.

EPA will establish and maintain a permanent file to document EPA's classified reviews under the National Environmental Policy Act (NEPA). The EPA policy establishing this permanent file will address transport, storage, review, and permanent recordkeeping of classified NEPA documents and EPA review comments. EPA will notify all Federal agencies of its new classified filing and review procedures and will provide Congress with information on request.