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SCIENTIFIC RESEARCH

Continued Vigilance Critical to Protecting Human Subjects

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Mr. Chairman and Members of the Committee:

I am pleased to be here today to testify on our report to the Committee on efforts to protect human research subjects.[1] Concerns have been raised about the effectiveness of today's safeguards in light of the recent disclosures of unethical Cold War-era radiation experiments and reports of infringements on subjects' rights, such as in a contemporary study of breast cancer.

Over the past 3 decades, the Department of Health and Human Services (HHS)—the primary federal sponsor of biomedical and behavioral research—has established procedures to minimize risks experienced by patients and healthy volunteers who participate in research that it supports or regulates. We reviewed HHS' human subject protection system, concentrating on the prevention, monitoring, and enforcement activities of the National Institutes of Health's (NIH) Office for Protection from Research Risks (OPRR) and the Food and Drug Administration (FDA). Within FDA, we examined the human subject protection activities of the Center for Drug Evaluation and Research because drug research is the largest segment of biomedical research.[2] We interviewed federal and research institution officials; medical and behavioral researchers; representatives of the drug industry; and experts in bioethics, law, and social science. We also reviewed HHS and FDA regulations, guidelines, and records and human subject protection procedures and records at research institutions.

I would like to highlight three key findings from our report. First, HHS' oversight of tens of thousands of studies appears to have reduced the likelihood that serious abuses of human subjects, comparable to past tragic events, will occur. Second, no practical level of oversight can guarantee that each researcher will protect subjects with complete integrity. The detection of recent instances of potential or actual harm to subjects both demonstrates that abuses can occur and also suggests that the current oversight activities are working. Finally, various time, resource, and other pressures have reduced or threaten to reduce the effectiveness of such oversight.

[1]Scientific Research: Continued Vigilance Critical to Protecting Human Subjects (GAO/HEHS-96-72, Mar. 8, 1996).

[2]FDA's Center for Biologics Evaluation and Research and Center for Devices and Radiological Health also carry out activities to protect human subjects of product testing. These activities were not included in the scope of our review.

Background

Since the 1960s, there have been significant advances in protecting the rights and welfare of human subjects in biomedical and behavioral research. The federal presence has grown in this area, establishing and enforcing regulations for protecting human subjects in federally funded and federally regulated research. HHS' regulation of biomedical and behavioral research consists of two principal tiers of review: one at the federal level and one at the research institution level. Both tiers are responsible for ensuring that individual researchers and their research institutions comply with federal laws and regulations for protecting human subjects. When the core of HHS' human protection regulations was adopted by 15 other federal departments and agencies in 1991, it became known as the Common Rule.[3]

Within the HHS oversight system there are several entities overseeing compliance with human protection regulations. At the federal level are the NIH's OPRR and the FDA. At the local level, institutional review boards (IRB)—that is, review panels that are usually associated with a particular university or other research institution—are responsible for implementing federal human subject protection requirements for research conducted at or supported by their institutions. In general, IRB members are scientists and nonscientists who volunteer to review proposed studies.

The Common Rule requires research institutions receiving federal support and federal agencies conducting research to establish IRBs to review research proposals for risk of harm to human subjects and to perform other duties to protect human research subjects. It also stipulates requirements related to informed consent—how researchers must inform potential subjects of the risks to which they, as study participants, agree to be exposed. HHS regulations contain additional protections not included in the Common Rule for research involving vulnerable populations—namely, pregnant women, fetuses, subjects of in vitro fertilization research, prisoners, and children.

[3]Currently, these regulations have been adopted by 17 federal departments and agencies: the Departments of Agriculture, Energy, Commerce, Health and Human Services, Housing and Urban Development, Justice, Defense, Education, Veterans Affairs, and Transportation; the National Aeronautics and Space Administration; the Social Security Administration; the Consumer Product Safety Commission; the Agency for International Development; the Environmental Protection Agency; the National Science Foundation; and the Central Intelligence Agency.

Preventive Efforts Have Been Important in Reducing Likelihood of Abuses

Preventing harm to human subjects' rights and welfare is the overarching goal of HHS' protection system. The organizational components of the system—OPRR, FDA, and local IRBs—have heightened the compliance of the research community with human protection guidelines through a variety of activities.

Oprr Requires a Formal Commitment to Federal Regulations

OPRR's chief preventive measure is its assurance process. Assurances are contract-like agreements made by research institutions to comply with federal human subject protection requirements. Assurances include the following: a statement of ethical conduct principles, a guarantee that an IRB has been designated to approve and periodically review the institution's studies, and the specifics of the IRB's membership, responsibilities, and process for reviewing and approving proposals. An institution must have an assurance approved by OPRR before the institution can receive HHS research funding.

Depending on an institution's willingness and expertise, as well as the requirements of specific research studies, OPRR can negotiate several different types of assurances. Through a multiple project assurance, for example, OPRR can delegate broad authority to an institution, allowing it to approve a wide array of research studies. Or, through a single project assurance, OPRR can retain the authority to approve studies one by one. As of November 1995, OPRR had 451 active multiple project assurances and over 3,000 active single project assurances. OPRR also had over 1,300 active cooperative project assurances, which pertain to multiple-site research projects.

Fda Reviews Subject Protections Before Permitting Drug Studies

FDA works to prevent the occurrence of human subject protection violations in the drug research it regulates. Before permitting drug research with human subjects, FDA requires researchers to submit a brief statement that they will uphold ethical standards and identify the IRB that will examine their study. FDA can request modifications to proposals or reject proposals deemed to present unacceptable risk.

Irbs Examine Researchers' Plans to Protect Subjects' Rights and Welfare

IRBs play a major role in the protection of patients and healthy volunteers, according to federal officials and members of the research community alike. For each study conducted using human subjects, researchers must first get IRB approval.[4] In fact, HHS will neither fund new human subject research nor authorize ongoing research to continue without IRB approval. The IRB's basic role when deciding whether to approve new research is to determine if the rights and welfare of subjects will be safeguarded. IRB members ensure that a study's procedures are consistent with sound research design and that the consent document conforms to federal rules for adequate informed consent. IRB reviews, however, generally do not involve direct observation of the research study or the process in which a subject's consent is obtained.

IRB members are expected to recognize that certain research subjects—such as children, prisoners, the mentally disabled, and individuals who are economically or educationally disadvantaged—are likely to be vulnerable to coercion or undue influence. The local nature of most IRBs enables members to be familiar with the research institution's resources and commitments, the investigators' capabilities, and community values.

IRBs are also required to review previously approved research periodically. The purpose of these continuing reviews is for IRBs to keep abreast of a study's potential for harm and benefit to subjects so that boards can decide whether the study should continue.

Federal Monitoring and Enforcement Identify and Address Human Subject Protection Violations

No system of prevention is foolproof. Therefore, FDA's and OPRR's monitoring and enforcement efforts include review of results of IRB operations, clinical trials, and allegations of researcher misconduct.

[4]Six categories of research are exempt from IRB review, such as many types of studies that evaluate educational techniques. Federal regulations also allow for expedited review of research that presents only minimal risk to subjects (that is, no greater harm than encountered in daily life). The Secretary of Health and Human Services has approved 10 categories of research that may be reviewed using expedited review procedures. Voice recording and collection of nail clippings, for example, are considered minimal risk research. The IRB chairman or a chairman-appointed IRB member, rather than the full board, conducts expedited reviews.

Fda's Monitoring of Irbs and Drug Researchers Identifies Violations

FDA's primary tool for monitoring human subject protection is its on-site inspections of the IRBs that oversee drug research. FDA's inspections of IRBs demonstrate that, at some institutions, compliance with federal oversight rules is uneven. Between January 1993 and November 1995, FDA issued 31 Warning Letters to institutions regarding significant deficiencies in the performance of their IRBs' oversight of drug research. Among the more serious violations cited were the following: participation of researchers as IRB members in reviewing their own studies, absence of a process for tracking ongoing studies, and failure to ensure that required elements of informed consent were contained in consent documents. The FDA Warning Letters terminated the IRBs' authority to approve new studies or to recruit new subjects into ongoing studies until FDA received adequate assurance of corrective action. From October 1993 to November 1995, FDA found less serious deficiencies involving about 200 other IRBs, such as failure to document the names of IRB members and failure of IRB minutes to identify controversial issues discussed.

In addition to monitoring IRBs, FDA must be satisfied that manufacturers have complied with human subject protection regulations during clinical trials. To this end, FDA conducts on-site inspections of individual drug studies. When examining how a trial was conducted, FDA determines, for example, if subject selection criteria were followed, if subjects' consent was documented, and if adverse events were reported. FDA's principal focus in these efforts, however, is to verify the accuracy and completeness of study data as well as the researcher's adherence to the approved protocol.

Most of the drug study violations FDA identifies are relatively minor. From 1977 to 1995, about one-half of the violations related to the adequacy of the informed consent forms. FDA also identifies more serious violations. Since 1980, FDA has taken 99 actions against 84 clinical investigators regarding their conduct of drug research with human subjects. It cited such instances of serious misconduct as failure to obtain informed consent; forgery of subjects' signatures on informed consent forms; failure to inform patients that a drug was experimental; and failure to report subjects' adverse reactions to drugs under study, including a subject's death.

Fda Can Impose Penalties for Serious Violations

FDA has used four types of actions to enforce its regulations: (1) obtaining a promise from a researcher to abide by FDA requirements for conducting drug research, (2) invoking a range of restrictions on a researcher's use of

investigational drugs, (3) disqualifying a researcher from the use of investigational drugs, and (4) criminally prosecuting a researcher.

Oprr Investigates Allegations of Noncompliance

OPRR also responds to inquiries and investigates allegations of potential harm to human subjects. These inquiries and investigations are largely handled by telephone and correspondence; few investigations result in site visits. Over the past 5 years, OPRR has investigated numerous allegations of serious human subject protection violations. One such example was OPRR's investigation of whether informed consent procedures clearly identified the risk of death to volunteers in the tamoxifen breast cancer prevention trial. OPRR found that informed consent documents at some sites failed to identify some of tamoxifen's potentially fatal risks, such as uterine cancer, liver cancer, and embolism. In another instance, OPRR compliance investigators found deficiencies in informed consent and in IRB review procedures in a joint NIH-French study of HIV-positive subjects in Zaire. Among cases currently under investigation are allegations that researchers at a university-based fertility clinic transferred eggs from unsuspecting donors to other women, without consent of the donors.

Oprr Can Restrict Research Until Violations Are Corrected

In many cases, OPRR has required institutions to take corrective action. In some instances, OPRR has suspended an institution's authority to conduct further research in a particular area until problems with its IRBs were fixed. From 1990 to mid-1995, there were 17 instances in which OPRR imposed some type of restriction on an institution's authority to conduct human subject research.

Multiple Factors Weaken Institutional and Federal Human Subject Protection Efforts

Oversight systems are by nature limited to minimizing, rather than fully eliminating, the potential for mishap, and HHS' system for protecting human subjects is no exception. Various factors reduce or threaten to reduce the effectiveness of IRBs, OPRR, and FDA.

First, pressure from heavy workloads and competing priorities can weaken IRB oversight.

- In some cases, the sheer number of studies necessitates that IRBs spend only 1 or 2 minutes of review per study.

- Some IRBs allow administrative staff with no scientific expertise—not board members themselves—to review continuing review forms, ensuring only that the information has been provided.
- The independence of IRB reviews can be compromised in cases in which IRB members have close collegial ties with researchers at their institutions, when there are pressures from institution officials to attract and retain funding, when IRB members have financial ties to the study, and when IRB members are reluctant to criticize studies led by leading scientists.
- The increasing complexity of research makes it difficult for some IRBs to adequately assess human subject protection issues when members are not conversant with the technical aspects of a proposed study, or when studies raise ethical questions that have not been satisfactorily resolved within the research community.
- Given the growing number of large-scale trials, if most involved IRBs have approved a proposed study, then IRBs at other institutions may feel pressured to mute their concerns about the study.
- Pressures to recruit subjects can lead some researchers and IRBs to overlook informed consent deficiencies.

Second, various factors may hamper OPRR oversight.

- OPRR staff make no site visits during assurance negotiations; instead, they review an institution's written application and conduct written or oral follow-up. In contrast, on the basis of experience gained from on-site investigations for compliance purposes, OPRR staff told us that their ability to evaluate an institution's human protection system is greatly enhanced by direct observation and personal interaction with IRB staff, IRB members, and researchers. In the future, OPRR expects to conduct from 12 to 24 technical assistance visits annually to institutions holding OPRR assurances.
- NIH's organizational structure may hamper the independence of OPRR with respect to its oversight of studies conducted by NIH's Office of Intramural Research. From a broad organizational perspective, a potential weakness exists because NIH is both the regulator of human subject protections as well as an agency conducting its own research programs. The NIH Director, therefore, has responsibility for both the success of NIH's intramural research programs and the enforcement of human subject protection regulations by OPRR.

Third, FDA's inspections of drug research may permit violations to go undetected.

- FDA's inspection program is geared more toward protecting the eventual consumer of the drug than the subjects on whom the drug was tested. FDA does not inspect all drug studies but concentrates its efforts on commercial products likely to be approved for consumer use. Furthermore, FDA's routine on-site inspections of drug studies are conducted only after clinical trials have concluded and subjects have completed their participation.
- Gaps also exist in FDA's inspection of IRBs. FDA's Center for Drug Evaluation and Research annually issues the results of about 158 inspections of the approximately 1,200 IRBs reviewing drug studies, although its goal has been to complete and issue reports on about 250 inspections each year. We found that in one of FDA's 21 districts—one that contains several major research centers conducting studies with human subjects—12 IRBs had not been inspected for 10 or more years. Furthermore, FDA is 3 to 5 years behind in its scheduled reinspection of some IRBs with which it had noted problems.
- FDA officials told us that some of its inspectors may be inadequately prepared to understand the human subject protection implications of drug studies and to ask meaningful follow-up questions on the research protocols they review.

Fourth, additional pressures make it difficult to guarantee the protection of human subjects.

- When seriously ill individuals, such as some HIV patients, equate experimental and proven therapies, some question the need for protections that appear only to restrict their access to therapy.
- When physician-researchers do not clearly distinguish between research and treatment in their attempt to inform subjects, the possible benefits of a study can be overemphasized and the risks minimized.
- When physicians use an innovative but unproven technique to treat patients, they may not consider the procedure to be research. Such treatments, however, could constitute unregulated research, placing people at risk of harm from unproven techniques.

Conclusions

Our work suggests that over the last 3 decades federal regulators and members of the research community have improved the protection of human research participants. However, holes inevitably exist in the regulatory net because no oversight system can guarantee complete protection for each individual. The goals remain to encourage researchers' ethical behavior without hobbling scientific research and to refine

regulations and oversight activities to further improve subject protections. Given the many pressures that can weaken the effectiveness of the protection system, continued vigilance is critical to ensuring that subjects are protected from harm.

Mr. Chairman, this concludes my prepared statement. I will be happy to answer any questions you or the other Members may have.

For more information about this testimony, please call Bruce D. Layton, Assistant Director, at (202) 512-7119. Other major contributors included Frederick K. Caison, Linda S. Lootens, and Hannah F. Fein.

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