

GAO

Report to the Ranking Minority Member,
Committee on Governmental Affairs,
U.S. Senate

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SCIENTIFIC RESEARCH

Continued Vigilance Critical to Protecting Human Subjects



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**Health, Education, and
Human Services Division**

B-259279

March 8, 1996

The Honorable John Glenn
Ranking Minority Member
Committee on Governmental Affairs
United States Senate

Dear Senator Glenn:

The 40-year Tuskegee study in which treatment was withheld from black men with syphilis, the injection of live cancer cells into elderly patients in the 1960s, and the recent disclosure of unethical Cold War-era radiation experiments¹ have demonstrated breakdowns in the protection of human subjects in scientific experiments sponsored by the federal government and others. Much of the concern focuses on whether participants in these experiments knew and understood what they would be subjected to and had an adequate opportunity to decline to participate. These and other issues related to protecting human research subjects were recently addressed by the President's Advisory Committee on Human Radiation Experiments.²

Since the 1960s, significant advances in protecting the rights and interests of human subjects in biomedical and behavioral research have occurred. The federal presence has grown in this area, establishing and reinforcing ethical practices for protecting human subjects in federally funded and federally regulated research. The Department of Health and Human Services (HHS) is the primary federal department sponsoring biomedical and behavioral research. Its regulatory apparatus for overseeing such research, which has evolved over the past three decades, consists of two principal tiers of review: one at the research institution level and the other at the federal level. Both tiers are responsible for ensuring that individual researchers and their research institutions comply with federal laws and regulations for protecting human subjects.

Despite the presence of institutional and federal oversight, abuses still occur, as evidenced by the recent infringement of patients' rights in breast cancer research. Concerned about the adequacy of current oversight, you asked us to determine (1) whether federal oversight procedures have

¹We have testified previously on this issue: see Human Experimentation: An Overview on Cold War Era Programs (GAO/T-NSIAD-94-266, Sept. 28, 1994) and Health and Safety: Status of Federal Efforts to Disclose Cold War Radiation Experiments Involving Humans (GAO/T-RCED-95-40, Dec. 1, 1994).

²Advisory Committee on Human Radiation Experiments, Final Report, Washington, D.C.: Oct. 1995.

reduced the likelihood of abuses of human subjects and (2) whether weaknesses exist that could limit the effectiveness of the current oversight apparatus.

Because of HHS' annual \$5 billion investment through about 16,000 awards involving human subjects and its lead role in setting, monitoring, and enforcing subject protections, we reviewed HHS' oversight system. Within HHS, we concentrated our review on the Office for Protection from Research Risks (OPRR) and the Food and Drug Administration's (FDA) Center for Drug Evaluation and Research (CDER). We interviewed federal and research institution officials; reviewed HHS and FDA regulations, procedures, and records; examined institutional procedures, guidelines, and records; and interviewed scientific researchers, as well as experts in human subject protection, from universities, medical centers, and subjects' rights groups. These researchers and experts included representatives drawn from the fields of bioethics, law, medicine, and social science. We also interviewed representatives of the drug industry. We performed our work from September 1994 to December 1995 in accordance with generally accepted government auditing standards. See appendix I for a detailed discussion of our scope and methodology.

Results in Brief

Today's oversight of tens of thousands of HHS-funded research and FDA-regulated drug studies appears to have reduced the likelihood that serious abuses of human subjects, comparable to past tragic events, will occur. The conspicuous activity of local institutional review boards and human subject protection efforts by federal agencies have heightened the research community's awareness of ethical conduct standards, increased compliance with federal regulations, and served as deterrents to abuse of subjects' rights and welfare. However, little data exist that directly measure the effectiveness of human subject protection regulations.

No practical level of oversight can guarantee that each researcher will protect subjects with complete integrity. The detection of instances of potential or actual harm to subjects both demonstrates that abuses can occur and suggests that the current oversight activities are working. The government and the research community, whose ultimate goal is the advancement of scientific knowledge, struggle to balance two sometimes competing objectives—the need to protect research subjects from avoidable harm and the desire to minimize regulatory burden on research institutions and their individual scientists. Various time, resource, and other pressures, however, have reduced or threaten to reduce the

effectiveness of local review board and federal agency oversight. In this context, the need for continued vigilance over human subject research should remain a priority for the research community and agencies charged with oversight.

Background

From 1962 through 1991, HHS' system for protecting human research subjects was created, piece by piece, largely in response to disclosures of dangerous or controversial biomedical and behavioral research. (See app. II for more historical information.) The tragic consequences of thalidomide use in the United States³ and revelation of the Tuskegee syphilis study shocked the public and convinced national policymakers that unregulated biomedical research represented a clear threat to research subjects. Two expressions of this concern were the passage of the National Research Act and the promulgation of human subject protection regulations by the Department of Health, Education, and Welfare (HEW)⁴ in 1974. The act also established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research to guide federal human subject protection policy.⁵ When the core of the human subject protection regulations was adopted by 15 other departments and agencies in 1991, it became known as the Common Rule.⁶

³Thalidomide is a sedative that was approved for use in Europe in the late 1950s and was widely used by pregnant women at risk of premature delivery and miscarriage. Although not dangerous to the mother, the drug caused severe birth defects. Although FDA had not approved the drug for use in the United States, the manufacturer supplied the drug to U.S. physicians to establish its safety, as was the common practice of that time. By 1962 it had become evident in Europe that thalidomide was harmful, and the investigational studies were stopped in this country. In that same year, it was also revealed that many of the patients participating in the U.S. clinical trials had not been informed that they were part of an investigational study nor had many given their consent.

⁴Now the Department of Health and Human Services.

⁵Between 1974 and 1995, six blue-ribbon panels were established to address ethical issues in biomedical and behavioral research: the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (1974-78), the HEW Ethics Advisory Board (1978-80), the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research (1980-83), the Biomedical Ethics Advisory Committee (1985-89), and the Advisory Committee on Human Radiation Experiments (1994-95). In addition, in October 1995, the President established the National Bioethics Advisory Commission with a mandate to report on current human subject protections.

⁶Currently, 17 departments and agencies that conduct or support biomedical and behavioral research involving human subjects have adopted regulations for protecting human research subjects. The first 15 to adopt the Common Rule, based on the core of HHS' regulations, were the Departments of Agriculture, Energy, Commerce, Housing and Urban Development, Justice, Defense, Education, Veterans Affairs, and Transportation; the National Aeronautics and Space Administration; the Consumer Product Safety Commission; the Agency for International Development; the Environmental Protection Agency; the National Science Foundation; and the Central Intelligence Agency. In addition, when the Social Security Administration became an independent agency in 1995, its enabling statute bound it to follow HHS' regulations.

The Common Rule requires research institutions receiving federal support and federal agencies conducting research to establish committees 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. (See fig. 1 for Basic Elements of Informed Consent.) 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. In the late 1970s and early 1980s, HHS considered but did not adopt recommendations by two national commissions for specific regulations to protect institutionalized mentally disabled subjects.

Figure 1: Basic Elements of Informed Consent

- ▶ A statement stipulating that research is involved, what the purpose of the research is, what the duration of the subject's involvement will be, and what procedures the subject will undergo.
- ▶ A description of foreseeable risks or discomforts to the subject.
- ▶ A description of expected benefits, if any, to the subject and others.
- ▶ The disclosure of alternative procedures or courses of treatment.
- ▶ A statement describing the extent to which confidentiality of records identifying the subject will be maintained.
- ▶ For research that poses more than minimal risk to subjects, an explanation of the availability and nature of any compensation or medical treatment if injury occurs.
- ▶ Names of people to contact for further information about the research, the subjects' rights, and notification of research-related injury.
- ▶ A statement stipulating that participation is voluntary and no penalties will be imposed for refusal to participate in research; subject can choose to discontinue participation at any time.

Within the HHS oversight system, OPRR and FDA are the key federal entities overseeing compliance with informed consent and other human subject protection regulations.⁷ Both entities carry out oversight functions central to the operation of the human subject protection system, including policy setting, prevention, monitoring, and enforcement. Institutional review boards (IRB)—that is, review panels that are usually associated with a particular university or other research institution—are responsible for

⁷FDA's regulations covering human subject research are nearly identical to HHS' human subject protection regulations. One difference concerns the requirement for informed consent from patients involved in emergency medical care research. FDA and OPRR are working to harmonize these rules.

implementing federal human subject protection requirements for research conducted at or supported by their institutions.

OPRR is located within the National Institutes of Health (NIH), the principal federal agency responsible for supporting biomedical and behavioral research. About one-half of OPRR's 28 full-time employees are responsible for overseeing protections in the approximately 16,000 HHS awards involving human subjects. The other half are devoted to ensuring the humane care and use of laboratory animals. Three physician volunteers augment OPRR's human subject protection staff. OPRR has an annual budget of \$1.9 million, about one-half of which is targeted to human subject protection activities.

FDA is responsible for protecting the rights of human subjects enrolled in research with products it regulates—drugs, medical devices, biologics, foods, and cosmetics. Our review focused on oversight activities of FDA's Center for Drug Evaluation and Research, which carries out most of FDA's human subject protection activities.⁸ At CDER, responsibility for human subject protection activities is shared between the Office of Drug Evaluation and the Division of Scientific Investigations. The Office of Drug Evaluation reviews manufacturers' and researchers' requests to conduct drug studies on human subjects. The Division of Scientific Investigations reviews FDA's field inspection reports on IRBS and investigators and makes final determinations regarding compliance violations. Routine and for-cause on-site inspections are conducted by field staff, who are also responsible for examining the integrity of research data, assessing compliance with good manufacturing practices, and examining other issues related to FDA's oversight of all its regulated products.

Within research institutions, oversight is done primarily by IRBS responsible for examining research proposals and ongoing studies.⁹ No data exist on the exact number of IRBS in the country but estimates range from 3,000 to 5,000. Most are found at universities, hospitals, and private research facilities; a few are free standing. Human subject research

⁸FDA's Center for Biologics Evaluation and Research (CBER) and Center for Devices and Radiological Health (CDRH) also carry out activities to protect human subjects of product testing. These activities were not included in the scope of our review.

⁹Additional reviews occur at local institutions. At some institutions, researchers are required to obtain approval from departmental officials, and if necessary, from such issue-specific groups as the radiation safety committee or the cancer research group. In addition, data and safety committees monitor ongoing research for data indicating safety and efficacy. They can recommend modification to the informed consent form or clinical trials. In addition, they can recommend stopping the study if problems arise or if the therapeutic effect has been demonstrated. Private companies also audit drug research that they sponsor.

conducted by NIH itself, for example, is governed by the 14 IRBS of the NIH Intramural Research Program.¹⁰ In general, IRBS are composed chiefly of scientists at their respective institutions. They are required to have a minimum of five members, at least one of whom is a scientist, one a nonscientist, and one a person not otherwise affiliated with the research institution. They are also required to have a diverse membership; in determining membership, consideration must be given to race, gender, and cultural background.

Preventive Efforts Have Been Important in Reducing Likelihood of Abuses

The presence of local review bodies and federal oversight agencies appears to have heightened the awareness and sensitivity of the research community to the importance of respecting subjects' rights and welfare. Written commitments, which bind research institutions to comply with human subject protection requirements, are an important element of the protection system. By requiring individual researchers and IRBS to uphold their institution's commitments, the system works to prevent harm to participants in most experimental studies. However, the effectiveness of the HHS human subject protection regulations in ensuring compliance by institutions and individual researchers has not been systematically studied.

Assurances Commit Institutions to Uphold Human Subject Protection Requirements

Research institutions must commit to uphold human subject protection requirements before engaging in research with human subjects conducted or funded by any of the departments or agencies that adopted the Common Rule. To be eligible to receive such funding, an institution must enter into a contract-like agreement, called an assurance. This is the written promise of an institution housing research studies to comply with federal ethical conduct standards. OPRR, the federal office within NIH that approves assurances for research funded by HHS, requires assurances to (1) include a statement of ethical conduct principles, (2) stipulate that a review board has been designated to approve and periodically review the institution's studies, and (3) specify the review board's membership, responsibilities, and process for reviewing and approving proposals. Assurances serve as one of the system's chief preventive measures.

¹⁰In addition to IRB review, NIH requires panels of in-house experts and nongovernment scientists to review research proposals' protections for human subjects and scientific merit before funding intramural and extramural research grant applications. The NIH Office of Intramural Research supports research in NIH's own laboratories, whereas the Office of Extramural Research supports research of nonfederal scientists in universities, medical hospitals, and research institutions throughout the United States and abroad.

OPRR's authority to require assurances derives from the 1974 National Research Act, which formalized the practice of obtaining from institutions receiving HHS funding written assurances of their commitment to the ethical conduct of research. When the legislation was enacted, NIH had already developed assurance-type documents with many universities, which OPRR reviewed. Approving an assurance involves no site visits by OPRR to the institution; rather, negotiations are handled through correspondence and telephone calls with institution officials.

OPRR assurances are of several types. Multiple project assurances are approved for universities and other major research centers that conduct a substantial number of studies and have demonstrated a willingness and the expertise to comply with human subject protection requirements. Through a multiple project assurance, an institution does not need to reapply through OPRR for eligibility to receive HHS funds for each new study approved by its IRB. An assurance covers the institution's human subject studies for 3 years, at which time the institution must renew its assurance.¹¹ Renewals are for a 5-year period. As a practical matter, multiple project assurances allow institutions to conduct research with no further OPRR involvement until the assurance is up for renewal. As of November 1995, 451 active OPRR multiple project assurances covered more than 500 research institutions. These institutions receive most of HHS' funding for research with human subjects. Primary responsibility for negotiating all multiple project assurances in OPRR rests with a retired physician who used to be employed for this purpose by OPRR. Since retiring, she has continued this work on an unpaid, part-time basis. Currently, the assurance branch chief is responsible for approving all multiple project assurances OPRR negotiates.

At institutions without a multiple project assurance, an assurance agreement must be negotiated with OPRR for each individual study. These are called single project assurances and require OPRR to review, for each study, documentation similar to that required for a multiple project assurance. In addition, OPRR reviews the study's informed consent form before approving a single project assurance. As of November 1995, OPRR had 3,063 active single project assurances. Primary oversight of these assurances rests with three full-time staff in OPRR's assurance branch.

A third type of assurance—the cooperative project assurance—recognizes that research is frequently conducted at multiple sites under joint

¹¹Almost all institutions holding multiple project assurances commit themselves to apply the terms of the assurance to all their human subject studies, not just those funded by HHS.

institutional sponsorship. One example is the National Surgical Adjuvant Project for Breast and Bowel Cancers, sponsored by the National Cancer Institute and conducted at over 300 sites. OPRR requires each participating institution to have a cooperative project assurance for all its joint research, regardless of other assurances held by the institution. For projects conducted under cooperative project assurances, OPRR designates reviewers to approve each research protocol and a prototype informed consent form. IRBS at the participating institutions must also approve the protocol and the informed consent document. IRBS can require additional explanations to be included in the informed consent document. However, they cannot modify the core elements of the protocol, which is to be consistent across all sites. Nor can they delete or substantially modify the discussion of risks and alternative treatments in the prototype consent document without notice and justification. As of November 1995, OPRR had 1,333 active cooperative project assurances. Assurance branch staff responsible for single project assurances also review cooperative assurances with additional support provided by other OPRR staff and others.

**FDA Requires
Commitment to Human
Subject Protection
Standards**

FDA also 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 institutional review board that will examine the study. Sponsors are required to provide the results of chemical and animal studies with the new drug, submit the proposed study procedures for using human subjects, and commit to ensuring that a properly constituted IRB will review the proposed study. FDA reviews this information to ensure the study poses no unacceptable risks to subjects, is ethically sound, and is likely to achieve the study objectives. FDA can request modifications to or reject proposals deemed to present unacceptable risk. FDA's prevention efforts overlap OPRR's if the drug study is supported by HHS funds.

**Federal Entities' Education
of Research Community Is
Another Preventive
Measure**

Both OPRR and FDA educate the research community on issues related to protecting human research subjects. Both respond directly to questions from individual researchers, IRBS, and institutional officials. They cosponsor about four human subject protection workshops annually across the country that are attended on a voluntary basis by IRB members, research institution officials, and researchers. OPRR also issues written guidance that defines terms and clarifies ambiguities in human subject

protection requirements. OPRR may provide additional information to individual institutions during its negotiation of assurances. FDA also provides guidelines on informed consent, research proposal review, and recordkeeping to IRBs, research sponsors, and researchers.

IRBs Serve as Gatekeepers in Approving Research

Federal officials and the research community alike commonly cite IRBs as a key line of defense protecting patients and healthy volunteers participating in research. Federal regulations authorize IRBs to approve, approve with modification, or withhold approval from new research projects. Researchers must get approval from the appropriate IRB associated with their institution before beginning research with human subjects.¹² IRBs are required to review ongoing projects annually or more often depending on the level of risk. HHS will not fund new human subject research or authorize ongoing research to continue without the local IRB's approval.

Specifically, IRBs are required to ensure that, for each project reviewed, risks are minimized and reasonable in relation to anticipated benefits, subjects are properly informed and give consent to participate, and the rights and welfare of subjects are maintained in other ways as well. IRBs are required to include scientists and nonscientists as members. IRBs must also consider gender, racial, and ethnic diversity in their membership selection in order to be sensitive to a broad range of social as well as scientific issues. IRB members are also 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 reputations, and the prevailing values and ethics of the community and subject population.

In deciding whether to approve new research, IRBs are required to determine that a study's procedures are consistent with sound research design and do not unnecessarily expose subjects to risk. In addition, IRBs are required to examine the study investigators' efforts to obtain subjects'

¹²Six 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 (i.e., 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 recordings and collection of nail clippings, for example, are considered minimal risk research. The IRB chair or a chair-appointed IRB member, rather than the full board, conducts expedited reviews.

consent, including examining the informed consent document when applicable.¹³ They do this to ensure that the document specifies the procedures the subject will undergo in language and terminology the subject can understand, the risks to the subject, and alternative treatments available and that the document makes explicit, among other things, the right of individuals to decline to participate in the study or to withdraw at any time.

IRB members told us that they spend most of their time reviewing the informed consent document associated with a study. IRB reviews generally do not involve direct observation of the research study or of the process in which a subject's consent is obtained, however. As a result, IRBs must rely on investigators' and consent monitors' assessments of subjects' reading skills, fluency in English, and mental capacity. An IRB can authorize the use of a consent monitor to observe the delivery of informed consent, for example, when potential subjects might not have the mental capacity to understand all aspects of the consent process.

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 IRBs can decide whether the study should continue. Principal investigators must therefore report the presence of adverse effects on study subjects, which allows the IRB to assess whether the seriousness of risk has changed. IRBs should also consider whether advances in knowledge or technology have occurred that would require reconsidering the appropriateness of the study's purpose or protocol. In addition, they should review such details as whether the number of subjects in the study corresponds to the number initially approved.

Federal Monitoring and Enforcement Identify and Address Human Subject Protection Violations

No system of prevention is foolproof—indeed, FDA's and OPRR's monitoring identifies abuses and other evidence of noncompliance. Federal monitoring efforts for human subject protection violations include reviews of study documentation, IRB operations, and allegations of misconduct. Federal enforcement activities serve to stem further adverse consequences. In fact, FDA officials, researchers, and drug industry representatives we interviewed told us that the FDA's oversight of drug

¹³IRBs may waive documentation of informed consent under certain circumstances. For example, under HHS regulations, informed consent can be waived when the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Informed consent can also be waived under HHS and FDA regulations when the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

research motivates researchers and IRBs to follow proper human subject protection procedures.

FDA Has a Variety of Monitoring Activities and Enforcement Options

FDA monitors drug research for compliance with human subject protections. By conducting on-site inspections of IRBs, reviewing progress reports from researchers and sponsoring drug companies, and making on-site inspections of clinical studies and investigators, FDA becomes aware of noncompliance with federal regulations. FDA officials told us that most institutions and researchers respond quickly and positively to inspection findings, and the presence of an FDA inspection process deters human subject protection violations.

FDA's inspection of IRBs is its primary monitoring tool for human subject protection. FDA inspects IRBs to determine their adherence to federal human subject protection requirements.¹⁴ FDA inspections of IRBs consist primarily of an on-site examination of the IRBs' minutes, written operating procedures, and other documentation that substantiates initial and continuing review and proper IRB membership. During these inspections, FDA interviews the chair or the administrator of the IRB to learn details about the IRB's operation. FDA also determines whether consent forms contain all required elements and are signed by subjects.

FDA has three levels of priority for inspecting the roughly 1,200 IRBs that oversee drug research. FDA gives top priority to the reinspection of IRBs for which it found serious deficiencies in the IRBs' review of studies. FDA's next priority is examining IRBs that were unknown to FDA until identified by researchers in their applications to begin drug studies with human subjects. FDA's lowest priority is the routine reinspection of IRBs. Between fiscal years 1990 and 1995, CDER issued each year, on average, the results of 158 inspections of IRBs overseeing drug research.¹⁵

¹⁴Because of the commonalities among IRB inspections performed for CDER, CBER, and CDRH, an inspection conducted for one of FDA's centers—for example, CDER—can serve to protect subjects in studies regulated by CBER or CDRH. Furthermore, FDA's IRB inspections enable it to monitor human subject protection aspects of some of the ongoing and completed studies that were reviewed by the IRB.

¹⁵In fiscal year 1995, FDA allocated about 13 full-time-equivalent positions in its field offices for the on-site inspection of IRBs reviewing research on drugs, medical devices, and biologic products. At CDER, FDA allocated about 6 full-time-equivalent positions to the Division of Scientific Investigations for its oversight of IRB inspections. These positions are also responsible for inspections of Radioactive Drug Research Committees, which are located at certain research institutions. FDA conducts about five such inspections each year.

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.¹⁶ These Warning Letters imposed sanctions—until CDER received adequate assurance that the IRB had taken corrective action—on the IRBs' ability to approve new studies, allow entry of new subjects into ongoing studies, or both. Among the more serious violations cited were the following: researchers participated as IRB members in the review of their own studies; institutional officials falsely claimed no trials had been conducted that would have required IRB review; IRBs had no process to track ongoing studies; IRBs used expedited rather than full review to approve major study changes; IRBs failed to correct deficiencies noted during a previous FDA inspection; IRBs failed to ensure that required elements of informed consent were contained in consent documents; and IRBs allowed their members to vote by telephone instead of convening the board.

FDA officials told us that FDA has never had to invoke its ultimate sanction—disqualification—for seriously deficient IRBs. On about 60 occasions, institutions disbanded their IRBs upon FDA's findings of serious noncompliance. In most of these instances, the research projects approved by the IRBs had already been completed.

FDA's examination of individual drug studies is another component of its human subject protection monitoring. Before a manufacturer can receive FDA approval to market a drug, it must satisfy FDA that it has complied with FDA's human subject protection regulations during clinical trials. The monitoring includes reviews of progress reports and on-site inspections. Although FDA examines documentation on protection matters, its principal focus in these efforts is to verify the accuracy and completeness of study data as well as the researcher's adherence to the approved protocol.

When researchers begin clinical trials, FDA's Office of Drug Evaluation requires them, through their sponsors, to submit annual progress reports and also to report within 10 working days any serious and unexpected adverse incidents involving subjects as well as major changes to the study protocol. If these reports indicate potential or actual harm to subjects, FDA can suspend or terminate the study.

¹⁶In January 1993, FDA instituted a new system with two categories of IRB noncompliance findings. In the first category, FDA issues Warning Letters for the most serious problems. The second category—voluntary action indicated—applies to less serious findings of IRB noncompliance. From October 1993 to November 1995, FDA requested voluntary actions from about 200 IRBs for a variety of reasons, such as failure to identify IRB members, failure of IRB minutes to identify controversial issues discussed, and too little time spent reviewing studies.

FDA's on-site inspections of drug studies generally occur after clinical trials have concluded. There are two types of inspections: routine and for-cause. Routine inspections are conducted after a manufacturer has completed its clinical trials and submits a new drug application (NDA) to FDA for approval to market the product. During fiscal years 1990 through 1995, FDA issued each year, on average, the results of about 265 routine inspections of drug studies.¹⁷ The sites visited are typically university-based research facilities, independent testing laboratories, and the offices of physicians participating in drug trials.

Inspections of drug studies also include an assessment of how well subjects were protected during the study: whether the consent document, study protocol, and required revisions to them were reviewed and approved by an IRB before enrolling subjects; whether signed consent forms were obtained from each enrolled subject;¹⁸ whether adverse incident and status reports were submitted to the IRB once research began; and whether subjects were recruited properly. FDA inspectors look for evidence that researchers reported all safety-related information to the sponsor, reasons why subjects dropped out of the study, and other matters related to the integrity of study data. In addition, FDA often interviews researchers and sometimes interviews subjects.

While routine inspections generally occur after completion of clinical trials, for-cause inspections can occur at any time during the course of drug testing with humans. FDA conducts for-cause inspections when its review of status reports submitted by researchers indicates possible misconduct, or when it receives allegations of serious misconduct. FDA conducts about a dozen for-cause inspections annually.

Most of the violations FDA identifies through its routine inspections of individual drug studies are relatively minor. From 1977 to 1995, about one-half of the violations related to the adequacy of the informed consent forms. For example, FDA frequently found violations of the requirement to specify in the informed consent document whom subjects can contact if they have concerns about research, subjects' rights, or research-related injury.

¹⁷In fiscal year 1995, FDA allocated about 45 full-time-equivalent positions to its field staff for inspecting studies of drugs, medical devices, and biologic products. In addition, FDA allocated about 9 full-time-equivalent positions to CDER's Division of Scientific Investigations for inspecting drug studies and investigators.

¹⁸Because FDA has had problems verifying that informed consent was obtained from a research subject before participation in a study, it published a proposed rule in December 1995 that would require dating the written consent form at the time consent was obtained.

FDA also identified more serious violations in its routine and for-cause inspections. We reviewed 69 of the 84 letters describing deficiencies that FDA issued to drug researchers between April 1980 and November 1995. These letters cited instances of serious misconduct, including failure to obtain informed consent; forgery of subjects' signatures on informed consent forms; failure to inform patients that a drug was experimental; fabrication of data to make subjects eligible for study; submission of false electrocardiograms, X rays, and lab test results to the company underwriting the research; failure to report subjects' adverse reactions to drugs under study, including a subject's death; failure to obtain informed consent and an IRB's approval for a study touting a human growth hormone as a cure for Alzheimer's disease; proceeding with a cancer study after FDA had suspended it for protocol deficiencies; and failure to inform patients that a drug sold to them was experimental and contained a steroid.

Since 1980, FDA has taken 99 actions against 84 clinical investigators regarding their conduct of drug research with human subjects. 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 using investigational drugs; and (4) criminally prosecuting a researcher.

OPRR Investigates Allegations of Noncompliance and Requires Corrective Action

OPRR also responds to inquiries and investigates allegations, but few investigations result in site visits; inquiries and investigations are largely handled by telephone and correspondence. OPRR receives complaints about human subject protection issues from a variety of sources, including NIH inspection teams, FDA, subjects and their families, staff from research institutions, news media, and the Congress. The majority of noncompliance reports come from the institutions themselves, which are required to report unanticipated problems, such as injuries and serious or continuing noncompliance, to OPRR as part of the assurance agreement. The number of compliance cases investigated by OPRR grew from 32 open cases in January 1993 to 107 cases under investigation in June 1995. OPRR officials and others attribute the increase to a heightened awareness of human subject protection issues and more extensive media coverage of untoward research events rather than to an increase in the actual occurrence of noncompliance.

Over the past 5 years, OPRR's compliance staff of four full-time employees and two volunteers have investigated several studies for allegations

involving 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 subjects who had tested positive for the human immunodeficiency virus (HIV) in Zaire. In a third case, OPRR compliance staff investigated a study of schizophrenia at a major university because of complaints from families of two subjects associated with the study. In that investigation, OPRR found that the informed consent documents failed to adequately describe the research procedures, research risks, and alternative courses of treatment. In addition, OPRR found that the researchers inappropriately obtained the subjects' oral consent rather than written consent as required by HHS regulations. Among cases currently under investigation, OPRR is reviewing allegations that researchers at a university-based fertility clinic transferred eggs from unsuspecting donors to other women without the consent of the donors.

Our review of OPRR files showed that OPRR found such deficiencies as the failure of an IRB to give full review of projects at a convened meeting or to adequately review ongoing research. OPRR also found IRB approval of informed consent documents that did not clearly state the study's purpose, did not identify the study's risks of the research, and did not present information that would be understandable to the subjects.

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. For example, in some cases, OPRR suspended the enrollment of new subjects; in others, OPRR excluded certain types of research from coverage by multiple project assurances, thereby requiring single project assurances and the direct involvement of OPRR in reviewing each study's informed consent forms and other documents. To document corrective actions, institutions are generally required to submit quarterly reports to OPRR. OPRR lifts a restriction when it is satisfied that the institution has taken appropriate corrective actions—in most cases, after receiving quarterly reports for about a year to 18 months.

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's system for protecting human subjects is no exception. Various factors reduce or threaten to reduce the system's effectiveness. IRBS face the pressure of heavy workloads and competing professional demands. OPRR is often remote from the institutions it oversees. FDA's processes, while including on-site inspections, may permit human subject protection violations to go undetected. Moreover, the complexity and volume of research under review and the difficulty of ensuring that individuals truly understand the risks they may experience as research subjects can weaken the effectiveness of human subject protections.

Workload and Other Demands Impair IRB Oversight

Federal officials, experts, and research community members we interviewed consistently mentioned several concerns about the operations of IRBS. First, IRB reviews are labor intensive and time consuming, forcing boards to balance the need to make reviews thorough against the need to get them done. IRB members are usually physicians, scientists, university professors, and hospital department heads who are not paid for their IRB service. Board members themselves told us they face a heavy workload, and others in the research community have raised concerns that heavy workload impairs IRB review.

In some cases, the sheer number of studies necessitates that IRBS spend only 1 or 2 minutes of review per study. FDA found one IRB that had reviewed as many as 200 proposals and ongoing studies at a meeting. Several experts told us of other instances in which IRBS had reviewed 100 to 150 studies in one meeting. In many such cases, one, two, or several individuals—known as “primary reviewers”—may be assigned to examine a study comprehensively in advance of the IRB meeting, often held monthly. In these cases the other IRB members rely on the conclusions drawn by the primary reviewers and may be less prepared to identify and discuss potential problems with proposals. In addition, IRB members and researchers told us that, given the time constraints, a good portion of the meetings is devoted to assessing the adequacy of the consent forms at the expense of reviewing research designs.

Second, federal officials and experts in IRB issues have been particularly concerned with IRBS' conduct of continuing reviews. They assert that these reviews are typically either superficial or not done at all. According to OPRR officials, IRBS have not always understood the requirements for continuing review, and, in other cases, IRB workload demands have

reduced the quality of this review.¹⁹ In some cases, IRB administrative staff with no scientific expertise—not IRB members themselves—review continuing review forms, ensuring only that the information has been provided. Heavy workload also necessitates that IRBs rely largely on investigators’ self-assessments in conducting continuing reviews. That is, IRBs review statements completed by the study’s investigators and, with rare exceptions, do not verify the accuracy of the reported information. Although experts disagree on the desired level of IRB verification, its value was demonstrated recently in a report by HHS’ Office of Inspector General.²⁰ The report cited one instance in which nine researchers failed to notify their IRBs, as required, of major deviations from a study protocol. In another instance, a surgeon reported to the IRB the implantation of an experimental device in 37 subjects. The HHS review team found that this surgeon and his coinvestigators had actually implanted the device in 258 subjects, thus far exceeding the limit of 75 subjects specified in the research protocol and approved by the IRB. In cases such as these, the possibility exists that a researcher could selectively report favorable results.

Third, experts we interviewed raised concerns about the independence of IRB reviews. For example, they told us that close collegial ties with researchers at their institutions, pressures from institution officials to attract and retain government or corporate research funding,²¹ financial ties to the research study, and reluctance to criticize studies led by leading scientists can compromise the independence of IRB reviews. Although most experts we interviewed agreed that instances of these problems occur, they did not have enough evidence to determine the frequency or the extent of the problem.

Finally, some IRBs are viewed by their institutions and by researchers as a low-priority administrative hurdle. As a result, these IRBs have difficulty securing the administrative and computer support they require. For example, OPRR has found instances of IRB staff working in office space insufficient to conduct review board business effectively, manual filing

¹⁹The January 1995 issue of *OPRR Reports* addressed the subject of continuing review of research—institutional and IRB responsibilities. OPRR periodically distributes *OPRR Reports* to about 5,500 institutions, IRB members, and others in the research community.

²⁰Department of Health and Human Services, Office of Inspector General, *Investigational Devices: Four Case Studies* (OEI-05-94-00100) (Washington, D.C.: HHS, Apr. 1995).

²¹IRB “shopping” has been cited as a threat to human subject protection. In several instances, corporate sponsors shifted projects away from institutions where local reviewers raised concerns about the sponsor’s study. See Sherertz, Robert J., and Stephen A. Streed, “Medical Devices: Significant Risk vs. Nonsignificant Risk,” *Journal of the American Medical Association*, Vol. 272, No. 12, Sept. 28, 1994, pp. 955-956.

systems too primitive to ensure that continuing reviews were conducted at the required times, and lack of privacy for IRB staff to take the sensitive telephone calls of subjects who may want to register complaints. At such institutions, researchers may not always follow IRB requirements, such as revising informed consent forms or reporting adverse events.

Various Factors May Hamper OPRR Oversight

OPRR's reliance on the assurance process for preventing the violation of human subject protections requires that OPRR have sufficient basis for judging an institution's ability to satisfy human subject protection requirements. At times, however, OPRR's assurance negotiation process falls short of that goal. OPRR staff are rarely direct observers of the institutions they oversee. They make no site visits during assurance negotiations, but instead review solely an institution's written application and conduct written or oral follow-up. Usually, document review does not include an examination of the manuals that detail the human subject protection procedures that the institution requires its IRBs and researchers to follow. Similarly, almost all of OPRR's compliance investigations—reviews in response to allegations of misconduct—are carried out through correspondence. In the 5 years preceding April 1995, OPRR made 15 site visits as part of the 202 compliance investigations it completed.

What OPRR has found in its site visits made in the course of investigating allegations of violations illustrates the value of such visits. For example, when we accompanied OPRR on a compliance site visit to a major research university, OPRR learned details about the institution's IRB operations and reporting chain idiosyncrasies that it was previously unaware of despite having reviewed the institution's assurance documents. This visit resulted in the temporary suspension of the human subject research under the surveillance of one of the university's two IRBs.

OPRR officials told us that they lack the time and funds for more site visits for assurance negotiations or compliance. They acknowledged, however, that when they did make site visits, their investigations were significantly enhanced by communicating face-to-face with officials, researchers, and the administrative staff assigned to the institution's IRB. On-site investigations have also been more thorough and expeditious because OPRR had ready access to study files and IRB records and could quickly follow leads. Site visits also provided OPRR the opportunity to educate institutional staff about ethical conduct practices by enabling OPRR staff to be immediately available to discuss and answer questions about human subject protection issues. Through these exchanges, OPRR staff learned

about problems, such as those with continuing review, that other institutions could be experiencing. Experts we interviewed also said that OPRR's prevention efforts would be more effective if it were to make site visits to institutions in the process of approving and renewing assurances.

In addition, NIH's organizational structure may hamper OPRR's independent oversight and enforcement of human subject protection regulations, although we found no specific instance in which this occurred. Although OPRR is located within the Office of Extramural Research, OPRR is responsible for enforcing compliance with human subject protection regulations for research conducted or supported by both the Office of Intramural Research and the Office of Extramural Research. Under this structure, the OPRR Director reports to the Deputy Director for Extramural Research, who, in turn, reports to the Director of NIH. Because the Deputy Director for Intramural Research also reports to the Director of NIH, OPRR has no direct authority over the research conducted by the intramural program. As a result, when OPRR cited NIH's Office of Intramural Research in 1991 for compliance violations, for example, OPRR had to depend on that office's good will and professional conduct to implement the corrective action plan proposed by OPRR, since OPRR did not have direct authority to require NIH to correct violations. According to OPRR, NIH will complete implementation of the plan by April 1996, 5 years after the problems were noted.

From a broader organizational perspective, a potential weakness exists because NIH is both the regulator of human subject protection issues as well as an institution conducting its own human subject research. The Director of NIH, therefore, has responsibility for both the success of NIH's intramural research program and for the enforcement of human subject protection regulations by OPRR.

FDA Oversight Has Certain Limitations

In some instances, FDA's oversight efforts may permit violations of human subject protections to go undetected. For example, researchers who use human subjects in drug research are required to submit to their sponsor periodic progress reports during the course of the trials. These reports include adverse events, project status, and changes to the research protocol. The sponsor, in turn, reports adverse events to FDA. The reporting process, however, is a passive one in which FDA relies on researchers and their sponsors to report potential or actual adverse medical events during clinical trials. Violations of subjects' rights, such as

inadequate informed consent or IRB review, however, are not required to be reported.

Two gaps in FDA's inspection of drug studies have implications for human subject protections. First, FDA only conducts routine on-site inspections after clinical trials have concluded and subjects have completed their participation. Second, FDA officials told us that because of resource limitations, FDA does not inspect all studies; instead, it concentrates its efforts on those products that both are likely to be approved for consumer use and could pose high risk to consumers.²² FDA officials told us that the primary reason for these inspections is to review the integrity of the study's data before initiating a review of the drug's safety and effectiveness. In essence, then, FDA's inspection program is geared more toward protecting the eventual consumer of the drug than the subjects on whom the drug was tested.²³

Gaps also exist in FDA's inspection of IRBs. CDER 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—a district that contains several major research centers conducting studies with human subjects—12 IRBs had not been inspected for 10 or more years on behalf of CDER, CBER, or CDRH. Furthermore, although FDA's policy is to accelerate the timetable for reinspecting IRBs found to have significant problems, we noted instances in which FDA conducted its reinspection 3 to 5 years later. FDA officials told us that, because of resource constraints, IRB inspections receive lower priority than inspections of FDA-regulated products or manufacturing practices.

Finally, experts we interviewed raised concerns about the unevenness of FDA inspectors' expertise, which they believe could enable human subject protection violations to go undetected. FDA officials acknowledge that some 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. FDA officials

²²Studies for certain products, such as vitamins, antimicrobial handwashes, and saline solutions, are not inspected by FDA because they pose low risk for consumers.

²³FDA calls drug studies that are sponsored by pharmaceutical companies and are intended to lead to a marketable product "commercial" studies. Commercial studies can involve thousands of subjects. In contrast, "research" studies are typically sponsored by individual researchers, do not result in commercial products, and usually involve a small number of subjects. FDA does not routinely inspect research studies. FDA officials told us, however, that FDA inspects studies that are important to the approval of all NDAs containing clinical data.

also noted that some inspectors lack practical experience in reviewing drug studies because they work in districts with few bioresearch sites and therefore usually inspect other types of regulated products.

Other Pressures in the Research Environment May Weaken Oversight Effectiveness

Several additional pressures make guaranteeing the protection of human subjects difficult. Many of the experts we interviewed raised concerns about the growing complexity of science, the increasing number of multicenter trials, and the vulnerability of certain subject populations. The extent of these problems, however, has not been studied.

First, the increasing complexity of research makes it difficult for IRBS to assess human subject protection issues when members are not conversant with the technical aspects of a proposed study. In such cases, the IRB's ability to assess the risks or benefits posed to subjects and the adequacy of language found in the consent document is questionable. In addition, cutting edge science can present new ethical dilemmas for IRBS to confront. Experimental human reproductive techniques and ownership of genetic material, for example, have raised ethical questions that thus far have not been satisfactorily resolved.

Second, the growing number of large-scale trials carried out at multiple research sites presents other problems for IRBS, both at initial and continuing review. Proposals for multicenter trials are reviewed by an IRB associated with each local research site. If most involved IRBS have approved a proposed study—that is, determined that the study is safe, ethical, and appropriately described in consent forms—then remaining IRBS at other institutions may feel pressured to mute their concerns about the study. Furthermore, during the course of a multicenter trial, each participating IRB receives numerous reports of adverse events from other research sites. Because of the volume of reports, IRB members may have difficulty discerning which adverse events are both relevant and serious enough to warrant their taking note of them.

Third, IRBS and researchers may not always be sensitive to subjects who have a stake in believing that research is at worst benign and at best beneficial. For many seriously ill individuals—such as HIV patients, for example—experimental therapies represent the best source of hope. Such subjects often equate experimental and proven therapies, leading some of them to question the need for protections that appear only to restrict their access to therapy. The Advisory Committee on Human Radiation Experiments notes that

“...patient-subjects who have serious illnesses may have unrealistic expectations both about the possibility that they will personally benefit by being a research subject and about the discomforts and hardships that sometimes accompany research.”²⁴

Volunteers who want to be included in biomedical or behavioral studies because they believe in the advancement of science or because researchers offer financial incentives are another group whose personal stake in the research may go unnoticed by IRBS and researchers, thereby weakening oversight.

Fourth, an inherent conflict of interest exists when physician-researchers include their patients in research protocols. If the physicians 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.

Fifth, pressures to recruit subjects can lead researchers and IRBS to overlook deficiencies in efforts to inform subjects of potential risks. This problem has been exacerbated, a consultant to IRBS told us, by NIH and FDA guidelines that now require that subjects selected for the studies over which the agencies have jurisdiction reflect the gender and racial composition of potentially affected populations. These guidelines are in place for the purpose of generalizing research results to the widest possible range of population groups.

Finally, the line between research and medical treatment is not always clear to clinicians. Controversy exists regarding whether certain medical procedures should be categorized as research. For example, in some cases physicians may use an innovative but unproven technique to treat patients without considering the procedure to be research. From the standpoint of the physicians, they are providing treatment to individual patients rather than conducting a clinical trial. Given this view, they do not seek IRB approval. From the standpoint of experts we interviewed, however, such treatments could constitute unregulated research and place people at risk of harm from unproven techniques.

Conclusions

With the issuance of federal regulations covering much human subject research and the maturation of the HHS oversight system, researchers have become more aware of ethical conduct standards and more often comply with them. Because no oversight system can be designed to guarantee

²⁴Advisory Committee on Human Radiation Experiments, Final Report, p. 798.

complete protection for each individual, holes inevitably exist in the regulatory net. Federal and IRB reviewers rarely observe the interaction between researchers and subjects during the informed consent process or throughout the course of the study. Whether research institutions are examined by OPRR for eligibility to receive HHS funding, research studies are assessed by IRBs for their compliance with HHS regulations, or applications to conduct drug trials are reviewed by FDA, oversight is present, but at a distance.

There is consensus among experts and regulators about the benefits of first-hand review, but continuous on-site inspections of every research institution and its studies are neither feasible nor desirable because of the regulatory burden this would impose on both the research community and regulators. Finding the balance, however, between that extreme and a process that relies almost exclusively on paper reviews is the fundamental challenge facing regulators and IRBs in the current HHS oversight system.

Individuals participating in biomedical and behavioral research are essential to the advancement of science and medicine. Federal regulators and research institutions, therefore, continually strive to improve the protection of human participants without imposing an unwieldy, burdensome regulatory apparatus. To continue to prevent the occurrence of human subject protection violations and to identify and correct violations that do occur remain essential objectives of the system. 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.

Agency Comments

NIH and FDA reviewed a draft of this report and provided comments, which are reproduced in appendixes III and IV. NIH and FDA found the report to be generally accurate and suggested revisions to clarify specific aspects of our discussion of the human subject protection system. We incorporated these as appropriate, basing the changes in some instances on further discussions with officials from each agency.

In its comments, NIH recognized the importance of on-site visits to research institutions by OPRR staff and noted that the number of technical assistance visits would be increased to 12 to 24 per year. This action should help strengthen human subject protection efforts by institutions and investigators as well as improve OPRR's assurance, monitoring, and enforcement efforts.

In its comments, NIH also stated that OPRR's independent oversight and authority to enforce human subject protection regulations within NIH are not compromised by OPRR's location within the NIH organizational structure. NIH said that the lines of authority of the NIH Deputy Director for Intramural Research and the OPRR Director do not cross within NIH and, therefore, that OPRR's authority is not compromised. We disagree with NIH's conclusion and believe that a potential weakness exists in OPRR's ability to enforce human subject protection regulations within NIH. This weakness results from the chain of command within NIH and the NIH Director's dual responsibilities for the success of the intramural research program and OPRR's enforcement of human subject protection regulations. We have amplified our discussion of these issues in the report.

In its comments on our draft report, FDA raised concerns that our work understates FDA's accomplishments and the efforts to protect human subjects of product testing by the industries regulated by FDA. Because human subject protection activities in drug research account for most of FDA's efforts in this area, we limited the scope of our work to an examination of CDER's oversight. We have modified the report to acknowledge the human subject protection activities of the Center for Biologics Evaluation and Research and the Center for Devices and Radiological Health. Furthermore, we have clarified that the inspection reports and actions to enforce regulations we discuss are for CDER's oversight of IRBS and drug studies, and we have included additional information FDA provided on fiscal year 1995 activities.

FDA also focused on our presentation of aspects of its IRB inspection programs. FDA commented that (1) the IRB inspection program is the principal way in which FDA addresses the issue of human subject protection, (2) IRB inspections can enhance protection for subjects in specific studies, and (3) an IRB inspection conducted for one center—for example, CDER—can serve to protect subjects in studies regulated by CBER and CDRH. We have modified the report to address these points.

As agreed with your office, unless you publicly announce its contents earlier, we plan no further distribution of this report until 7 days from the date of this letter. At that time, we will send copies of this report to the Secretary of HHS, the Director of NIH, the Commissioner of FDA, and other interested parties.

This report was prepared under the direction of Mark V. Nadel, Associate Director for National and Public Health Issues. If you or your staff have any questions, please call me at (202) 512-7119 or Bruce D. Layton, Assistant Director, at (202) 512-6837. Other major contributors to this report include Frederick K. Caison, Linda S. Lootens, and Hannah F. Fein.

Sincerely yours,

A handwritten signature in black ink that reads "Sarah F. Jaggar". The signature is written in a cursive style with a long, sweeping underline that extends to the left.

Sarah F. Jaggar
Director, Health Financing and
Public Health Issues

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Figure 1: Basic Elements of Informed Consent

Abbreviations

CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
FDA	Food and Drug Administration
HEW	Department of Health, Education, and Welfare
HIV	human immunodeficiency virus
HHS	Department of Health and Human Services
IRB	institutional review board
NDA	new drug application
NIH	National Institutes of Health
OPRR	Office for Protection from Research Risks

Scope and Methodology

We focused our work on the Department of Health and Human Services (HHS)—the federal department sponsoring biomedical and behavioral research with the largest human subject research budget, over \$5 billion in fiscal year 1995. Within HHS, we examined the policy and oversight roles of the two entities with primary responsibility for protecting human research subjects: the National Institutes of Health’s (NIH) Office for Protection from Research Risks (OPRR) and the Food and Drug Administration (FDA). OPRR is responsible for enforcing compliance with HHS human subject protection regulations when human subject research is conducted or supported by HHS. FDA is responsible for protecting the rights of human subjects enrolled in research with products it regulates—drugs, medical devices, and biologics. We limited our review to FDA’s Center for Drug Evaluation and Research (CDER) because drug research is the largest segment of biomedical research. Because of this volume, FDA conducts more oversight activities in the drug products area than it does for medical devices and biological products, with CDER carrying out most of FDA’s human subject protection activities. Although FDA’s Center for Biologics Evaluation and Research and Center for Devices and Radiological Health also have programs to protect human subjects, these Centers were not included in our review.

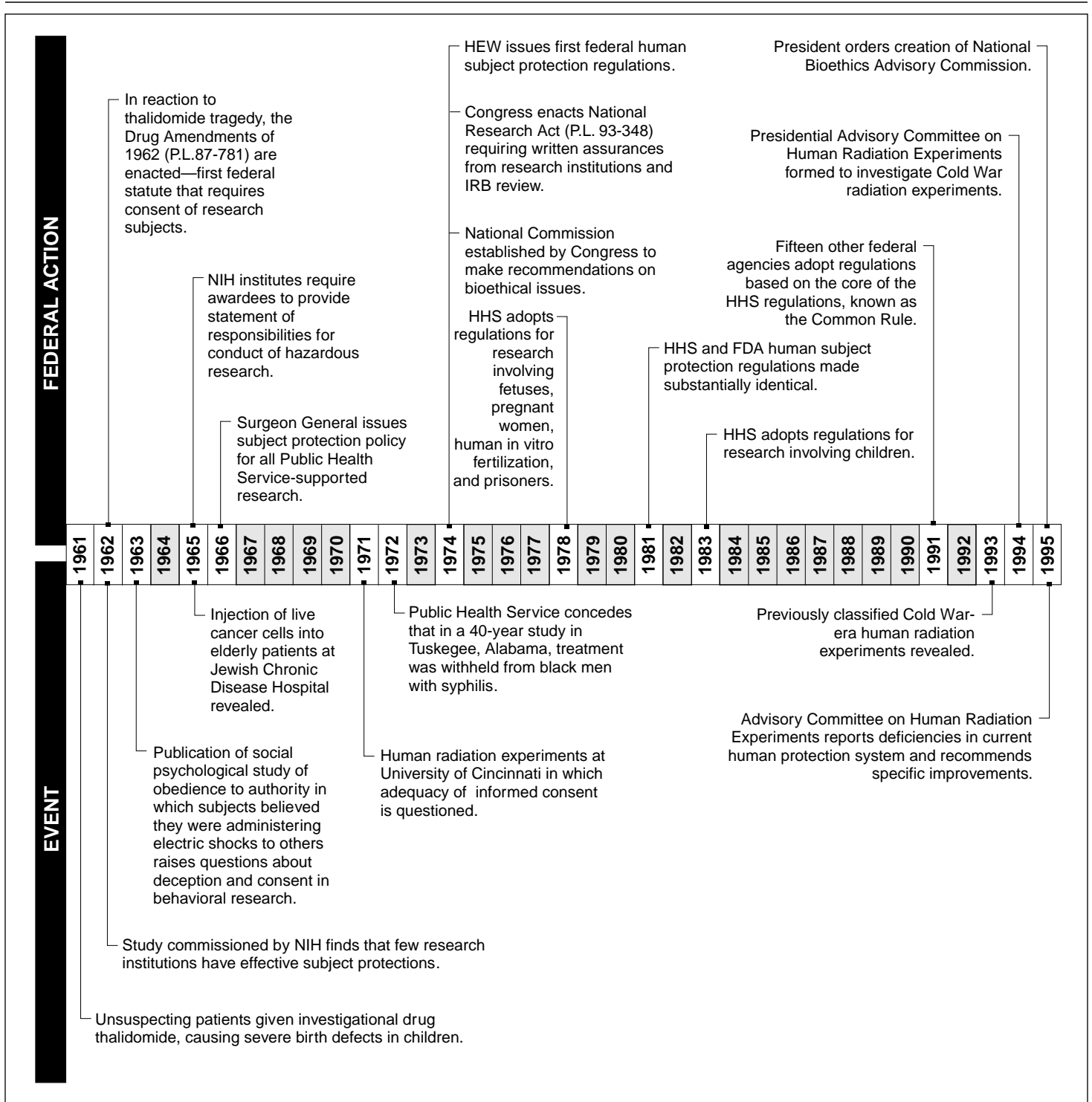
To gather information about the federal role in protecting human subjects, we interviewed NIH, OPRR, and FDA officials and reviewed regulations, policies, procedures, guidelines, and educational materials the entities provide to institutional review boards (IRB) and researchers. To learn about the nature of OPRR findings and corrective actions, we reviewed 40 of the 166 compliance case files handled by OPRR from 1988 through March 1995, including 30 files we randomly selected and 10 files OPRR officials selected as representing the most serious violations. We accompanied OPRR staff on a compliance site visit to a major research institution and reviewed OPRR site visit reports from compliance visits conducted from September 1990 through December 1994. We also reviewed examples of inspection files, 69 of the 84 letters describing deficiencies that FDA issued to drug researchers from April 1980 through November 1995, and all 31 Warning Letters issued to IRBs regarding their oversight of drug research between January 1993 and November 1995. In addition, we reviewed correspondence between FDA and institutions in cases where FDA inspections found that IRBs did not comply with human subject protection regulations.

To examine how local level protections work, we reviewed the professional literature, including the reports of presidential and

congressional commissions; interviewed research institution officials, IRB members, and researchers; and reviewed research documents, such as institutional guidelines for IRBS and researchers, IRB minutes, and informed consent forms. We attended an IRB meeting to observe an IRB review of proposed research. We interviewed numerous experts from across the nation with experience in bioethics, medicine, social science, law, and human subject protection issues. These experts included university and hospital researchers, subjects' rights advocates, IRB members, human subject protection consultants, and representatives from the drug industry.

We performed our field work from September 1994 to December 1995 in accordance with generally accepted government auditing standards.

Landmark Events Affecting the Development of HHS' Human Subject Protection System



Comments From the National Institutes of Health



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20892

FEB 15 1996

Ms. Sarah F. Jaggar
Director, Health Financing and Public Health Issues
United States General Accounting Office
Washington, DC 20548

Dear Ms. Jaggar:

The National Institutes of Health (NIH) appreciates the opportunity to comment on the Draft GAO Report, *Scientific Research: Continued Vigilance Critical to Protecting Human Subjects*. The report accurately describes the overall functions of the NIH Office for Protection from Research Risks (OPRR) related to human research subjects, including education by means of guidance and workshops; prevention in the form of negotiating written assurances; and oversight through inquiries and investigations.

In particular, it acknowledges that current oversight activities are working. The review of forty OPRR compliance case files, accompaniment of OPRR staff on a compliance site visit to a major research institution, and interviews found that OPRR effectively identifies noncompliance, requires institutions to take corrective actions, and, in most cases, achieves satisfactory resolution of institutional noncompliance within 12 to 18 months.

Further, the report identifies a consensus among experts and regulators about the benefits of first-hand review of institutional oversight of human subject research. Accordingly, OPRR expects to enhance its assurance efforts to include a program of technical assistance site visits. Such visits, to number from 12 to 24 per year, are of mutual educational benefit--strengthening both the institution's program of human subject protections and ensuring the fidelity of OPRR's assurance negotiations and documents. The OPRR expects to continue its program of for-cause and not-for-cause compliance site visits.

The report also notes that primary responsibility for OPRR's negotiating Multiple Project Assurances of compliance covering the 450 to 500 institutions that receive most of the Health and Human Services' (HHS) funding for human subjects research rests with one individual. I honored this part-time, unpaid, retired physician in June 1995 with the NIH Director's Award for her extraordinary service, and I am pleased that OPRR is proceeding to recruit for a health scientist administrator to join her in negotiating Multiple Project Assurances.

The NIH is described by the GAO Report as "in the position of regulating itself" and the OPRR as in a position of "potential weakness," when it oversees human subjects research conducted by NIH (i.e., by the NIH Intramural Research Program.) In fact, the OPRR oversees and interacts

**Appendix III
Comments From the National Institutes of
Health**

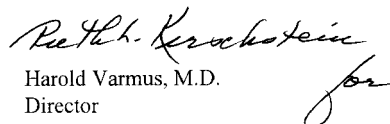
Page 2 - Ms. Sarah F. Jaggard

with the NIH just as with any extramural research institution. The NIH holds a Multiple Project Assurance approved by OPRR. The NIH institutional official and Multiple Project Assurance signatory is the NIH Deputy Director for Intramural Research, who heads the NIH Intramural Research Program. The OPRR's independent oversight and authority are not compromised, as the lines of authority of the NIH Deputy Director for Intramural Research and the OPRR Director do not cross within NIH. The NIH Intramural Research Program's need for 5 years to implement corrective actions after being cited by the OPRR in 1991 for compliance violations is best viewed as an index of the complexity of fully implementing the corrective actions rather than a function of weakness in the OPRR's ability to enforce human protection regulations within the NIH organizational structure.

In the face of constraints on time and resources that threaten to reduce the effectiveness of oversight by local Institutional Review Boards and OPRR, the report warns of the need to retain as a priority continued vigilance over human subject protections. The Secretary of HHS, on whose behalf OPRR implements the HHS Regulations for Protection of Human Subjects (Title 45, Code of Federal Regulations, Part 46), identified six priorities for HHS in December 1995. One of those six--making bioethics "as sophisticated as our science"--embraces the advice of the GAO and reemphasizes the OPRR's charge.

Finally, the NIH appreciates the diligent fieldwork of GAO investigators Bruce D. Layton, Frederick K. Caison, and Linda S. Lootens and their informed analysis of the operations of OPRR. Additional technical comments on the Report are enclosed.

Sincerely,


Harold Varmus, M.D.
Director

Enclosure

**Appendix III
Comments From the National Institutes of
Health**

Suggested Technical Revisions of Draft Report GAO/HEHS-96-72
SCIENTIFIC RESEARCH
Continued Vigilance Critical to Protecting Human Subjects

<u>Citation</u>	<u>Technical revision</u>
Now on p. 2.	page 4, line 1: "of" should be "for"
Now on p. 2.	p.5, 1.3-4: "demonstrates that abuses can occur, but" should be "both demonstrates that abuses can occur and"
Now on p. 3.	p.6, 1.4: "led to the" should be "accompanied"
	The HEW regulations were promulgated in May 1974, prior to the July 1974 enactment of the National Research Act.
Now on p. 3.	p.6, 1.5: "HHS" should be "HEW"
Now on p. 3.	p.6, 1.8: "When these" should be "When the core of these"
	Only Subpart A of the HHS regulations (which are comprised of Subparts A, B, C, and D) was adopted by 15 other departments and agencies in 1991.
Now on p. 3, footnote 5.	p.6, footnote 3, 1.1: "five" should be "six"
Now on p. 3, footnote 5.	p.6, footnote 3, 1.4: Insert after comma "the HEW Ethics Advisory Board (1976-80),"
Now on p. 4.	p.7, 1.1: "HHS has considered but has yet to" should be "In the late 1970s and early 1980s, HHS did not"
	As written, the draft report conveys a false impression of pending action. In a December 16, 1982 letter to the Chairman of the President's Commission for the Study of Problems in Medicine and Biomedical and Behavioral Research (Morris B. Abram), the Secretary of Health and Human Services (Richard S. Schweiker) indicated that the Department was not intending to issue such regulations.
Now on p. 6.	p.8, 1.14: "studies" should be "awards involving human subjects"
Now on p. 5, footnote 7.	p.8, footnote 4, 1.2: "The major" should be "One"

Appendix III
Comments From the National Institutes of
Health

Suggested Technical Revisions of Draft Report GAO/HEHS-96-72
SCIENTIFIC RESEARCH
Continued Vigilance Critical to Protecting Human Subjects

(continued)

Citation Technical revision

Now on p. 5, footnote 7.

p.8, footnote 4, 1.4: Delete the balance of the footnote text beginning with "While..." and replace with the following:

"The Common Rule permits IRBs to alter or waive informed consent in a research protocol when four criteria are met. FDA regulations permit single exceptions to informed consent, with followup notification to the IRB, when different criteria are met. In September 1995, aiming toward harmonization of the two rules, FDA proposed revision of its regulations. OPRR officials told us that they will seek Secretarial action under 45 CFR 46.101(i) to achieve harmony with a final FDA rule."

Footnote 4 appears as an explication of the "Common Rule" (p.8, 1.3), but it actually describes action solely under the HHS regulations (45 CFR Part 46) that would affect no other Common Rule departments or agencies.

Now on pp. 6-7.

p.10, 1.2-3: Revise "NIH has 14 IRBs, ..." to read "Human subjects research conducted by NIH itself, for example, is governed by the 14 IRBs of the NIH Intramural Research Program. In general, IRBs..."

Now on p. 7.

p.11, 1.5-6: Revise "conducting federally funded research..." to read "engaging in research with human subjects conducted or funded by any of the 17 departments or agencies pledged to the Common Rule. To be eligible to receive such funding,..."

The Common Rule applies to research conducted or supported by 17 departments or agencies, not to all federally funded research.

Now on p. 8.

p.12, 1.1: Delete "the"

Now on p. 8.

p.12, 1.9: After "willingness" insert "and the expertise"

**Appendix III
Comments From the National Institutes of
Health**

Suggested Technical Revisions of Draft Report GAO/HEHS-96-72
SCIENTIFIC RESEARCH
Continued Vigilance Critical to Protecting Human Subjects

(continued)

<u>Citation</u>	<u>Technical revision</u>
Now on p. 8.	p.12, l.17-18: "OPRR had granted 451 multiple project assurances covering" should be "451 active OPRR multiple project assurances covered" OPRR both grants--and deactivates--multiple project assurances, in a dynamic process. An MPA may be deactivated, for example, because of lack of recent research activity involving human subjects.
Now on p. 8, footnote 11.	p.12, footnote 7, l.1: "Most" is more accurately "Ninety-eight percent of"
Now on p. 9.	p.13, l.18: "of any other assurances" should be "of other assurances that do not apply which are"
Now on p. 9.	p.14, l.1: Delete "the protocol or delete information from the prototype consent document" and replace with "core elements of the protocol that must be consistent across all sites or delete or substantially modify risks and/or alternative treatments of the prototype consent document without certain notice given and IRB justification"
Now on p. 10, footnote 12.	p.16, footnote 8, l.1: "certain" should be "six"
Now on p. 10, footnote 12.	p.16, footnote 8, l.3: "Other" should be "Other, nonexempt"
Now on p. 10, footnote 12.	p.16, footnote 8, l.4: Insert after closed parenthesis "and falls into any of 10 categories approved by the Secretary of Health and Human Services"
Now on p. 11.	p.17, l.13: "make assumptions about" should be "rely on investigators' and consent monitors' assessments of"
Now on p. 11.	p.17, l.18: After "harm" insert "and benefit"
Now on p. 11.	p.17, l.20: "adverse medical" should be "general adverse"
Now on p. 11.	p.18, l.2: "increased" should be "changed"
Now on p. 11.	p.18, l.3: "technological advances" should be "advances in knowledge or technology"

**Appendix III
Comments From the National Institutes of
Health**

Suggested Technical Revisions of Draft GAO/HEHS-96-72
SCIENTIFIC RESEARCH
Continued Vigilance Critical to Protecting Human Subjects

(continued)

<u>Citation</u>	<u>Technical revision</u>
Now on p. 15.	p.23, l.21: Insert "news media" and "Congress" as additional, important sources.
Now on p. 15.	p.24, l.7: "misconduct" is more properly "noncompliance"
Now on p. 17.	p.27, l.10: "monthly board meeting" should be "board meeting, often held monthly"
Now on p. 19.	p.29, l.18: "effects" should be "events"
Now on p. 30.	p.41, l.5: After "largest" insert "human subjects"
Now on p. 30.	p.41, l.12-13: Delete "and individuals supported by HHS funds" and replace with "when human subjects research is conducted or supported by HHS"
Now on p. 3, footnote 6.	p.41, footnote 17, l.1: "Fifteen" should be "Sixteen" The Social Security Administration, which became an independent agency in 1995, is bound by its enabling statute to the Common Rule.
Now on p. 3, footnote 6.	p.41, footnote 17, l.2: After "subjects" insert "have also"
Now on p. 3, footnote 6.	p.41, footnote 17, l.9: After semicolon insert "the Social Security Administration;"
Now on p. 32.	p.46, l.10-16: On 1974 time line, "HEW issues first human protection regulations" should precede "Congress enacts National Research Act..."
Now on p. 32.	p.46, bottom: Insert "1978 Adoption of current Subparts B and C of 45 CFR Part 46"
Now on p. 32.	p.47, l.3: Insert "1983 Adoption of current Subpart D of 45 CFR Part 46"
Now on p. 32.	p.47, l.4: 1991 entry should be "Fifteen other federal agencies adopt regulations based on core of HHS regulations"
Now on p. 32.	p.47, l.7-9: 1993 entry should be: "Dept. of Energy follows <u>Albuquerque Tribune</u> and Rep. Edward J. Markey in holding previously classified Cold War-era human radiation experiments up to public scrutiny"

Comments From the Food and Drug Administration



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

FEB 6 1996

Ms. Sarah F. Jaggar
Director, Health Financing and
Public Health Issues
U.S. General Accounting Office
1 Massachusetts Avenue, N.W.
Room 650
Washington, D.C. 20001

Dear Ms. Jaggar:

Attached are the Food and Drug Administration's comments on the GAO draft report entitled, SCIENTIFIC RESEARCH: Continued Vigilance Critical to Protecting Human Subjects.

Sincerely,

for Melinda Plam
Diane E. Thompson
Associate Commissioner
for Legislative Affairs

Attachment

**Appendix IV
Comments From the Food and Drug
Administration**

**Comments on the GAO Report Entitled "SCIENTIFIC RESEARCH:
Continued Vigilance Critical to Protecting Human Subjects"**

We appreciate the opportunity to review the report and find it to be generally acceptable. However, the report also contains some errors, and we offer the following suggestions to correct them. The report omits any reference to human subject protection activities carried out by the Food and Drug Administration's (FDA) Centers for Biologics Evaluation and Research (CBER) and Devices and Radiological Health (CDRH), and thus significantly understates FDA's accomplishments and efforts to protect the human subjects of product testing by the industries regulated by FDA. We recognize that GAO focused on the Center for Drug Evaluation and Research's (CDER) program only, and would, therefore, have no data regarding the activities of the other Centers. However, both CBER and CDRH also have active Institutional Review Board (IRB) inspection programs, as GAO was informed. Although CDER does most of the inspections, last year 30% (94) of the 306 inspections accomplished were done by CDRH and CBER. The report indicates that FDA only accomplished around 150 IRB inspections, which is less than half the number actually done.

Not only does this understate FDA accomplishments, it also overlooks the fact that inspections performed for one center enhance subject protection for subjects involved in studies as well. IRB inspections, in particular, affect all studies within the purview of the inspected IRB, not just those relative to the specific Center responsible for the inspection. Inspections focus on how the IRB carries out its responsibility to ensure that human research is ethical and that subjects are protected from undue risks and are appropriately informed about all aspects of the study in which they are participants. If the IRB is appropriately constituted and meets the requirements of the regulation for studies of devices, for example, it most likely meets the requirements in studies of biologics and drugs as well. We suggest that the report be revised to incorporate a more complete statement of the activities carried out by FDA with respect to Human Subject Protection and make clear that GAO only evaluated approximately two-thirds of FDA's activities in this field.

The report seems to focus first on the Clinical Investigator (CI) program as the principal mechanism for overseeing the protection of human research subjects. In fact, the IRB inspection program is the principal way by which FDA addresses the issue of human subject protection. Although FDA investigators examine physicians' records concerning IRB approval and oversight, and documentation of informed consent and adverse experiences reporting by the physician investigator, the principal focus of the CI program is auditing study performance against protocol

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requirements and verifying the accuracy and completeness of scientific data.

The report also overstates the resources FDA expends in these programs by implying that all 1000 FDA inspectors are engaged in inspections of CIs and IRBs. While it is true that all FDA inspectors may conduct these inspections, they do not do so full time. As indicated below in comments on specific statements in the draft report, the actual number of FTEs devoted to inspections of CIs and IRBs is significantly less than 1000.

TECHNICAL COMMENTS

Throughout the report.

1. As an over-all observation, the report frequently refers to "human protection," when "human subject protection" is meant. We suggest that the word "subject" be inserted wherever "human protection" is currently used. This would make it clear that the report addresses protection of the human subjects of research only.

Now on p. 1.

2. Page 2, first sentence: This sentence groups Tuskegee, thalidomide and the radiation experiments together. Although there are parallels, the thalidomide "disaster" does not really belong. The other two were clearly research activities that, among other problems, involved failures in obtaining informed consent. Thalidomide was approved for use in Europe, and although still "experimental" thinly disguised as research, was being used in the practice of medicine in the U.S. when the birth defects began to surface. It is seen as a "triumph" that the FDA did not approve the drug for use in the U.S.

Now on p. 5.

3. Page 7, Bottom of the box: We suggest adding the following footnote:

Six additional elements, listed in Title 21, Code of Federal Regulations 50.25(b), are required when appropriate to the study. The HHS regulation is 45 CFR 46.116(b).

Now on p. 5.

4. Page 8, first paragraph, last sentence: The description of an IRB assumes that all IRBs are associated with an institution. FDA permits review by "independent" IRBs; that is, IRBs that are not affiliated with the institution in which the research is to be conducted. Independent IRBs may be "local" or they may be located at a distant location. Their responsibilities do not differ from those IRBs that are associated with an institution--i.e., they must take into account community values, etc. Therefore, the statement in the report should be qualified to state something like: "...review panels that are usually associated...."

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Now on p. 5, footnote 7.

5. Page 8, footnote 4: This footnote needs to be substantially revised to be accurate. FDA's current regulations permit an exception from informed consent in emergency life-threatening situations if certain conditions are met. See 21 C.F.R. § 50.23. The footnote suggests that FDA's proposed regulation modifies the existing regulation by requiring prior FDA approval "in these situations." FDA's proposal applies to situations other than those described in § 50.23. FDA is not proposing to change § 50.23. See 60 Fed. Reg. 49086 (Sept. 21, 1995).

The footnote should be changed to read:

FDA's regulations covering human subjects research are nearly identical to those found in the Common Rule. One major difference concerns the criteria under which informed consent can be waived. The common rule permits the IRB to waive the requirement to obtain informed consent provided the IRB finds and documents that (1) the research involves no more than minimal risk to the subjects; (2) the waiver will not adversely affect the rights and welfare of the subjects; (3) the research could not practicably be carried out without the waiver; and (4) whenever appropriate, the subjects will be provided with additional pertinent information after participation. FDA's regulations provide an exception from the general requirements of obtaining informed consent if both the investigator and a physician who is not otherwise participating in the clinical investigation certify in writing all of the following: (1) the human subject is confronted by a life-threatening situation necessitating the use of the test article; (2) informed consent cannot be obtained from the subject because of an inability of communicate with, or obtain legally effective consent from, the subject; (3) time is not sufficient to obtain consent from the subject's legal representative; and (4) there is available no alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the subject. This documentation is required to be submitted to the IRB within 5 working days after the use of the test article.

In September 1995, FDA proposed regulations that would provide a narrow exception to the requirement for obtaining and documenting informed consent for a limited class of research activities involving human subjects who, because of their life-threatening medical

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condition and the unavailability of legally authorized persons to represent them, are in need of emergency medical intervention and cannot provide legally effective informed consent. It is the intent of HHS to bring the HHS (45 CFR part 46) and FDA (21 CFR part 50) regulations into harmony on this matter at the time this rule is made final.

Now on p. 6.

6. Page 9, 1st paragraph, last sentence: Change to read as follows: "Routine and for-cause on-site inspections are conducted by a small number of FDA's about 1000 investigators. For FY'95, the field allocated approximately 13 FTEs for domestic IRB and inspections and 45 FTEs among the three Centers for domestic Clinical Investigator, and Sponsor/Monitor/Contract Research Organization inspections. The inspectors are also responsible for examining the integrity of research data, assessing compliance with good manufacturing practices and carrying out all of FDA's investigations, inspections and sample collections necessary to enforce the Food, Drug and Cosmetic Act. Of the roughly 14,500 inspections conducted in FY 1995, 306 covered Institutional Review Boards and 632 covered clinical trials."

In addition to the field investigators allocated to clinical investigators and IRBs, CDER's Bioresearch Monitoring Program is carried out by the Division of Scientific Investigations (DSI). One of the primary purposes of this program is the protection of human subjects involved in clinical research. DSI has 7 full-time employees dedicated to IRB/RDRC investigations and 9 full-time employees dedicated to clinical investigations.

Other agency offices are also involved; e.g., the Office of Health Affairs and CDER Review Divisions (whose Medical Officers evaluate informed consent documents submitted in INDs).

Now on p. 9.

7. Page 14, third line from the bottom: FDA doesn't modify protocols. It requests sponsors to make modifications where appropriate. Change the words "can modify" to "can request modifications."

Now on p. 11, footnote 13.

8. Page 17, footnote: The material following (1) in the footnote is not contained in FDA's regulations. See 21 CFR 56.109(c). Change to read, "Under the Common Rule"

Now on p. 12.

9. Page 19, second paragraph, sentence 4: Although the Clinical Investigations inspection program does address protection of human research subjects, this is a relatively limited objective of this program. The IRB program provides the principal program for oversight of human subject

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protection. The sentence tends to understate FDA's activity in this area. It reports that FDA conducts about 250 routine inspections. It refers to for-cause inspections, but does not assign numbers.

The report would more accurately reflect FDA efforts by noting that last fiscal year, among the three Centers monitoring human clinical trials, 632 (almost 3 times the number cited in the report) inspections were performed. This included 376 for drugs, 197 for devices and 59 for CBER, both for-cause and routine.

Now on p. 14, footnote 18.

10. Page 21, next-to-last sentence: A footnote should be added to refer to a new notice of proposed rulemaking, as follows:

On December 22, 1995, FDA published a proposed rule to amend current informed consent regulations to require that the written consent form signed by the subject or the subject's legally authorized representative, be dated by the subject or representative at the time consent is given. FDA is proposing this requirement because the agency has had problems on occasion verifying that informed consent was obtained from a research subject prior to participation in a study because the consent document was not dated. The agency believes that by explicitly requiring that the consent form be dated at the time it is signed, the agency will be able to help ensure that informed consent was, in fact, obtained prior to entry into the study as required by FDA regulations.

Now on p. 12.

11. Page 22, second line: The report should make clear that action against a single IRB has a protective effect multiplied by the number of studies for which the IRB is responsible. Unlike action against a single clinical investigator concerning the limited number of patients in one or two trials, one large research university IRB may be responsible for a thousand or more ongoing clinical trials involving tens of thousands of patients. Action to limit research at such an IRB serves to protect an exponentially greater number of human subjects than action against a single clinical investigator. Also, unlike the clinical trials inspections, IRB inspections cover studies that are both completed and ongoing. Thus, it affords protection before-the-fact by stopping or preventing unacceptable practices.

Now on p. 13.

12. Page 22, first complete paragraph, fourth line: It would be more accurate to state that "...researchers participated as IRB members in the review of their own studies;..." There

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is nothing wrong with a researcher being an IRB member as long as the researcher does not participate in the review of his or her research, other than to provide information requested by the IRB.

Now on p. 13.

13. Page 23, top paragraph, line 4, sentence beginning, "Over the past 30 years...": The term, "enforcement actions," is not defined, but seems to refer only to disqualifications. Also, the paragraph does not reflect the "teeth" of the FDA regulations. It would be appropriate to mention that FDA regulations (unlike the HHS regulations) have administrative sanctions that can be taken against IRBs and their institutions (21 CFR 56.120 and 56.121). As a result of inspection findings, FDA has restricted subject enrollment and suspended the ability of IRBs to approve FDA-regulated studies. These restrictions are generally in place only a short time because the research community is very responsive to FDA concerns. Also, in accordance with 21 CFR 56.124, FDA has successfully pursued prosecution through the Department of Justice. Material needs to be added that shows the entire range of FDA's actions against researchers who fail to comply with FDA's regulations pertaining to the use of investigational drugs and protection of human subjects. "From June 1977 through November 1995, FDA conducted over 3600 inspections of clinical studies performed in support of new drug applications. Of these, FDA found over 300 clinical investigators who were severely deficient in their use of investigational drugs.

Now on p. 15.

It should also be noted that, during the same period, FDA conducted over 430 inspections of specific clinical investigators whose work, for some reason, was thought to be deficient. Over 200 of these inspections revealed objectionable conditions or practices that represented significant departures from good clinical practices. FDA disqualified 83 investigators, and imposed restrictions on the investigational drug use of 34 others. In addition, FDA successfully pursued criminal prosecution of 17 clinical investigators, with penalties ranging from probation and public service, to fines and restitution (\$2 million in one case), to prison sentences. Since April 1982, FDA inspections revealed 298 instances in which IRBs were not following FDA's regulations for the protection of human subjects involved in drug research; from January 1993 to November 1995, the Center for Drug Evaluation and Research issued 31 Warning Letters to deficient IRBs. FDA Warning Letters require immediate corrective actions. Those few IRBs that could not comply chose to go out of business, so FDA did not formally disqualify any IRBs."

14. Page 28, last paragraph and top of page 29: A footnote should be added to update FDA's recent actions. On

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September 22, 1994, FDA published a proposed rule which would require that the sponsor certify to the absence of certain financial interests of clinical investigators or disclose those financial interests when clinical studies are submitted to FDA in support of product marketing. A number of comments were received on the proposal and, on July 20, 1995, FDA held a Part 15 hearing in order to hear public testimony on this topic. The rule is being revised based on the written comments and the Part 15 hearing. When the regulation is finalized, FDA will use this financial interest information in conjunction with other information about the study and on-site inspections to assess the reliability of data.

Now on p. 20.

15. Page 32, 1st full paragraph, 2nd and 3rd sentences: Change to read, "For example, researchers who use human subjects in drug research are required to submit to their sponsor periodic progress reports during the course of the trials. These reports include adverse events, project status, and changes to the research protocol. The sponsor, in turn, reports adverse events to FDA."

Now on p. 21, footnote 23.

16. Page 34, footnote 15: FDA does not have the resources to inspect "all studies ... etc." Restate to say that "with rare exceptions FDA inspects the conduct of studies that are important to the approval of all product approval applications containing clinical data."

Now on p. 30.

17. Page 42, 9 lines from the bottom of the page: It should be clarified that the "31 letters issued to IRBs" were "warning letters" issued by CDER.

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