

GAO

Statement

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HUMAN SUBJECTS
RESEARCH

HHS Takes Steps to
Strengthen Protections,
But Concerns Remain



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Considerable attention to the protection of human subjects in biomedical research was sparked in the mid-1990s following disclosures of federally sponsored experiments in which research investigators did not properly obtain the consent of the subjects.¹ Congressional concern was heightened after the death in September 1999 of Jesse Gelsinger, an 18-year-old participant in a gene transfer trial funded by the National Institutes of Health (NIH) in the Department of Health and Human Services (HHS).

Responsibility for the protection of human subjects in biomedical research exists at three levels: at the federal level are agencies, such as HHS; at the institutional level are research institutions, including universities and academic medical centers; and at the individual investigator level are physicians, scientists, and other professionals. Each level plays a role in meeting federal requirements for protecting human research subjects or in ensuring that the requirements are met. However, with the Gelsinger death and other instances of research misconduct, questions are being raised about the progress of federal efforts to ensure the safe and ethical conduct of biomedical research.

This summer we will report in more detail on federal efforts to protect human subjects in biomedical research, including efforts to address financial conflict of interest issues. This statement focuses on HHS' efforts to date to address human subjects protection issues at the federal, institutional, and individual investigator levels and on areas of concern that remain. My comments are based on interviews with key officials at HHS agencies and other organizations, reviews of recent reports on human subjects protection, and an analysis of relevant HHS regulations and policies. We conducted our work from September 2000 through May 2001 in accordance with generally accepted government auditing standards.

In summary, at the federal level HHS is seeking to strengthen protection of human subjects in biomedical research by enhancing the visibility of its human subjects protection activities, improving its monitoring of compliance with relevant regulations by institutions and investigators, and strengthening enforcement of those regulations. HHS has also issued new

¹Advisory Committee on Human Radiation Experiments, *Final Report* (Washington, D.C.: Oct. 1995). *Scientific Research: Continued Vigilance Critical to Protecting Human Subjects* (GAO/HEHS-96-72, Mar. 1996).

guidance and is collecting information intended to improve oversight and monitoring at the institutional level. HHS activities directed at the investigator level consist largely of educational efforts to heighten investigators' awareness of and compliance with ethical policies and practices in conducting research. Overall, HHS' actions appear promising, but we have some concerns about the pace and scope of the department's efforts to ensure the safety and protection of participants in clinical trials.

Background

A significant proportion of biomedical research is conducted through clinical trials, which involve testing new drugs, devices, or treatments with human subjects. Many of these trials are spread across hundreds of sites, sometimes at sites outside of the United States, and are performed not only in academic medical centers but also by physicians and other providers in the community. Although there are no comprehensive data on the number of individuals enrolled in research studies, this number has likely increased as federal spending for medical and health research has doubled in recent years and industry spending has been growing even faster.

Common Rule Requirements for Protecting Human Subjects in Federally Supported Scientific Research

The principal federal policy for protecting human research subjects is called the Common Rule. It is a set of requirements, embodied in regulation, agreed to by 17 federal departments and agencies, including HHS,² and applies only to federally funded or sponsored research. Broadly speaking, the Common Rule focuses on

- obtaining the research subject's voluntary, informed consent by specifying, among other things, that subjects must be told of the expected benefits and potential risks to which they could be exposed;
- setting criteria for review panels—known as institutional review boards (IRB)³—that are responsible for performing initial and ongoing reviews of research; and
- obtaining a formal written assurance of compliance with federal standards from institutions engaged in research studies.

²HHS regulations contain additional protections not included in the Common Rule for research involving certain vulnerable populations—namely, pregnant women, children, fetuses, subjects of in vitro fertilization research, and prisoners.

³Some IRBs are associated with particular universities or research institutions. Others are independent for-profit or not-for-profit entities.

A federal agency cannot change the Common Rule without the agreement of the other 16 agencies that agreed to and are governed by the rule. Thus, to adapt regulations to emerging ethical issues or new scientific developments, some agencies have issued their own regulations or guidance, which has produced a varied array of policies across the federal agencies.

Structure in Place to Oversee Human Subjects Protections in HHS- Related Research

Major responsibility for federal oversight of human subjects protection in HHS-related clinical research rests with three entities: the Office for Human Research Protection (OHRP), NIH, and the Food and Drug Administration (FDA). OHRP oversees all research conducted or funded by HHS that uses human subjects. OHRP's oversight activities are directed chiefly at HHS-supported research, including research conducted at universities, hospitals, and other medical and behavioral research institutions. One of OHRP's principal duties is to approve and renew an institution's "assurance," which is a written and signed agreement that details the terms of the institution's promise to comply with federal human subjects protection requirements and policies. In addition, OHRP investigates problems involving noncompliance with human subjects protection that have been identified at institutions and conducts occasional on-site evaluations.

NIH, the principal federal agency that provides funds for biomedical research, is charged with ensuring that the research it funds is in compliance with HHS regulations and with any additional terms it negotiates with an individual research institution. NIH also issues its own guidelines for certain aspects of human subjects research, such as data and safety monitoring and the education of investigators.

FDA is responsible for ensuring the protection of the rights and welfare of human subjects enrolled in research on the products it regulates—drugs, medical devices, biological products,⁴ foods, and cosmetics. It oversees public and private research investigators, sponsors of research, such as pharmaceutical companies and biotechnology companies, and IRBs that review FDA-regulated research. Some of this research is not federally funded and thus does not fall under the Common Rule, but FDA has

⁴A "biological product" means "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, . . . , applicable to the prevention, treatment, or cure of a disease or condition of human beings" (42 U.S.C. Section 262(i)).

adopted a separate set of human subjects protection regulations that are similar, but not identical, to the Common Rule that apply to the research on products it regulates. A primary concern for FDA is assuring the quality and integrity of research data involved in the testing or licensing of medical products. FDA enforces compliance with its regulations through on-site inspections of IRBs, clinical investigators, and sponsors.

Recent Studies Highlighting Human Subjects Protection Concerns

In recent years, a number of concerns have been raised about human subjects protection. In a 1996 study, we found that various time, resource, and other pressures had reduced or threatened to reduce the effectiveness of oversight by federal agencies and IRBs.⁵ Two years later, a series of reports issued by the HHS Office of the Inspector General (OIG) confirmed the intense pressures on IRBs and the limitations of their effectiveness and made specific recommendations for action.⁶ In April 2000, the OIG reported that HHS had taken few actions in response to these recommendations.⁷

In 1999 the National Bioethics Advisory Commission (NBAC) was asked to conduct a thorough review of the federal oversight system for human subjects protection.⁸ NBAC has released a series of drafts of its report entitled “Ethical and Policy Issues in Research Involving Human Participants” and is scheduled to issue a final report in the summer of 2001. NBAC’s report is expected to address all federal oversight for research involving human participants, and NBAC is not expected to limit its recommendations to areas within HHS’ purview.

⁵[GAO/HEHS-96-72](#).

⁶*Institutional Review Boards: A Time for Reform* (OEI-01-97-00193, 1998); *Institutional Review Boards: The Emergence of Independent Boards* (OEI-01-97-00192, 1998); *Institutional Review Boards: Promising Approaches* (OEI-01-91-00191, 1998); *Institutional Review Boards: Their Role in Reviewing Approved Research* (OEI-01-97-00190, 1998).

⁷*Protecting Human Research Subjects: Status of Recommendations* (OEI-01-97-00197, 2000).

⁸NBAC was established in October 1995 to advise the National Science and Technology Council and other government entities regarding bioethical issues arising from research on human biology and behavior.

HHS Components Seek to Improve Their Diverse Federal Oversight Efforts

In response to concerns raised by Congress and the research community, HHS, in particular, three of its components—OHRP, NIH, and FDA—has begun several initiatives to enhance the protection of subjects in HHS-funded and FDA-regulated research. These efforts are largely in the initial stages of implementation.

Efforts to Enhance Visibility of Human Subjects Protection Activities

HHS has taken steps to give the issue of human subjects protection greater prominence. Until recently, NIH's Office for Protection from Research Risks (OPRR) was responsible for oversight and enforcement of regulations when HHS funding was involved. Because the office was located at NIH, it was not clear that its authority extended beyond NIH-funded research. There was also the perception that its autonomy was compromised by its location within an agency that also funds research. To address these concerns about authority and autonomy, HHS established OHRP in the Office of the HHS Secretary, Office of Public Health and Science in June 2000, enhancing the status and visibility of human subjects protection activities. OHRP assumed the human subjects protection functions of the former OPRR. OHRP has a 2-year plan to organize and coordinate the department's diverse human subjects protection activities and reengineer the system for protection of human subjects in research.

In March 2001, FDA formally elevated and centralized its human subjects protection activities by creating the Office for Human Research Trials and locating it in the Office of the Commissioner. At FDA, human subjects protection activities previously were diffuse, dispersed across various centers and the Office of the Commissioner. The new office is involved with intra-agency coordination of policy, education, and oversight relating to human subjects protection. OHRP, FDA, and NIH officials told us they are now working together more closely to coordinate and utilize resources for human subjects protection activities.

Efforts to Improve Oversight, Compliance, and Enforcement

The three HHS components have also sought to improve the mechanisms they use to conduct oversight and enforcement activities related to human subjects protection. To reduce regulatory burden and enhance its oversight capabilities, OHRP has recently revised its assurance process. The research community had concerns about the assurance approval and renewal processes. They contended that the processes had been unnecessarily burdensome and created disproportionate workload demands on HHS and research institution staff who are needed to meet other, equally important and time-consuming human subjects protection

requirements. To address these problems, OHRP undertook, as one of its first major initiatives, implementation of a simplified assurance process that is less administratively burdensome. The streamlined assurance process, which is currently being phased in, is designed to reduce the paperwork burden that characterized the former process.

OHRP, in collaboration with FDA, has initiated IRB registration as another step to improve its ability to conduct oversight and facilitate compliance. Previous HHS efforts to monitor IRBs and communicate with them about policies and guidance had been hampered because HHS did not have a comprehensive list of all IRBs, estimated to number in the thousands. As part of the new assurance process, institutions will be required to register their IRBs.⁹ Registration will enable HHS to build an IRB database, which will facilitate the identification of and communication with officials who actively review projects using human subjects.

OHRP also seeks to enhance IRB compliance by adopting a monitoring and quality improvement strategy intended to prevent problems before they occur. We and others have reported that this office's predecessor made few site visits to review compliance. Those conducted, moreover, were "for cause," that is, in response to complaints of noncompliance. OHRP has plans to conduct quality improvement evaluations (although not necessarily through site visits) at every major medical school in the United States within the next 18 months, insofar as resources permit. OHRP seeks to expand its compliance activities through enhanced coordination and communication with FDA's inspection program. In fiscal year 2000, NIH also began a process of not-for-cause site visits, intended to assess institutional understanding of federal policies and regulations (including those involving human subjects protection), minimize or eliminate noncompliance, and foster a productive partnership between NIH and its grantee institutions. To date, it has completed 10 of these visits; NIH officials told us that more are planned for fiscal year 2001.

HHS is also considering ways to address the research community's concerns that its range of options for enforcement of regulations is too limited. In the event that serious violations are uncovered, OHRP can restrict or suspend an institution's assurance. Such an action would

⁹This registration procedure seeks for the first time to register all IRBs overseeing HHS-funded research, whether independent or based at academic institutions. The new procedures do not, however, require all IRBs to register. FDA intends to require registration by all IRBs that are subject to its regulation.

seriously disrupt ongoing research at that institution because federally funded human subjects research cannot be conducted without an assurance in place. FDA can withhold approval of new studies, withhold approval for enrollment of new subjects, and terminate studies. FDA can also issue warning letters and restrict or disqualify investigators, IRBs, or institutions from conducting or reviewing research. As a granting agency, NIH can place a restriction on an award if the grantee institution is not in compliance with regulations. Nonetheless, some critics have argued that there are too few sanctions to match the range of violations that occur. Acknowledging this problem, HHS is considering a proposal for legislation that would enable FDA to levy civil monetary penalties for violations of the informed consent process and other important research practices.

Recent and Planned Protection Efforts Involve Strengthening Oversight Performed by Research Institutions

HHS has taken some actions to improve the review and monitoring of clinical trials by research institutions. HHS has taken steps to improve institutional research reviews while reducing IRB workload by issuing guidance regarding adverse events and financial relationships. It is also initiating efforts to develop standards for evaluating IRBs.

Efforts to Improve Institutional Review and Monitoring of Research

Recent HHS guidance regarding IRB use of information from other entities involved in monitoring research has the potential to improve IRB reviews and reduce their workload. Our 1996 report noted that workload and other demands impaired IRB oversight, and subsequent studies found that review of adverse event reports presents a particular challenge to IRBs. Adverse event reports describe untoward occurrences experienced by research subjects during the course of a clinical trial. IRBs have been overwhelmed by large numbers of adverse event reports from investigators, as can happen when clinical trials are conducted at multiple sites. IRB review can be difficult because adverse event reports can lack key information, such as whether the individual experiencing the adverse event was part of the trial's treatment group or control group. One mechanism that is sometimes used to help evaluate data collected during a trial is data and safety monitoring boards (DSMB). These are special committees composed of statisticians and other scientists that monitor information about the safety and effectiveness of clinical trials and that may recommend that a trial be continued or stopped. Because DSMBs have access to adverse event data, they are in a good position to assess

certain risks to subjects. Until recently, however, IRBs were to review a clinical trial's adverse event reports even if a DSMB had also evaluated them.

In May 2000, OHRP's predecessor issued guidance stating that an IRB, in its continuing reviews of a trial, could rely on a statement by a DSMB attesting that it had reviewed a trial's adverse event reports, interim findings, and any recent literature that may be relevant to the research. This policy expedites the IRB's own review of adverse event reports, thus freeing IRB resources to concentrate more appropriately on assessments of other potential study risks. Recognizing the potential benefits of DSMBs, both NIH and FDA are taking steps to encourage their use when appropriate. For example, NIH, which had issued guidance in 1998 directing the use of DSMBs in certain NIH-funded multisite trials,¹⁰ issued new guidance in June 2000 suggesting in part that DSMBs be used for additional studies, such as early-stage clinical trials that employ particularly high risk interventions or use vulnerable populations. FDA, which recommended DSMBs for certain studies in 1998 guidance, is currently developing additional guidance on their use, which is expected to be released for comment this summer.

HHS' anticipated guidance on financial relationships may also facilitate the ability of IRBs to appropriately review research. In today's environment, financial relationships sometimes exist between investigators, institutions, and industry sponsors.¹¹ These relationships have the potential to inappropriately influence the professional judgment and independence of those responsible for the protection of human subjects. In particular, they can affect the study's recruitment, enrollment, conduct, and analyses of results in ways that would financially benefit the investigator or institution, and IRBs must ensure that such financial relationships do not pose a risk for human subjects. As financial relationships continue to multiply, IRBs may need to address an increasingly complex range of issues associated with possible conflicts of interest. Some research institutions have special committees to examine financial relationships in

¹⁰NIH's 1998 guidance reaffirmed a 1979 policy directing the use of DSMBs in certain NIH-funded multisite trials.

¹¹The Bayh-Dole Act (P.L. 96-517, Section 6(a)), which was designed to allow universities, not-for-profit corporations, and small businesses to patent and commercialize their federally funded interventions, has fostered ties between industry and clinical investigators.

detail, and these committees may be able to supplement IRB review in this area.¹² In January 2001, HHS developed Draft Interim Guidance on Financial Relationships, which discussed points that IRBs and other participants in the research process should consider when addressing issues of financial interests and human subjects protection. This document generated a broad range of reactions and debate, and HHS is currently revising the document to address those comments.

Efforts to Develop Standards for IRBs

HHS has initiated efforts to develop standards for accreditation and evaluation of IRBs, standards that might help improve performance by allowing assessment of strengths and weaknesses. The OIG has stated that oversight at the federal or institutional level is not geared toward evaluating IRB effectiveness and that little is known about how well IRBs are accomplishing their mission to protect human subjects. As a first step toward evaluating the effectiveness of IRBs, HHS requested that the Institute of Medicine (IOM) explore the option of accreditation for IRBs and other human research protection entities. IOM released its report in April 2001, recommending pilot testing of accreditation by nongovernmental organizations.^{13,14} HHS also asked IOM to conduct an analysis, scheduled for completion in 2002, of the structure and functioning of IRBs and other entities involved in ensuring protection of human subjects and to develop criteria for evaluating their performance. These efforts constitute a preliminary step toward establishing benchmarks for IRB performance.

¹²Institutions receiving research funds from the Public Health Service or the National Science Foundation are required to have policies and procedures to examine financial relationships. Institutions must ensure that any significant relationships are managed, reduced, or eliminated.

¹³IOM, *Preserving Public Trust, Accreditation and Human Research Participant Protection Programs* (Washington, D.C.: National Academy Press, 2001).

¹⁴NIH plans to have its intramural human subjects program evaluated later this year using draft accreditation standards issued by the Association for the Accreditation of Human Research Protection Programs. The Department of Veterans Affairs has contracted with the National Committee for Quality Assurance to develop an accreditation process for the IRBs it uses.

HHS Initiates Efforts to Raise Investigators' Awareness of Human Subjects Protections

HHS has efforts under way to improve investigators' understanding of and compliance with human subjects protection requirements. The efforts focus on instructing clinical trial investigators on the ethical conduct of research, including pertinent regulations, proper ways to obtain informed consent from research subjects, and obligations to report adverse events.

HHS has taken several recent actions to inform investigators about human subjects protection policies and practices. We, OHRP, and OIG have all noted that educational programs are critical to ensuring that investigators understand their responsibilities to protect human subjects. Some recent instances in which investigators violated informed consent or adverse event reporting may have been due to a lack of understanding of key issues by investigators. In June 2000, NIH established an education requirement for all investigators submitting NIH applications for grants and proposals involving human subjects. Effective October 1, 2000, NIH grantees are required, as a condition of project funding, to attest to having received training—through on-line workshops, published materials, or live presentations—on the protection of human subjects. In February 2001, OHRP held an educational “summit” of key agency officials and representatives of the research community to develop an educational initiative, possibly as a public-private partnership.¹⁵ HHS has taken some steps to improve awareness through education, which build on previous educational efforts sponsored by OHRP's predecessor. This past year, FDA, OHRP, the Department of Veterans Affairs, and others jointly sponsored educational workshops on human subjects protection in Washington, D.C., and Newark, New Jersey, and held a town meeting in Dallas, Texas for investigators, IRBs, and others on human subjects protection issues. Plans are in place for continuing these joint educational workshops and town meetings in the coming year. In addition, FDA is conducting educational programs for clinical investigators, jointly sponsored with industry and academic representatives.

HHS has some plans to address concerns relating to investigators' practice of obtaining informed consent. Experts have suggested that some investigators may tend to emphasize the disclosure of information and documentation of consent, rather than ensuring that participants fully understand the risks and benefits of the study and that their participation is voluntary. Over the years, HHS components have provided information

¹⁵The summit was co-hosted by the Office of Research Integrity, a separate HHS component that directs research integrity activities on behalf of the HHS Secretary.

and guidance on informed consent. For example, OHRP's predecessor discussed informed consent in its IRB Guidebook and other supplemental materials. NIH's institutes and centers have provided guidance to their grantee investigators and to in-house clinical researchers and IRBs. FDA informed consent guidance has been issued to IRBs and clinical investigators in the form of "Information Sheets." While the guidance and information on informed consent are extensive, NBAC has suggested that in general, the federal guidance continues to emphasize documenting the subject's consent rather than focusing on the ethical practices for obtaining this consent.

FDA officials told us they are revising all of the agency's Information Sheets for investigators and IRBs, including the guidance on informed consent. The revised guidance is intended to emphasize the importance of informed consent as a process of achieving understanding and voluntary participation. It will also address issues involved in obtaining consent from study participants who might not be able to provide consent on their own behalf. Beginning in 1999, NIH has funded 12 studies on informed consent and research ethics. The studies include an evaluation of the cognitive ability required to comprehend different aspects of a research project and an analysis of how potential participants weigh risks and benefits; the results are not yet available.

Some HHS efforts are aimed at improving investigators' understanding of adverse event reporting obligations. Although the ultimate responsibility for reporting adverse events in clinical research lies with investigators, they have sometimes misunderstood their responsibilities because there are inconsistencies between HHS and FDA regulations and guidance. These differ in what is to be reported, the entity to which it should be reported, and the required time frames for reporting. NIH is planning to make its adverse event reporting requirements—as they apply to gene transfer research—compatible with those of FDA.¹⁶

¹⁶In the specific area of human gene transfer research, the NIH has special guidelines regarding reporting of serious adverse events that are different from FDA's requirements.

Concerns Remain Regarding the Pace and Scope of HHS' Actions to Protect Human Subjects

Although problems with the oversight of human subjects protection have received increasing attention since the 1990s, it is only recently that HHS has made a concerted effort to address these issues. We have some concerns, however, that the pace of some actions is too slow and that gaps remain at each of the three levels of oversight we reviewed.

At the agency level, for example, HHS has not increased OHRP's budget in proportion to the office's increased scope of work—including its quality improvement evaluations at medical schools—and the office has not been able to hire the staff it planned to because of the federal hiring freeze that went into effect in early 2001. OHRP is still addressing a backlog of compliance cases. In addition, NIH appears to have lost momentum regarding its not-for-cause site visits. In the first two-thirds of fiscal year 2001, it has not made any not-for-cause site visits. FDA officials told us that HHS has not finalized a legislative proposal that, if enacted, would broaden FDA's authority to apply civil monetary penalties for investigator violations. Furthermore, FDA units that monitor and inspect clinical trials are seeking additional resources. According to an FDA acting associate commissioner, in 2000 the agency inspected fewer than 800 clinical investigators, or about 2 percent of an estimated 35,000 clinical sites. Although the agency has asked for additional resources to allow it to increase the number of inspections by 275, this would extend the inspections by less than 1 percentage point.

At the research institution level, HHS' efforts to support IRBs and enhance their performance appear promising, but the subject of financing IRBs remains largely unexplored. Although institutions bear the ultimate responsibility for supplying needed resources for IRBs, HHS can help facilitate the appropriate allocation of resources by providing information about resource benchmarks. HHS officials have acknowledged that little is known about the actual cost of the human subjects protection process, and there is debate about what constitutes appropriate funding and what the sources of funding should be. A Regulatory Burden Working Group at NIH has begun to study IRB operations and intends to address these financing questions. In addition, while HHS has begun to examine the issues relating to financial conflicts of interest at research institutions, it is not yet clear how, or how quickly, the department plans to move to address these serious concerns.

At the investigator level, HHS has taken little action to improve the informed consent process and to clarify adverse event reporting requirements. A year ago, HHS announced that it would issue new guidance on informed consent, but it has not yet done so. OHRP officials

told us that other issues, such as implementing the new assurance process and educational initiatives, have higher priority and that they need time to get expert and public input on the informed consent process and how it can be improved. Despite concerns about problems with adverse event reporting and confusion among investigators over differing requirements, HHS has not yet taken any steps to address these concerns. The only announced plans to improve this process have been limited to harmonizing the gene transfer research reporting requirements.

Concluding Remarks

The actions of HHS components to improve oversight are in the right direction, but in some areas, the extent of change could be greater. At the three key levels of human subjects protection—federal agency, research institution, and individual investigator—more could be done to fill the gaps in protection efforts.

GAO Contacts and Acknowledgments

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