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VA RESEARCH

System for Protecting Human Subjects Needs Improvements

Statement of Victor S. Rezendes, Assistant Comptroller General
Health, Education, and Human Services Division

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VA Research: System for Protecting Human Subjects Needs Improvement

Mr. Chairman and Members of the Subcommittee:

I am pleased to be here to discuss the report we are issuing today to you and other requesters on the Department of Veterans Affairs (VA) system for protecting the rights and welfare of veterans who volunteer to participate in research at VA medical centers.[1] It has been 18 months since research was suspended at the West Los Angeles VA Medical Center[2] because officials failed to correct longstanding problems in its human subject protection system. Since that suspension, four additional VA medical centers have felt the repercussions of sanctions by regulatory agencies against their affiliated universities. My testimony summarizes our assessment of VA's implementation of human subject protections, highlights systemwide weaknesses we identified in those protections, and evaluates VA's actions to better protect human subjects at medical centers that have been affected by sanctions and throughout VA's healthcare system.

Based on our review of eight medical centers, we concluded that VA needs to take action to strengthen the protection of human research subjects. Although the extent of the problems was uneven, we documented a disturbing pattern of noncompliance across the centers we visited. The cumulative weight of the evidence indicated failures to consistently safeguard the rights and welfare of research subjects. We also identified three specific weaknesses that have compromised VA's ability to protect human subjects—lack of adequate guidance to medical centers about human subject protections, insufficient monitoring of local protections, and inadequate attention to ensuring that funds needed for human subject protection activities are allocated and available for those purposes. To VA's credit, at three other medical centers we visited, substantial corrective actions have been implemented in response to sanctions by regulatory agencies taken against their human research programs. In contrast, VA's systemwide efforts at improving protections have been slow to develop.

Background

Conducting medical research is one of VA's core missions. VA researchers have been involved in a variety of important advances in medical research, including development of the cardiac pacemaker, kidney transplant

[1] *VA Research: Protections for Human Subjects Need to Be Strengthened* (GAO/HEHS-00-155, Sept. 28, 2000).

[2] The West Los Angeles VA Medical Center is now part of the VA Greater Los Angeles Healthcare System.

technology, prosthetic devices, and drug treatments for high blood pressure and schizophrenia. Funds from the appropriations for VA medical research and VA medical care support VA researchers and the indirect costs of research, which includes support for the human subject protection system. VA researchers receive additional grants and contracts from other federal agencies such as the National Institutes of Health (NIH), research foundations, and private industry sponsors including pharmaceutical companies. In fiscal year 2000, biomedical or behavioral research involving human subjects is being conducted at about 70 percent of VA medical centers.

VA is responsible for ensuring that all human research it conducts or supports meets the requirements of VA regulations, regardless of whether that research is funded by VA, the subjects are veterans, or the studies are conducted on VA grounds. Responsibility for administration and oversight of the research program has rested primarily with the Office of Research and Development (ORD). Recently, VA created the Office of Research Compliance and Assurance (ORCA) to advise the Under Secretary for Health on matters affecting the integrity of research protections, to promote the ethical conduct of research, and to investigate allegations of research impropriety. In addition, some VA research is subject to oversight by two components of the Department of Health and Human Services (HHS). The Food and Drug Administration (FDA) is responsible for protecting the rights of human subjects enrolled in research with products it regulates—drugs, medical devices, biologics, foods, and cosmetics. HHS-funded research is subject to oversight by its Office for Human Research Protections (OHRP).[3]

Research offers the possibility of benefits to individuals or to society, but it is not without risk to research subjects. To protect the rights and welfare of human research subjects, 17 federal departments and agencies, including VA, adopted regulations designed to safeguard the rights of subjects and promote ethical research. These regulations establish minimum standards for the conduct and review of research to ensure that studies are conducted in accordance with the ethical principles outlined in the Belmont Report, issued by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. These principles require that subjects voluntarily give informed consent to

[3]The Office for Human Research Protections (OHRP) is in the Office of the Assistant Secretary for Health. HHS established OHRP in June 2000 to assume the human subject protection functions of the former Office for Protection from Research Risks (OPRR), which was part of NIH. We refer to both organizations as OHRP. Actions taken before June 18, 2000, were taken by OPRR.

participate in research and that the expected benefits of research to the individual or to society outweigh its anticipated risks.

Federal regulations create a system in which the responsibility for protecting human subjects is assigned to three groups. Investigators are responsible for conducting research in accordance with regulations. Institutions are responsible for establishing oversight mechanisms for research, including local committees known as institutional review boards (IRB) that are responsible for reviewing both research proposals and ongoing research. Agencies, including VA, are responsible for ensuring that their IRBs comply with applicable federal regulations and have sufficient space and staff to accomplish their obligations. VA requires that each of its medical centers engaged in research with human subjects establish its own IRB or secure the services of an IRB at an affiliated university. As of August 2000, approximately 40 percent of the VA medical centers conducting research with human subjects relied on an IRB at an affiliated university.

Implementation of Human Subject Protections Uneven

We found various degrees of noncompliance with VA regulations and policies involving protections for human subjects at the eight medical centers we visited. Although we recognize that the results of our visits cannot be projected to VA as a whole, we found sufficient patterns of noncompliance to be concerned. We saw multiple problems at some sites, but relatively fewer problems at others. The five sites we visited that relied on VA-run IRBs had the most extensive problems. The three university-run IRBs we visited, however, were not without problems.

We found that medical centers and their affiliated universities did not comply with all the regulations designed to protect the rights and welfare of research participants in four areas: (1) informed consent; (2) IRB review; (3) IRB membership, staff, and space; and (4) IRB documentation. OHRP noted similar compliance problems in letters to universities and hospitals it has found to be out of compliance with federal regulations. As shown in fig. 1, some sites we visited had more problems than others.

Figure 1: Noncompliance with VA Regulations at Eight Sites

		Informed Consent			IRB Review				IRB Membership, Staff, and Space			IRB Documentation			
		Percentage													
		IRB-Approved Consent Forms That Provided Incomplete or Unclear Information[a]	Studies in Which the Investigator Used a Nonapproved Consent Form[b]	Research Conducted Without Consent	Initial Review–IRB Held Meetings Without a Quorum	Initial Review–High-Risk Study Improperly Approved by IRB Chair	Continuing Review–Not Conducted on Time	Continuing Review–Analysis Based on Insufficient Information	Potential Conflict of Interest in IRB Membership	Insufficient IRB Staff	Insufficient Space for IRB Operations	Inadequate Documentation in IRB Project Files	Written IRB Procedures Did Not Meet Standards	Incomplete Documentation in Minutes of IRB Discussions	IRB Votes Not Recorded as Required
VA-Run IRBs	A	100						●		●	●		●		
	B	88		●					●	●	●	●	●		
	C	25					●	●		●		●	●		●
	D	78	28				●	●	●	●		●	●	●	●
	E	87			●		●	●				●	●	●	●
University-Run IRBs	F	59	25									●			●
	G	44	33			●									
	H	26	12								●				

We did not compare consent forms signed by subjects with IRB-approved consent forms at these sites.

We did not assess the timeliness of continuing review at these sites.

● We observed noncompliance at these sites.

[a]We reviewed from 14 to 20 IRB-approved consent forms at each site, for a total of 138 forms.

[b]We compared consent forms signed by subjects to IRB-approved consent forms for 17 to 20 studies at each of 4 sites. We compared forms for a total of 73 studies.

We found problems with the content or use of informed consent forms at all of the medical centers we visited. We found that some informed consent documents that had been approved for use by IRBs provided incomplete or unclear information. For example, we found that a consent form given to subjects did not mention possible risks of a biopsy in a study designed to test a treatment for esophageal cancer. We found another that did not indicate who would have access to data obtained during a study on treatment for cirrhosis of the liver. We found a third that did not describe alternative treatment options in a study comparing two drug treatments for schizophrenia. Obtaining informed consent is a primary ethical requirement of research with human subjects. The ability of competent subjects to make their own informed decisions about whether to participate in research and the ability of legally authorized representatives to protect those unable to provide consent because they are incapacitated are undermined when IRBs fail to ensure that all required information is included in consent forms or when investigators fail to obtain consent using approved procedures.

We also found that five of the sites we visited did not implement certain required procedures for IRB review of research. For example, one IRB held meetings without having all required members in attendance. Studies, such as those on new drug treatments for unstable coronary symptoms and pneumonia, were thus initiated without legitimate approval. In addition, three review boards did not meet the requirement that each study be re-reviewed at least once a year. At one of these, a VA-run IRB, re-review delays of up to 14 months occurred in one-half of the projects we sampled. Regular re-review allows reassessment of a study's ratio of risks to benefits in light of data obtained since a study was begun, such as data about adverse events.

We found problems with IRB membership, staff, and space. Two IRBs we visited did not ensure that their members had no potential conflict of interest, four IRBs did not have adequate staff to support review activities, and IRB staff at three sites did not have sufficient space to conduct their work or store all necessary documents. IRBs must have secure, private areas for the review, discussion, and storage of confidential materials. But we observed IRB file folders stacked loosely on top of filing cabinets and on floors at one of these sites.

In addition, six of the eight IRBs we visited did not maintain all the records required by VA regulations. We found incomplete documentation of IRB activities, such as local written IRB procedures that were inadequate, IRB

meeting minutes that did not document substantive discussions, and votes that were improperly recorded. One medical center we visited had been cited by the FDA in June 1999 for failure to have adequate written procedures. The center agreed to have them in place by August 1999 but did not do so until December 1999. The written procedures we reviewed from three other VA-run IRBs did not include required descriptions of procedures for conducting project review, determining when additional project monitoring is necessary, or responding to investigator noncompliance. Although inadequate documentation does not alone place subjects at risk, documentary failures prevent appropriate monitoring and oversight activities. For example, records of actions, deliberations, and procedures can help identify problems and corrective actions.

Specific Weaknesses Compromise VA's Protection of Human Subjects

We identified three specific weaknesses in VA's system for protecting human subjects: not ensuring that research staff have appropriate guidance, insufficient monitoring and oversight activity, and not ensuring that the necessary funds for human subject protection activities are provided. These weaknesses indicate that human subject protection issues have not historically received adequate attention from VA headquarters.

VA headquarters had not provided medical center research staff with adequate guidance about human subject protections and thus had not ensured that research staff had all the information they need to protect the rights and welfare of human subjects. We found that VA had not developed a systemwide educational program or ensured that each of its facilities had an appropriate training program in place. A need for increased educational guidance from headquarters was one of the most commonly identified issues regarding human subject protections in a VA-sponsored survey of network managers. Educational programs are critical to ensuring that IRBs and investigators can implement appropriate protection for human research subjects.

The second weakness we identified is that VA did not have an effective system for monitoring protections of subjects, thus allowing noncompliance with regulations to go undetected and uncorrected. For example, we found that VA headquarters and affected medical centers were generally unaware of regulatory investigations and impending actions by OHRP and FDA against university-run IRBs until after the regulatory sanctions were applied. Also, VA headquarters has not provided medical centers with guidance on ensuring access to minutes or other key information when they arrange for the services of a university-run IRB. As a result, one medical center we visited did not have access to the minutes of its university-run IRB, and two medical centers affected by regulatory

sanctions against their affiliated universities had not monitored IRB minutes to assess compliance with regulations. Seven of the eight medical centers we visited did not routinely check whether investigators provided subjects with the correct IRB-approved consent form.

The third weakness we identified is that VA has not ensured that funds needed for human subject protections are allocated for that purpose at the medical centers. Officials at some medical centers told us that they did not have sufficient resources to accomplish their mandated responsibilities. We found that responsibility for funding human subject protections is diffused across several decisionmakers: the medical center's associate chief of staff for research and development, the medical center's director, and the board of directors of the medical center's nonprofit research foundation, which has discretion over the use of funds from non-VA research sponsors. Each of these may also have competing priorities for the same funds. The result is that no one official is responsible for ensuring that medical center research programs have the resources they need to support IRB operations and provide training in human subject protections. Research officials at five of the eight medical centers we visited reported that they had insufficient funds to ensure adequate operation of their human subject protection systems. Moreover, headquarters research officials told us that VA has not determined the funding needed for human subject protection activities at the medical centers.

Local Actions Address Problems Identified by Regulators but Systemwide Focus Slow to Develop

To VA's credit, substantial corrective actions have been implemented at three medical centers we visited in response to regulatory sanctions taken against their human research programs. However, VA's systemwide efforts to improve protections have been slow to develop.

Medical centers and affiliated universities affected by sanctions have taken numerous steps to improve human subject protections. They have, for example, hired and trained IRB staff and developed written procedures for their IRB operations. These medical centers and affiliated universities have made progress, and each has resumed human research activities.

We identified several issues of concern at some of these medical centers, however. For example, VA's authorization of a resumption of IRB operations at the West Los Angeles VA Medical Center on April 19, 1999—less than 1 month after OHRP's sanctions against the medical center—was premature. At that time, the medical center still lacked approved, written procedures for operation, relied on untrained administrative staff to assist newly formed IRBs, and had not provided investigators with training in

human subject protection issues. We are also concerned that officials at the medical center were particularly slow to respond to the issues OHRP identified over a 5-year period, including the requirement to establish a data and safety monitoring board to oversee studies involving subjects with severe psychiatric disorders.

VA also has been slow to identify systemwide deficiencies and obtain necessary information about the human subject protection systems at its medical centers. Although OHRP identified problems with human subject protections at the West Los Angeles VA Medical Center in 1994, VA did not have a plan to address systemwide concerns involving research until July 1998. VA did not begin to implement systemwide changes until after OHRP took regulatory action against the medical center in March 1999.

Only recently has VA headquarters begun to implement systemwide changes to improve its human subject protections. Its steps have included providing information to investigators and research staff and obtaining information about medical centers' research programs, such as identifying medical centers that use their own IRBs and those that use university-run IRBS, which will allow headquarters officials to determine the additional steps that may be needed locally or systemwide to ensure compliance with regulations and protection of human subjects.

In addition, VA is making two organizational changes to enhance monitoring and oversight of human research. The changes are designed to allow routine onsite monitoring of medial centers' research programs, thereby helping medical centers identify weaknesses and develop strategies to improve compliance with human subject protection regulations. Although promising in concept, it is too soon to determine whether these initiatives will fulfill their objectives. The first, the creation of ORCA, was announced in April 1999, but VA did not appoint the chief officer until December 1999. As of September 2000, staffing of ORCA, which includes four regional offices, was incomplete. Although ORCA's specific plans for monitoring medical center research activities are still under development, ORCA officials told us they planned to conduct a site visit to each medical center on a rotating basis. In its second initiative, VA has awarded a contract for external accreditation of its IRBs. The contractor is expected to conduct a site visit to each medical center conducting research with human subjects every 3 years to review IRB performance and assess compliance with regulations. VA officials told us VA expects that the university-run IRBs it uses will grant access to the accreditation team. VA is the first research organization to seek external accreditation of its human research programs.

VA needs to do more systemwide to protect the rights and welfare of human subjects who participate in research at VA medical centers. In the report we issue today, we make recommendations to the Acting Secretary of Veterans Affairs to take immediate steps to provide staff training and resources and to take other measures to ensure that VA medical centers, their IRBs—whether operated by VA or not—and VA investigators comply with all applicable regulations for the protection of human subjects.

In concurring with the recommendations, VA identified the steps it has taken and its planned initiatives. Critical to timely and effective implementation will be sustained commitment to a program of heightened vigilance regarding the protection of human subjects. Without this, the rights and welfare of veterans who participate in VA research remain vulnerable.

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

GAO Contact and Staff Acknowledgments

For more information regarding this testimony, please contact Cynthia A. Bascetta at (202) 512-7101. Key contributors to this testimony include Bruce D. Layton, Cheryl Brand, and Kristen Joan Anderson.

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