



Department of Veterans Affairs Office of Inspector General

Healthcare Inspection

Comparison of VA and University Affiliated IRB Compliance with VHA Handbook 1200.5

Contents

	Page
Executive Summary	i
Introduction	1
Purpose.....	2
Background.....	2
Scope and Methodology	4
Results	7
I. IRB Chairpersons, Members and Coordinators	7
II. IRB Compliance with Documentation Requirements of VHA Handbook 1200.5..	10
III. Principal Investigator Profiles and Documentation Requirements.....	14
IV. Reporting of Adverse Events and Protocol Modifications in Multi-Center Trials	16
Conclusions.....	18
Recommendations.....	19
Appendixes	
A. Requirements for IRB Standard Operating Procedures.....	20
B. IRB Meeting Minutes Requirements	22
C. Under Secretary for Health Comments.....	24
D. OIG Contact and Staff Acknowledgments	29
E. Report Distribution.....	30

Executive Summary

The Veterans Health Administration (VHA) supports and participates in a large research program that has made major contributions, including the development of cardiac pacemakers, liver transplants, and prosthetic devices. Resources available for VHA's Research and Development Program in fiscal year 2007 totaled \$1.6 billion.

VA adheres to the Common Rule, a set of Federal regulations requiring that all research involving human subjects be approved by an Institutional Review Board (IRB). VHA Handbook 1200.5, *Requirements for the Protection of Human Subjects in Research*, July 15, 2003, describes the means by which IRB review occurs in the VA, including documentation standards and required standard operating procedures. The Office of Research Oversight (ORO) within VHA provides oversight of these human subjects protections. Consistent with this function, VHA Handbook 1058.1, *Reporting Adverse Events in Research to the Office of Research Oversight*, November 19, 2004, requires reporting of certain adverse events to ORO.

The Office of Inspector General conducted a national review of VHA research to assess compliance with certain requirements of Handbook 1200.5 and Handbook 1058.1, focusing on compliance with IRB standard operating procedures (SOPs), IRB minutes, progress reports, and reporting of adverse events and protocol modifications in 23 phase IV clinical trials. We conducted a total of 41 site visits, reviewed documents for 58 separate reviews from 47 unique IRBs, and interviewed IRB coordinators, chairpersons, and members at each site.

While our review disclosed overall good compliance with IRB documentation requirements found in VHA Handbook 1200.5, we found that fewer university IRB representatives stated that they disclosed reportable adverse events to medical center officials than did VA IRB representatives. Both VA and University IRB SOPs did not consistently address the requirement to report privacy or information security violations to appropriate personnel. Finally, while not a policy requirement, we note a lack of communication between IRBs in multicenter trials concerning adverse events and protocol modifications.

We recommended that VHA ensure that all IRBs reviewing VA protocols comply with the requirements of VHA Handbook 1058.1 and VHA Handbook 1200.5 in the reporting of adverse events. We further recommended VHA examine current SOPs of IRBs reviewing VA protocols to ensure that they include mechanisms for the reporting of privacy or information security violations in accordance with the requirements of VHA Handbook 1200.5. The Under Secretary for Health agreed with the findings and recommendations and provided acceptable improvement plans. We will follow up on the planned actions until they are completed.



DEPARTMENT OF VETERANS AFFAIRS
Office of Inspector General
Washington, DC 20420

TO: Under Secretary for Health (10)

SUBJECT: Healthcare Inspection – Comparison of VA and University Affiliated IRB Compliance with VHA Handbook 1200.5

Introduction

The Department of Veterans Affairs specifies that research is part of its core mission. Historically, Veterans Health Administration (VHA) supported research contributed to such landmark developments as the cardiac pacemaker, the first successful liver transplant, and multiple advances in prosthetic limbs. VHA's Medical and Prosthetic Research Program (more commonly referred to as VHA's Research and Development (R&D) Program) currently maintains four organizational units for the selection of funding applications and administration of awards: Biomedical Laboratory Research and Development Service, Clinical Science Research and Development Service, Health Services Research and Development Service, and Rehabilitation Research and Development Service. In 2004, these services conducted more than 15,000 research projects at more than 115 facilities nationwide. Resources available for VA's Research and Development Program in fiscal year 2007 total \$1.6 billion.

VA and 17 other Federal agencies adhere to the Common Rule, a set of Federal regulations governing research involving human beings. All VHA institutions that perform Federally funded or supported research must file a Federalwide Assurance (FWA) stating that the institution will comply with the Common Rule. The Office of Research Oversight (ORO), located within VHA and charged with oversight of VHA research, manages the FWA program and is responsible for oversight and compliance with the Common Rule and VA policies. VHA has codified the Common Rule at 38 CFR Part 16. It is estimated that there were 120 facilities holding FWAs on April 30, 2007.

Compliance with the Common Rule requires a significant investment of resources. "Top professional staff must perform necessary, labor-intensive activities associated with research involving human subjects, including education and training of clinician investigators and research staff, ensuring compliance with applicable regulations,

credentialing of research staff, and operation of Institutional Review Board (IRB) committees.”¹ IRBs are committees constituted at the level of the medical center or institution conducting the research that provide the “primary mechanism for ensuring the adequacy of informed consent and other aspects of human subjects protections....” The Common Rule requires that an IRB review all research involving human beings, that the research subjects give informed consent, and that institutions give assurances that they will comply with the regulations.

VHA Handbook 1200.5, *Requirements for the Protection of Human Subjects in Research*, adopted July 15, 2003, outlines agency policy for compliance with the Common Rule’s requirements for the ethical conduct of research involving human subjects. The Handbook requires all such research to be approved by an IRB, but permits a VA medical center to use an affiliate university’s IRB if it executes a written Memorandum of Understanding (MOU) with the affiliate and reflects the arrangement in the VAMC Federalwide Assurance. However, VHA Handbook 1200.5 states: “An IRB established by an affiliated medical or dental school that is serving as an IRB of record for a VA facility must agree to comply with...the provisions of this Handbook when reviewing VA research.”

In addition to the IRB’s responsibilities to approve research and ensure the execution of a proper informed consent, IRBs must conduct continuing reviews not less than once per year on previously approved protocols to ensure ongoing compliance with Handbook 1200.5 (38 CFR 16.109(e)). They must also have Standard Operating Procedures (SOPs) describing how they meet this obligation (see Appendix A). So that IRBs may be updated on the status of ongoing research projects, investigators are required to submit progress reports at least annually as part of the continuing review process. VHA Handbook 1200.5 describes what information must be contained within those progress reports. In addition, IRBs must record minutes of meetings that contain certain elements as described in VHA Handbook 1200.5 (see Appendix B) and reflect decisions relative to the review process.

Purpose

The Office of Inspector General, Office of Healthcare Inspections (OHI), conducted this national project to assess compliance with certain requirements of VHA Handbook 1200.5 in the IRB review of 23 Phase IV protocols within VHA.

Background

VHA Handbook 1200.5 describes IRB composition and functions in detail. IRBs within the VA, or those IRBs that the VA uses to review its protocols, must conform to certain standards. These standards include having at least five members with sufficient

¹ VHA Directive 2003-031, June 13, 2003.

qualifications to review the research. Members must include at least one scientific and one non-scientific member. IRBs then review protocols for their compliance with the requirements of the Common Rule; they have the authority to approve, disapprove or require modifications to such protocols. IRBs ensure that risks to human subjects are minimized by using sound research techniques, that the risks to human subjects are reasonable in relation to any anticipated benefits, and that the protocol contains adequate provisions for monitoring the safety of participants. Other areas reviewed by IRBs include educational requirements of principal investigators (PIs) and all other investigators in the protection of human subjects, as well as protocol provisions to ensure the privacy and confidentiality of research subjects.

As part of its obligation to oversee the safety of research subjects, IRBs “are responsible for reviewing and managing adverse events (AEs) in research,”² as described in VHA Handbook 1058.1, *Reporting Adverse Events in Research to the Office of Research Oversight*, November 19, 2004. Handbook 1058.1 includes a requirement that IRBs develop SOPs that provide detailed instructions on how to report and manage AEs. VA facilities must report certain types of AEs to ORO. The AEs that must be reported to ORO include AEs that result in either an IRB taking substantive action or an unexpected death of a research subject, regardless of IRB action. Substantive action is defined as “[a]n action taken by an IRB that materially alters the substance and meaning of a protocol, informed consent form or process, or investigator status, including, but not limited to, restriction, suspension or termination of a study or investigator participation, and actions taken to prevent future occurrence(s) of the AE in research.”³

In 2003, prior to the enactment of VHA Handbook 1200.5, VA’s Office of Research and Development (ORD) identified the need for ongoing quality assurance programs at facilities conducting research involving human subjects. ORD specified four broad compliance-related activities that need to be carried out at every research site:

- Training and education of lead investigators and research staff.
- Credentialing of research staff.
- Ensuring compliance with applicable human research protection standards.
- Accrediting of the facility Human Subjects Protection Program by the National Committee for Quality Assurance (NCQA).

ORD contracted with the National Committee for Quality Assurance (NCQA), to assess standards through site surveys conducted by researchers. Beginning December 1, 2005, ORD awarded a new contract for accreditation of VHA research facilities to the Association for Accreditation of Human Research Protection Programs, Incorporated

² VHA Handbook 1058.1, p. 1.

³ VHA Handbook 1058.1, p. 1.

(AAHRPP). As of April 30, 2007, 9 facilities were accredited by AAHRPP, 52 by NCQA, and 25 facilities had AAHRPP accreditation pending.

Additional initiatives undertaken by ORD to ensure human subjects protections in research include the Program for Research Integrity Development & Education (PRIDE). “PRIDE is responsible for all policy development and guidance, and all training and education in human research protection throughout the VA.”⁴ VHA Directive 2003-036, *Credentials and Training of Employees Involved in Human Subjects Research*, issued July 7, 2003, required facility directors with human research programs to ensure appropriate training for those individuals engaged in research activities. This Directive specifically indicates that all investigators and all members and staff of a VA IRB must complete an educational or web-based course on the protection of human research subjects and Good Clinical Practice (GCP) as required by Food and Drug Administration (FDA) regulations.

The FDA divides clinical trials into different phases, depending upon the stage of development of the regulated drug. Phase 4⁵ clinical trials are those research protocols that involve a drug already approved for general use by the FDA that is subjected to further testing or tested on a different population for the purpose of expanding its FDA-approved indications. Information on FDA trials may now be found on several websites, including ClinicalTrials.gov. ORD registers VA-sponsored research on ClinicalTrials.gov and assists VA investigators in completing this registration process. The U.S. National Institutes of Health (NIH) developed this website in collaboration with the FDA as a result of the FDA Modernization Act of 1997. “The website ClinicalTrials.gov currently contains more than 41,000 clinical studies sponsored by the National Institutes of Health, other Federal agencies, and private industry. Studies listed in the database are conducted in all 50 States and in over 120 countries. ClinicalTrials.gov receives over 20 million page views per month and hosts approximately 31,000 visitors daily.”⁶

Scope and Methodology

This review examines specific requirements of VHA Handbook 1200.5 as applied to the continuing review of 23 Phase IV protocols within VHA. It is not a comprehensive compliance review of all applicable human subjects protections regulations nor of all provisions of VHA Handbook 1200.5. This review focuses on four areas of compliance: documentation of IRB standard operating procedures (SOPs), IRB minutes, investigator progress reports, and the reporting of adverse events and protocol modifications. Comparisons are made between VA and university affiliated IRBs. The relative training

⁴ Overview, Program for Research Integrity Development and Education, www.research.va.gov/programs/PRIDE 10/2/2006

⁵ FDA regulations use the convention of Arabic numbers for designating phases, rather than the Roman numerals used elsewhere.

⁶ About Clinical Trials.gov: <http://www.clinicaltrials.gov/ct/info/about>; June 15, 2007.

and experience of IRB chairpersons, coordinators, IRB members, and PIs are reported only for general profiling and background purposes.

Sample Selection

We utilized ClinicalTrials.gov to identify a sample for this review. On December 1, 2005, a search of this database revealed a total of 24 Phase IV clinical trials (subject protocols) conducted at VA medical centers (VAMCs) during the past 3 years. One protocol was not ongoing and had enrolled no subjects. The remaining 23 protocols were included in this review. The 23 protocols involved a total of 41 VAMCs and 47 different IRBs. The subject protocols included eight industry-sponsored trials, nine trials sponsored solely by the Department of Veterans Affairs, and six sponsored by other agencies and nonprofits. They ranged in size from single site protocols to one protocol that involved 17 different VAMCs. Because multicenter trials were involved, this resulted in a total of 58 unique IRB reviews.

Document Review

OHI conducted a total of 41 site visits from February 2006 to June 2006 to determine compliance with specific aspects of VHA Handbook 1200.5. We first determined which IRB(s) at the facility reviewed the subject protocol or protocols, and grouped these IRBs by VA or affiliate status. Inspectors obtained the following while at the facility: SOPs for the IRB(s) reviewing subject protocols, the most recent IRB minutes, investigator progress reports pertaining to the subject protocol(s), IRB rosters, consent forms, and copies of all adverse events and protocol modifications. Inspectors obtained information both from IRB files and from the files of the PIs. When the subject protocol was conducted at more than one facility, inspectors also obtained all correspondence pertaining to adverse events and protocol modifications between facility IRBs, investigators, and data safety monitoring boards (DSMB).

Interviews

Following the identification of the specific IRBs evaluating the subject protocols, we prepared for interviews. Each interviewer received 8 hours of training in use of the instruments. We began with interviews of each IRB chairperson, each IRB coordinator, and one scientific IRB member. The scientific IRB member was chosen at random, utilizing a sequential numbering system of IRB members from rosters obtained prior to site visits by OIG inspectors. In addition, we interviewed the PI of each subject protocol at each facility. Administering a standard set of questions to all, we asked each individual about his/her educational requirements and attainments pertaining to human subjects protections, as well as his/her relevant professional experience and knowledge of reporting requirements for adverse events.

Statistical Analysis

Pearson Chi-square statistics were used to examine associations between IRB type (VA or university affiliated) and compliance with certain requirements of VHA Handbook 1200.5. When at least one of the table cell sizes was fewer than 5, Fisher's exact test was used, instead of the Chi-square test. All p-values were two-sided. The association was considered statistically significant if its corresponding p-value was less than 0.05. All analyses were performed using SAS (Cary, North Carolina) Version 9.1.

Results

Forty-seven IRBs at 41 separate sites reviewed the clinical trials in our sample. Of these 47 IRBs, 23 were VA IRBs, and 24 were university affiliated IRBs, reviewing VA protocols pursuant to Memoranda of Understanding. All 47 IRBs had at least five members as required by VHA Handbook 1200.5.

I. IRB Chairpersons, Members and Coordinators

A. IRB Chairpersons, Coordinators, and Members of VA and University IRBs

We categorized our interviews with IRB chairpersons, members, and coordinators by whether their respective IRBs were VA or university affiliated IRBs. In general, university affiliated IRBs tended to review more protocols than VA IRBs ($p = 0.01$). Further, 11 of 24 (46 percent) university IRBs employed certified IRB professionals as coordinators compared to only 2 of 23 (8 percent) VA IRBs that utilized a certified IRB professional in this capacity ($p = 0.01$). While this represented a significant difference in the utilization of certified IRB professionals between VA and university IRBs, the experience of IRB coordinators as defined by the number of years of service at the facility did not vary significantly by IRB type ($p = 0.29$).

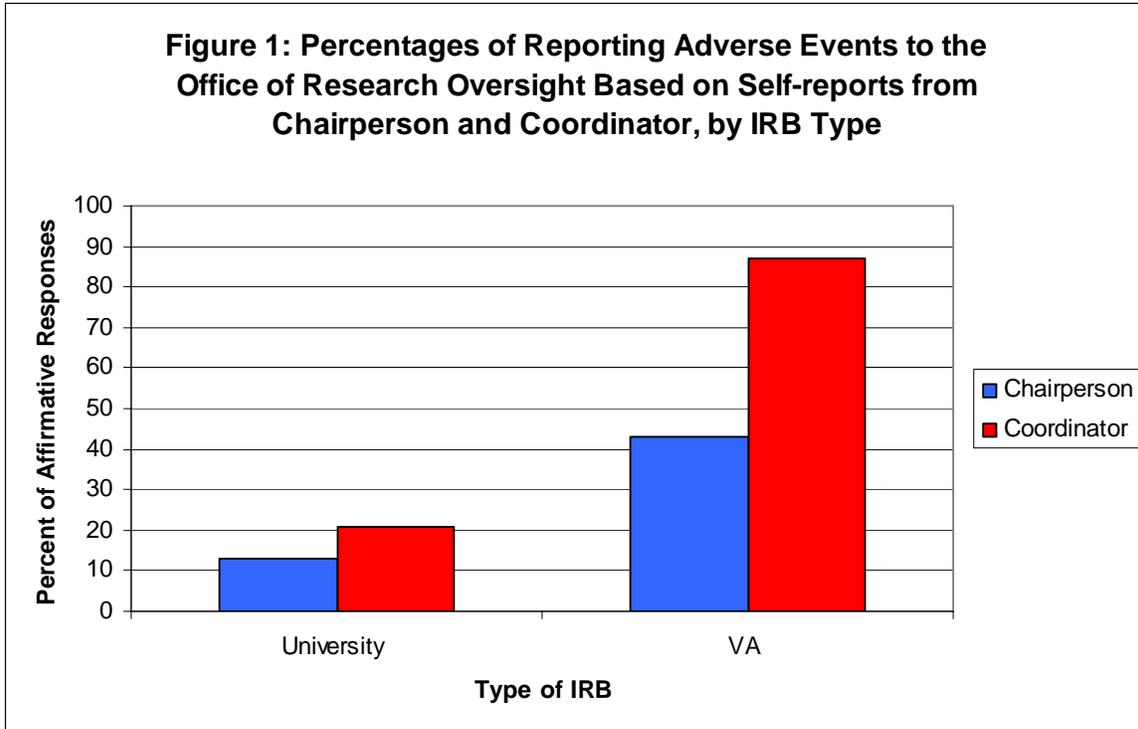
IRB chairpersons were in all cases either Medical Doctors (M.D.s) or held scientific doctorate degrees (Ph.D.s). VA or university affiliation of the IRB made no difference in the likelihood of holding one degree or the other ($p = 0.45$). IRB chairpersons self-reported the total number of publications listing themselves as a first author. Most chairpersons reported between 6 and 50 publications listing themselves as first author (VA = 12 (52 percent); university = 16 (66 percent)) with no significant difference between chairpersons of VA and university affiliated IRBs ($p = 0.32$). Forty-six of 47 chairpersons reported receiving some training in human subjects protections during 2004 or 2005.

More of the 47 IRB scientific members interviewed were M.D.s (VA = 55 percent, university = 58 percent) rather than Ph.D.s (VA = 29 percent, university = 39 percent). While all but one of the university IRB scientific members interviewed were M.D.s or Ph.D.s, 16 percent of VA IRB scientific members held degrees at the Master's level or less. However, this difference in educational attainment between VA and university IRB scientific members was not statistically significant ($p = 0.26$). The difference in the number of publications listing the scientific members interviewed as the first author between VA and university IRB members was statistically significant ($p = 0.015$) with university IRB members having more publications than VA IRB members. Forty-six of the 47 IRB scientific members reported that their IRBs required that they take some human subjects protection training annually.

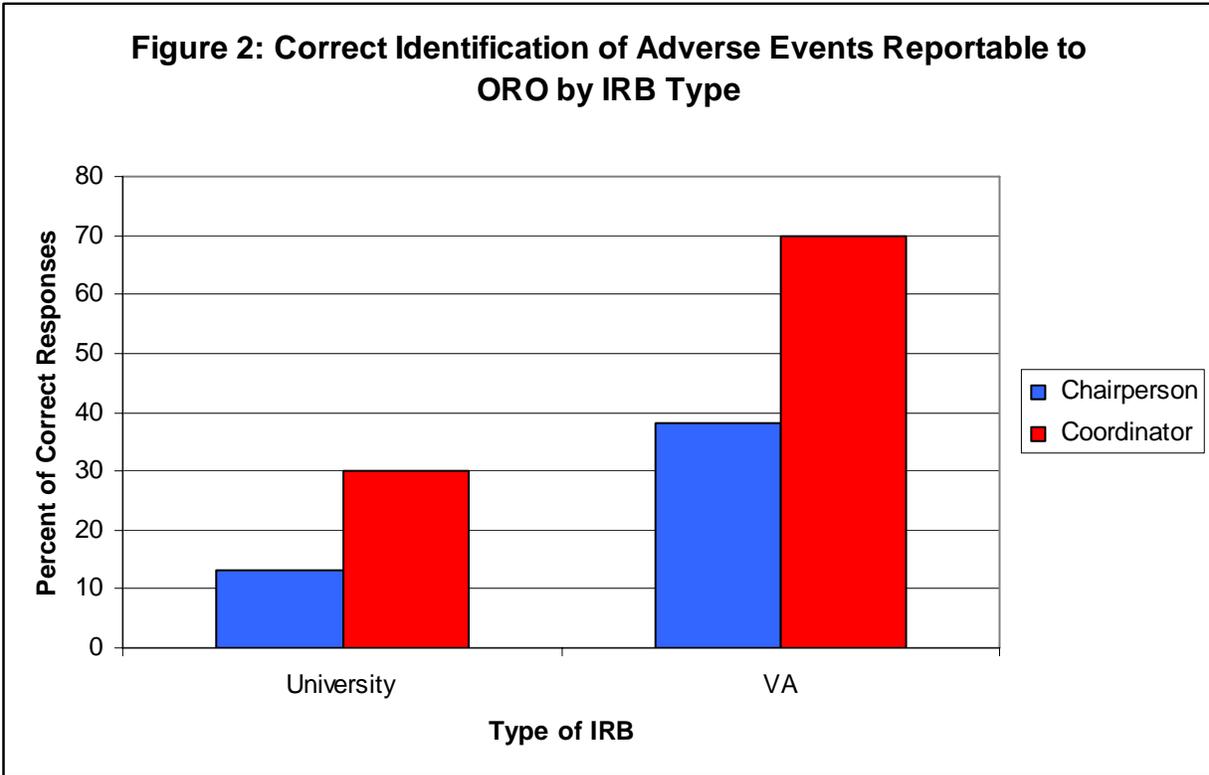
B. Institutional Adverse Event Reporting Practices as Described by IRB Chairpersons and IRB Coordinators

We also asked all IRB chairpersons and coordinators whether or not their institutions disclosed reportable adverse events to certain entities. Based on the chairpersons' responses, the VA IRB chairpersons indicated that their facility disclosed reportable adverse events to the medical center director (VA = 26 percent, university = 11 percent; $p = 0.03$), the Associate Chief of Staff for Research (VA = 38 percent, university = 21 percent; $p = 0.01$), and other IRBs in the event that the clinical trial involved multiple sites (VA = 19 percent; university = 2 percent; $p < 0.01$) more frequently than their university counterparts. Twenty-one of 23 (91 percent) VA and 18 of 24 (75 percent) university IRB Coordinators indicated that their facility did not report adverse events to other IRBs in the event that a clinical trial was ongoing at multiple sites. The responses of VA IRB Chairpersons indicated a higher reporting rate.

VA IRB chairpersons also indicated that their facilities commonly reported adverse events to ORO (VA = 43 percent). In contrast, only 3 of 24 (13 percent) university IRB chairpersons stated that their facilities reported adverse events to ORO ($p < 0.0001$). IRB coordinators generally reported similar practices. We were told by ORO that university IRBs were not required to report adverse events to ORO, but were instead required only to report them to the facility through the medical center director as specified in VHA Handbook 1200.5 section 7d(5). The expectation was that the medical center would then report the events to ORO. However, as previously discussed, university IRBs did not consistently report adverse events to medical center directors either. In addition, IRB coordinator responses indicated that VA coordinators reported adverse events to the medical center director (VA = 30 percent, university = 13 percent; $p = 0.01$) and the Associate Chief of Staff for Research (VA = 38 percent, university = 23 percent; $p = 0.02$) more frequently than university IRB coordinators. Twenty of 23 (87 percent) VA IRB coordinators stated that their institutions reported adverse events to ORO, compared to 5 of 24 (21 percent) university IRB coordinators ($p < 0.0001$), as seen in Figure 1:



When IRB chairpersons were interviewed regarding their understanding of the definition of adverse events reportable to ORO, 18 of 23 (78 percent) VA IRB chairpersons correctly identified the definition compared to 6 of 24 (25 percent) university IRB chairpersons ($p = 0.01$). Seven of 23 (32 percent) university IRB coordinators compared with 16 of 23 (70 percent) VA IRB coordinators correctly identified the definition of an adverse event reportable to ORO ($p = 0.02$). IRB chairperson responses are compared to IRB coordinator responses in Figure 2:



II. IRB Compliance with Documentation Requirements of VHA Handbook 1200.5

A. IRB Standard Operating Procedures

To better assess adverse event reporting practices at VHA facilities as well as to determine compliance with the requirements of VHA Handbook 1200.5, we reviewed IRB SOPs from all 47 IRBs. However, institutions with more than one IRB utilized the same SOPs, giving a total of 41 unique sets, 22 for VA IRBs and 19 for university IRBs. VHA Handbook 1200.5 requires facilities to develop SOPs in a number of different areas. We reviewed facility compliance in nine areas listed in Table 1:

Table 1: Frequency and Percent Compliance with VHA Handbook 1200.5 Requirements for Standard Operating Procedures

Standard Operating Procedure*	VA IRB Frequency (Percent Compliance)	University IRB Frequency (Percent Compliance)	P Value
Initial and continuing review.	21 (95.5)	19 (100)	0.35
More frequent review.	22 (100)	19 (100)	0.46
Verification of no protocol changes.	21 (95.5)	17 (89.5)	0.47
Reporting of protocol amendments or consent form changes.	22 (100)	18 (94.7)	0.28
Reporting to IRB noncompliance by study personnel.	20 (90.9)	18 (94.7)	0.64
Informed consent observation.	20 (90.9)	14 (73.7)	0.15
Audits of protocols.	18 (81.8)	17 (89.5)	0.49
Reporting to privacy officer.	4 (18.1)	5 (26.3)	0.53
Reporting of VA information security violations.	3 (13.6)	6 (31.6)	0.17

* See Appendix A for a full listing of IRB Standard Operating Procedures required by VHA Handbook 1200.5.

There was no statistically significant difference in compliance in these nine areas between VA and university IRBs (Table 1). Of 41 unique sets of IRB Standard Operating Procedures, we found that the majority of facilities complied in seven of the nine areas reviewed. The two areas in which the majority of facilities failed to maintain standard operating procedures involved “reporting to the privacy officer any unauthorized use, loss or disclosure of individually identifiable patient information” and “reporting violations of VA information security requirements to the appropriate VHA Information Security Officer.” Only 4 of 22 (18 percent) VA IRBs and 5 of 19 (28 percent) university IRBs maintained a standard operating procedure for reporting events to the privacy officer while only 3 (14 percent) VA IRBs and 6 (32 percent) university IRBs maintained procedures for reporting information security violations to a VHA Information Security Officer.

With regard to reporting adverse events, VHA Handbook 1200.5 requires the IRB to maintain a written procedure for notifying medical center officials and VA central office

of adverse events occurring that cause harm or risk of harm to human subjects. It further requires a written procedure stating that facilities will report adverse events “as required by VA and Federal policy and regulations.” While most facilities maintain SOPs for reporting as required by VA and Federal policy and regulations (VA = 100 percent, university = 90 percent), fewer facilities maintained a procedure for notifying medical center officials or VA central office (VA = 55 percent, university = 37 percent). Differences in adverse event SOPs between VA and university IRBs were not statistically significant.

To better clarify the type of adverse event reporting procedure maintained by each facility, we asked whether the procedure contained the following three elements: (1) Definition of events that should be reported to a given agency, (2) Time frame for reporting an event to a regulatory agency, and (3) Specific agencies to which those events should be reported. We found that most facility SOPs contained at least those three elements for reporting of adverse events. [For (1), VA = 86 percent, university = 94 percent; (2) VA = 91 percent, university = 79 percent; (3) VA = 95 percent, university = 95 percent]. However, there was wide variability in whether the SOP required notification of medical center directors (VA = 50 percent, university = 53 percent), Associate Chiefs of Staff for Research (VA = 55 percent, university = 47 percent), other IRBs (VA = 9 percent, university = 10 percent), and ORO (VA = 95 percent, university = 55 percent).

While there were no statistically significant differences in reporting requirements between VA and university IRBs for most areas, we did find that university IRBs were less likely to have an SOP requiring reporting of adverse events to ORO ($p = 0.009$).

This was consistent with IRB chairperson and IRB coordinator responses indicating that VA IRBs reported adverse events to ORO and/or the medical center director with greater frequency than university IRBs. We also note that only two (9 percent) VA IRBs and two (10 percent) university IRBs maintained an SOP that referenced reporting of adverse events to other IRBs. This was more consistent with responses obtained from IRB coordinators indicating that most IRBs do not report adverse events to other IRBs. VA IRB Chairpersons described a higher rate of reporting between IRBs.

Addressing the reasons for the differences between VA and university IRBs is beyond the scope of this review. However, during the course of our inspection, one facility’s SOP was noted to contain the following statements:

Under an IRB Authorization Agreement and Memorandum of Understanding (MOU) between the [university IRB] and the [VAMC], the [university IRB] provides IRB review for human subjects research conducted at the VAMC. The agreement specifies that IRB-01 operates under the condition of the

[university’s] FWA only and does not obligate the IRB-01 to operate under any additional VAMC-specific regulations or policies.⁷

This is contrary to VHA policy that VAMCs with university affiliated IRBs reviewing VHA research comply with the same standards for human subjects protections required of VA IRBs.

B. IRB Documentation Standards: Review of IRB Minutes by Protocol

We also examined whether IRB minutes contained eight necessary elements described in VHA Handbook 1200.5. We reviewed 58 sets of minutes referencing our 23 subject protocols. Thirty (52 percent) of these reviews were conducted by VA IRBs, while 28 (48 percent) reviews were conducted by university IRBs. Among the required elements, IRB rosters must list member names, earned degrees, affiliated or nonaffiliated status, and voting status of all IRB members. Because IRB members change, however, we looked at IRB minutes to determine whether there was sufficient information to determine member names, earned degrees, affiliated or nonaffiliated status and voting status of IRB members. All 30 sets of VA IRB minutes contained member names and degrees while 26 (87 percent) recorded affiliation, and 28 (93 percent) recorded voting status. This compared to 28 sets of university IRB minutes in which 27 of 28 (96 percent) contained names, but only 23 (82 percent) contained degrees, 17 (61 percent) described affiliations, and 19 (68 percent) listed voting status. VA IRBs were more likely to record degree ($p = 0.02$), affiliation ($p = 0.03$), and voting status ($p = 0.01$) than were their university counterparts. Information about degrees and voting status (other than recusals) is not specifically required to be in the minutes. The remaining required elements discussed in this review are presented in Table 2:

Table 2: Frequency and Percent Compliance with Handbook 1200.5

Required Elements for the 58 IRB Minutes

	VA IRB Minutes	University IRB Minutes	P Values
	Frequency (Percent Compliance)	Frequency (Percent Compliance)	
The minutes include sufficient information to determine that a quorum is present.	28 (93.3)	15 (53.27)	0.002
A non-scientific member of the IRB is recorded as present.	30 (100)	21 (75)	0.003

⁷ ORO stated they were aware of the language in the MOU and were working with the VA facility at the time of the OIG visit to ensure correction of the MOU.

The minutes record votes on actions including the number of members voting for, against, or abstaining.	29 (96.7)	27 (96.4)	0.96
The minutes describe the basis for required changes in the research.	29 (96.7)	12 (42.9)	<0.0001
At least one of the two VA employees on the IRB is listed as present and as a voting member.	30 (100)	14 (50)	<0.0001

As presented in Table 2, VA IRB minutes contained information that a nonscientific member and VA employee were present and voting members more often than did university IRB minutes ($p = < 0.0001$). In addition, VA IRB minutes were more likely to indicate the presence of a quorum than were university IRB minutes. Both VA and university IRB minutes indicated high rates of compliance in recording the number of members voting for or against issues or abstaining from voting.

III. Principal Investigator Profiles and Documentation Requirements

A total of 57 different PIs were involved in the 23 subject protocols. We interviewed all of them regarding their publication history, human subjects protection training status, and IRB documentation, including progress reports, adverse event reporting, and protocol modifications. These PIs varied widely in terms of their publication history. Six of the 57 (10 percent) PIs indicated they were not the first author on any publication; 18 (32 percent) were first authors on 1–5 publications; 17 (30 percent) had 6–20 such publications; and 16 (28 percent) PIs had more than 20 publications listing themselves as first author. All 57 indicated that they were required by their local IRB to participate in some form of human subjects protection training.

We reviewed 58 continuing review applications, one submitted for each IRB that reviewed any one of the 23 subject protocols. We assessed whether the reports contained 11 elements required under the terms of VHA Handbook 1200.5. Results are described in Table 3:

**Table 3: Frequency and Percent Compliance with Handbook 1200.5
IRB Progress Report Requirements**

	VA IRB Submissions Total = 30 Frequency (Percent Compliance)	University IRB Submissions Total = 28 Frequency (Percent Compliance)	<i>P</i> Values
Summary of research methodology and procedures.	23 (76.7)	21 (75.0)	0.88
Number of subjects entered and withdrawn.	30 (100)	26 (92.9)	0.14
Gender and minority status of those entered into protocol.	25 (83.3)	18 (64.3)	0.10
Number of subjects that are members of specific vulnerable populations.	15 (50)	11 (39.2)	0.41
Copy of the current consent document.	30 (100)	26 (92.9)	0.14
Copy of the current HIPAA Authorization.	28 (93.3)	25 (89.3)	0.58
Adverse events, unanticipated problems and complaints.	29 (96.7)	28 (100)	0.33
Research findings to date.	17 (*)	16 (57.1)	0.62
Summary of Data Safety Monitoring Board or Committee Meetings.	16 (*)	14 (*)	0.16
An assurance that all SAEs and UAEs have been reported.	23 (76.7)	20 (71.4)	0.65
New scientific findings in the literature.	16 (53.3)	16 (57.1)	0.62

*No percentage compliances were calculated for these specific elements because the requirement did not apply to all protocols. For example, a total of 13 continuing review applications (4 for VA IRBs, 9 for university IRBs) were reviewed for protocols that did not use a data safety monitoring board. Therefore, the requirement for a summary of meetings of the data safety monitoring board would not be applicable.

While in some areas, compliance rates exceeded 90 percent, we find that certain measures revealed reduced compliance. For example, compliance rates for documentation of new scientific findings in the literature were 53.3 percent and 57.1 percent respectively, and documentation of the involvement of vulnerable populations occurred in only 50 percent and 39.2 percent of VA and university IRBs. Differences in compliance rates between VA and university IRBs were not statistically significant in these areas.

IV. Reporting of Adverse Events and Protocol Modifications in Multi-Center Trials

A total of 40 of the 58 unique protocol reviews examined in this report involved multi-center trials. We examined IRB files for evidence of communication regarding adverse events. Table 4 below describes the number of protocol reviews in which evidence was found of communication regarding adverse events between the IRB and the sponsor, PI, IRBs at other sites, and PIs at other sites.

Table 4: Frequency and Percent of IRBs Communicating With Other Entities Regarding Adverse Events

	VA IRB Total = 26 Frequency (Percent Communicating AEs)	University IRB Total = 17 Frequency (Percent Communicating AEs)	P Value
Sponsors.	8 (31)	1 (6)	0.05
PI.	19 (73)	12 (71)	0.86
Other IRBs.	0 (0)	1 (6)	0.21
Other PIs.	2 (8)	3 (18)	0.32

While most files contained correspondence regarding adverse events between the PIs and IRBs at the individual sites, we note that very few contained evidence of correspondence between IRBs or between an IRB and a PI at another site. This was consistent with IRB chairperson and coordinator interviews, as well as evaluation of facility SOPs that determined it was not common practice for one IRB to notify another IRB of adverse events occurring at a given facility. VHA policy does not currently require IRBs to notify other IRBs in multicenter trials of adverse events. This is generally the role of the sponsor, data coordinating center, or DSMB.

For example, one protocol (Protocol #9) enrolled two subjects at a single site. One subject subsequently decided not to participate in the study. The second subject experienced six adverse events before the decision was made to terminate the study at that site. There was no evidence in either the PI’s files or the IRB files that IRBs at other sites were notified of these adverse events or of the decision to discontinue the study at that site. It is also not documented as to whether the adverse events experienced by the sole participant in the study at that site resulted in the decision to close the protocol.

In addition to IRB reporting practices relating to adverse events, we also reviewed the subject protocols for numbers of modifications. Of 30 unique protocol reviews by VA IRBs, 29 contained evidence that at least one protocol modification or amendment was reported to the IRB compared with only 12 of 28 unique protocol reviews by university IRBs ($p \leq 0.0001$). In multi-center trials, 33 of 40 sites’ IRB files contained correspondence describing protocol modifications. Table 5 below describes correspondence between the site IRBs and sponsors, PIs, PIs at other sites, and IRBs at other sites regarding protocol modifications.

Table 5: Frequency and Percent of IRBs Communicating With Other Entities Regarding Protocol Modifications

	VA IRB Total = 26 Frequency (Percent Compliance)	University IRB Total = 17 Frequency (Percent Compliance)	<i>P</i> Value
Sponsors.	10 (39)	2 (12)	0.06
PI.	22 (85)	14 (82)	0.85
Other IRBs.	2 (8)	0 (0)	0.25
Other PIs.	3 (12)	1 (6)	0.53

The IRB files maintained by VA IRBs were more likely to contain correspondence between the IRB and the sponsor regarding protocol modifications than were university IRB files. There were no other significant differences in documentation of communication regarding protocol modifications between VA and university IRBs. The vast majority of IRB files reviewed contained no documentation of correspondence regarding protocol modifications between IRBs or between one IRB and the PI at another site.

Conclusion

Overall, we found good compliance with the documentation requirements of VHA Handbook 1200.5 for IRBs and PIs. In the area of standard operating procedures for IRBs, we noted the lowest compliance rates with the requirements of standard operating procedures ensuring reporting of privacy or information security violations to the appropriate officials. However, data collection occurred prior to a number of significant information security developments and initiatives within VHA. IRB minutes maintained by VA IRBs demonstrated excellent compliance, with all rates above 90 percent. However, we note significantly lower compliance rates in at least three areas in the maintenance of minutes by university IRBs. Both VA and university compliance with the required elements of PI progress reports should target improvement in the description of vulnerable populations and documentation of new scientific findings in the literature that might affect the research.

Because of the lack of communication between IRBs in multi-center trials as well as the lack of consistent procedures for reporting adverse events to medical center officials among university affiliates, we identify the reporting of adverse events and protocol modifications as an area for potential improvement within VHA. In the sample of protocols discussed in this report, there was not a consistent mechanism by which those multi-center trials that did not maintain data safety monitoring boards communicated with other sites. Neither IRB files nor PI files consistently contained evidence that IRBs or individual PIs communicated with any other site. We note that this is not currently required under VHA policy. While PI files contained some evidence of correspondence with the sponsor regarding these events, we found that affiliate IRBs were less likely to have documentation from the sponsor in their files describing protocol modifications or adverse events occurring at other sites.

In addition, the individuals interviewed as well as IRB standard operating procedures and documentation in PI and IRB files did not demonstrate that university IRBs consistently notified the medical center director of reportable adverse events. If adverse events are not properly reported to ORO by the medical center director, this would circumvent another means by which VHA could centrally monitor at least certain types of adverse events in multi-center trials.

While identification of potential causes for non-compliance or differences in compliance is beyond the scope of this review, we do note that there were no significant differences in the background and experience of IRB Chairpersons between VA and university IRBs. In addition, while university IRBs as a whole reviewed more protocols and employed more certified IRB professionals, we found that, where significant differences existed in compliance between VA and university IRBs, these differences reflected less compliance by university IRBs rather than VA IRBs.

Recommendations

1. We recommend that the Under Secretary for Health ensure that all IRBs reviewing VA protocols disclose reportable adverse events to the VA facility, which must then report adverse events to ORO in compliance with the requirements of VHA Handbook 1058.1.
2. We recommend that the Under Secretary for Health ensure that VHA compliance offices review current standard operating procedures of IRBs reviewing VA protocols to ensure that they include mechanisms for the reporting of privacy or information security violations in accordance with the requirements of VHA Handbook 1200.5.
3. We recommend that the Under Secretary for Health ensure that VHA facilities require university affiliated IRBs to follow VHA Handbook 1200.5 and to verify that corrections are made to address deficiencies identified in this report.

Comments

The Under Secretary for Health agreed with the findings and recommendations and provided acceptable improvement plans. (See Appendix C, pages 24–28, for the full text of comments.) We will follow up on the planned actions until they are completed.

(original signed by)

JOHN D. DAIGH, JR., MD
Assistant Inspector General for
Healthcare Inspections

Requirements for IRB Standard Operating Procedures (From VHA Handbook 1200.5)

The IRB must establish written procedures for, but not limited to:⁸

1. Conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the R&D Committee.
2. Determining which projects require review more often than annually and which projects need verification from sources, other than the investigator, that no material changes have occurred since previous IRB review.
3. Ensuring that investigators promptly report proposed changes in a research activity including amendments to the protocol, or the consent form, to the IRB, and ensuring that such changes in approved research are not initiated without the IRB's review and approval, except when necessary to eliminate apparent immediate hazard to the subject.
4. Reporting promptly to the IRB regarding non-compliance by study personnel.
5. Notifying medical center officials and VA Central Office of any AEs that cause harm or risk of harm to human subjects or groups as required by this Handbook, other VA policies, or Federal regulations, any instance of serious or continuing noncompliance with this Handbook or the requirements or determinations of the IRB; and suspension or termination of IRB approval.
6. Reporting any AE as required by VA and Federal policy and regulations.
7. Termination and/or suspension of IRB approval.
8. Observing the informed consent process when the IRB determines it to be appropriate.
9. Conducting audits of protocols and other IRB activities.
10. Ensuring that initial and continuing education requirements for the IRB Chair, IRB members, and IRB alternate members are met.
11. Notifying members of expedited reviews and decisions about exemptions.
12. Reporting to the Privacy Officer any unauthorized use, loss, or disclosure of individually-identifiable patient information.

⁸ VHA Handbook 1200.5, *Requirements for the Protection of Human Subject in Research*, July 15, 2003, pages 13, and 14.

13. Reporting violations of VA information security requirements to the appropriate VHA Information Security Officer.

IRB Meeting Minutes Requirements (From VHA Handbook 1200.5)

1. Proceedings must be written and available for review within 3 weeks of the meeting date. Once approved by the members at a subsequent IRB meeting, the minutes must not be altered by anyone including a higher authority. Minutes of IRB meetings must contain sufficient detail to show:⁹
 - a. The presence of a quorum throughout the meeting including the presence of one member whose primary concern is in a non-scientific area.
 - b. Attendance at the meetings including those members or alternate members who are participating through videoconference or teleconference and documentation that those attending through videoconferencing or teleconferencing received all pertinent material prior to the meeting and were able to actively and equally participate in all discussions.
 - c. Alternate members attending the meeting and for whom they are substituting.
 - d. Actions taken by the IRB including those involving full review. The IRB may choose to use the minutes to notify IRB members of actions taken through expedited review and those studies that have been determined to be exempt from IRB review.

NOTE: *These required notifications may be carried out through other mechanisms.*

- e. Documentation of the four required findings (36CFR 16.116(d)) when approving a consent procedure that does not include or that alters some or all of the required elements of informed consent, or when waiving the requirement to obtain an informed consent.
- f. The vote on actions including the number of members voting for, against, and abstaining.
- g. A note indicating that when an IRB member has a real or potential conflict of interest relative to the proposal under consideration, that the IRB member was not present during the deliberations or voting on the proposal (and that the quorum was maintained).

⁹ VHA Handbook 1200.5, *Requirements for the Protection of Human Subject in Research*, July 15, 2003, pages 16 and 17.

Appendix B

- h. The basis for requiring changes in or disapproving research and documentation of resolution of these issues when resolution occurs.

Under Secretary for Health Comments

**Department of
Veterans Affairs**

Memorandum

Date: September 25, 2007

From: Under Secretary for Health (10)

Subject: OIG Draft Report: **Healthcare Inspection: Comparison of VA and University Affiliated IRB Compliance with VHA Handbook 1200.5** (Project No. 2006-00980-HI-0257/ WebCIMS 385907)

To: Assistant Inspector General for Healthcare Inspections (54)

1. I have reviewed this draft report and am pleased that your findings reflect overall good compliance by VA and university-affiliate Institutional Review Boards (IRB) in meeting the documentation requirements included in VHA Handbook 1200.5. As you are aware, VHA has a long-standing commitment to ensuring that protection of human subjects in research remains a top priority, and we will continue to strive for ongoing improvements in this broad and complex area. I concur with your findings and recommendations and include, as an attachment, our planned corrective actions in response to each recommendation.

2. I agree that there is considerable confusion in the field about how to implement established IRB adverse event reporting protocols, and the Offices of Research Oversight (ORO) and Research and Development (ORD) are taking immediate steps to address this situation. For example, ORO will revise and clarify VHA Handbook 1058.1, outlining definitive processes involved with the reporting of adverse events by the IRBs to medical facility management, who then submit the report directly to ORO. As part of their efforts to better define the reporting process, ORO will also identify oversight monitoring tools that can be implemented at various organizational levels to assess IRB and facility compliance with Handbook guidance for disclosing reportable adverse events. As detailed in our action plan, these compliance requirements will also be points of discussion at a variety of educational seminars that will be attended by VA research professionals, including a series of ORD-sponsored regional meetings on research accountability at the local level, as well as the five regional

Network Cluster Meetings for VISN and medical center directors. ORO and ORD will also jointly sponsor training sessions about adverse event reporting during the upcoming annual meeting of the Society of Research Administrators International, which will be attended by a large number of both VA and university-affiliate research managers. These educational forums will also address issues that you raise about the reporting of privacy or information security violations in accordance with the requirements of VHA Handbook 1200.5, dealing with the protection of human subjects in research.

3. Another planned VHA research initiative also responds directly to your recommendations. I recently requested that ORO fully explore VA's use of university-affiliated IRBs. This comprehensive endeavor will include targeted on-site reviews of the effectiveness of university IRBs for VA research programs. ORO has additionally been directed to strengthen newly required annual facility research program assessments and facility director certification of research oversight to include use of university IRBs. ORD will also be actively involved in these expanded functions, particularly in relation to reviewing accreditation standards and findings for VA use of university IRBs, in reviewing the effectiveness of oversight by VA Research and Development Committees, and in developing and implementing education programs addressing VA use of university IRBs.

4. In summary, your focused findings have assisted in helping us to prioritize some specific improvement actions. VHA's planned actions are responsive to the issues that you identify, and I look forward to sharing ongoing progress with you. If additional information is requested, please contact Margaret M. Seleski, Director, Management Review Service (10B5), at 565-7638.

(original signed by)

Michael J. Kussman, MD, MS, MACP

Attachment

VETERANS HEALTH ADMINISTRATION
Action Plan Response
**OIG Draft Report: Healthcare Inspection: Comparison of VA and University
Affiliated IRB Compliance with VHA Handbook 1200.5**
(Project No. 2006-00980-HI-0257)

Recommendations/ Actions	Status	Completion Date
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Recommendation 1. We recommend that the Under Secretary for Health ensure that all IRBs reviewing VA protocols disclose reportable adverse events to the VA facility, which must then report adverse events to ORO in compliance with the requirements of VHA Handbook 1058.1.

Concur

VHA acknowledges the need to refine and clarify existing guidance on the required steps that the IRBs and field facilities must take in reporting adverse events to Office of Research Oversight (ORO) and to assure that all involved parties understand and comply with that guidance. Specific actions are already planned by both ORO and the Office of Research and Development (ORD) to address issues identified in this report. As a first step, ORO will revise and update VHA Handbook 1058.1, *Reporting Adverse Events in Research to the Office of Research Oversight*, with emphasis on defining step-by-step processes involved with the reporting of adverse events by the IRBs to medical facility management, who will then submit the reports directly to ORO.

Compliance requirements for research-related adverse event reporting will be reinforced at a variety of educational forums that will be attended by VA research professionals. For example, beginning in October 2007, ORD will conduct five regional meetings on “Local Accountability for Research in VA Facilities.” ORO program managers will also participate in these meetings, as will up to five representatives from each VA facility performing research. Included on the planned agenda of these meetings is training on adverse event reporting as defined in VHA Handbooks 1058.1 and 1200.5 (*Requirements for the Protection of Human Subjects in Research*).

At the October 2007 annual meeting of the Society of Research Administrators International, which is widely attended by both VA and university affiliated research professionals, ORO and ORD will jointly

Recommendation 3. We recommend that the Under Secretary for Health ensure that VHA facilities require university affiliated IRBs to follow VHA Handbook 1200.5 and to verify that corrections are made to address deficiencies identified in this report.

Concur

This will be a core goal in ORO's expanded mission to ensure the efficacy and effectiveness of affiliated IRBs that review VA research protocols. ORO will be directly involved with strengthening newly required annual facility research program assessments and facility director certification of research oversight to include use of university IRBs. ORD will also be an active participant with ORO in reviewing the effectiveness of oversight of the IRBs by VA Research and Development Committees and in developing and implementing educational programs to address identified issues.

Planned

February 2008 and Ongoing

OIG Contact and Staff Acknowledgments

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Acknowledgments	Annette Acosta Gail Bozzelli Limin Clegg, Ph.D. Marnette Dhooghe Dorothy Duncan Donna Giroux Jeanne Martin, Pharm.D. Nelson Miranda Roxanna Osegueda Katherine Owens Michelle Porter Reba Ransom Annette Robinson Sunil Sen-Gupta, Ph.D. Randall Snow, J.D. Carol Torczon John Tryboski
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