Department of Veterans Affairs
Office of Inspector General

Healthcare Inspection

Human Subjects Protections Violations at the Central Arkansas Veterans Healthcare System Little Rock, Arkansas

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VA Office of Inspector General
Washington, DC 20420

To Report Suspected Wrongdoing in VA Programs and Operations
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Contents

Executive Summary

The VA Office of Inspector General received allegations related to research integrity and human subjects protection violations in research projects conducted at the Central Arkansas Veterans Healthcare System. To evaluate these allegations, we made three site visits, catalogued thousands of pages of source documents, interviewed dozens of individuals with relevant information, and met with officials from the Food and Drug Administration, the Office of Research Oversight, and the Office of Research and Development (ORD). We reviewed 13 research projects and described the facility's research program in detail.

We substantiated the allegations of human subjects protection violations in the areas of informed consent and adverse event reporting. We found that researchers obtained Human Immunodeficiency Virus tests on subjects without their consent; could not provide informed consent documents for all subjects enrolled in the protocols; and did not appropriately obtain witness signatures for demented patients enrolled in research protocols. We further found that researchers did not report deaths occurring during the course of the protocol, although these deaths were most likely not related to the research.

In addition to missing informed consents, four protocols were missing other key information and data related to the subjects recruited in the study. There were discrepancies in the number of subjects reported as being recruited to the Institutional Review Board (IRB) and to ORD. Other issues identified included the failure of principal investigators to obtain the requisite skills, training and experience to conduct the research.

We further found that the IRB was aware of many of these deficiencies well before our review, and had failed to suspend or terminate the researchers or research projects involved. In one instance, a single protocol had been audited at least six times, with the results communicated to the IRB on each occasion. For this reason, we found that the IRB failed to identify and address serious and continuing noncompliance.

We note the facility has made several attempts to address these problems. The Medical Center Director, Associate Chief of Staff for Research and Development, and Chief of Staff are all relatively new to the facility. The facility formed its own IRB, and embarked on an educational program for its researchers regarding human subject protections. Despite these efforts, we remain concerned about the status of human subject protections at the facility. We therefore recommended that the Under Secretary for Health determine whether research involving human subjects should continue at the facility; and if it should continue, develop a comprehensive plan for addressing the problems identified in this report. We further recommended that appropriate administrative action be taken based upon the findings contained within this report.

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

TO: Under Secretary for Health (10)

SUBJECT: Healthcare Inspection – Human Subjects Protection Violations at the Central Arkansas Veterans Healthcare System, Little Rock, Arkansas

Purpose

The VA Office of Inspector General (OIG), Office of Healthcare Inspections (OHI) conducted an inspection to determine the validity of allegations regarding human subjects protection violations in research at the Central Arkansas Veterans Healthcare System (CAVHCS) in Little Rock, Arkansas, which is a part of Veterans Integrated Service Network (VISN) 16.

Background

VA and 17 other Federal agencies adhere to the Common Rule, a set of Federal regulations governing research involving human beings. Among the principles embodied in the Common Rule are the concepts of informed consent and that the benefits of the research must outweigh the risk to human subjects. Researchers, or investigators, must document informed consent according to certain Federal regulations and policies and report adverse events so that risks may be assessed on an ongoing basis. All Veterans Health Administration (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.

Role of Institutional Review Boards

Compliance with the Common Rule requires a significant investment of resources. Professional staff must be involved in every aspect of research regulation, instructing primary researchers or principal investigators (PIs) in regulations addressing human subjects protections; overseeing research budgets and operations; and forming and managing institutional review boards (IRBs). 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, the research subjects give informed consent, and 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 it 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 medical center's FWA. 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 proper informed consent, IRBs must conduct continuing reviews not less than once per year on previously approved protocols to ensure ongoing compliance with VHA Handbook 1200.5 (38 Code of Federal Regulations (CFR) 16.109(e)). IRBs may also utilize procedures for expedited reviews if the matter to be reviewed involves minor changes to the research. The IRB Chairperson can do that expedited review alone and must then notify the IRB, typically at the next meeting. 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. In addition, IRBs must record minutes of meetings that contain certain elements as described in VHA Handbook 1200.5 and reflect decisions relative to the review process. IRBs must also maintain standard operating procedures, including a procedure to audit study protocols. Many facilities perform such audits through a Research Compliance Officer (RCO). No VHA policy specifies minimum qualifications or appropriate grade ranges for this position.

At the time our review began in August 2007, VHA policy did not further describe a facility's obligation to conduct protocol audits. However, on March 12, 2008, VHA issued Directive 2008-014, *Auditing of VHA Human Subjects Research to Determine Compliance with Applicable Laws, Regulations and Policies.* This directive now requires facilities to create standard operating procedures that describe the expertise required for auditing protocols, the frequency of audits, and areas to be audited. The directive does outline a number of areas to be included in the audit, and it further specifies that such standard operating procedures should address corrective actions to be taken based on the findings of the audit as well as the results of any corrective actions taken. We note this directive had not been issued at the time of our review, and we therefore did not consider facility compliance with this directive.

Role of Research and Development Committees

In VHA, the IRB is a subcommittee of the Research and Development (R&D) Committee. Research at every VHA facility must be reviewed by the full R&D Committee as well as by the IRB. To ensure adequate oversight of human subjects protections, VHA Handbook 1200.5 requires an IRB, regardless of whether it is a VA IRB or a university IRB reviewing VA protocols, to provide the R&D Committee with all records pertaining to the protocols the R&D Committee reviews, as well as all IRB minutes.

VHA policy also designates the R&D Committee, reporting through the Chief of Staff to the Medical Center Director, as the entity responsible for ensuring the overall quality of research activities at a given facility, including the protection of human subjects engaged in research activities. Research studies cannot begin prior to R&D Committee approval.

Responsibilities of Principal Investigators

PIs or the lead researchers responsible for a research study must comply with VHA Handbook 1200.5 and the Common Rule in the protection of human subjects. VHA Handbook 1200.5 specifies, among many other requirements, that non-veterans can be enrolled in VA approved research studies "only when there are insufficient veterans available to complete the study . . . ." However, where non-veterans are enrolled in VA approved research, all protections under the handbook, which apply to veterans, also apply to these subjects.

One of the core responsibilities of a PI outlined in VHA Handbook 1200.5 is the duty to ensure that adverse events are appropriately reported to the IRB and oversight agencies. VHA Handbook 1200.5 defines an adverse event (AE) as "any untoward physical or psychological occurrence in a human subject participating in research…. An adverse event does not necessarily have to have a causal relationship with the research, or any risk associated with the research or the research intervention, or the assessment." The handbook goes on to define a serious adverse event (SAE) as death; a life threatening experience; hospitalization (for a person not already hospitalized); prolongation of hospitalization (for a patient already hospitalized); persistent or significant disability or incapacity; congenital anomaly and/or birth defect; or an event that jeopardizes the subject and may require medical or surgical treatment to prevent one of the preceding outcomes." SAEs must be reported to various agencies, including ORO. Continuing reviews require the PI to certify that all SAEs have been reported appropriately.

Research Activities at CAVHCS

CAVHCS conducts an active research program, occupying 54,760 square feet at the facility. The Office of Research and Development's (ORD's) electronic tracking system disclosed that, as of March 18, 2008, CAVHCS had 294 active research projects utilizing

106 investigators. Of these projects, 208 involved human subjects; 55 evaluated investigational drugs; and another 4 gathered data regarding investigational devices. Of the 294 projects, 44 received VA funding and 96 received National Institute of Health (NIH) funding; the rest were either unfunded or received funding from other governmental agencies, academic institutions, or private sources. Total expenditures for research at the facility during fiscal year (FY) 2007 totaled $8,483,946.

At the time our review began, CAVHCS utilized the IRBs at its affiliated university (hereinafter "the affiliate"). As of June 12, 2007, the affiliate reported the use of five IRBs to the Office of Human Research Protections (OHRP), the office in the Department of Health and Human Services (HHS) that oversees human subject protections. The affiliate formed one of these IRBs on January 30, 2007, for the purpose of reviewing audits of protocols. We were informed that this IRB did not conduct any other activities related to human subject protections or protocol reviews. It was, however, listed as an IRB on the institution's FWA. Collectively, the other 4 IRBs reported that they reviewed 2,948 protocols during that reporting period on an OHRP self-assessment tool on June 12, 2007.

In 2005, the affiliate research program was fully accredited by the Association for the Accreditation of Human Research Protection Programs (AAHRPP). According to correspondence received from the affiliate, it was one of the first 24 entities to be voluntarily accredited.

CAVHCS supplied us with a protocol list suggesting that the affiliate IRB reviewed over 300 protocols involving VA resources or VA patients. The institution reported to OHRP that adverse events for all protocols were tracked in a computerized database used by the affiliate. In accordance with VHA policy, CAVHCS maintained its own R&D Committee.

CAVHCS also maintained an active compliance program, employing a full-time RCO. The RCO performed protocol audits to assess compliance with Federal regulations on a regular basis. Because of time constraints, the protocols to be audited were not always selected randomly, but were at times targeted to protocols known or suspected to be in noncompliance with Federal regulations. The university also employed compliance officers, who at times conducted audits of studies which involved both VA and university researchers.

In addition to engaging in research activities with individuals employed by the affiliate, VA researchers also performed certain research activities in conjunction with investigators at the National Center for Toxicology Research (NCTR), a Food and Drug Administration (FDA) funded research facility in Little Rock, AR. NCTR began by Executive Order in 1971 and conducts primarily animal studies to support FDA decision making on regulated products. We were told that the NCTR had more than 500 employees on site, about 200 of whom were Federal employees. Others were contractors

providing support services such as animal husbandry. NCTR conducted some research activities in collaboration with both the affiliate and CAVHCS.

Under 45 CFR 46.114, for research involving multiple institutions, each institution is responsible for ensuring the protection of human subjects. Despite this provision, a January 26, 2005, IRB Authorization Agreement between FDA and the affiliate authorized the affiliate's IRB to review research from NCTR. In March 2005, however, the FDA notified NCTR personnel by letter of a recommendation by OHRP that FDA maintain responsibility for continuing reviews of all FDA funded research regardless of the site. The FDA maintained its own IRB, the Research Involving Human Subjects Committee (RIHSC). This letter also formally revoked the previous IRB authorization agreement.

In a memorandum to the IRB Chairperson dated March 2, 2007, the FDA also expressed concern that the IRB had not notified the FDA of the results of an audit formalized on October 27, 2006, or of apparent ongoing compliance problems with certain research protocols at NCTR. These protocols involved VA researchers. Further, the FDA expressed concern that the IRB expedited a request to anonymize data from these studies just prior to an audit and that the IRB permitted the researcher to destroy records pertaining to subjects with missing or unsigned consent forms. The FDA also expressed its intent to perform its own audit of the protocols and requested that the records be sequestered. The VA Medical Center Director requested permission from the VISN Director to release a copy of this memorandum to ORO.

On March 28, 2007, the affiliate's IRB Chairperson responded in a memorandum to the Associate Commissioner for Science at the FDA. This memorandum stated that the affiliate's IRB did not receive notification that the IRB Authorization Agreement was revoked; noted that the PI of the study was not the person listed by the NCTR, but instead was another PI at CAVHCS; agreed that they had approved the PI's request to remove data where consent forms were missing or unsigned; and stated that, because the IRB did not declare that there was serious or continuing noncompliance in any of the studies reviewed, it was unclear what should have been reported to the FDA's IRB.

The FDA conducted its own audit of three protocols involving CAVHCS staff and FDA research from April 30 to May 4, 2007. In a letter to the Director of the NCTR dated July 3, 2007, the FDA indicated the audits were "requested and conducted because of ongoing concerns of noncompliance with the HHS' human subjects protection regulations (45 CFR 46) and a general lack of oversight with studies conducted by NCTR in conjunction with the [affiliate]."

The FDA summarized the results of its audit, concluding that documentation did not ensure that the protocol was followed in any of the three studies; noting that one NCTR investigator had "exhibited a continuing pattern of disregard for IRB rules and the Federal regulations," and that in several instances, there was no documentation that

informed consent was obtained from subjects prior to their participation in the studies. The FDA terminated all three studies and suspended a fourth involving the same researcher until an audit could be performed of that research. On July 12, 2007, CAVHCS's Medical Center Director requested an onsite review of its entire research program by ORO.

At the time of FDA's action, the PI about whom FDA was concerned had a total of nine active protocols approved by the facility's R&D Committee. Also on July 12, 2007, the Associate Chief of Staff (ACOS) for R&D at CAVHCS sent a memorandum to the Medical Center Director, requesting that all nine studies be suspended. On July 16, 2007, a co-PI on another study involving the subject PI asked that the subject PI's name be removed so that the research could proceed.

The Complaint

On August 13, 2007, ORO referred to the OIG allegations of forged informed consent documents and improper de-identification of records from studies involving VA researchers at NCTR. As documentation, we were supplied with a summary of the FDA audit findings dated June 29, 2007. Significant findings relevant to VA research activities included the following:

- Critical information appeared to be missing from study files, including evidence of subject eligibility and laboratory data.

- Documentation irregularities raised concerns about the accuracy of study records including informed consents, although the audit did not find clear evidence of forgery.

- Documentation was destroyed immediately prior to a Federal audit with the permission of the IRB.

During the course of our review, additional allegations were made, including:

- The affiliate's IRB and the VA's R&D Committee were aware of problems with these protocols prior to the FDA's audit and failed to address them appropriately.

- The affiliate's IRB and VA's R&D Committee generally did not appropriately identify and respond to serious or continuing noncompliance by PIs.

- Unlicensed research personnel performed certain minimally invasive procedures, such as muscle biopsies.

Scope and Methodology

We referred the allegations of forgery and improper de-identification of study records elsewhere and do not further review them here. This inspection report is therefore limited to human subjects protections violations and administrative responses to these issues.

General Overview of Methodology

To evaluate complaints pertaining to the specific protocols addressed in the FDA's audit, we conducted extensive document reviews, cataloging thousands of pages of PI source documents, IRB files, R&D Committee files, research compliance audits, memoranda, emails, and correspondence with ORO. We examined electronic databases for patient identifiers and compared data contained in those databases to PI source documents. We sequestered records pertaining to the protocols audited by the FDA and obtained documents from the affiliate's IRB.

We interviewed numerous facility research personnel, conducting three separate site visits. The first such visit occurred from August 15–17, 2007. Based upon allegations received onsite, we conducted protocol reviews to determine how audit findings were addressed by the IRB and R&D Committees; chart reviews to determine whether adverse events were reported and whether unlicensed personnel performed procedures requiring licensure; and obtained information regarding changes in the leadership and administration of research services at CAVHCS.

We also interviewed officials from the ORD, ORO, and NCTR. We met with FDA representatives regarding their concerns. We also interviewed former employees of the facility's research program who had knowledge of the specific issues involved.

Identification of Sample Population for Review of Protocols Audited by the FDA

To assess the allegations of documentation irregularities in the protocols audited by the FDA, we first identified an electronic database containing patient identifiers which purported to represent patients enrolled in these four protocols. We then took this list of names and social security numbers and matched them to Austin Automation Center's Beneficiary Identification Records Locator Subsystem (BIRLS) to identify the population of veterans in each study. Once veteran participants in the studies were identified, we then matched these veterans against the Social Security Death Index File to define the population of deceased veteran participants.

This process disclosed a total of 105 individuals, 75 of whom we were able to verify in the electronic medical record as being deceased. We then sought to locate study records for all 105 patients, the results of which are presented below. We chose to obtain our sample from deceased veterans in order to ensure that adverse events were accurately

reported among this group because, by definition, any death occurring during the course of a protocol should be reported whether or not it is related to the study. This was not an effort to identify the total number of individuals on all four protocols who were deceased or who were veterans, nor was it an effort to obtain a representative population sample. Furthermore, validation of the accuracy of the data obtained from the Austin Automation Center or protocol databases is beyond the scope of this review.

Identification of a Sample of Audits for Assessment of IRB & R&D Committee Oversight

To appropriately address the additional allegation that the IRB and R&D Committees failed to properly oversee human subjects protections, we reviewed all protocol audits conducted by the facility's RCO from January 1–July 1, 2006. We also reviewed all protocol audits conducted by the RCO during FY 2007 for reasons identified in the report. We then reviewed IRB and R&D Committee minutes to assess IRB and R&D Committee responses to the issues identified in the audits, as well as correspondence to and from oversight and regulatory agencies.

We conducted the inspection in accordance with *Quality Standards for Inspections* published by the President's Council on Integrity and Efficiency.

Inspection Results

Issue 1: Alleged Human Subjects Protections Violations in Protocols Conducted by CAVHCS and NCTR Staff

We substantiated the allegations of documentation irregularities and human subjects protection violations in the execution of four protocols conducted by CAVHCS and NCTR researchers. We further substantiated that the affiliate IRB was aware of problems in these studies prior to the FDA audit and failed to appropriately follow up on these issues.

A. Human Subjects Protections Violations and Missing Documentation in Protocols A, B, C, and D

Protocols A, B, C, and D were all conducted by the same PI at CAVHCS. We note that allegations of forged witness signatures on informed consent forms were presented to the affiliate IRB prior to the FDA's audit. We found the following statements in the affiliate IRB's January 30, 2007, minutes referencing Protocol B:

> This study, currently open for data analysis and writing only, raised allegations of forged witness signatures on consent forms, totaling 753 (for instance, one subject appeared on two different forms). The audit report supported no revelation of forged signatures. A motion was made to accept

> the audit report, which indicates no level of non-compliance. The motion carried unanimously, with no abstensions.

The audit referenced in these minutes is the affiliate's own audit report, dated October 25, 2006. While the IRB minutes reference "no level of non-compliance," the affiliate compliance officer's own audit report contains many findings of noncompliance including that: handwriting styles on subject initials or other written elements did not match on 62 consent forms; an unapproved consent form was used for 49 subjects; the times and/or dates of subject and witness signatures differed on 103 forms; the PI's signature on the consent forms was more than 2 months after the subject's signature on 173 forms; and the same person timed and/or dated the subject and witness signatures on 142 forms. The compliance staff, noting that they did not have formal handwriting analysis training, did state that "No evidence was found allowing confirmation that any signature appearing on any informed consent form was not authentic." We could find no evidence that this allegation of forged informed consent signatures was evaluated further, or referred to the OIG prior to the referral from ORO following FDA's audit.

FDA's initial audit addressed findings relative to Protocols A, B, and C, deferring an audit of Protocol D because of time considerations. Findings related to Protocol A included the absence of any study records documenting the eligibility of subjects. The FDA also found that, although certain lab specimens were time-limited following the administration of an over-the-counter medication, there were no records documenting receipt of these medications from the pharmacy, when or how much of the medication was administered, and when specimens were obtained. There were inconsistencies regarding the number of subjects enrolled, missing informed consent documents, and an incorrect statement regarding whether or not an audit had been performed on the study.

Findings relative to Protocol B were similar, with additional findings of multiple irregularities in the execution of the informed consent regarding witness signatures, times, dates, and PI signatures. FDA personnel also reported receiving allegations of forged witness signatures on informed consent documents. The audit report stated that auditors saw no definitive evidence of forgery but said they could reach no conclusion as they were not experts in the area of forgery. The FDA audit described additional informed consent irregularities in Protocol C, with the addition that there was no documentation that seven subjects met inclusion criteria, as required laboratory test results could not be located. The FDA further noted that none of these documentation issues were reported to RIHSC prior to FDA's audit, despite similar findings by the affiliate's compliance staff in previous audits.

Audit findings from CAVHCS's RCO also raised concerns regarding the reporting of adverse events and missing documentation in all three protocols audited by the FDA at that time. Both the FDA and ORO addressed the issue of any potential research misconduct based upon absence of documentation. We focused our review on the

absence of documentation as it related to human subjects protections issues and IRB actions taken as a result of audit findings.

Failure to Report Serious Adverse Events

Our review of the records of 105 deceased veterans and the source documents for Protocols A, B, C, and D revealed that the PI for these protocols failed to disclose all adverse events to the IRB. Annual continuing review forms submitted to the IRB require the PI to report the number of deaths occurring from the time of subject enrollment in the study to the time of study closure, whether or not those deaths are related to study interventions. For those studies which involve long-term follow-up, the investigator is required to report any death to the IRB within 60 days of becoming aware that such a death occurred.

Our review of the 105 deceased veterans disclosed that 21 of them had no electronic medical record. Of the remaining 84 patients, compensation and pension record interchange (CAPRI) records contained verification of death of 75 patients. Fifteen of these 75 patients had a cause of death documented in the medical record. None of these 15 patient deaths appeared to be related to study interventions. While we do not know the cause of death in the remaining 60 patients, the nature of the study interventions would make it unlikely that study participation contributed in any way to their deaths. Nevertheless, continuing review forms submitted by the PI to the affiliate IRB disclosed 0 deaths in response to the question of how many patients died between the time of enrollment in the study protocol until the time of study disclosure. Despite an April 2006 recommendation by the VA RCO to report these deaths, when we conducted this review in October 2007, none of the 75 verified deaths had been reported. We therefore found that the PI failed to report adverse events as required by VHA policy, and the IRB failed to take action to ensure compliance with this requirement.

Missing Documentation in Protocols A, B, C, and D

We also checked this sample of patients to determine whether documentation was in fact missing as alleged in the FDA audit. We substantiated the allegation that documentation was missing from all four protocols. Of the 105 deceased patients, 97 patients were enrolled in protocols C and D; 3 in Protocol A; and 5 in Protocol B. For the 97 patients enrolled in Protocols C and D, there were no complete packets of paperwork found for any patients.

For Protocols C and D, we found one document for each of the 69 patients, which consisted of 8 contact sheets, 1 freezer inventory specimen log, 58 history abstraction forms, and 2 history and physical inquiries. There were no documents pertaining to four patients. The remaining 24 patients had a combination of documents that included 20 consent forms, 6 freezer inventory specimen logs, 21 health habits questionnaires,

19 health habits and diet questionnaires, 13 tracking database follow-up sheets, 20 men's health sections, and 5 specimen processing records.

For the three deceased subjects enrolled in Protocol A, we were able to locate one document for each, which were history abstraction forms. For four of the five deceased subjects enrolled in Protocol B, there were no documents. We located a contact sheet and questionnaires for the fifth patient. However, we note that the IRB had authorized de-identification of records in Protocol B, which is discussed below. This may indicate the reason why records could not be matched to subjects in Protocol B.

Because of the missing documentation, we were unable to validate the information contained within the database. Documents were missing in no discernible pattern, and we were not able to validate a complete data set for any patient in our sample.

B. Failure of the IRB to Address Human Subjects Protections Violations: The Example of Protocol D

Because audits were performed by the affiliate and VA RCOs identifying these problems prior to both the FDA audit and our review, we examined IRB documentation pertaining to Protocol D to assess the IRB's response to these findings. It is our opinion that the IRB failed to adequately follow up significant audit findings, which prevented the identification of potential continuing noncompliance. We present the example of Protocol D below.

The VA RCO conducted an audit of Protocol D; the report was completed March 13, 2006. Audit findings included that the first veteran was enrolled in 1996, but the study was not submitted to the R&D Committee for approval until the year 2000. The RCO looked at 100 consent forms, finding that 23 had incorrect dates or times; and that there were numerous problems with versions of the consent. Further, computerized patient record system (CPRS) contained no documentation of the consent process. Of the 100 participants reviewed, 25 had died. No SAE or deaths had been reported for the study. The RCO recommended that the PI report adverse events and deaths and that the PI ensure all subjects were properly consented on the appropriate consent forms.

On April 13, 2006, the affiliate IRB notified the PI of the decision to disallow use of data for two subjects with informed consent irregularities. Further, the PI was required to perform a self-audit on this protocol within 60 days. Finally, the IRB recommended a random audit of another of the PI's studies in 6 months. The R&D Committee reviewed the results of Protocol D's audit on April 17, 2006. The R&D Committee's recommendation was to re-audit the study in 6 months. This was reported to ORO on May 2, 2006. On May 16, 2006, ORO responded that because both the IRB and the R&D Committee voted to allow these protocols to continue, they considered the matter closed. The PI performed a self-audit on May 31, 2006, which indicated that of 1,314

study participants in this study, 40 were missing informed consents. The self-audit contained no reference to the reporting of deaths or SAEs.

Neither the affiliate nor CAVHCS audited this protocol again. Between May 31, 2006, and the date of the FDA audit in March 2007, we could find no evidence that the IRB or R&D Committee responded to the PI's failure to report deaths as recorded in the initial VA RCO audit or further followed up to determine if deficiencies identified were corrected. On November 1, 2006, Protocol D underwent continuing review by the affiliate IRB. No deaths were reported. The PI did report a vasovagal response after a biopsy, but no other adverse events. The study was approved by the affiliate IRB despite the prior audit report disclosing unreported deaths. We therefore found that the IRB failed to follow up on audit findings relative to the reporting of deaths and other SAEs; they also further failed to address significant documentation issues described in multiple audits in terms of the validity of the study data. This prevented the identification of continuing noncompliance and appropriate reporting as required by Federal regulations.

IRB Authorization to De-Identify Subject Records in Protocol B Prior to an Audit

In addition, we substantiated that the IRB authorized the de-identification of study records immediately prior to an audit. On September 25, 2006, an investigator on Protocol B requested that the IRB authorize de-identification of study records as the study was closed to recruitment. This request stated that the de-identification would occur by removing all identifiers from consent forms, contact information sheets, questionnaires, and the database. On September 26, 2006, the next day, the IRB Chairperson approved the request by expedited review. On September 27, 2006, the affiliate's RCOs arrived to retrieve the materials for an audit. An official from the affiliate informed us that this occurred as a result of a complaint received through the affiliate's compliance hotline on September 27, 2006.

In examining the consent forms obtained one day after the IRB's approval to de-identify study materials, the affiliate's compliance staff found that all study numbers had been removed from each page of 753 consent forms. Subject signatures were still legible. The affiliate's compliance staff concluded:

> Because study identifiers have been removed from the informed consent documents, data from any subjects whose informed consent may be determined to be invalid cannot be identified or removed from the dataset, and it may no longer be possible to determine if valid informed consent was obtained prior to obtaining particular data.

While our review disclosed that some study information had indeed been de-identified, we do note that the database contained identifiers at the time of our review, defeating the rationale for de-identifying study source documents. In addition, we find it disturbing that the affiliate's compliance staff noted that all 753 consent forms had been

de-identified in less than one day following approval by the IRB and immediately prior to an audit.

Issue 2: Alleged Failure of IRB to Protect Human Subjects

We substantiated the allegation that the affiliate's IRB failed to adequately protect human subjects in that it did not: (1) address serious and/or continuing investigator noncompliance with informed consent and SAE reporting requirements in a timely fashion; and (2) ensure that researchers had the requisite skills, training, and experience to conduct the research.

A. Failure to Identify and Address Serious and/or Continuing Noncompliance

January 1–July 1, 2006, CAVHCS RCO conducted 18 protocol audits of which we reviewed 14. Of these audits, two disclosed no significant deficiencies; six disclosed deficiencies that were promptly addressed with cooperative efforts between the involved PIs and the RCO; and the remaining six audits required IRB intervention.

These six audits included one of the three protocols audited by the FDA, as well as the fourth protocol which the FDA could not audit due to time constraints (Protocol D, discussed above). The remaining four audits demonstrated problems with informed consent; protocol deviations; documentation of adverse events; and missing study data such as required labs. We present examples of how the IRB responded to those problems.

Protocol E: IRB's Failure to Identify Serious and/or Continuing Noncompliance

While Protocol D is an example of the IRB's failure to require research compliance personnel to follow up on deficiencies previously identified to determine if they had been rectified, Protocol E is an example of the IRB's response when multiple audits did demonstrate continuing noncompliance. Protocol E is one of the five non-FDA studies audited January 1 through June 30, 2006, by CAVHCS's RCO which required IRB action. We found that this study was audited on multiple occasions with continuing demonstrations of deficiencies without the IRB taking action to suspend or restrict either the study or the PI.

Protocol E involved the application of a different technique during coronary artery bypass graft (CABG) surgery. It required an angiogram after CABG, and then another angiogram at one year post-CABG to assess graft patency. This study began as a multicenter trial on October 1, 2002. At CAVHCS, it was suspended August 29–November 10, 2005, following irregularities noted in source documentation and data acquisition by the coordinating center and outside auditors. Auditors dispatched from the VA Cooperative Studies Program stated the following in a letter to the RCO and Medical Center Director: "In short, while we consider the audit findings disturbing, we feel the study is indeed salvageable at this site . . . ." It reopened in November 2005, and on

January 17, 2006, ORO recommended continued adherence to recommendations described in the audit and closed the case. Five additional patients were enrolled, bringing the number of total enrollees to 70. The RCO performed an audit on February 15, 2006. While this audit described study records that were well-organized, the RCO noted that the 12-month follow-up coronary angiogram required by the protocol to assess graft patency had not been performed in many patients. The RCO suggested documentation of all attempts to contact patients regarding follow-up and that the PI send certified letters if unable to contact the participants.

In the spring of 2006, a patient received follow-up coronary angiogram performed for study purposes and was subsequently discharged. The day after surgery, the patient required air evacuation to an outside hospital for hemorrhage related to bilateral femoral artery perforations and blood loss resulting in bowel ischemia. A month later, a reviewer for the affiliate IRB indicated that a fellow, who was not listed on the study protocol, performed the procedure. Minutes from that meeting also contain the following statement: "The report shows an attending physician was present during the procedure, but he was in the next room." The facility reviewed the case and found it acceptable.

On May 31, 2006, the IRB approved the addition of a statement to the study informed consent requiring disclosure of bleeding risks. The facility directed a memorandum to ORO on June 21, 2006, reporting the event.

VA RCO audit reports of July 2006 and January 2007 cite continued failure to re-consent subjects to advise them of this risk associated with the protocol. The January 2007 audit disclosed that 19 of the 83 patients enrolled remained active; and of the 64 inactive participants, 31 received an angiogram at 1 year following CABG to assess graft patency. Others were noted to be either lost to follow-up or refusing coronary catheterization. The RCO again advised recording attempts to contact those not receiving the coronary catheterization at 1 year to assess graft patency.

Minutes from the January 30, 2007, meeting of the IRB Special Committee on Audit and Compliance reflect discussion of audit findings. This committee was created to determine whether audit findings met the definition of serious or continuing noncompliance. If findings met either the definition of serious or continuing noncompliance, Federal regulations require that the IRB report these instances to oversight agencies, such as OHRP or the FDA. The affiliate's standard operating procedures define serious noncompliance as "an action or omission taken by an investigator or study personnel that any other reasonable investigator would have foreseen as compromising the rights and/or welfare of a subject." Continuing noncompliance is defined as "a pattern of repeated actions or omissions taken by an investigator or study personnel that indicates a deficiency in the ability or willingness to comply with federal regulations . . . ." The affiliate's standard operating procedures also created a third category, known as simple noncompliance, meaning that the deficiencies identified did not comport with Federal regulations but did not meet requirements for

reporting to any Federal oversight agency. The committee found that failure to re-consent subjects in Protocol E constituted noncompliance but not serious or continuing noncompliance. One member "added the principal investigator, whose schedule is very rigorous and difficult, is showing significant improvement in this study."

The audit committee addressed this protocol again in the April 19, 2007, meeting. Minutes from that meeting contain the following statements:

> This VA study has undergone monitoring in 3-month intervals, the last report compiled in January 2007. The spokesperson from the VA said the newly hired study coordinator has conducted no human research until recently. Compared with previously disorganized documentation, recent materials appear more complete. The spokesperson requested no report from this coordinator. [A member] told the committee that [the protocol] is part of a major national study that entails a topic very much in vogue, with the local principal investigator generating the most recruitment among all researchers in the U.S. A motion was made to accept the quarterly report with no response necessary. The motion carried, with no abstensions.

The next day—on April 20, 2007—the CAVHCS RCO conducted an additional audit on this protocol. The CAVHCS RCO found that 7 of 7 subjects undergoing 12 month cardiac catheterization follow-up had not been reconsented with the revised consent form advising them of the risk of internal bleeding associated with coronary catheterization. The RCO stated in her audit:

> The failure to report in January 2007 as well as the July 26 audit report (no one returned that needed to be re-consented during the October 2006 review) yet the participants have continued to come in for final angiogram without being re-consented. The July 2006 and January 2007 oversights were explained as just that but this now indicates continuing non-compliance.

The CAVHCS RCO and the IRB Chairperson met with the PI and study coordinator on May 2, 2007, to "impress the importance of re-consenting participants prior to another angiogram if they have not signed the 6/07/06 version of the Informed Consent." On July 23, 2007, three of the seven subjects had been reconsented, in part because some of the patients did not have scheduled appointments. On September 17, 2007, the affiliate IRB approved the study for continuing review.

We reviewed the medical record of 93 patients enrolled in Protocol E as of July 30, 2008, to determine how many had received two follow-up coronary angiograms as described in the protocol. Our review disclosed that, 24 of 93 medical records reviewed did not contain documentation that the initial angiograms post-CABG were done. For the coronary angiogram due 12 months following CABG, 16 of the subjects were not

included in our sample because of death or withdrawal of consent to the study. Thirty-one of the 77 remaining subjects had no documentation in the medical record that they received the 12-month follow-up angiogram as of July 30, 2008.

Following the September 17, 2007 IRB approval, the study was not reviewed again by CAVHCS compliance staff until January 28, 2008. Findings and actions of that date and later are discussed under Issue 5, regarding facility responses. There remained, however, persistent issues with the reporting of SAEs and various issues pertaining to appropriate documentation of the informed consent process. We therefore found that, despite multiple audits demonstrating continuing deficiencies, the IRB failed to identify continuing noncompliance and to report it appropriately in this instance.

Protocols G&H: IRB's Failure to Respond Appropriately to Serious and Continuing Noncompliance

Noting that both Protocol D and E began more than 5 years ago, and acknowledging the greater difficulty of record keeping in older studies, we sought to determine whether studies approved within the last 3 years reflected similar noncompliance. To do this, we requested and reviewed audits for FY 2007. The RCO supplied us with 24 audits completed during this time frame. Six of these audits were of protocols addressed elsewhere in this report. Of the remaining 18 audits, 10 identified issues with informed consent. These issues included such deficiencies as no Health Insurance Portability and Accountability Act (HIPAA) authorizations for 96 of 157 participants (the PI allegedly thought the clinic HIPAA authorization was sufficient); the performance of Human Immunodeficiency Virus (HIV) tests that were not discussed in the informed consent; subjects were consented for a different but similar study; missing PI signatures on informed consents; informed consent forms approved by the IRB that did not contain all the required elements; and numerous documentation issues, including documentation of signature times and initials on consent forms. In the one case identified regarding HIV tests, the RCO noted that the first several participants received an HIV test without their knowledge, but the investigators decided to withdraw future HIV testing from their "routine research practice." HIV testing was also not specified as part of the protocol.

IRB minutes identified two of these protocols in which findings were made of serious or continuing noncompliance. We examined both cases to determine how the IRB responded to serious or continuing noncompliance once it identified these conditions.

Protocol G

Protocol G involved the use of a Humanitarian Use Device (HUD). HUDs are devices intended to benefit patients with conditions that generally affect less than 4,000 individuals per year in the United States. They can be approved by the FDA for marketing as a Humanitarian Device Exemption (HDE) without the data typically required where devices are used more commonly, and data on efficacy is therefore more

readily available. HUDs may be used at an institution after IRB approval. IRB review must include verification that the device will be used in accordance with the indication specified in the HDE (21 CFR 814.124(a)).

An HUD may be used in an emergency without IRB approval, if: (1) the patient has a life-threatening condition that needs immediate treatment; (2) no generally acceptable alternative treatment for the condition exists; and (3) because of the immediate need to use the device, there is no time to get approval for its use (21 CFR 812.35(a) (2)). If used for an emergent indication, the physician should obtain, to the greatest extent possible, informed consent, clearance from the institution, an independent assessment from another physician, authorization from the manufacturer, and concurrence of the IRB Chairperson. The physician must notify the IRB and the manufacturer within 5 days following the procedure with the above supporting documentation.

One such device was approved under an HDE for treatment of free coronary artery perforations. We found that the device was used at CAVHCS at least twice for off-label indications without IRB approval. Further, the facility was unable to track who received the device for off-label indications reliably.

The manufacturer sent a letter to the affiliate IRB on October 12, 2006, stating that they had determined the device was used for an off-label indication. This letter included the following statement: "Under the current Food and Drug Administration regulations [the manufacturer] is required to track all use of this device . . . . If it is determined that unapproved off label use of this device is continuing at your facility, all sales to our facility will be immediately suspended." The RCO performed an audit during November and December 2006 following identification of this issue. On November 8, 2006, the CAVHCS RCO emailed the coronary catheterization laboratory manager to request a list of persons receiving the device other than the individual identified by the sponsor. On November 9, 2006, the RCO received identifiers for two veterans purportedly receiving the device. We reviewed both records. One patient's medical record made no reference to the use of the device, although he did have a coronary catheterization on the date provided by the study personnel. The medical record documents that the second patient received the device.

On November 13, 2006, the PI wrote a letter to CAVHCS Chief of Staff indicating that he would follow the regulations concerning the off-label use of HUDs and would submit a protocol concerning such uses to the IRB and R&D Committee. He also indicated that he obtained verbal consent from the patient to use the device in the case reported to the sponsor. There is no documentation in the medical record that the patient was aware at all of the use of an HUD. This was reported to the former ACOS for R&D and the former Chief of Staff on November 2, 2006.

The CAVHCS RCO completed an audit of the case on December 6, 2006. This audit disclosed that a peer review found medical necessity in the case, although peer reviewers

acknowledged that the protocol had not been followed. The RCO also added: "There is no notation anywhere that indicated that the patient realized he would or did receive a humanitarian use device."

On December 7, 2006, the IRB Chairperson sent a letter to the sponsor indicating that the Chairperson discussed the regulations with the PI and instructed him to apply formally to the IRB for an emergency use protocol. To the date of this report, the PI had not submitted any such protocol.

Correspondence between all parties involved do cite several contributing factors to the use of this HUD without IRB approval, including a change in PI for the study; a change in sponsor for the product; and some interruption of field support services by the sponsor. Further, the RCO reported that the sponsor rescinded a complaint letter following the discovery that the researcher notified the sponsor's field representative of the off-label use of the device.

While we could not locate primary documentation of this rescission, we did find that, on January 15, 2007, the sponsor reported that they had received all documentation supporting the August 4, 2006, use of the device, including a concurrence from the IRB Chairperson dated December 7, 2006. The affiliate IRB did not review this case until the January 30, 2007, meeting of the Audit Committee, which was the first meeting of the Audit Committee. The IRB identified three issues before it: (1) the original violation regarding use of the HUD without IRB approval; (2) determination of whether this was an emergency procedure; and (3) submission of a protocol covering emergent off-label uses. We found no reference in the IRB minutes or the documents submitted to ORO or OHRP of any other past off-label use of this device.

On May 22, 2007, the current ACOS for R&D sent a memorandum to ORO which included the following statements regarding the delay in notification:

> [Affiliate] officials also decided not to place any documentation regarding audits or the meetings in the electronic IRB records. Minutes for this meeting [the January 30th meeting] were not available until they were approved on 4/19/07 at the second special audit IRB meeting. The minutes that were provided and approved by the R&D committee at the 4/23/07 meeting did not have the complete information regarding [the device] discussion including the IRB finding of this as "serious non-compliance". The error was discovered by CAVHCS research compliance officer . . . .

Following this report, the affiliate and CAVHCS notified OHRP of the August 4, 2006, incident, described as serious noncompliance, on May 24, 2007.

The audit performed on the protocol stated that all previous recipients of the device had received it for the approved indication. When we reviewed the two cases identified by

the coronary catheterization laboratory nurse manager, the device had been used for the repair of a vessel demonstrating aneurismal dilation in 2005. Records do not reflect any free perforation, the approved indication for this device. The patient initially presented with a myocardial infarction and received an urgent coronary catheterization and stent placement within 24 hours of presentation. Eight days following the patient's presentation, another cardiac catheterization was performed to assess other vessels, including those supplying the right side of the heart. The coronary catheterization report records use of the device for repair of an aneurysm. We could find no documentation in the record that this was considered to be an emergency by any staff physicians. IRB documentation supplied to us pertaining to this device did not contain documentation that this off-label use was reported to the IRB, OHRP, FDA, or ORO. In correspondence to the OIG, dated October 4, 2007, the RCO disclosed that neither CAVHCS nor the IRB had ever been informed of this off-label usage to her knowledge.

As of the date of this report, the PI still had not submitted a protocol for the off-label use of this device. He did, however, indicate that he was not going to use the device off-label in the future.

Protocol H

We also examined Protocol H, a minimal risk protocol, but one which involved a vulnerable population—those patients with dementia. The R&D Committee initially suspended the study in 2005 for failure of the PI to comply with training requirements. An audit conducted on February 16, 2007, revealed noncompliance in multiple areas, including failure to obtain witness signatures and/or patient representative signatures in patients with dementia who were recruited for the study. The affiliate IRB suspended the protocol in June 2007 following failure of the PI to respond at all to the audit findings. The affiliate conducted its own audit of Protocol H in July 2007. Findings were similar. In August 2007, the affiliate IRB informed the PI that Protocol H was suspended for serious noncompliance. The PI was told to surrender all data, including videotapes of subjects, for destruction by the IRB on August 10, 2007.

At the time of our last site visit in April 2008, the PI had not surrendered the study data and told us he "didn't know where it was." We asked for an enrollment list, which he has yet to provide. We were provided with no evidence that caretakers or other informed consent surrogates were notified of patient enrollment. Further, we were informed that the PI continued to conduct research at the facility. We therefore chose to evaluate a second protocol by this PI.

Protocol I

On February 7, 2006, the same PI submitted another research study (Protocol I) to the affiliate IRB, which approved it under expedited review. The affiliate IRB Chairperson completed VA Form 10-1223, *Report of Subcommittee on Human Studies*, on February 9,

2006, and checked "yes" by the following statement: "The information given in the Informed Consent under the Description of Research by Investigator is complete, accurate, and understandable to a research subject or a surrogate who possesses standard reading and comprehension skills." In March 2006, the R&D Committee informed the PI that they were tabling this same protocol because of the lack of a consent form and confusion over a requirement to contact subjects although it was otherwise described as a research project involving only chart review. He was asked to resubmit the proposal. We were provided with no documentation that he ever resubmitted the proposal.

In January 2007, when questioned about the status of the project, the PI stated that he began data collection in March 2006 and had reviewed 678 veterans' medical records. He stated he had IRB and R&D Committee approval. The R&D Committee had not granted approval for this study. The R&D Committee discussed this protocol on July 16, 2007, and stated that the PI should suspend any activity on the study until obtaining final approval. Further, the R&D Committee indicated that failure to respond to the March 2006 letter requesting re-submission of the protocol by August 20, 2007, could result in suspension of his research privileges at CAVHCS. The PI did not respond, and the committee voted to indefinitely suspend all VA research activities for which this physician served as PI.

On January 5, 2008, the PI submitted the suspended Protocol I to the IRB for approval under expedited review procedures. On January 10, 2008, the Chairman of the affiliate IRB approved the suspended study despite the fact that the study enrolled veterans, and the PI had no active research privileges at CAVHCS. The Chairman of the IRB could not explain how the IRB approved Protocol I with the above history. The IRB Chairman said he would notify the PI and suspend the study.

B. Failure to Ensure that Investigators Have the Requisite Skills, Training, and Experience to Conduct the Research

While evaluating Protocol H, the study suspended in 2005 for failure of the PI to maintain training requirements, we could find no evidence that the PI ever completed those training requirements despite continuing the research until 2007. Further, we were provided with documentation suggesting that the former ACOS for R&D permitted evidence that PIs satisfied the affiliate's requirements in lieu of VA mandatory training. We therefore found that the affiliate IRB failed to ensure that PIs had the requisite skills, training, and experience as defined in VA educational requirements to conduct research at a VA facility.

In addition, we received allegations onsite that the IRB permitted unlicensed research personnel to perform muscle biopsies at the facility, an activity which may constitute the practice of medicine. To evaluate this issue, we requested scopes of practice for unlicensed PIs performing muscle biopsies and received a scope of practice for three investigators. Two scopes of practice permitted the investigator to perform muscle

biopsies, but one of these was a Registered Nurse and therefore had some type of licensure authorizing that person to administer medical care to patients. The other was a Doctor of Philosophy (Ph.D.). We were supplied with no documentation that the Ph.D. had any license authorizing him to conduct any type of procedure on patients. Both his scope of practice and that of one other Ph.D. also permitted them to give xylocaine anesthesia injections; inject patients with stable isotopes, sodium bicarbonate, glucose, insulin, and saline; make rounds, and advise the responsible physician "of significant changes in the patients' condition." The scopes of practice for the two Ph.D.s were signed on June 18, 2003, and February 22, 2005, respectively. Neither had executed a revised scope of practice at the time of our initial site visit.

CAVHCS was aware of this problem and attempted to address it on February 23, 2007. Following a call by the current ACOS for R&D to the Arkansas Medical Board, the Medical Center Director issued a memorandum stating that all such procedures had to be done by licensed and credentialed physicians, stating that the memorandum superseded all scopes of practice extended previously. On June 5, 2007, the affiliate's Dean from the College of Medicine wrote a letter in support of permitting a particular unlicensed individual to continue to perform muscle biopsies, despite the above memorandum.

To verify that PIs were complying with the Medical Center Director's prohibition against this activity, we asked CAVHCS for a list of all protocols involving muscle biopsies. The medical center listed 18 different protocols requiring muscle biopsies, with 9 having a Ph.D. as the PI and 9 listing a medical doctor (M.D.) as the PI.

We reviewed two protocols (Protocols J and K) for evidence that unlicensed personnel continued to perform muscle biopsies following the Medical Center Director's intervention. In Protocol J, we reviewed the study records of 16 enrolled patients. Of those 16 patients, 14 had documentation that an M.D. performed the muscle biopsies. The remaining two were performed by an advanced practice nurse (APN). In Protocol K, we were supplied with the records of two veterans recruited for the study, both of whom received muscle biopsies performed by an APN. Intravenous medications appeared to be administered by licensed nursing staff. Therefore, while scopes of practice were inappropriate at the time of our initial review, we found no evidence that unlicensed individuals continued to perform muscle biopsies in the protocols we reviewed.

We therefore found that, while scopes of practice for existing research personnel did permit activities which might constitute the practice of medicine, the Medical Center Director had addressed the issue of performance of muscle biopsies by these individuals. We were not, however, supplied with any documentation of training by these individuals to administer intravenous isotopes, insulin, and glucose, activities which would otherwise require licensure, training, or certification.

On a repeat site visit, we were provided with revised scopes of practice for unlicensed personnel listed as the PI on protocols requiring muscle biopsies. None of these revised

scopes of practice permitted unlicensed individuals to perform muscle biopsies, although we note that they did permit the continued performance of certain other activities such as exercise testing. The facility attached two scopes of practice guidelines from the American College of Sports Medicine. These guidelines contained the following statement: "The degree of physician supervision may vary with local policies and circumstances, the health status of the patient, and the experience of the laboratory staff. The appropriate protocol should be based on the age, health status, and physical activity of the person being tested."

While we describe the efforts of the CAVHC leadership to address this problem, we were not supplied with any documentation that the IRB, despite its responsibility to ensure that researchers have the requisite skills, training, and experience to conduct the research, evaluated researchers in these protocols to ensure licensure where research activities would require it prior to the Medical Center Director's memorandum. Further, a letter from an official of the affiliate was actually written in support of allowing the practice to continue. We therefore found that the IRB did not ensure that PIs had the appropriate training to conduct research at CAVHCS.

Issue 3: Alleged Failure of R&D Committee to Ensure Human Subjects Protections

We substantiated the allegation that the facility's R&D Committee failed to protect human subjects. While the IRB is the subcommittee of the R&D Committee primarily responsible for ensuring human subjects protections, the R&D Committee bears responsibility for oversight of IRB actions. While the R&D Committee cannot approve a research proposal that the IRB has disapproved, it may disapprove a proposal that has IRB approval. Therefore, by not ensuring that the IRB acted appropriately to protect human subjects, we found that the R&D Committee also failed to protect human subjects. We provide one additional example.

Protocol L was initially approved on December 21, 1999, by the affiliate IRB. It involved the performance of muscle biopsies by the PI (hereafter referred to as PI 1). We found no evidence that this protocol was audited prior to March 2006. In March of 2006, however, the RCO performed an audit in conjunction with the affiliate's compliance staff at the request of PI 1, who stated in a memorandum to the Chairperson of the IRB: "My office (CAVHCS Research Administration) was notified in early 2006 that the federal Inspector General would be coming to Little Rock to audit specific VA research projects. I asked CAVHCS RCO to look over the clinical trial with the intent of checking for any problems that might be targeted by the IG audit."

The audit conducted by the CAVHCS RCO identified numerous deficiencies; these included failure to notify the IRB of compensation provided to a veteran for persistent mild pain and numbness around the biopsy site, numerous irregularities in informed consent documents, and missing HIPAA forms. In addition, the RCO indicated that

while subjects were supposed to receive a computed tomography (CT) scan as part of the protocol, this was not performed; not all subjects met inclusion or exclusion criteria; and there were numerous areas in which documentation was insufficient to support protocol adherence. PI 1 responded to the audit, stating that he did not perform the CT scans because he received less funding than anticipated. We were supplied with no documentation suggesting that the PI obtained IRB approval for modification of the protocol prior to his decision to not perform the CT scans. On April 17, 2006, the RCO requested permission to present the results of the audit even though the IRB had not yet considered the audit results. She made this request because "there were major findings of the protocol not being followed . . . ." The R&D Committee decided to defer evaluation of audit findings to the IRB.

On July 24, 2006, the IRB notified the PI that he could use the data collected "when minor mistakes where [sic] made during the collection of the data." On August 8, 2006, ORO responded to the facility's reporting of audit findings, indicating that, because the IRB accepted the revised research protocol and granted the PI's request to use the data already collected, they believed that sufficient action had been taken to protect human subjects. The IRB made a final determination of noncompliance on August 30, 2007, more than 1 year after the date of the audit. We could not find any reference to what constituted a "minor mistake" for purposes of determining whether data could be used from this study, nor could we determine that the R&D Committee ever addressed this protocol again prior to August 30, 2007.

Issue 4: Other Human Subjects Protections Allegations

In the course of evaluating all of the protocols described in this report, we identified a number of systemic issues which place human subjects at risk. First, we found that PIs were not reliably accounting for subject recruitment, nor were they differentiating between veteran and non-veteran subjects. Many of the protocols we reviewed onsite failed to demonstrate a need for the use of non-veterans in documentation submitted to the IRB, despite recruiting veterans and non-veterans alike. Even during the course of our review, we found that the means of differentiating veterans from non-veterans was often to determine whether the subjects recruited had a medical record at CAVHCS. In addition to being unable to differentiate veteran from non-veteran subjects, we identified other recruitment discrepancies.

Inaccuracies in the Reporting of Subject Recruitment

During the course of examining the muscle biopsy protocols, we noted a discrepancy in the number of subjects reported as being recruited for Protocol M to ORD, and that which had been reported to the IRB. We therefore elected to review the protocols of PI 1 to determine the source of this discrepancy.

Documentation supplied by the CAVHCS RCO revealed that PI 1 was listed as the PI on three protocols and as an individual performing muscle biopsies on an additional four protocols. We requested documentation of PI 1's active studies and received documentation pertaining to eight different studies.

PI 1 received a merit review award for a research proposal in 2003 in the amount of $559,000 for a period of 4 years for Protocol M. When we requested numbers of subjects enrolled in this study, the study coordinator informed the RCO on September 28, 2007, that no subjects were enrolled in this study. Continuing review documents submitted to the affiliate IRB also indicated that there were no subjects enrolled. However, we find that the PI submitted a Human Subjects Enrollment Report to the VA Clinical Science Research and Development Service on March 1, 2007, indicating that 47 patients had been enrolled in the study. The PI added:

> You may wish to note that the funding of my Clinical merit was the basis for data leading up to the funding of two other grants . . . . In addition, my clinical merit provided preliminary data and provoked additional questions that led to a new NIH grant . . . .

The PI listed seven publications as deriving in whole or in part from this data. We requested expenditures for this research project from CAVHCS. Financial documents supplied indicate a deposit of $138,000 on October 1, 2006. Following this deposit, expenditures for laboratory supplies, salaries, and other expenses occurred. On September 27, 2007, the balance in this account had a negative balance of $658.40.

When we discussed these findings with the PI, he stated that the subjects were actually recruited into another study (Protocol N), which was a pilot and separately funded. He also said that a research official at ORD had informed him that it was acceptable to roll these subjects over from the pilot to the active study, and this accounted for the discrepancy. We interviewed the ORD official, who denied having this conversation with the PI.

We requested consent forms for all subjects enrolled in Protocols M or N. We were supplied with 67 consent forms for subjects enrolled under Protocol N, which carried the same name as Protocol M but was listed under a different PI (hereafter PI 2).

Protocol N began as a study funded by a pharmaceutical company. Then, reference is made in a letter dated December 16, 2003, between PI 2 and the IRB to an additional funding source in the form of a merit review grant for this proposal. However, the merit review grant listed PI 1, not PI 2, as the PI for that study. PI 2 is listed as a fellow devoting a 50 percent effort to the study. The PI of Protocol M stated that he was the mentor of PI 2.

Finally, our review disclosed a third proposal of the same name, which received initial approval on November 20, 2001, under PI 1. This study was funded by a non-profit entity and was closed on January 11, 2005. None of the consent forms we were provided with referenced this study. All listed PI 2 as the PI and appeared to refer to Protocol N. We therefore found significant discrepancies in the number of enrolled patients reported to the IRB and to VA's ORD.

Issue 5: Facility Responses to Concerns Raised in Our Initial Review

While we identified many problems in the area of human subjects protections, we find the facility has made significant progress towards remedying some of the issues identified in this report. The leadership today is not the leadership in place when many of these events transpired. The current Medical Center Director became the director on November 26, 2006. Prior to that date, a current VISN Director served in that position from January 9, 2005, through August 18, 2006. The former Chief of Staff retired from the VA May 31, 2007. The current Chief of Staff became Acting Chief of Staff on June 1, 2007, with a permanent appointment effective October 28, 2007. The former ACOS for R&D stepped down from that position on December 24, 2006, after more than a 10-year term in that position.

The new leadership has made significant changes in response to concerns identified during our site visits. On August 23, 2007, ORO directed CAVHCS to ensure that IRB protocol files and relevant IRB meeting minutes were made available to R&D Committee members. ORO also directed the facility to comply with requirements that the IRB approve all planned HUD uses; to notify the IRB of any emergency use of an HUD for an unapproved indication; and to require investigators likely to use HUDs in the future to receive mandatory training.

On August 28, 2007, CAVHCS sent a letter to the Vice-Chancellor for Academic Affairs and Research Administration requiring that the CAVHCS ACOS for R&D and the R&D Committee Chairperson obtain a copy of all audits conducted after January 1, 2007, and identify unanticipated problems and serious or continuing noncompliance. This memorandum also required CAVHCS to develop and implement standard operating procedures for conducting protocol audits and required the IRB to review the results of any such audit within 3 weeks. ORO recommended the addition of a second protocol auditor and that the facility increase the number of audits performed in a memorandum dated August 23, 2007.

On August 30, 2007, CAVHCS was directed to establish its own IRB; to develop an MOU with another VA IRB to use in the interim; and to restrict research activities to include not initiating any new projects or enrolling new subjects, but permitting new grant submissions and the continuation of ongoing treatment studies. A memorandum from the Medical Center Director dated August 31, 2007, communicated these decisions to CAVHCS investigators. As of September 14, 2007, CAVHCS selected its own IRB

Chairperson. From September 18–19, 2007, ORD conducted training sessions for CAVHCS leadership, researchers, information technology staff, IRB members, and R&D Committee members. Ongoing protocols were prioritized with the assistance of ORO for review.

The facility routed protocols for review to another facility, but encountered some difficulties in the transmission of documents and information. This second facility had oversight responsibilities for 12 protocols as of April 8, 2008. CAVHCS formed its own IRB, which began meeting in December 2007. At the time of our last site visit on April 8, 2008, CAVHCS's new IRB had reviewed 93 protocols, and approved 54, with 21 pending approval (they were sent back for additional information or clarification). 18 were in the process of getting IRB approval. Fifty-five protocols had been reviewed by the R&D Committee since obtaining CAVHCS IRB approval.

The affiliate's IRB policies permitted the Vice Chancellor for Academic Affairs and Research Administration or his or her designee to assess incidents of noncompliance and to assign them to categories based on institutional and Federal policies. At the time of our last site visit, the Vice Chancellor was making this determination himself. We were further supplied with correspondence indicating that the affiliate has made numerous improvements in its human subjects protection program since this review began.

Unfortunately, while this transition occurred, the facility ceased conducting protocol audits. We note the absence of any VHA directive or policy specifying the appropriate frequency, contents, or method of selection of protocol audits. In January 2008, the RCO began auditing protocols again. The results of one such audit are presented below.

Follow-Up of Protocol E Since Implementation of the Above Measures

Protocol E, the protocol involving the use of different grafts in coronary artery bypass surgery previously discussed in this report, was suspended by the VA between October and December 2007 as it was transitioned to another VA facility's IRB. It remained open under the affiliate's IRB because the surgical procedures involved in the audit were conducted there. The VA IRB approved it in December 2007. On January 28, 2008, the VA RCO conducted an audit. During the course of that audit, "numerous Serious Adverse Events were discovered as being documented in CPRS." These events had not been reported to the IRB, and included hospitalizations for sternal wound infection, chest pain, atrial flutter, and infection at the graft site.

CAVHCS R&D Committee discussed the findings during the February 25, 2008, meeting. The committee noted that the other VA facility's IRB had not reported their recommendations regarding the audit; they further noted that the affiliate's IRB also had not reported any recommendations. They requested a re-audit in 1 month. The re-audit, conducted on March 27, 2008, could not be completed because the study coordinator did not have regulatory documents prepared for review. The study coordinator was given

until the close of business on April 4, 2008, to reschedule completion of the audit. During the week of April 7–11, 2008, while we were onsite at the facility, we were informed that the study was suspended for continuing noncompliance.

The current CAVHCS IRB consists of seven voting members who were on the affiliate's IRB in August 2007. Four of these remain on both the affiliate and CAVHCS's IRB, including CAVHCS IRB Chairperson. The new members of CAVHCS IRB include two alternating community members and one other investigator. The current R&D Committee consists entirely of members who were also on the R&D Committee in August 2007.

Conclusions

While we found that current facility leadership has made significant improvements to the R&D program, the persistence of problems in Protocol E is of concern, as is the number of findings relative to the 13 different protocols assessed in this report. Many of these deficiencies revolve around informed consent, verification that subjects recruited met inclusion or exclusion criteria, and the reporting of adverse events to the IRB.

As outlined in the FDA audit, Protocols A through C presented significant problems with documentation regarding informed consent, verification that subjects met inclusion and exclusion criteria, and the reporting of adverse events. As we identified in Protocol D, the affiliate IRB knew or should have known of some of these issues, and failed to verify compliance.

Protocol E demonstrated the affiliate IRB's failure to identify and address continuing noncompliance where it existed, while Protocol G reflected a failure to follow-up on serious noncompliance when found in the context of the use of a humanitarian use device. Protocols H and I demonstrate both serious and continuing noncompliance that was not addressed in a timely fashion. While certain PIs had inappropriate scopes of practice at the time of our initial review, we found no evidence that unlicensed personnel performed muscle biopsies or other invasive procedures in Protocols J and K.

In Protocols L and M, however, we did identify discrepancies in the number of subjects recruited as compared to those reported to the IRB and ORD. Because of the number, nature, and severity of some of the issues identified, we are concerned that the R&D program as a whole at this facility may reflect a culture of noncompliance. In addition, the number of members currently on the IRB, who also either currently or formerly served on the affiliate's IRB, is of concern.

Among the PIs discussed in this review, were two individuals who had served for many years in senior leadership positions at CAVHCS, including serving as the Chief of Staff and as ACOS for R&D. It is of particular concern that both of these individuals had every reason to know and understand the requirements of human subject protection at

CAVHCS. In fact, they had responsibility for encouraging and enforcing compliance with VHA policy.

Even with the addition of a second RCO, CAVHCS may lack the resources to audit a representative sample of all research protocols conducted at the facility in a timely fashion to ensure the protection of human subjects. The need to perform these audits is particularly clear when one considers the example of Protocol E described above. Further, documentation discrepancies of the magnitude identified in this report may compromise the validity of research results if they have already been published. Audits are needed to fully assess whether and to what extent CAVHCS may be obligated to notify professional journals of potentially erroneous or non-verifiable results.

Recommendations

Recommendation 1. The Under Secretary for Health should determine if it is appropriate to continue human research at CAVHCS, and if the decision is to continue human research, should provide a plan to ensure that CAVHCS research complies with VHA standards and addresses the issues identified in this report.

Recommendation 2. The Under Secretary for Health should require the VISN Director to take appropriate administrative actions against VHA employees based upon the issues identified within this report.

Comments

The Under Secretary for Health agreed with the findings and recommendations and provided acceptable improvement plans. (See Appendix A, pages 29–32, 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., M.D.
Assistant Inspector General for
Healthcare Inspections

Appendix A

Under Secretary for Health Comments

Department of Veterans Affairs **Memorandum**

Date: July 11, 2008

From: Under Secretary for Health

Subject: **Healthcare Inspection – Human Subjects Protections Violations at the Central Arkansas Veterans Healthcare System, Little Rock, Arkansas**

To: Assistant Inspector General for Healthcare Inspections (54)

1. I have reviewed the draft report and I concur with the recommendations. The report highlights several serious issues in Central Arkansas Veterans Healthcare System's (CAVHCS) research and development (R&D) program that require my continuous attention and oversight. As your report notes, VHA has already made significant progress towards remedying some of the issues identified in this report, and I am encouraged by the progress being made. In addition to those actions identified in your report, VHA Office of Research Oversight (ORO) has conducted six on-site reviews at CAVHCS since August 2007 to ensure implementation of remedial actions and development of an effective human subjects research protection program. These site visits have included a verification of appropriate review of protocols by the newly established CAVHCS Institutional Review Board and the reconstituted CAVHCS R&D Committee. I have directed ORO to continue on-site and remote monitoring of the CAVHCS human subjects research protection program until all remedial actions have been successfully implemented. Upon complete implementation, I will make a final decision on continuing human research at this facility.

2. Additionally, on March 12, 2008, VHA published Directive 2008-014, Auditing of VHA Human Subjects Research to Determine Compliance with Applicable Laws, Regulations and Policies. This new Directive clearly outlines auditing requirements for VA-approved human subjects research and defines responsibilities for each VA facility director for establishing an auditing program within the facility. Compliance with the requirements of this Directive will help prevent the kind of deficiencies that took place at CAVHCS from occurring again in the future.

3. Thank you for the opportunity to review the report. Attached is VHA's complete plan of corrective action. If you have any questions, please contact Margaret Seleski, Director, Management Review Service at (202) 461-8470.

(original signed by)

Michael J. Kussman, MD, MS, MACP

Under Secretary for Health's Comments to Office of Inspector General's Report

The following Under Secretary for Health's comments are submitted in response to the recommendation in the Office of Inspector General's report:

OIG Recommendations

Recommendation 1. The Under Secretary for Health should determine if it is appropriate to continue human research at CAVHCS, and if the decision is to continue human research, should provide a plan to ensure that CAVHCS research complies with VHA standards and addresses the issues identified in this report.

Concur **Target Completion Date:** 12/31/08

Since August 2007, the VHA Office of Research Oversight (ORO) has conducted six on-site reviews at CAVHCS to ensure implementation of remedial actions and development of an effective human research protection program, including a verification of appropriate review of protocols by the newly established CAVHCS Institutional Review Board (IRB) and the reconstituted CAVHCS Research and Development (R&D) Committee. ORO will continue to monitor implementation of remedial actions through weekly conference calls with CAVHS leadership and periodic written reports from the CAVHCS Director. ORO will continue on-site and remote monitoring of the CAVHCS human research protection program until all remedial actions have been successfully implemented.

During this period of continuous monitoring, ORO, VHA Office of Research and Development (ORD), and VHA Office of the Deputy Under Secretary for Health for Operations and Management (ODUSHOM) will continue to discuss CAVHCS' progress and provide input to the Under Secretary for Health in order to ultimately determine if it is appropriate to continue human research at CAVHCS. Commensurate with the OIG's recommendation, if the ultimate decision is to continue human research, VHA will outline a plan to ensure that CAVHCS research complies with VHA standards and addresses the issues identified in this report.

Recommendation 2. Require the VISN Director to take appropriate administrative actions against VHA employees based upon the issues identified within this report.

Concur **Target Completion Date:** 12/31/08

Since most of the employees associated with the issues identified in this report are no longer at the facility, OIG has recently clarified that the recommendation is intended for the [VHA employees] still at the facility. As such, VHA ODUSHOM will work with the VISN Director to take appropriate administrative action against the remaining [VHA employees].

Appendix B

OIG Contact and Staff Acknowledgments

OIG Contact	Andrea Buck, M.D., J.D., Medical Consultant Washington, DC (202) 461-4669
Acknowledgments	Linda Delong, Director Debbie Crawford, Investigator Shirley Carlile, Healthcare Inspector Karen Moore, Associate Director Christa Sisterhen, Associate Director Marilyn Stones, Program Support Assistant Annette Robinson, Healthcare Inspector

Appendix C

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