



Department of Veterans Affairs Office of Inspector General

Healthcare Inspection

Human Subjects Protections in One Research Protocol VA Medical Center, Washington, DC

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Executive Summary

On June 17, 2008, the Office of Inspector General received a letter from Representative Steve Buyer, Ranking Member of the House Committee on Veterans' Affairs, requesting an investigation into the circumstances surrounding the use of a medication called varenicline (Chantix[®]) in a particular research study sponsored by the Veterans Health Administration (VHA). This complaint followed an incident in which a veteran treated at the VA Medical Center in Washington, DC, (VAMCDC) alleged that Chantix[®] caused him to become aggressive and engage in inappropriate activities. The Food and Drug Administration (FDA) had reported the possibility of an association with changes in mood, behavior, or suicidal thoughts and Chantix[®] on November 20, 2007. The FDA upgraded this warning to a public health advisory on February 1, 2008.

To respond to this complaint, we conducted an investigation at VAMCDC, focusing on the timeliness of patient notification following warnings from FDA related to this study, on the adequacy of the informed consent process, and on the reporting of adverse events at the VAMCDC. During the course of our investigation, we also received allegations of inappropriate documentation in connection with this study at the VAMCDC, which are also described in this report.

We found that the VAMCDC Pharmacy Service responded appropriately to FDA communications concerning Chantix[®] in November 2007 and in February 2008 in notifying providers of these newly defined risks. However, we found that the Research Service did not ensure that patients with post-traumatic stress disorder (PTSD) who were also enrolled in a smoking cessation study received adequate and timely notice of these risks. We further found that the facility failed to ensure that patients in this study who had taken Chantix[®] signed an addendum to the consent form disclosing these risks. While the facility mailed information letters to participants in late February or early March 2008, we also noted that the facility did not document or ensure that participants actually received this notification.

The Association for the Accreditation of Human Research Protection Programs, Inc. (AAHRPP), the organization responsible for accrediting VA facilities conducting human subjects research, noted significant deficiencies in informed consent processes and procedures at the VAMCDC as a whole during an October 2007 site visit. We further found that the facility's research compliance program did not conduct protocol audits in accordance with current VHA policy. Finally we found that in at least one instance, a form designed to describe a clinician's interview with a subject was completed from other data rather than from a direct patient interview. Numerous documentation irregularities related to this study at this site were also reported to the Coordinating Center for this study.

Therefore, we made the following recommendations:

Recommendations

Based upon these findings, we made the following recommendations.

Recommendation 1: The Under Secretary for Health will ensure that all patients who currently take Chantix[®] have been informed of the possible association between Chantix[®] and suicidal thoughts.

Recommendation 2: The Under Secretary for Health will develop a formal mechanism for ensuring that Institutional Review Boards are directly notified of FDA communications concerning medications when they are responsible for protocols involving those medications.

Recommendation 3: The Under Secretary for Health will ensure that all patients involved in the smoking cessation study are informed of risks associated with Chantix[®] by VHA study personnel and given the opportunity to sign the addendum to the informed consent disclosing those risks.

Recommendation 4: The Under Secretary for Health will take appropriate administrative action, to include a research misconduct inquiry, based upon the findings contained within this report.

Recommendation 5: The VISN 5 Director will require that the smoking cessation study data collected at VAMC Washington, DC, be validated to ensure its accuracy.

Recommendation 6: The VISN 5 Director will require the medical center director to audit a representative sample of all active protocols involving human subjects for compliance with VHA informed consent requirements, including whether an informed consent can be located for each study participant.

Recommendation 7: The VISN 5 Director will require the medical center director to ensure that protocols are being audited in accordance with VHA Directive 2008-014.

Comments

The Under Secretary for Health concurred with the recommendations in this report and submitted acceptable improvement plans to implement all recommendations. In addition, the Under Secretary made extensive comments concerning the report findings. (See Appendix A, pages 16–25, for the full text of these comments.) Following a careful review of the Under Secretary’s comments and VHA’s action plan to implement our recommendations, we stand behind the findings, conclusions, and recommendations as stated in this report. We will follow up on all corrective actions until the plan has been fully implemented.

(original signed by:)

JOHN D. DAIGH, JR., M.D.
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Part I. Introduction

Purpose

The purpose of this inspection was to determine whether the Veterans Health Administration (VHA) protected human research subjects appropriately following notification from the Food and Drug Administration (FDA) of potentially harmful effects associated with the drug varenicline (Chantix[®]).

Background

On June 17, 2008, the Office of Inspector General received a letter from Representative Steve Buyer, Ranking Member of the House Committee on Veterans' Affairs, requesting an investigation into the circumstances surrounding the use of Chantix[®] in a particular research study sponsored by VHA. Chantix[®] is a medication approved by the Food and Drug Administration (FDA) for use in helping patients to quit smoking. The request followed an incident reported in the media in which a veteran taking Chantix[®] while enrolled in a research study at the VA Medical Center in Washington, DC, (VAMCDC) allegedly experienced an episode of agitated and/or aggressive behavior. The research study enrolling the veteran compared the effectiveness of smoking cessation treatment administered by mental health providers to that administered by primary care providers in patients with post-traumatic stress disorder (PTSD); it will hereafter be referred to as "the smoking cessation study" or "the study."

The protocol, a written document describing the method for conducting the smoking cessation study, stated that patients assigned to mental health providers for their smoking cessation therapy would receive medications for smoking cessation unless contraindications existed. While Chantix[®] was not available when this research study began in 2004, the protocol was modified on January 17, 2007, to include circumstances under which Chantix[®] could be used. Specifically, the protocol indicated that Chantix[®] would be provided, "at the discretion of prescribing clinicians for subjects who cannot tolerate or who have failed adequate trials of other smoking cessation medications." Subjects enrolled were required to have the diagnosis of PTSD and to be actively receiving treatment for that disorder. Subjects could not be enrolled if they had a psychotic disorder not in remission, were at imminent risk for suicide or violence, or had severe psychiatric symptoms.

The Cooperative Studies Program (CSP) provided us with a list of 10¹ different VA medical centers which enrolled patients receiving Chantix[®] in this smoking cessation study. The various sites were overseen by the Cooperative Studies Program (CSP), a VHA program designed to coordinate research occurring at multiple facilities. CSP

¹ Houston, Hampton, Minneapolis, New Orleans, Philadelphia, Portland, Providence, San Diego, Tuscaloosa, and Washington, DC.

maintains five coordinating centers, a clinical research pharmacy, four epidemiological research and information centers, and a health economics resource center. The coordinating centers provide statistical and methodological guidance to VA researchers involved in clinical trials. CSP trials have resulted in numerous important contributions to research, including demonstrating the efficacy of a vaccine for shingles and coordinating multiple trials involving cardiovascular treatments that resulted in major innovations in the treatment of hypertension and coronary artery disease.

The research protocol in question utilized the Palo Alto CSP Coordinating Center (the Coordinating Center). The Coordinating Center received all study data from the sites. It forwarded information pertaining to serious adverse events (SAEs) to the Albuquerque Pharmacy Coordinating Center. In an e-mail of June 20, 2008, CSP reported that as of June 18, 2008, there were 158 subjects nationwide who had received Chantix[®] while enrolled in the research study. This CSP data was based on self-reporting by research subjects during the course of the study. VHA indicated that there is no single data source that can completely and accurately portray actual Chantix[®] use by those in this study. In addition, VHA reported to us that there was a total of 945 subjects in the study nationwide.

CSP had also reported in the June 20, 2008, e-mail that 11 of the VAMCDC subjects received Chantix[®]. However, the senior researcher (also known as the senior investigator (SI)) conducting the smoking cessation study at VAMCDC informed us on June 19 (the date of our first onsite visit), that there were a total of 109 subjects in the study at VAMCDC and that 12 of those 109 subjects received Chantix[®]. Following chart review for these 12 subjects, we found that 1 patient had never actually taken Chantix[®]. Later, on June 27, 2008, the SI informed us of an additional 4 patients at VAMCDC who received Chantix[®] at some time during the course of the study; this made a total of 15 patients who received Chantix[®] as part of this study at VAMCDC. It is these 15 patients whom we discuss throughout this report.

VAMCDC is part of the VA Capitol Health Care Network (Veterans Integrated Service Network (VISN) 5). In addition to acute care services, it maintains a 120 bed long-term care unit and four Community Based Outpatient Clinics. It is affiliated with three medical schools and is a medical readiness partner with three Department of Defense facilities. The VAMCDC also has an active research program, with 70 researchers and 185 active protocols as of June 27, 2008. It also maintains one of two VA War Related Illness and Injury Study Centers.

A. FDA Notifications Pertaining to Chantix[®]

The FDA approved Chantix[®] on May 10, 2006, as an aid for smoking cessation. During pre-marketing studies, more than 4,500 people received Chantix[®]. Recorded adverse psychiatric reactions included frequent anxiety, depression, emotional disorders,

irritability, and restlessness. Initial product labeling did not include any warning regarding any suicidal ideation. VHA added the product to its National Formulary as a third line agent, following failure of nicotine replacement strategies and bupropion, another medication for smoking cessation.

As additional information became available during post-marketing studies, the sponsor modified the patient package insert on November 20, 2007, to include possible adverse reactions such as depression, suicidal thoughts, and agitation. At this time, the FDA issued an “Early Communication About an Ongoing Safety Review” because of post-marketing cases involving suicidal ideation and behavior. This communication specifies that the FDA had not concluded that a causal relationship existed, nor did they advise health care professionals to discontinue the product. On January 31, 2008, in response to additional reported adverse events, the FDA requested that all advertising materials be modified to reflect the additional risks. On February 1, 2008, the FDA issued a public health advisory stating that “. . . it appears increasingly likely that there may be an association between Chantix[®] and serious neuropsychiatric symptoms.”

B. Human Subjects Protections in Research

Determining if and to what extent this public health advisory altered the relative risks and benefits of the smoking cessation study was the responsibility of the facility’s Institutional Review Board (IRB). Each facility in VHA conducting research involving human subjects must have an IRB, which is a committee vested with the responsibility of protecting human research subjects. The IRB is composed of scientists, physicians, and community members. In the VA, the IRB is a subcommittee of the Research and Development (R&D) Committee. Any research project must have both IRB and R&D Committee approval.

In research protocols conducted at multiple sites, each site’s IRB must approve the protocol, as well as any substantive modifications. In approving the protocol, the IRB must determine that the potential benefits outweigh any risks to subjects involved in the research. Further, the IRB must approve any modifications to informed consent and ensure that each protocol has an adequate plan for monitoring the safety of subjects enrolled in the protocol.

IRBs are required to meet regularly and to maintain minutes of those meetings. They must review all protocols at least annually. IRB Chairpersons may unilaterally approve minor changes to previously approved research using expedited review procedures, providing that the IRB reviews these actions at the next regularly convened meeting.

In addition, IRBs review adverse events (AEs) and serious adverse events (SAEs) occurring during the course of research studies. AEs are defined as “any untoward occurrence (physical, psychological, social, or economic) in a human subject participating in research.” SAEs include “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 defects; or an event that jeopardizes the subject and may require medical or surgical treatment to prevent one.”

IRBs do not, however, routinely review files maintained by the researchers, including whether there is a signed informed consent for each research subject. This type of information would be gathered through protocol audits, a process of reviewing the actual implementation of the protocol in accordance with human subjects protections. VHA Directive 2008-014, dated March 12, 2008, mandated that facilities perform such audits. Audit requirements included an evaluation of informed consent. Prior to this Directive, facilities were not required to fully audit research protocols. Rather, IRBs were only required to have a procedure for conducting such audits.

IRBs in VHA are evaluated as part of an accreditation process in VHA. VHA contracted with the Association for the Accreditation of Human Research Protection Programs, Inc. (AAHRPP) to accredit its human subjects protection programs. Accreditation Standards used by AAHRPP include multiple measures of IRB compliance with Federal regulations and VHA policy. They conducted a site visit at the VAMCDC from October 30, 2007 – October 31, 2007. Accreditation was not granted. The facility received a status of Accreditation-Pending and was given the opportunity to submit an Improvement Plan.

Scope and Methodology

To address the concerns regarding the use of Chantix[®] in this research study, we chose to focus our review on issues of informed consent, patient notification of potential adverse effects associated with Chantix[®], and the tracking and reporting of adverse events occurring during the course of this research study. The scope of this review is limited to the VAMCDC. Our first site visit to VAMCDC was on June 19, 2008. While conducting our inspection, we received allegations of potential inappropriate documentation, which we also reviewed.

We addressed issues of informed consent by obtaining study records for the research subjects who we were told received Chantix[®] during the course of the study at VAMCDC. We compared these records to the patients’ electronic medical records. As discussed on page 2 of this report, we had identified 15 patients who had received Chantix[®] at some time during the research. We then attempted to contact 14 of the 15 patients by telephone to determine when and if they had consented to enrollment in a smoking cessation study. As of June 30, 2008, we have been able to speak with 10 of 15 patients; 1 of the 10 was hospitalized and could not be interviewed. An 11th patient was deceased as the result of an unrelated illness. We have called 3 patients whom we have been unable to contact. Therefore, we interviewed 9 of 15, spoke to 1 we could not interview, and were unable to reach 3 of 15; 1 of 15 was deceased as a result of unrelated causes, and 1 we did not attempt to contact.

In addition, we reviewed IRB files, files maintained by the SI at the VAMCDC, e-mail, and pharmacy correspondence pertaining to this protocol. We interviewed the SI, Associate Chief of Staff (ACOS) for Research and Development, the IRB Administrator, study personnel, the research compliance officer, and the Acting Chief of Staff. We obtained and reviewed records from the CSP Coordinating Center in Palo Alto, California, and interviewed staff located at that facility. We reviewed CSP policies and procedures, adverse event reports, and numerous documents from VHA's Office of Research and Development pertaining to the smoking cessation study as conducted by VAMCDC. We also asked the FDA for an opinion regarding whether the November 20, 2007, early communication should have prompted a modification to the protocol. As of the date of this report, we have not received this opinion.

In this report we did not review or comment upon the medical care provided to individual veterans. We reported our findings only in the aggregate form. We performed the inspection in accordance with the *Quality Standards for Inspections* published by the President's Council on Integrity and Efficiency.

Part II. Results and Conclusions

Issue 1: Patient Notification of FDA Communications Concerning Chantix®

The CSP Coordinating Center and the facility's Pharmacy Service appropriately notified providers following the FDA's Early Communication of November 20, 2008. However, following the February 1, 2008, Public Health Advisory, we found that the facility's research service did not ensure that patients involved in the smoking cessation study were notified of the risk of suicidal thoughts or behavior in a timely manner.

The November 20, 2007, Early Communication from FDA

The VAMCDC IRB approved the smoking cessation study on August 16, 2004. The R&D Committee there initially approved the smoking cessation study on August 27, 2004. R&D Committee minutes describe the study as a greater than minimal risk study involving patients with PTSD. The study further required monitoring of PTSD and depression symptoms to determine whether smoking cessation would worsen these conditions.

The IRB re-approved the study under continuing review procedures on July 11, 2005; on May 15, 2006; and on April 9, 2007. The R&D Committee also re-approved the study annually, with the last such approval occurring on April 24, 2008. On April 30, 2007, the IRB approved an amendment to the study, adding Chantix® as a study medication.

Further, the consent form was amended to reflect the risks of Chantix[®] which were known at that time; these included insomnia, unusual dreams, headache, and constipation.

On November 20, 2007, the FDA issued its early communication notifying health care professionals of post-marketing cases involving suicidal ideation and occasional suicidal behavior. The Associate Chief of Pharmacy at the facility received this alert the same day via e-mail through a subscription to a service informing health care professionals of medication alerts. E-mails describing the risks were sent to providers at the facility on November 21, 2007. The Associate Chief of Pharmacy generated lists of patients by prescriber between November 23, 2007, and November 26, 2007, and indicated that these lists were distributed. They were paper rather than electronic, because all the providers at the facility do not have encrypted e-mail to ensure the privacy and security of the patients' personal information. The Chief of Primary Care confirmed that these lists were distributed.

CSP conducted three conference calls with site researchers between November 20, 2007, and December 31, 2007. The first of these conference calls occurred on November 26, 2007. These minutes record the following statement: "...because this is not a drug study, it is not necessary to take action on this [the FDA communication] unless your local IRB requires that you report it to them." On December 3, 2007, minutes reiterate that it was considered the decision of the local IRB as to what actions should be taken following an FDA warning. On December 4, 2007, minutes state the following:

Given that this is not a drug study and use of varenicline is optional, the Chairs don't feel that sites need to inform their IRBs of this issue unless particular subjects report adverse events related to the medication.

On January 18, 2008, a communication from the VHA Pharmacy Benefits Management Service to health care providers stated the following: "FDA's preliminary assessment indicates that many cases presented with new-onset of depressed mood, suicidal ideation, and behavior and emotional changes within days to weeks of starting varenicline [Chantix[®]]." Further, the communication described a warning from the European Medicines Agency of suicidal ideation and suicidal attempt in some patients taking Chantix[®]. The communication recommended that providers "monitor patients taking varenicline for changes in mood and behavior." We could find no documentation that the SI formally reported this to the IRB, or that the IRB addressed any of the events related to the November 20, 2007, communication. Documentation supplied regarding CSP conference calls between November 20, 2007, and December 31, 2007, make it clear that the CSP believed that local IRBs should decide whether this communication warranted action.

This lack of action is concerning, because it is evident that the pharmacy service considered the November 20, 2007, communication important information requiring dissemination to providers and the creation of lists of patients on this medication. This

was particularly important in the smoking cessation study, as it by definition enrolled only those veterans who had PTSD. Because not all the research subjects in the smoking cessation study received their medications from VA providers, and because all providers prescribing Chantix[®] for patients involved in the study were not listed on the protocol, we were unable to determine whether all providers notified patients of these events.

The February 1, 2008, Public Health Advisory

The CSP Coordinating Center and the IRB reacted following FDA's Public Health Advisory of February 1, 2008. Minutes from a February 5, 2008, conference call between study coordinators and assessment technicians and Coordinating Center staff indicated that the new safety information should be passed along to site clinicians to ensure patient notification. The Human Rights Committee at Palo Alto sent a memorandum to the Director of the Coordinating Center on February 8, 2008. This memorandum stated that, "it is appropriate that veterans who are or who might be prescribed this medication while participating in the study be informed, and given the opportunity to discuss alternative treatments with their provider." This memorandum also contained the following statement:

The proposed procedure is that all participants be given the information at their next follow up visit; this will be documented by their signature on the addendum. While this is acceptable for participants who are not receiving the medication, those who are taking varenicline should be notified more urgently.

The CSP Coordinating Center sent a memorandum dated February 13, 2008, to researchers at the VAMCDC stating that patients currently on Chantix[®] "will receive a copy of the consent addendum in the mail, along with a cover letter explaining the reason for the addendum." The Center provided a draft of the letter. The letter described risks of "anxiety, nervousness, tension, and depression as well as untoward changes in behavior." It did not contain any information regarding increased risks of suicidal thoughts or behavior. While the letter did not describe these risks, the informed consent addendum did state that side effects included "thoughts of suicide, and attempted and completed suicide". However, CSP indicated that patients could sign the addendum at their next study visit. The SI at each site was responsible for ensuring that the letters were sent following IRB approval.

The IRB at VAMCDC subsequently met on March 3, 2008. Minutes from that meeting document that the IRB Chair and Administrator met with the SI on February 29, 2008, to discuss patient notification issues following that advisory. The IRB Chair approved the addendum to the consent form addressing these risks by expedited review on the same day. The SI was to notify all study participants by mail with the letter in addition to the informed consent addendum. The SI planned to notify all study participants, whether or

not they were on Chantix[®]. The minutes include the following sentence: “The FDA states that some patients on varenicline [Chantix[®]] have an increased risk of depression and suicidality.” Minutes also state that patient notification issues were reported to the research compliance officer for followup.

We interviewed the SI, IRB Administrator, IRB Chair, and study coordinator for the smoking cessation trial at VAMCDC. The IRB Administrator and Chair indicated that it was the SI’s responsibility to actually send the letters. The SI stated the letters were sent to all 109 participants. The study coordinator reported assisting in this task. The letters were not sent with any return receipt requested, or with any other means of verifying delivery to the appropriate individuals. There was no consistent documentation in the electronic medical record that such letters were sent. We interviewed nine of the patients by phone. Three of these patients recalled receiving a letter. The study coordinator indicated that a few letters came back, but we were unable to locate documentation of any follow-up actions to address these returned letters, or exact numbers of how many were returned.

While we believe these letters were sent, we have no reliable way of determining how many of the veterans actually received notification. Further, we concluded that the letter did not adequately explain the risks associated with Chantix[®] at that time. We were told that the informed consent addendum was included with the letter when the letters were mailed, but we were unable to find any documentation of sending these items to all affected veterans. Therefore, we found that the notification procedures for patients in the smoking cessation study at the VAMCDC following the February 1, 2008, Public Health Advisory did not adequately ensure that all patients were notified of this risk in a timely manner.

On May 30, 2008, VHA’s Pharmacy Benefits Management Service sent an e-mail to VISN formulary leaders and pharmacy chiefs asking them to distribute a letter to veterans taking Chantix[®] that informed them of the risk of suicide associated with the medication. Two of the six veterans who did not recall receiving the initial letter from the SI recalled getting this letter recently.

While the facility’s Pharmacy Service appropriately notified providers of the risks associated with Chantix, we do not find that the research service ensured that subjects enrolled in the smoking cessation study were notified of these risks. We therefore concluded that the facility notified providers of the adverse effects of Chantix[®] in an appropriate and timely manner but did not ensure that patients enrolled in the smoking cessation study received this information.

Issue 2: Adequacy of Informed Consent

Federal informed consent regulations govern the use and participation of human subjects in research. The purpose of the regulations is to safeguard the welfare of humans and to assure that the subjects are given enough information about the research so that they may make informed decisions about whether or not to participate.

Patients enrolling in the smoking cessation study were initially required to sign two consent forms. The first indicated the patient's consent to be screened for the study to determine whether they were eligible. If a patient was found eligible for the study, the patient would then sign a second consent form to participate in the research and be informed of any medications which might be used in the study. Over time there were three versions of this second consent form. The first version, we call "the original second consent form." The second version of this form we refer to as the "revised consent form"; it introduced Chantix[®] to the study and informed the patients of the earliest known risks. The third version of this form we refer to as "the addendum"; it disclosed the greater risks of Chantix[®] as of February 2008.

Thus, the "original second consent form" to participate in the study contained information pertaining to the risks of nicotine patches, nicotine gum, and bupropion, another medication used for smoking cessation. The original second consent did not contain a mention of Chantix[®], which at that time had not yet received FDA approval and was not a part of the research study.

On April 9, 2007, the IRB approved a new second consent form to participate in the study, which is referred to here as the "revised consent" form; it replaced the original second consent. This revised consent form included information on the risks of Chantix[®] that were known at that time, to include changes in dreams and nausea. We reviewed all the consent forms for all 15 patients identified by the SI as being on Chantix[®] at some time during the course of the study. We could locate the revised consent form for only 5 of the 15 patients on Chantix[®]. The SI indicated that patients entering the study after April 9, 2007, were to sign that revised consent form, but that individuals who had already signed the original second consent form were not re-consented during the research study.

Following the February 1, 2008, FDA Advisory, an addendum was created and added to the revised consent form to include information about the risks of suicidal thoughts or behavior for patients taking Chantix[®]. In this report, we refer to the addendum to the informed consent, which is essentially the third version of the second consent form, as "the addendum." The addendum was initially approved through expedited review on February 29, 2008, and disclosed that Chantix[®] could cause "changes in behavior, anxiety, nervousness, tension, depression, thoughts of suicide, and attempted or completed suicide." The SI stated that she mailed the addendum to all patients within the study, not just to those on Chantix[®]. On April 1, 2008, minutes from a CSP conference

call between study personnel and the Coordinating Center indicated that the study coordinator and assessment technician from the VAMCDC site reported that “a number of patients have signed the consent addendum.”

Chantix[®] next appears in the VAMCDC IRB minutes of May 5, 2008. These minutes document a discussion between a patient who experienced an episode of aberrant behavior while on Chantix[®] and the SI and the Chief of Psychiatry. The patient wanted to withdraw from the study and a letter to that effect was signed by these parties and witnessed by the IRB Chair. On May 6, 2008, another CSP conference call occurred in which VAMCDC study personnel stated that they were “actively approaching subjects about the varenicline (Chantix[®]) addendum and obtaining signatures.”

We reviewed only those charts of the 15 patients identified as having taking Chantix[®] at some time during the course of the review. We could locate signed addendums including information about the risks of suicidal thoughts or behavior for only 6 of these 15 patients as of June 23, 2008. Of these 6, only 2 were signed prior to June 20, 2008. We do note that, of the patients without a signed addendum in their chart, one had died as the result of an unrelated illness and another had moved out of the area. Medical records demonstrate that 11 of the 15 patients had visited the medical center between March 3, 2008, and June 20, 2008.

Despite evidence that study personnel at the VAMCDC reported that the consent process was going well on numerous occasions, we found that the facility failed to obtain patient signatures on the addendum to the informed consent describing the risk of suicidal thoughts in patients taking Chantix[®]. Patients also were not re-consented with the April 9, 2007, consent form, which added Chantix[®] to the list of medications already utilized by study prescribers and disclosed risks known to be associated with the drug at that time. Minutes from a June 2, 2008, conference call between CSP and research personnel at the VAMCDC once again record that VAMCDC told the CSP that “[T]he varenicline [Chantix[®]] consent process is going well.”

Further, we found that the facility’s research compliance program failed to appropriately monitor the adequacy of the informed consent process at the facility. The research compliance officer obtained her current position in October of 2007. Since that time, she told us she has “been in training mode.” She reviewed the consent forms for this study but did so only from the perspective of whether the informed consent process was documented appropriately. She did not verify that there were consents for all patients enrolled in this study. AAHRPP noted several deficiencies relating to the informed consent process in its October 2007 visit. Standards described as “NOT MET” by AAHRPP included:

- (1) Researchers “develop an informed consent process and method of documentation appropriate to the type of research and the study population, emphasizing the importance of participant comprehension and voluntary participation.”

- (2) The Research Review Unit has and follows “written policies and procedures requiring that the investigator has and follows a procedure for properly documenting informed consent.”
- (3) The Research Review Unit “reviews the content of the consent process including the consent document, and the process through which informed consent is obtained from each participant, focusing on measures to improve patient understanding and voluntary decision-making.”

We do note, however, that the facility did not receive a copy of the Final Site Visit Report from AAHRPP until March 19, 2008. AAHRPP did not accredit the VAMCDC; rather, they gave it a status of Accreditation Pending. An Improvement Plan is due to AAHRPP on July 14, 2008.

Issue 3: Psychiatric Adverse Events and Serious Adverse Events in Patients Enrolled in the Smoking Cessation Study Receiving Chantix®

We also reviewed whether the VAMCDC appropriately monitored AEs and SAEs occurring during the course of the smoking cessation study. Our review of SAEs was limited to psychiatric events occurring at the VAMCDC in patients who had taken Chantix® at some time during the course of the study. We did not evaluate all adverse events from the VAMCDC or SAEs from any of the other sites.

At the VAMCDC, we found reports for 4 SAEs relating to psychiatric hospitalizations for 3 of the 15 patients; 1 of those patients was on Chantix® at the time. Three SAEs were dated in early 2007; the fourth was in early 2008.

We then sought to determine whether the Coordinating Center had evaluated the communications from FDA in terms of the study results nationwide. We did find that they considered this problem. They initially decided not to change reporting requirements of AEs following the November 20, 2007, communication. Prior to the February 1, 2008, warning, sites were required to report SAEs but not all AEs. However, following the February 1 warning, sites were required to report AEs and SAEs. The Data and Safety Monitoring Board for the nationwide Chantix® study met on February 27, 2008. Minutes from this meeting contain the following statements:

[A Board member] reported that the number of SAEs [includes all SAEs, not just psychiatric SAEs] continues to be high. Often one or two life-threatening events are reported in a day, but most are not study related. . . The study chose to include varenicline [Chantix®] when it became available. [The Board member] noted that the original [market-related] studies [on Chantix®] did not include people with active mental disorders, so we are starting to see the affect [sic] now in our population. We are

asking sites to report these side effects on the SAE forms even if they are only AEs [adverse events].

Also on February 27, 2008, the human rights committee at the CSP Coordinating Center in Palo Alto met and discussed Chantix[®]. Minutes reflect a discussion of the fact that the initial Chantix[®] studies evaluating its safety did not include subjects with comorbid mental health diagnoses. Minutes state that the “study Co-Chairs agreed to check with sites and review how those participants who are taking varenicline, but are not in therapy, are being monitored.” We were not provided with any written documentation regarding if or when this occurred.

Study results provided to us described 25 serious adverse events of a psychiatric nature which occurred while patients were enrolled in the study nationwide. This did not mean that these events were related to the study or that they occurred while the patient was actually taking Chantix[®]. By definition, all patients in the study had pre-existing mental illness. The 25 events disclosed included 16 patients with suicidal ideation; 1 who attempted suicide; and 1 who had homicidal thoughts.

We are concerned, however, by the comment in the Data Safety and Monitoring Board minutes stating that we are seeing the effects now “in our population.” This made the human rights committee decision to review how patients taking Chantix[®] were to be monitored all the more important. However, we do note that data provided reflected that only a single possible Chantix[®]-related event occurred during the course of this study nationwide. Interpreting nationwide data for this study, however, is expressly beyond the scope of this review.

Issue 4: Alleged Documentation Irregularities in the Smoking Cessation Study at VAMCDC

During the course of our review, we received allegations that study personnel had falsified certain study records at VAMCDC. The smoking cessation study required study personnel to fill out a number of written documents based upon direct patient interviews. One such document was the Clinician Administered PTSD Scale (CAPS) form. This is a structured interview used in part to assess the severity of PTSD symptoms in study participants. At VAMCDC the study coordinator could not complete this form because he was not a clinician. The assessment technician typically completed these forms at the VAMCDC.

On June 24, 2008, the ACOS for R&D notified ORO of allegations he received regarding inappropriate documentation of information contained on the CAPS form for two patients associated with the smoking cessation study. It was reported that the study coordinator completed these forms based on information contained in other documents, rather than from a direct patient interview.

We reviewed the CAPS forms, and interviewed the study coordinator. We were unable to interview the assessment technician because of reported health problems. The study coordinator admitted that in two instances, he completed these forms from information obtained from other forms. He further stated that he had the assessment technician on the telephone who offered advice as to how to complete these forms. We verified that in at least one of these instances, the assessment technician was on leave without pay on the day of the patient's visit.

Based upon this information, we conclude that the CAPS form in at least one instance was not completed by a clinician during a direct patient interview as required by the protocol. Further, we were told that this particular record was faxed to the Coordinating Center along with the other data collected at this site. We therefore found that this employee did not complete the form in accordance with the protocol, and we question the accuracy of the data contained on that form.

In addition, we reviewed quality control reports sent from the Coordinating Center concerning their evaluation of study data submitted from the VAMCDC. These reports were provided on a weekly basis. The Coordinating Center reports contain numerous entries concerning VAMCDC's missing pages, missing data, and inconsistent data. While data entry errors are exceedingly common, we are concerned about these reports in light of the information described above.

Conclusions

The actions of study personnel regarding the completion of the smoking cessation study records suggest that the accuracy of such records may be in dispute. Data used in the type of important trials described in this report may be used to define the standard of care for PTSD patients who want to stop smoking. The quality control reports reflect that CSP monitored data submissions regularly. However, the Coordinating Center could not be expected to detect whether the CAPS form was appropriately completed from a direct patient interview or extrapolated from other study data. These kinds of documentation irregularities may affect the credibility of study results. While in this case we have no reason to believe that the problem is not remediable, it reinforces the need for monitoring of data collection and researcher records at a local level.

The human rights committee at the Coordinating Center suggested special monitoring for study subjects taking Chantix[®] and not receiving therapy. We were not able to locate documentary evidence that this recommendation was ever implemented at VAMCDC. Further, the VAMCDC did not initially supply us with an accurate number of patients having ever taken Chantix[®] during the course of the study, suggesting that local sites may not have been tracking which patients were and were not taking Chantix. This makes it unlikely that they ever identified the subgroup of those patients who were not actively receiving therapy while taking Chantix[®].

In addition, the absence of signed informed consent addendums describing the effects of Chantix[®] after they were known to researchers at the VAMCDC is also of concern. While the SI at the VAMCDC did send out a letter in late February or early March 2008 to at least some participants in the study, we have no documentary evidence of who received it or when. This prevents us from ensuring that patients were notified in a timely fashion once side effects of Chantix[®] were known. We also did not find that the letter contained sufficient warning regarding the possible risk of suicidal thoughts or actions, but note that this information was in the enclosed addendum to the consent form.

We also found that the pharmacy service provided timely notification to clinical care providers, including lists of patients on the medication. The VA sent letters dated May 30, 2008, to identified patients on Chantix[®] to alert them to medication side effects. We believe that this was sufficient for the general population of patients in the facility taking Chantix[®]. However, research subjects, who by definition had active PTSD, represented a group uniquely susceptible to neuropsychiatric side effects. We believe that the Coordinating Center recognized this in deciding to modify the informed consent and mail letters to patients. The local implementation of this directive, however, is at issue in that the VAMCDC did not ensure that these patients signed informed consent addendums or received letters notifying them of the additional risks.

Finally, the deficiencies involving informed consent identified in the AAHRPP review suggest that the VAMCDC may not be adequately monitoring the informed consent process on a systemic scale. The scope of this review prevents us from making a definitive statement with regard to the VAMCDC's research program overall, but deficiencies identified in the AAHRPP report suggest that some issues may be systemic in nature. Therefore, we make the following recommendations:

Recommendations

Recommendation 1: The Under Secretary for Health will ensure that all patients who currently take Chantix[®] have been informed of the possible association between Chantix[®] and suicidal thoughts.

Recommendation 2: The Under Secretary for Health will develop a formal mechanism for ensuring that Institutional Review Boards are directly notified of FDA communications concerning medications when they are responsible for protocols involving those medications.

Recommendation 3: The Under Secretary for Health will ensure that all patients involved in the smoking cessation study are informed of the risks associated with Chantix[®] by VHA study personnel and given the opportunity to sign the addendum to the informed consent disclosing those risks.

Recommendation 4: The Under Secretary for Health will take appropriate administrative action, to include a research misconduct inquiry, based upon the findings contained within this report.

Recommendation 5: The VISN5 Director will require that the smoking cessation study data collected at VAMC Washington, DC, be validated to ensure its accuracy.

Recommendation 6: The VISN 5 Director will require the medical center director to audit a representative sample of all active protocols involving human subjects for compliance with VHA informed consent requirements, including whether an informed consent can be located for each study participant.

Recommendation 7: The VISN 5 Director will require the medical center director to ensure that protocols are being audited in accordance with VHA Directive 2008-014.

Under Secretary for Health Comments

**Department of
Veterans Affairs**

Memorandum

Date: July 30, 2008

From: Under Secretary for Health (10)

Subj: OIG Draft Report, *Healthcare Inspection – Human Subjects Protections in One Research Protocol*, VA Medical Center, Washington, DC, Project No. 2008-02346-HI-0140 (WebCIMS 408201)

To: Assistant Inspector General for Healthcare Inspections (54)

1. I have reviewed the draft report, and I concur with the recommendations. While I strongly believe that VA has an outstanding research program, it is evident that the circumstances involved in this case have resulted in veterans who believe that they have been improperly treated, and I regret the extent to which our actions may have contributed to that belief. This draft report cites valuable opportunities for improvement, and I will utilize your recommendations to ensure the best, most ethical and safest scientific inquiries into the health care needs of our Nation's veterans.

2. While I concur with the recommendations, there are a number of comments I would like to make concerning the report findings. First, in considering the events surrounding this study, it is important to emphasize that this research project is not a drug study. It is an examination of the most effective treatment for heavy smokers who have post-traumatic stress disorder (PTSD), using medications approved by the Food and Drug Administration (FDA). The specific drug that is the focus of your report, Chantix®, is in fact considered to be the most effective medication available for smoking cessation. Any veterans receiving Chantix® in the study, or anywhere in VA, have been prescribed this drug by their doctors following an individual doctor-patient decision, with continued monitoring of the patient's health status. When information suggested that some patients taking Chantix® experienced potential psychological side effects, VA promptly notified its clinical providers. VA also sent letters discussing possible side-effects to every individual participating in the study, as well

as to every veteran prescribed Chantix® by VA. Within this letter, VA encouraged all patients to contact their provider immediately if they experienced side effects and assured them that VA will help them find another way to quit smoking if they are concerned about Chantix® or are experiencing side effects. As far as I am aware, VA is the only health care organization that notified patients following issuance of FDA's Public Health Advisory on February 1, 2008, despite no requirement to do so.

3. I am also concerned that your presentation of particular findings in the report may lead readers to misinterpret VHA's actions related to this research protocol. The draft report concludes that the Washington, DC VA Medical Center (VAMCDC) did not ensure that patients with PTSD, who were also enrolled in a smoking cessation study, receive adequate and timely notice of the risks associated with Chantix®.

FDA did not require that notifications be made to patients on Chantix®; nevertheless, given the vulnerability of the patients in the study, the VAMCDC Research Service took positive action to notify patients of the risks involved. The senior investigator (SI) and study coordinator conducting the smoking cessation study at VAMCDC indicated that they mailed out letters and informed consent addendums describing the risks associated with taking Chantix® to all 109 participants in the study, including the 16 patients who were prescribed Chantix®. You acknowledged that you believe VA did send out these patient notifications.

4. Your report also finds fault with the adequacy of our patient notification and concludes that the notification procedures following the FDA February 1, 2008, Public Health Advisory did not adequately explain the risks associated with Chantix®. Your conclusion is based upon the finding that while the letter described risks of anxiety, nervousness, tension, and depression as well as untoward changes in behavior associated with taking Chantix®, only the informed consent addendum contained information regarding increased risks of suicidal thoughts or behavior. While the argument that inclusion of information regarding increased risks of suicidal thoughts or behavior in both the letter and the informed consent addendum would have resulted in a stronger notification may have some validity, I believe that since the addendum included the information and the addendum was a part of the notification package, our notification was appropriate.

5. Additionally, the draft report finds fault with the timeliness of our patient notification and concludes that while VAMCDC's Pharmacy Service appropriately and timely notified providers of the risks associated with Chantix®, the facility did not ensure that patients enrolled in the study

received this information in a timely manner. Following the FDA's February 1, 2008 Public Health Advisory, by February 13, 2008, the Cooperative Studies Program (CSP) Coordinating Center drafted the notification letter and informed consent addendum for submission to the facility's Institutional Review Board (IRB), which has sole authority to approve any modifications to informed consent and patient communications. Realizing the importance of this notification, the IRB Chair and Administrator met with the SI on February 29, 2008, to expedite review and approval of the notification letter, addendum, and subsequent patient notification. The SI mailed out the notifications on March 3, 2008. I believe that this timeline and expedited IRB approval process indicate that VAMCDC's Research Service acted appropriately and timely notified patients of the risks associated with Chantix®.

6. In regards to your finding that VAMCDC failed to ensure that patients in this study who had taken Chantix® signed an addendum to the consent form disclosing these risks, I agree that a stronger effort to follow-up with these patients was warranted. Since the discovery that not all 16 veterans who were prescribed Chantix® at any time signed the addendum, VAMCDC has worked diligently to try to obtain the remaining signatures. To date, the facility has documented that 10 of the 16 veterans have signed the addendum. The facility also verified that none of the 16 patients have active Chantix® prescriptions, and has no reason to believe that any of these patients are currently taking the drug. Of the six patients that have not signed the addendum: one is deceased; one moved to Florida, but has an appointment to come to VAMCDC to sign the addendum when visiting the DC area in August 2008; one withdrew from the study on May 2, 2008; two have appointments to come to the VAMCDC and sign the addendum, but have not yet reported for those appointments; and one, VAMCDC has not been able to make direct contact with despite repeated phone call, emails, and letters. It is also important to note that for the two patients who have appointments to sign the consent addendum, there have been no study related visits since mailing of the information letter and addendum on March 3, 2008. VAMCDC personnel continue to work diligently to reach these remaining three individuals and obtain the signed addendums.

7. Your report also states that the Association for the Accreditation of Human Research Protection Programs, Inc. (AAHRPP), the organization responsible for accrediting VA facilities conducting human subjects research, noted significant deficiencies in informed consent processes and procedures at the VAMCDC as a whole during an October 2007 site visit. I believe that the characterization of AAHRPP's review resulting in "significant deficiencies" is not an appropriate one. It would be more

accurate to state that AAHRPP found deficiencies at VAMCDC related to the lack of certain elements of disclosure in the consent template, documentation of its informed consent processes, and the consistency of its informed consent policies. In response to the AAHRPP's review, VAMCDC revised all informed consent templates and policies to adhere to AAHRPP's recommendations and has addressed all previously-cited elements in the Improvement Plan that it submitted to AAHRPP on July 14, 2008.

8. The draft report further states that AAHRPP accreditation was not granted to VAMCDC, and that the facility received a status of Accreditation Pending. While this is a true statement per se, I believe the report does not provide enough context regarding VAMCDC's accreditation status to give the reader a full understanding. AAHRPP has four accreditation categories: Full Accreditation, Qualified Accreditation, Accreditation Pending, and Accreditation Withheld. It is important to point out that AAHRPP did not place the VAMCDC in its Accreditation Withheld category. Instead AAHRPP placed VAMCDC in its Accreditation Pending category. This is not uncommon as 62 percent of VA facilities receive Accreditation Pending status following an AAHRPP visit.¹ By assigning VAMCDC this category, AAHRPP indicates that the organization is able and willing to commit to take corrective actions to meet the criteria for accreditation within a reasonable time period. Thus, it would be more accurate for the report to state that VAMCDC's AAHRPP accreditation is still in process.

9. Regarding, the report's conclusion that VAMCDC's research compliance program did not conduct protocol audits in accordance with VHA Directive 2008-014, Auditing of VHA Human Subjects Research to Determine Compliance with Applicable Laws, Regulations, and Policies, I must point out that VHA issued this policy on March 12, 2008, and implementation of new policy requires an adequate period of time. This directive, as you correctly point out, mandates that facilities conduct protocol audits. Prior to issuance of this directive, there was no such mandate; the only requirement was that each IRB have a procedure for conducting such audits. In response to this previous requirement, VAMCDC has had a research compliance program and procedures for conducting protocol audits since 2003. VAMCDC conducted a full audit on this protocol on

February 23, 2006, and found that all required original consents were present. Furthermore, VAMCDC has continuously audited consents as part

¹ Figure provided by VHA Office of Research and Development Program for Research Integrity Development & Education (PRIDE).

of an ongoing process, and previous consents have been found to be present for all participants in this protocol. Nonetheless, I agree that the Medical Center could improve how it monitors the adequacy of the informed consent process. I believe that VAMCDC leadership is taking the necessary actions to ensure that this takes place. Specifically, Medical Center leadership fully implemented VHA Directive 2008-014 on June 18, 2008, and appointed the Chief of Staff, who oversees the Research Compliance Office, as the official responsible for the auditing program.

10. In regards to the report's finding that in at least one instance, a form designed to describe a clinician's interview with a subject was completed from other data rather than from a direct patient interview, I request that you acknowledge that this is an allegation at this time. After the SI became aware of this allegation, she promptly notified all of the appropriate VA authorities. In response, VHA Office of Research Oversight (ORO) instructed VAMCDC to initiate a Research Misconduct Inquiry in accordance with VHA Handbook 1058.2, Research Misconduct. VAMCDC initiated an inquiry on July 1, 2008, and will report its findings to ORO by July 31, 2008.

11. 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 (10B5) at (202) 461-8470.

(original signed by:)

Michael J. Kussman, MD, MS, MACP

Attachment

**VETERANS HEALTH ADMINISTRATION
Action Plan**

**OIG Draft Report, Healthcare Inspection: Human Subjects Protections
in One Research Protocol, VA Medical Center, Washington, DC
Project No. 2008-02346-HI-0140**

| Recommendations/ Actions | Status | Completion Date |
|-----------------------------|--------|--------------------|
|-----------------------------|--------|--------------------|

We recommended that the Under Secretary for Health will:

Recommended Improvement Action(s) 1: Ensure that all patients involved in the smoking cessation study who currently take Chantix® have been informed of the possible association between Chantix® and suicidal thoughts.

Concur

VA sent letters to every patient prescribed Chantix® by VA to inform them of the possible association between Chantix® and suicidal thoughts. Within this letter, VA encouraged all patients to contact their provider immediately if they experienced side effects and assured them that the VA will help them find another way to quit smoking if they are concerned about Chantix® or are having side effects. Currently, there are 40 study patients in VA who are currently taking Chantix®, and VA will continue to closely monitor all of them.

Completed

7/8/08

Recommended Improvement Action(s) 2: Develop a formal mechanism for ensuring that Institutional Review Boards are directly notified of FDA communications concerning medications when they are responsible for protocols involving those medications.

Concur

VHA Office of Research and Development (ORD) is currently developing a directive that will address the direct notification of Institutional Review Boards (IRB) in the event of FDA communications concerning medications in which they are responsible for protocols involving those medications. After issuance of the directive, ORD will ensure that each medical center's

Research Service, Pharmacy Service, and Institutional Review Board are fully aware of and understand the tenets of the new directive.

In Process

9/30/08

Recommended Improvement Action(s) 3: Ensure that all patients involved in the smoking cessation study are informed of the risks associated with Chantix® by VHA study personnel and given the opportunity to sign the addendum to the informed consent disclosing those risks.

Concur

VA sent letters to every patient prescribed Chantix® by VA to inform them of the risks associated with Chantix®. Within this letter, VA encouraged all patients to contact their provider immediately if they experienced side effects and assured them that the VA will help them find another way to quit smoking if they are concerned about Chantix® or are having side effects. VA will continue to work diligently to obtain signed addendums for those patients prescribed Chantix® that have not yet signed the addendum. All study sites will inform VHA Office of the Deputy Under Secretary for Health for Operations and Management when this action is complete.

In Process

7/31/08

Recommended Improvement Action(s) 4: Take appropriate administrative action, to include a research misconduct inquiry, based upon the findings contained within this report.

Concur

The Secretary of Veterans Affairs directed VHA Office of Research Oversight (ORO) to conduct a comprehensive review of CSP Protocol #519, Integrating Practice Guidelines for Smoking Cessation into Mental Health Care for Posttraumatic Stress Disorder (PTSD). This was completed on July 18, 2008. Furthermore, ORO is currently coordinating a comprehensive review of all VHA research studies involving individuals with PTSD. The purpose of this review is to ensure (a) appropriate sensitivity to the PTSD study population; (b) consideration of relevant Food and Drug Administration (FDA) or Sponsor advisories, alerts, and warnings; (c) appropriate subject notification regarding such advisories, alerts, and warnings; and (d) review of risks associated with medications

likely to be used in the PTSD study population. This comprehensive review is projected for completion by August 25, 2008.

Lastly, ORO is exercising oversight of formal Research Conduct proceedings in this case in accordance with VHA Handbook 1058.2, Research Misconduct. Washington DC VA Medical Center (VAMCDC) initiated this Research Misconduct Inquiry on July 1, 2008, and it is projected for completion by July 31, 2008. The Medical Center Director chartered a committee to conduct the inquiry. The committee will present the results of its inquiry to the VAMCDC Research Integrity Officer, Medical Center Chief of Staff, Veterans Integrated Service Network (VISN) Office, and Medical Center Director. ORO will also review the results. If the inquiry finds the allegation has substance, VAMCDC will conduct a full investigation, which they have 90 days to complete. If the investigation finds misconduct, the next step is adjudication by the VISN Director, followed by ORO Review.

In Process

12/15/08

We recommended that the VISN Director will:

Recommended Improvement Action(s) 5: Require that the smoking cessation study data collected at VAMC Washington, DC, be validated to ensure its accuracy.

Concur

Consistent with VHA Office of Research Oversight's (ORO) comprehensive review of all VHA research studies involving individuals with post-traumatic stress disorder (PTSD), the Director, Washington, DC VA Medical Center (VAMCDC), has appointed three voting members from the Institutional Review Board (IRB) Committee and/or Research and Development (R&D) Committee to validate the accuracy of all data from the smoking cessation study (CSP 519). This panel will present the results of its review to the VAMCDC Associate Chief of Staff for Research, IRB Committee, R&D Committee, Medical Center Chief of Staff, Veterans Integrated Service Network (VISN) Office, and the Medical Center Director. VAMCDC will complete its audit no later than August 1, 2008. VISN 5 will also perform an audit of the VAMCDC smoking cessation study for data accuracy. The VISN will complete its audit no later than August 15, 2008. VAMCDC and VISN 5 will report the results of the reviews to ORO upon completion.

In Process

8/15/08

Recommended Improvement Action(s) 6: Require the medical center director to audit a representative sample of all active protocols involving human subjects for compliance with VHA informed consent requirements, including whether an informed consent can be located for each study participant.

Concur

The Director, Washington, DC VA Medical Center (VAMCDC), instructed the Institutional Review Board (IRB) Administrator to initiate a review of signed informed consents related to 548 research participants at VAMCDC for the period of January 1, 2007 – July 3, 2008. The IRB Administrator assembled an audit team and reviewed all research protocols. The IRB Administrator will present the results of this audit to the Associate Chief of Staff of Research, IRB Committee, Research and Development Committee, Medical Center Chief of Staff, Veterans Integrated Service Network (VISN) Office, and Medical Center Director. VAMCDC will complete its audit no later than August 5, 2008. VISN 5 will also perform an audit of the VAMCDC informed consent protocol for human subjects. The VISN will complete its audit no later than August 15, 2008. VAMCDC and VISN 5 will report the results of these reviews to VHA Office of Research Oversight upon completion.

In Process

8/15/08

Recommended Improvement Action(s) 7: Require the medical center director to ensure that protocols are being audited in accordance with VHA Directive 2008-014.

Concur

Washington, DC VA Medical Center (VAMCDC) Research Compliance Officer will complete protocol audits in accordance with VHA Directive 2008-014, Auditing of VHA Human Subjects Research to Determine Compliance with Applicable Laws, Regulations, and Policies, and will certify the conduct and results of all audits to the Medical Center Director. VAMCDC Research Compliance Officer began protocol audits on July 15, 2008, and will present the results of existing protocol audits to the Associate Chief of Staff of Research, Institutional Review Board (IRB) Committee, Research and Development (R&D) Committee, Medical Center Chief of Staff, Veterans Integrated Service Network (VISN) Office, and Medical Center Director. VISN 5 will also perform an audit of VAMCDC's compliance with VHA Directive 2008-014. The VISN will complete its audit no later than September 15, 2008. VISN 5 will report the

results of the reviews to VHA Office of Research Oversight upon completion.

In Process

9/15/08 and On-going

OIG Contact and Staff Acknowledgments

| | |
|-----------------|---|
| OIG Contact | Andrea Buck, M.D., J.D. Medical Consultant (202)-461-4669 |
| Acknowledgments | Randall Snow, J.D. Associate Director, Washington, DC, Regional Office Donna Giroux, Healthcare Inspector Nelson Miranda, Director of Washington, DC, Regional Office |

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