

**STATEMENT OF  
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DEPARTMENT OF VETERANS AFFAIRS  
BEFORE  
COMMITTEE ON VETERANS' AFFAIRS  
UNITED STATES HOUSE OF REPRESENTATIVES  
HEARING ON  
"WHY DOES THE VA CONTINUE TO GIVE SUICIDE-INDUCING  
DRUG TO VETERANS WITH PTSD"  
JULY 9, 2008**

Mr. Chairman and Members of the Committee, thank you for the opportunity to testify today on whether the Veterans Health Administration (VHA), Department of Veterans Affairs (VA), protected human research subjects appropriately following notification from the Food and Drug Administration (FDA) of potentially harmful effects associated with the drug varenicline (Chantix<sup>®</sup>). Accompanying me today is Dr. Andrea Buck and Mr. Randall Snow.

Chantix<sup>®</sup> is a medication approved by FDA for use in helping patients to quit smoking. Concerns involving the use of Chantix<sup>®</sup> escalated following an incident reported in the media in which a veteran taking Chantix<sup>®</sup> while enrolled in a VHA research study at the Veterans Affairs Medical Center, Washington, DC (VAMCDC) allegedly experienced an episode of agitated and/or aggressive behavior.

To address concerns regarding the use of Chantix<sup>®</sup>, we focused our review on issues of informed consent, patient notification of potential adverse effects associated with Chantix<sup>®</sup>, and the tracking and reporting of adverse events occurring during the course of the research study. The scope of our review was 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.

The Office of Inspector General initiated this review in response to requests from this Committee and other Members of Congress. My statement today is based on the results of our review, which have been provided to VHA in a draft report for comment. Until we receive VHA's official response and issue the final report, our findings are subject to further clarification.

## **BACKGROUND**

The VHA 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<sup>®</sup> was not available when this research study began in 2004, the protocol was modified on January 17, 2007, to include circumstances under which Chantix<sup>®</sup> could be used. Specifically, the protocol indicated that Chantix<sup>®</sup> 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 10<sup>1</sup> different VA medical centers which enrolled patients receiving Chantix<sup>®</sup> 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 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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup>. 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<sup>®</sup>. Following chart review for these 12 subjects, we found that 1 patient had never actually taken Chantix<sup>®</sup>. Later, on June 27, 2008, the SI informed us of an additional 4 patients at VAMCDC who received Chantix<sup>®</sup> at some time during the course of the study; this made a total of 15 patients who received Chantix<sup>®</sup> 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.

### **FDA Notifications Pertaining to Chantix<sup>®</sup>**

The FDA approved Chantix<sup>®</sup> on May 10, 2006, as an aid for smoking cessation. During pre-marketing studies, more than 4,500 people received Chantix<sup>®</sup>. Recorded adverse psychiatric

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

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<sup>®</sup> and serious neuropsychiatric symptoms.”

### **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<sup>®</sup> in this research study, we chose to focus our review on issues of informed consent, patient notification of potential adverse effects associated with Chantix<sup>®</sup>, 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<sup>®</sup> 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<sup>®</sup> 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 11<sup>th</sup> 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 draft, we have not yet 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.

## RESULTS

### 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 by the date of this draft report 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<sup>®</sup>. The minutes include the following sentence: “The FDA states that some patients on varenicline [Chantix<sup>®</sup>] 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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup>, 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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup>. 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<sup>®</sup>. 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<sup>®</sup> 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<sup>®</sup>. 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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup>) addendum and obtaining signatures.”

We reviewed only those charts of the 15 patients identified as having taking Chantix<sup>®</sup> 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<sup>®</sup>. 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 AEs and SAEs 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<sup>®</sup>] when it became available. [The Board member] noted that the original [market-related] studies [on Chantix<sup>®</sup>] 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<sup>®</sup>. Minutes reflect a discussion of the fact that the initial Chantix<sup>®</sup> 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<sup>®</sup>. 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<sup>®</sup> were to be monitored all the more important. However, we do note that data provided reflected that only a single possible Chantix<sup>®</sup>-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.

## **CONCLUSION**

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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup>.

In addition, the absence of signed informed consent addendums describing the effects of Chantix<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> to alert them to medication side effects. We believe that this was sufficient for the general population of patients in the facility taking Chantix<sup>®</sup>. 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**

1. The Under Secretary for Health will ensure that all patients who currently take Chantix<sup>®</sup> have been informed of the possible association between Chantix<sup>®</sup> and suicidal thoughts.
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.
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<sup>®</sup> by VHA study personnel and given the opportunity to sign the addendum to the informed consent disclosing those risks.
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.
5. The VISN5 Director will require that the smoking cessation study data collected at VAMC Washington, DC, be validated to ensure its accuracy.
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.
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.

Mr. Chairman, in closing, I would like to once again thank you and the other Members of the Committee for the opportunity to testify on this important matter. Dr. Buck, Mr. Snow, and I would be pleased to answer any questions.