# OFFICE OF RESEARCH OVERSIGHT
## Report to the
## Office of Special Counsel
## OSC File Number DI-12-1098

## Department of Veterans Affairs
## VA Boston Healthcare System
## Boston, MA

## Veterans Health Administration
## Washington, DC

## Report Date: June 4, 2012

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# Report to the Office of Special Counsel

## OSC File Number DI-12-1098
## Regarding the
## VA Boston Healthcare System
## Boston, Massachusetts

## On-Site Review Dates: May 1-3, 2012
## Date of Report: June 4, 2012

## EXECUTIVE SUMMARY

### INTRODUCTION

The Veterans Health Administration (VHA) Office of Research Oversight (ORO) conducted a Focused For-Cause Review of the conduct of VA Cooperative Studies Program (CSP) Protocol #562 *(The VA Keratinocyte Carcinoma Chemoprevention Trial)* at the VA Boston Healthcare System (VABHS) in Boston, Massachusetts. The on-site portion of this review occurred on May 1 – 3, 2012.

ORO's review was predicated on a whistleblower disclosure, referred to VA by the United States Office of Special Counsel (OSC) on April 4, 2012, concerning possible "violations of law, rule, or regulation and a substantial and specific danger to public health or safety" in accordance with Title 38 United States Code (38 U.S.C) §1213(a) and §1213(b). The disclosure was comprised of three allegations:

1. The Principal Investigator (PI) manipulated the research process of a VA skin cancer prevention clinical trial by instructing the Whistleblower to conduct skin examinations for research purposes in violation of protocol requirements.

2. The PI falsified data in this clinical trial by recording that she, rather than the Whistleblower, had conducted required research skin examinations.

3. The PI's research misconduct could lead to the improper approval by the Food and Drug Administration (FDA) of the drug studied in the clinical trial for use as a skin cancer preventative medication.

The purpose of ORO's review was to assess the nature and scope of the alleged violations, including possible **research misconduct** *(i.e., fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results)* and/or other **research impropriety** *(i.e., noncompliance with the laws, regulations, and policies regarding human subject protections,* etc.*)* as applicable to VA research (VHA Directive 1058 §6.g and §6.h).

## FINDINGS AND REQUIRED ACTIONS

ORO determined on April 16, 2012, that the allegations referred to VA by OSC did not fall within the Federal and VA policy definition of **research misconduct** (Volume 65 Federal Register (65 FR) 76260, December 6, 2000, and VHA Handbook 1058.2 §3) and, therefore, did not meet the threshold for initiating a research misconduct inquiry (VHA Handbook 1058.2 §13.e).

ORO further determined, however, that the allegations did warrant investigation as possible **research impropriety** and initiated a Focused For-Cause Review of the implementation of CSP #562 at the VABHS.

ORO interviewed key personnel and reviewed all research records related to CSP Protocol #562, including case records of all 61 enrolled subjects and relevant Computerized Patient Record System (CPRS) records (i.e., medical records) of selected subjects.

### Policy Concerns

ORO did not find a violation, or apparent violation, of any law, rule or regulation, nor was there a substantial and specific danger to public health. However, ORO did identify the following concerns regarding compliance with VA policy:

**1. The PI did not fulfill all responsibilities required of investigators.**

VHA Handbook 1200.05 includes the following investigator responsibilities:

> *§9e. Overseeing the Research Staff. This means overseeing and being responsible for ensuring the research staff under the investigator's direction comply with all applicable requirements including, but not limited to, implementing the research study in accordance with the approved protocol.*
>
> *§9.h. Implementing the Study as Approved. This means ensuring the study is implemented as approved by the IRB and in accordance with other required approvals and with all applicable local, VA, and other Federal requirements including, when applicable, those for research involving investigational drugs (see par. 39) or investigational devices (see par. 40).*
>
> *§9.q. Reporting Deviations and Complaints. This means reporting deviations from the protocol and subject complaints to IRB in a time frame specified in local SOPs.*

Specifically, ORO found that the PI did not oversee research staff sufficiently to ensure that CSP Protocol #562 was implemented in accordance with the approved protocol:

a. Having acknowledged Research Progress Notes indicating that the Un-Blinded AE Assessor had conducted full body skin examinations for research purposes,

the PI did not identify this practice as a protocol deviation and did not intervene to ensure protocol compliance by study staff.

b. The PI did not ensure that the required full body skin exam was documented prior to enrollment of at least one subject.

c. The PI did not ensure adherence to the protocol's "un-blinding" procedures.

d. The PI did not ensure that the study drug was prescribed only by an authorized provider.

**2. The VABHCS HRPP did not ensure compliance with all applicable VA research requirements.**

Specifically, ORO found that the Research Pharmacist dispensed the study drug to 20 subjects enrolled in CSP Protocol #562 on the basis of prescriptions from an unauthorized provider.

## Conclusions

ORO reached the following conclusions based on its review:

1. ORO was unable to determine whether the PI instructed the Whistleblower to perform full body skin examinations for research purposes (Allegation #1). However, ORO found that, having acknowledged Research Progress Notes indicating that the Whistleblower had conducted such skin examinations, the PI did not identify this practice as a protocol deviation and did not intervene to ensure protocol compliance by study staff.

2. ORO was unable to determine whether the PI falsified data in this clinical trial by recording that she, rather than the Whistleblower, had conducted research skin examinations (Allegation #2). However, ORO found that, in at least one instance, a subject was enrolled into CSP Protocol #562 prior to documentation by the PI that she had conducted the required skin exam.

3. Regarding the allegation of research misconduct (Allegation #3):

    a. ORO determined that the allegations as presented in the whistleblower disclosure did not fall within the Federal and VA policy definition of **research misconduct** and, therefore, did not meet the threshold for initiating a research misconduct inquiry. In reaching this determination, ORO noted that the PI's actions were not alleged to have resulted in an inaccurate representation of the ***scientific data or results*** obtained in CSP Protocol #562 (see Appendix 3).

    b. Relative to the allegation that the PI's actions could lead to improper approval of the study drug by FDA, the findings of ORO's Focused For-Cause Review did not suggest that the ***scientific data or results*** obtained in CSP Protocol #562 at VABHS were inaccurately represented.

4. ORO determined that noncompliance with VA requirements identified during its Focused For-Cause review warranted remedial action.

## Required Actions

The VABHS must provide ORO with a written Remedial Action Plan detailing specific steps and an implementation schedule to address each of the following Required Actions. The plan should be received by the ORO Central Office within 30 days after this report is transmitted to the facility.

1. The VABHS must ensure that all research currently involving the PI and the Study Coordinator (SC) adheres to the IRB-approved protocol and complies with all applicable VA research requirements by implementing an appropriate monitoring plan for their research.

2. The VABHS must ensure that all of its research studies are conducted according to the IRB-approved protocols and all relevant Federal regulations and VHA Policies.

3. The VABHS must ensure that pharmacy personnel dispense study medications only when prescribed by authorized prescribers.

4. The VABHS must determine whether any disciplinary action is warranted in light of ORO's findings.

VA will provide the Remedial Action Plan to OSC upon receipt and will update OSC as remedial actions are implemented.

# Report to the Office of Special Counsel

## OSC File Number DI-12-1098
## Regarding the
## VA Boston Healthcare System
## Boston, Massachusetts

## On-Site Review Dates: May 1-3, 2012
## Date of Report: June 4, 2012

## I. INTRODUCTION

The Office of Research Oversight (ORO) serves as the primary Veterans Health Administration (VHA) office for advising the Under Secretary for Health (USH), and for exercising oversight concerning all matters of research compliance and assurance in VA research, including human subject protections, laboratory animal welfare, research safety, research laboratory security, research information protection, research misconduct, and Governmentwide debarment for research impropriety. ORO is also responsible for developing and conducting VHA research compliance officer (RCO) education programs.

ORO conducted a Focused For-Cause Review of VA Cooperative Studies Program (CSP) Protocol #562 *(The VA Keratinocyte Carcinoma Chemoprevention Trial)* as implemented at the VA Boston Healthcare System (VABHS). The on-site portion of this review was conducted on May 1-3, 2012.

ORO's review was predicated on a whistleblower disclosure, referred to VA by the United States Office of Special Counsel (OSC) on April 4, 2012, concerning possible "violations of law, rule, or regulation and a substantial and specific danger to public health and safety" in accordance with Title 38 United States Code (38 U.S.C) §1213(a) and §1213(b).

## II. VABHS PROGRAM OVERVIEW

The VABHS, consisting of three campuses (Jamaica Plain, West Roxbury, and Brockton), is a tertiary care facility, academically affiliated with the Harvard Medical School and the Boston University School of Medicine, both in Boston. It conducts a research program involving human subjects as well as laboratory animals and hazardous chemicals, with a budget of approximately $58.4 million in FY2011, of which approximately $32.7 million came from the VA Office of Research and Development (ORD). The program includes approximately 780 active research protocols, including 585 studies involving human subjects, conducted by approximately 274 PIs.

The VABHS maintains its own Research and Development Committee (R&DC) and its own Institutional Review Board (IRB) for oversight of research involving human subjects. It also utilizes the VA Central IRB (VA CIRB) as an IRB of record for participation in VA-funded multi-site studies through a Memorandum of Understanding (MOU) with the VHA Central Office (VHACO). The VABHS has a Federalwide Assurance (FWA #00001270, expiring June 30, 2016) on file with the Department of Health and Human Services (HHS) Office for Human Research Protections (OHRP), and its Human Research Protection Program (HRPP) was awarded full accreditation by the Association for the Accreditation of Human Research Protection Program, Inc. (AAHRPP) on December 10, 2010.

ORO conducted a Routine On-Site Review of the VABHS' R&DC Oversight Program and HRPP on February 13 through March 1, 2012. While the VABHS maintained a comprehensive R&DC Oversight Program and HRPP, and there were no practices that might place human research subjects at significant risk, ORO identified a number of deficiencies that required remedial actions in order to bring the program into full compliance with Federal regulations and VHA policies. The VABHS is currently in the process of developing remedial action plans to address the deficiencies that ORO identified.

## III. BACKGROUND

### A. Allegations Leading to the Focused For-Cause Review

The whistleblower disclosure referred to VA by OSC was comprised of three specific allegations:

1. The Principal Investigator (PI), who was the VABHS Chief of Dermatology, manipulated the research process of a VA skin cancer prevention clinical trial by improperly instructing the Whistleblower to perform skin examinations for research purposes.

2. The PI falsified data in this clinical trial by recording that she, rather than the Whistleblower, had conducted required research skin examinations.

3. The PI's research misconduct could lead to the improper approval by the Food and Drug Administration of the drug studied in the clinical trial for use as a skin cancer preventative medication.

   ORO noted that Allegation #3 is comprised of two parts:

   a. The PI's actions constituted research misconduct.

   b. The PI's actions could lead to improper FDA approval of the study drug.

## B. Relevant Protocol Requirements

**CSP Protocol #562 (VA CIRB Project #08-01/12):** *The VA Keratinocyte Carcinoma Chemoprevention Trial – A randomized controlled trial of 5-fluorouracil (5-FU) compared to a vehicle control to the face and ears in a high-risk population*

ORO identified the following protocol-specific requirements pertinent to the allegations:

1. CSP #562 Protocol Description, v.1.0, June 2, 2008, page 18:

   *At baseline, all participants will have a **full body skin examination by a study dermatologist,** who will determine whether the potential participant meets criteria to be in the study. [Note: bold type added by ORO]*

2. CSP #562 Protocol Operations Manual, February 2009:

   *Full Body Skin Exam: The **dermatologist must find the patient free of any lesions** suspicious of skin cancer conducted for the purpose of this program. (Page 40) [Note: bold type added by ORO]*

   *Required Procedures and Forms:*
   *Baseline visit: **Site investigator or co-investigator performs complete skin examination** … Form 13: "Full Body Skin/Physical Exam" will be used by site investigator or co-investigator to determine if the patient is free of skin cancer at the time of randomization **as well as** assess AKs (actinic keratoses) present on the **face/ears**. (Page 42) [Note: bold type added by ORO]*

## C. Purpose and Method of Review

The purpose of ORO's review was to assess the nature and scope of the alleged violations, including possible **research misconduct** *(i.e., fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results)* and/or other **research impropriety** *(i.e., noncompliance with the laws, regulations, and policies regarding human subject protections, etc.)* as applicable to VA research (VHA Directive 1058 §6.g and §6.h).

ORO's review included individual interviews with the Whistleblower who filed the whistleblower disclosure; the Associate Chief of Staff for Research and Development (ACOS/R&D); the Administrative Officer for Research and Development (AO/R&D); the Chief of Medicine; and the Principal Investigator (PI) (i.e., local site investigator) and the Study Coordinator (SC) for CSP Protocol #562 at the VABHS site. (Appendix 1)

Documents reviewed included all research records related to CSP Protocol #562 and relevant Computerized Patient Record System (CPRS) records (i.e., medical records) of selected research subjects. (Appendix 2)

## D. Chronology of Events

| | |
|---|---|
| February 26, 2009 | The protocol was approved by the VA CIRB for implementation at the VABHS. A total of 61 subjects were subsequently enrolled into the study at this site. |
| April 4, 2012 | The OSC referred the whistleblower disclosure to VA, requiring VA to investigate the allegations and submit a report to OSC within 60 days. |
| April 10, 2012 | VHA referred the whistleblower disclosure to ORO for investigation. |
| April 12, 2012 | ORO notified the VABHS Medical Center Director (MCD) of the allegations and of ORO's pending investigation and requested that the MCD:<br><br>1. Notify the PI of the allegations and pending investigation; and<br>2. Immediately sequester all research records related to CSP Protocol #562, dated on or before April 12, 2012, including those in possession of the PI. |
| April 13, 2012 | The VHA CSP suspended conduct of Protocol #562 at the VABHS. |
| April 16, 2012 | ORO determined that the allegations did not fall within the Federal and VA policy definition of **research misconduct** and, therefore, did not meet the threshold for initiating a research misconduct inquiry. In reaching this determination, ORO noted that the PI's actions were not alleged to have resulted in an inaccurate representation of the ***scientific data or results*** obtained in CSP Protocol #562. Details of ORO's research misconduct threshold determination are provided in Appendix 3.<br><br>ORO determined that the allegations did warrant investigation as possible **research impropriety** and initiated a Focused For-Cause Review of the implementation of CSP Protocol #562 at the VABHS. |
| April 16 - 19, 2012 | The VHA CSP Site Monitoring, Auditing and Review Team (SMART) conducted an audit of CSP Protocol #562 at the VABHS. |
| April 18, 2012 | ORO notified the VABHS of its Focused For-Cause Review and of the on-site portion of the review on May 1-3, 2012. |
| April 19, 2012 | ORO contacted the Whistleblower and scheduled an interview with her at 3:00 PM on April 30, 2012, at the Boston Marriott Copley Place. |

April 30, 2012 — The Whistleblower notified ORO via an e-mail at 12:46 PM on April 30, 2012, that she could not make the 3:00 PM appointment and requested that the interview be rescheduled at her attorney's office. ORO declined to meet the Whistleblower at her attorney's office, but instead rescheduled her interview at 1:00 PM on May 2, 2012, at the VABHS, to which she agreed.

May 1, 2012 — The VHA CSP lifted its suspension of Protocol #562 at the VABHS.

May 1-3, 2012 — ORO conducted the on-site portion of its Focused For-Cause Review of the conduct of CSP Protocol #562 at the VABHS.

## IV. FINDINGS

### A. ORO Interviews and Record Reviews

1. **Roles of the Whistleblower.** The Whistleblower was a licensed nurse practitioner employed by the VABHS Department of Dermatology from 2004 through 2011. In this role, she provided clinical care to VAHBS dermatology patients within the parameters of her license. From March 2009 through November 2011, the Whistleblower was a member of the study team for CSP Protocol #562.

   According to the Operations Manual for CSP Protocol #562, dated February 2009, and the Site Personnel Signatures & Delegated Responsibilities Sheet (undated), the Complaint performed the following roles in CSP Protocol #562:

   - Study Coordinator (SC), March – August 2009, when the current SC (September 2009 – Present) was approved by the VA CIRB
   - Sub-investigator, March 2009 – August 2011
   - Un-Blinded Adverse Event (AE) Assessor, March 2009 – November 14, 2011
   - Prescriber of Triamcinolone, November 2009 – November 2011

   As the SC from March – August 2009, the Whistleblower's responsibilities were described in "The VA Keratinocyte Carcinoma Chemoprevention Trial Operations Manual" §2.B.2 (pages 13-14), dated February 2009. However, the first subject was not randomized until October 2009, so the Whistleblower never acted in the capacity of SC with respect to any enrolled subjects. In any event, her responsibilities as SC did not include full body skin examinations (FBSEs) for research purposes, either at baseline visits or semi-annual follow-up visits.

   As the Un-Blinded AE assessor and the Prescriber of Triamcinolone, the Whistleblower was responsible for direct medical care (i.e., clinical treatment) of subjects, evaluating adverse events, and prescribing Triamcinolone. Neither the protocol itself nor the protocol's Operations Manual allowed the Whistleblower to conduct baseline or semi-annual FBSEs of study patients for research purposes.

The Whistleblower's role as a local sub-investigator for CSP Protocol #562 was not clearly defined. At the study kickoff meeting, CSP personnel made clear that only the PI or a dermatologist co-investigator could perform the initial baseline FBSE and that, as a nurse practitioner, the Whistleblower was not eligible to perform FBSEs for the purposes of CSP Protocol #562. Both the PI and current SC stated that the Whistleblower had never functioned as either a co-investigator or a sub-investigator for this study.

The Whistleblower resigned from the VABHS on November 14, 2011. According to VABHS Time and Attendance Records, March 25, 2011, was the Whistleblower's last day physically present as an employee at the VABHS, after which she was granted various forms of leave until her resignation.

2. **Allegations from the Whistleblower**. The Whistleblower alleged that the PI, who was her supervisor, instructed her to conduct the initial baseline FBSEs on patients for study purposes, whenever the PI was not available, for a period of 6-9 months in 2009 and 2010. She stated that the PI's requests were usually conveyed to her through the SC. Sometimes, the SC would just bring potential subjects to her for skin exams. While she understood that she was not supposed to perform baseline FBSEs for the study, she maintained that she did so because she was following the instructions of her supervisor, the PI.

   a. The Whistleblower suggested that a review of the first 10 – 20 subjects' CPRS medical records would support her assertion that she had conducted initial baseline FBSEs for study purposes. In addition, she provided a copy of the following e-mail message to her from the SC, dated June 3, 2010:

      *In conclusion, I work best with positive motivation. Also, I create enough stress, pressure, criticism for the success of this terrific* ***Skin cancer research program*** *to make it a success or to do the best I can …. because* ***basically, it is just YOU and ME. You have the Skin exams and orders while I have everything else*** *(funding, follow up, adverse events, appointments, recruitment, phone calls, letters, filing, etc.) [Note: bold type added by ORO]*

      The Whistleblower stated that she had concerns about performing baseline FBSEs for subject enrollment purposes in violation of the protocol, and that she had expressed these concerns to the SC and the PI, both orally and in writing. An e-mail message from the Whistleblower to the PI, dated July 1, 2010, and provided to ORO by the PI, supports this assertion:

      *I was just wondering about the initial skin exams on study patients. I believe the protocol indicates it should be done by the principal investigator.* ***When I do them in your absence do you think that could be a deviation from the protocol?*** *[Note: bold type added by ORO]*

*Let me know what you think, otherwise I can contact [the CSP Program Manager] and see what she thinks.*

The PI responded to the Whistleblower in an e-mail dated that same day:

*Thank you very much for bringing this to my attention today. I will contact [the current SC] and cancel all study patients that are scheduled for the exams for today and tomorrow.*

The PI stated that the email message above was the first indication to her that, contrary to the protocol, the Whistleblower was scheduled to perform upcoming FBSEs on study subjects for research, rather than clinical, purposes.

b. The Whistleblower did eventually contact the CSP with the concerns expressed in her July 1, 2010, e-mail. On May 11, 2011, she sent an e-mail to the National Coordinator of CSP Protocol #562, stating that:

*My understanding is that my role as an unblinded subinvestigator is to evaluate and document adverse events. At the time of the initial patient enrollment a skin exam is supposed to be done by a Board Certified Dermatologist who remains blinded. In this case, that is [the PI]. She instructed me to do the initial skin exams on approximately the first 10 patients since she was unavailable. I followed her orders until [the current SC] and I discussed the possibility that this was a deviation from the protocol and then I told [the PI] I could not do the initial skin exam.*

The PI responded to CSP's inquiry on May 23, 2011, stating that:

*In July 2010, I received an e-mail from [the Whistleblower] stating that she was scheduled to perform the initial visits for the study patients. I also was informed by her in the same email that this may deviate [sic] the protocol.* ***This was the first time I was made aware of the potential deviation of the protocol.*** *I immediately emailed [the Whistleblower] back and stated that I will contact [the current SC] to cancel all potential study patients and have him schedule all initial visits are [sic] with me. I thanked [the Whistleblower] for bringing this to my attention.* ***This is the first and only time that I was notified.*** *[Note: bold type added by ORO]*

*[The current SC] had never reported to me any potential deviation of the protocol.*

c. The Whistleblower asserted that since she brought up her concerns regarding protocol deviations, she had been subjected to various retaliatory actions including progressive disciplinary actions and peer reviews that might lead to loss of her state license.

3. **Response from the PI**. The PI informed ORO that in no instance had she ever instructed the Whistleblower to conduct FBSEs of subjects for research purposes. The PI further stated that she herself had performed all required baseline and semi-annual FBSEs on all enrolled subjects. The PI indicated that the Whistleblower might have conducted skin examinations on some patients as part of her clinical care duties prior to referring the patients to the PI for evaluation for enrollment into the study. However, in these instances, the PI maintained that she herself always conducted the initial baseline FBSE as required by the protocol.

4. **Response from the Current SC**. The current SC informed ORO that the PI had always performed the initial baseline FBSEs on all enrolled subjects and that he had never used the results of any FBSEs performed by the Whistleblower to enroll subjects into the study. The SC further stated that, in most cases, he was in the examination room when the PI conducted the baseline FBSE on subjects.

   The SC stated that he had never communicated to the Whistleblower any instruction or request from the PI that the Whistleblower perform any initial baseline FBSEs for enrollment of subjects into CSP Protocol #562. The SC also stated that he could not recall any discussion or e-mail correspondence with the Whistleblower regarding potential protocol violations resulting from the conduct of initial baseline FBSEs by the Whistleblower.

5. **ORO Review of Case Records**. ORO reviewed case records of all 61 subjects enrolled into CSP Protocol #562 as well as the CPRS records of selected subjects.

   a. **CSP Good Clinical Practice Audit.** On March 10-12, 2010, reviewers from the CSP SMART Program conducted a Good Clinical Practice (GCP) audit of CSP Protocol #562 and noted the following:

      *Three subjects had both the PI and the Un-Blinded AE Assessor involved in the full body skin examination at baseline. Per protocol (page 19) the full body skin exam must be conducted by a study dermatologist; i.e., the PI or co-investigator. The problem arose in that the PI performed face and nose part of exam and the un-blinded AE Assessor the rest of evaluation. The PI signed the Full Body Skin/Physical Exam (CRF 13); however, the CPRS progress note states the Un-Blinded AE Assessor performed the evaluation.*

   Although she did not formally dispute the CSP SMART findings, the PI told ORO that she disagrees with the statement that she performed only part of the FBSE for selected subjects.

   (i) Nevertheless, **on March 15, 2010, the PI signed** the *Source Document Worksheet for Form 25: Protocol Deviation* for three subjects, i.e., **#111-0002, #111-0007** and **#111-011**, admitting the irregularity that the FBSE was *"completed by both the PI and practitioner"* and agreeing to take appropriate remedial actions, i.e., *"PI to complete FBSE solely"* and *"SC will correct notes."*

**This appears to refute the PI's assertion (see §IV.A.2.b) that she first became aware on July 1, 2010, of a potential protocol deviation related to the Un-Blinded AE Assessor (i.e., the Whistleblower) conducting FBSEs for research purposes.**

(ii) ORO verified that the CPRS Research Progress Note for subject #**111-0002**, dated November 4, 2009, included the following entry:

*Patient's full body skin exam performed by [the Un-Blinded AE Assessor].*

The note was electronically signed by the SC on November 4, 2009, and **acknowledged by the PI on November 7, 2009.**

**This demonstrates that the PI had been informed, prior to July 1, 2010, through the CPRS Research Progress Note, that the Un-Blinded AE Assessor had conducted FBSEs for research purposes. As the PI, it was her responsibility to ensure proper implementation of the protocol and to identify this as a protocol deviation.**

An Addendum was added by the SC on March 16, 2010, stating the following:

*Skin exam completed by both [the PI] and [the Un-Blinded AE Assessor].*

(iii) For subject **#111-0007**, the CPRS Research Progress Note included the following entry, dated November 27, 2009:

*Visit: November 23, 2009*
*Patient came in for baseline (randomization) visit for the study . . .*
*Patient's full body skin exam performed by [the Un-Blinded AE Assessor].*

The note was electronically signed by the SC on November 27, 2009.

An Addendum was added by the SC on March 16, 2010, stating the following:

*Skin exam completed by both [the PI] and [the Un-Blinded AE Assessor].*

Thus, in accordance with the SMART Monitor's recommendations, the SC amended the CPRS note, which had indicated only that the Un-Blinded AE Assessor performed the evaluation, to indicate that both the Un-Blinded AE Assessor **and** the PI performed an FBSE.

Subjects **#111-0002** and **#111-0007** were randomized and enrolled into CSP Protocol #562 on **November 4** and **November 24, 2009**, respectively. The SC stated that these two subjects came in for research screening immediately following their dermatology clinic visits and would have received an FBSE from the Un-Blinded AE Assessor **and** from the PI.

ORO confirmed that the PI signed the *Source Document Worksheet for Form 13* indicating that she had performed an FBSE for each subject on the date of enrollment.

However, ORO noted that a review of the PI's Time and Attendance records during the CSP SMART audit on April 16-19, 2012, indicated that the PI was on sick leave from November 4 (the FBSE/enrollment date for Subject #111-0002) to November 6, 2009. The PI stated that she may have worked a partial day on November 4 even though she took a full day of leave. Although given the opportunity, the PI has not provided ORO with any documentation to this effect.

b. **Subject #111-0011.** ORO found that Subject #111-0011 was randomized and enrolled into CSP Protocol #562 on **December 11**, 2009. However, the PI signed the *Source Document Worksheet for Form 01: Inclusion/Exclusion Criteria* and the *Source Document Worksheet for Form 13: Full Body Skin/Physical Exam*, on **December 14,** 2009, three days after enrollment.

(i) Review of the subject's CPRS record revealed that the **December 11,** 2009, Research Progress Note stated the following:

*Patient came in for baseline (randomization) visit for the study . . . Patient's skin exam performed by [the Un-Blinded AE Assessor].*

The note was electronically signed by the SC on December 11, 2009, and **acknowledged by the PI on December 17, 2009.**

**This demonstrates that the PI had been informed, prior to July 1, 2010, through the CPRS Progress Note, that the Un-Blinded AE Assessor had conducted FBSEs for research purposes. As the PI, it was her responsibility to ensure proper implementation of the protocol and to identify this as a protocol deviation.**

An Addendum was added by the SC on March 16, 2010, stating the following:

*Skin exam completed by both [the Un-Blinded AE Assessor and [the PI].*

This addendum, like the addenda for Subjects **#111-0002** and **#111-0007**, was added in accordance with the recommendations of the CSP SMART Monitor.

(ii) ORO noted that Subject **#111-0011** was randomized and enrolled on **December 11**, 2009, the same day that the **Un-Blinded AE Assessor** (i.e., the Whistleblower) conducted the *"skin exam"* documented in the above referenced CPRS Research Progress Note dated December 11, 2009. On the other hand, the *Source Document Worksheet for Form 13: Full Body Skin/Physical Exam* was signed by the PI on **December 14,** 2009, three days **after** the subject was randomized and enrolled into the protocol.

The SC insisted that he did not use the results of skin exams conducted by the Un-Blinded AE Assessor (i.e., the Whistleblower) to enroll Subject #111-0011. ORO noted that if that were the case, the SC would have had to fabricate the FBSE results in order to enroll the subject, since the PI did not sign the relevant *Source Document Worksheet* until December 14, 2009.

The SC and PI pointed out that the FBSE *Source Document Worksheet* listed **December 11,** 2009, as the date of the FBSE, even though the PI did not sign it until **December 14,** 2009. The SC suggested that the PI may have performed the FBSE on December 11, but did not sign the *Source Document Worksheet* until December 14. However, neither the SC and PI could explain the reason for a delayed signature in this instance.

c. **Dispensing of Study Drug.** The study required dispensing the blinded study drug as well as Triamicinolone and Sunscreen. Two *Investigational Drug Information Records* (VA Form 10-9012) were submitted. One for the blinded drug and the other for Triamcinolone. The Un-Blinded AE Assessor was authorized to prescribe Triamcinolone, but was not authorized to prescribe the blinded study drug, as she was listed on the VA Form 10-9012 for Triamcinolone, but not the VA Form 10-9012 for the blinded study drug.

However, the Un-Blinded AE Assessor prescribed the study drug and the Research Pharmacist then dispensed it to the first 20 subjects enrolled in CSP Protocol #562 at the VABHCS.

VHA Handbook 1108.04 §10.d(2) stipulates that *"Investigational drugs and supplies may be dispensed only after a provider, who is authorized to prescribe the drug, has submitted a proper written or electronic order."*

d. **Un-Blinding of Study Subject.** In January 2011, the VABHCS reported the death of a CSP Protocol #562 research subject to the VA CIRB as a serious adverse event (SAE). In order to determine whether the death was related to the study, the IRB reviewer requested and received a copy of the subject's death certificate from the VABHS on February 18, 2011. The death certificate listed the cause of death as "Pending." The IRB reviewer then requested that the VABHS SC break the treatment code, thereby "un-blinding" (i.e., identifying) the topical medication being prescribed to the affected subject.

The VABHS study team complied with the IRB request, but did not follow the process required under CSP Protocol #562 Drug Treatment and Handling Procedures (DTHP), v.2, October 2011, at §11.02:

*Authorization to break the Blind. Under unusual circumstances, chiefly related to participant safety, unblinding may be necessary. This is usually done after consultation with the study chairperson … If [the study chairperson] is not available, the PCC Clinical Research Pharmacist or the Biostatistician should*

*be contacted. Code envelopes should only be opened if the Site Investigator has been instructed to do so by one of the parties listed above or is unable to reach one of the parties listed above.*

As a result, the CSP suspended VABHS enrollment of new subjects into Protocol #562. The noncompliance case was reported to ORO on March 4, 2011. The remedial action plan included requiring the VABHS study team and VA CIRB reviewers to complete GCP training.

## B. Policy Concerns

ORO did not find a violation, or apparent violation, of any law, rule or regulation, nor was there a substantial and specific danger to public health. However, ORO did identify the following concerns regarding compliance with VA policy:

### 1. The PI did not fulfill all responsibilities required of investigators.

VHA Handbook 1200.05 includes the following investigator responsibilities:

*§9e. Overseeing the Research Staff. This means overseeing and being responsible for ensuring the research staff under the investigator's direction comply with all applicable requirements including, but not limited to, implementing the research study in accordance with the approved protocol.*

*§9.h. Implementing the Study as Approved. This means ensuring the study is implemented as approved by the IRB and in accordance with other required approvals and with all applicable local, VA, and other Federal requirements including, when applicable, those for research involving investigational drugs (see par. 39) or investigational devices (see par. 40).*

*§9.q. Reporting Deviations and Complaints. This means reporting deviations from the protocol and subject complaints to IRB in a time frame specified in local SOPs.*

Specifically, ORO found that the PI did not oversee research staff sufficiently to ensure that CSP Protocol #562 was implemented in accordance with the approved protocol (see §III.B above):

a. Having acknowledged Research Progress Notes indicating that the Un-Blinded AE Assessor had conducted FBSEs for research purposes (see §6.a(ii), Subject #111-0002 and §6.b(i), Subject #111-0011,), the PI did not identify this practice as a protocol deviation and did not intervene to ensure protocol compliance by study staff.

b. The PI did not ensure that the FBSE was documented prior to enrollment of Subject #111-0011 (see §IV.A.6.b).

c. The PI did not ensure adherence to the protocol's "un-blinding" procedures (see IV.A.6.d).

d. The PI did not ensure that the study drug was prescribed only by an authorized provider (see §IV.A.6.c).

**2. The VABHS HRPP did not ensure compliance with all applicable VA research requirements.**

Specifically, ORO found that the Research Pharmacist dispensed the study drug to 20 subjects enrolled in CSP Protocol #562 on the basis of prescriptions from an unauthorized provider.

## C. Conclusions

ORO reached the following conclusions based on its review:

1. ORO was unable to determine whether the PI instructed the Whistleblower to perform skin examinations for research purposes in violation of the protocol. However, ORO found that, having acknowledged Research Progress Notes indicating that the Un-Blinded AE Assessor had conducted such skin examinations for research purposes, the PI did not identify this practice as a protocol deviation and did not intervene to ensure protocol compliance by study staff.

2. ORO was unable to determine whether the PI falsified data in this clinical trial by recording that she, rather than the Whistleblower, had conducted research skin examinations. However, ORO found that, in at least one instance, a subject was enrolled into CSP Protocol #562 prior to documentation by the PI that she had conducted the required skin exam.

3. Relative to the allegation of research misconduct:

    a. ORO determined that the allegations as presented in the whistleblower disclosure did not fall within the Federal and VA policy definition of **research misconduct** and, therefore, did not meet the threshold for initiating a research misconduct inquiry. In reaching this determination, ORO noted that the PI's actions were not alleged to have resulted in an inaccurate representation of the ***scientific data or results*** obtained in CSP Protocol #562 (see Appendix 3).

    b. Relative to the allegation that the PI's actions could lead to improper approval of the study drug by FDA, the findings of ORO's Focused For-Cause Review did not suggest that the ***scientific data or results*** obtained in CSP Protocol #562 at VABHS were inaccurately represented.

4. ORO determined that noncompliance with VA requirements identified during its Focused For-Cause review warranted remedial action.

## V. Required Actions

The VABHS must provide ORO with a written Remedial Action Plan detailing specific steps and an implementation schedule to address each of the following Required Actions. The plan should be received by the ORO Central Office within 30 days after this report is transmitted to the facility.

1. The VABHS must ensure that all research currently involving the PI and SC adheres to the IRB-approved protocol and complies with all applicable VA research requirements by implementing an appropriate monitoring plan for their research.

2. The VABHS must ensure that all of its research studies are conducted according to the IRB-approved protocols and all relevant Federal regulations and VHA Policies.

3. The VABHS must ensure that pharmacy personnel dispense study medications only when prescribed by authorized prescribers.

4. The VABHS must determine whether any disciplinary action is warranted in light of ORO's findings.

VA will provide the Remedial Action Plan to OSC upon receipt and will update OSC as remedial actions are implemented.

## OFFICE OF RESEARCH OVERSIGHT

(b)(6)

(b)(6)
Deputy Chief Officer
ORO Review Leader

June 4, 2012

# APPENDIX 1: INDIVIDUALS INTERVIEWED

## I. ENTRANCE BRIEFING

### A. Members of VABHS Management:

| | |
|---|---|
| (b)(6) | Medical Center Director (MCD) (via Teleconference) |
| (b)(6) | Chief of Staff (COS) (via Teleconference) |
| (b)(6) | Associate Chief of Staff for Research and Development (ACOS/R) |
| (b)(6) | Administrative Officer for Research and Development (AO/R) |

### B. Members of ORO Review Team:

| | |
|---|---|
| (b)(6) | Deputy Chief Officer, ORO Central Office (CO) |
| (b)(6) | Associate Director, Research Information Security & Privacy (AD/RISP) |
| (b)(6) | Assistant Director, ORO CO |
| (b)(6) | Health Science Specialist (HHS), ORO Northeastern Regional Office (NERO) |

## II. INDIVIDUAL INTERVIEWS

| | |
|---|---|
| (b)(6) | Associate Chief of Staff for Research and Development (ACOS/R) |
| (b)(6) | Administrative Officer for Research and Development (AO/R) |
| (b)(6) | Research Pharmacist |
| (b)(6) | Local Site Investigator (LSI)/Principal Investigator (PI) for CSP #562 |
| (b)(6) | Study Coordinator for CSP #562 |
| (b)(6) | Chief of Medicine |
| (b)(6) | Informant (Whistleblower) |

## III. EXIT INTERVIEW (Conducted on May 15, 2012 by teleconference)

### A. Members of VABHS Management:

| | |
|---|---|
| (b)(6) | MCD |
| (b)(6) | COS |
| (b)(6) | ACOS/R |
| (b)(6) | AO/R |

### B. Members of ORO Review Team:

| | |
|---|---|
| (b)(6) | Deputy Chief Officer, ORO CO |
| (b)(6) | AD/RISP |
| (b)(6) | Assistant Director, ORO CO |
| (b)(6) | HHS, ORO NERO |

# APPENDIX 2: DOCUMENTS REVIEWED

## I. DOCUMENTS REVIEWED PRIOR TO ON-SITE REVIEW

### A. Documents from OSC, ORD and VA CSP:

1. OSC File No. DI-12-1098 (The Office of Special Counsel Letter to Secretary of VA dated April 4, 2012)

2. Suspension of CSP #562 Site Activities (Deputy CRADO and Director, ORD CSR&D memorandum to Director, VA Boston HCS dated April 13, 2012)

3. Suspension of CSP #562 Site Principal Investigator (Deputy CRADO and Director, ORD CSR&D memorandum to Director, VA Boston HCS dated April 12, 2012)

4. Study Suspension for "The VA Keratinocyte Carcinoma Chemoprevention Trial" VA Cooperative Program Study (CSP) #562 (VA CSP #562 Study Chair memo to Co-Chair, VA Central IRB dated April 16, 2012)

### B. VABHCS Research Service Records and LSI Records

1. Protocol "VA Cooperative Study #562: The VA Keratinocyte Carcinoma Chemoprevention Trial" (Version 3.0 dated January 30, 2012, Version 1.0 dated September 29, 2008, Version 1.1 dated June 25, 2010)

2. VA Cooperative Study #562: The VA Keratinocyte Carcinoma Chemoprevention Trial Operation Manual (Revised April 7, 2010)

3. VA Cooperative Study #562: The VA Keratinocyte Carcinoma Chemoprevention Trial Operation Manual (February 2009)

4. Site Personnel Signature and Delegated Responsibilities (Site 111-Boston, undated)

5. Informed Consent Documents approved by IRB between November 2008 and July 2011

6. HIPAA Authorization: Written Permission for Release Protected Health Information for Research Purposes (Approved by VA Central IRB on February 26, 2009)

7. Investigational Drug Information Record (VA Form 10-1092 for 5-Fluorouracil and Triamcinolone approved by IRB between January 2009 and August 2011)

8. Correspondence (Email correspondence among LSIs, CIRB and Coordinating Center between 2009 and 2011)

9. Conference calls (Coordinating Center and LSIs conference call agendas and minutes between June 2009 and February 2012)

10. Notes to File (Notes to File requirements for issues/irregularities in consent, subject management, conduct of study, and file maintenance; or anything else that needs explanation, and 13 notes filed by the LSI between March 15, 2010, and August 10, 2011)

11. Summary for Investigator (Report of a Good Clinic Practice audit conducted by Site Monitor Audit sand Review Team (SMART) on March 10 – 12, 2010)

12. Source Document Worksheet for Form 25: Protocol Deviations (Worksheets completed by the LSI and Study Coordinator on March 15, 2010 in response to the recommendations of SMART audit on March 10 – 12, 2010)

13. AE Form Intervention (Logs for 58 AEs occurred between February 11, 2010 and October 29, 2011 and issues regarding informed consent process identified by a SMART audit in 2011)

14. List of Studies (list of LSI's protocols since 2009)

15. IRB Submission Log Book (Current and previous versions of the protocols (Version 1.0, 1.1. & 3.0), ICDs, continuing review submissions)

16. *[PI]*_10249_C (Including documents of initial IRB approval in April 2009 to the latest R&DC approval in August 2011)

17. IRB Submission Binders 1 A (2009-2010 continuing review/amendment submission packets, previous versions of protocol, review and approval)

18. IRB Submission Binder 1 B (2008-2009 original LSI submission packets)

19. IRB Submission Binder 2 (2010-2011 continuing review/amendment submission packets, previous versions of protocol, review and approval)

20. SAE-Safety Reports (AE reports from Boston LSI and communications with VA Central IRB between February 2010 and October 2011)

## C. VA Central IRB Records

1. VA Central IRB initial and continuing review approvals for CSP #562 at VABHCS (Site 111) (February 2009 – July 2011)

2. VABHCS LSI reports of adverse events/unanticipated problems and IRB determinations (April 2010 – April 2012)

3. VABHCS LSI reports of protocol deviations, IRB review and determinations (March 2010 – March 2011)

4. VABHCS RCO memo to LSI on an audit conducted on December 6, 2011

5. LSI Report of Serious Noncompliance and IRB review and Determination (March – June 2011)

## II. DOCUMENTS REVIEWED ONSITE

### A. LSI Records

1. Subjects Binders for all 61 enrolled subjects at VABHCS (Site 111) (including 7 terminated/withdrew and 54 active)

2. LSI email communication with the informant (Whistleblower)

3. CSP #562 Electronic Data Capture System for subject treatment randomization

4. Study Coordinator's subjects appointment calendar from December 3 – 31, 2010

### B. Records on VA Computerized Patient Record System:

1. Research enrollment notes for subjects #0002, 0007, 0011, and 0045

2. Dermatology Clinic Note for subject #0011.

# Appendix 3

## ORO's Research Misconduct Threshold Determination

VA Boston Healthcare System
April 16, 2012

### Background

On April 4, 2012, the U.S. Office of Special Counsel (OSC) forwarded to the Secretary of Veterans Affairs (VA) a set of allegations from *[the "Informant"]*,, a former Nurse Practitioner in the VA Boston Healthcare System (VABHS) Department of Dermatology. OSC File No. DI-12-1098. The allegations were lodged against *[the "Respondent"]* in her role as local site investigator (LSI) in the Cooperative Studies Program (CSP) study #562, "The VA Keratinocyte Carcinoma Chemoprevention Trial."

### Allegations

The Informant's allegations included the following:

(1) The Respondent "manipulated the research process" in CSP #562. Specifically, the Respondent "improperly instructed [Informant] to conduct initial skin examinations on individuals seeking to be participants…. [T]he study protocol indicates that the lead investigator is to conduct all initial and follow-up skin examinations of study participants, and [Informant] was not eligible to be the lead investigator because the study protocol required lead investigators to be board certified dermatologists."

(2) The Respondent "falsified data recorded in the clinical trial." Specifically, the Respondent "falsely recorded data in the study to reflect that [Respondent], rather than [Informant], conducted the aforementioned initial skin examinations."

(3) The Respondent's "research misconduct could lead to the improper FDA-approval of the drug studied in the clinical trial for use as a skin cancer preventative medication."

### Definition of Research Misconduct

OSC's notice to VA categorized the above as allegations of research misconduct as defined under VHA Handbook 1058.2 ("Research Misconduct"), specifically, falsification.

"Falsification" is defined as "manipulating research materials, equipment, or processes, or changing or omitting data or results <u>such that the research is not accurately represented in the research record</u>." VHA Handbook 1058.2, §3.a(2) (emphasis added).

"Research record" is further defined as "the record of data or results that embody <u>the facts resulting from scientific inquiry</u>…." VHA Handbook 1058.2, §5.n (emphasis added).

*See also* Federal Policy on Research Misconduct at 65 Federal Register 76260 (December 6, 2000).

**Threshold Determination Requirement**
Under VHA Handbook 1058.2, in order to open an Inquiry into an allegation of research misconduct, the allegation must meet certain threshold requirements including that the allegation be one of research misconduct as defined above.

**ORO's Determination**
ORO has determined that the three allegations listed above do not meet the threshold for opening a research misconduct Inquiry. None of the three allegations are of research misconduct, specifically "falsification," as defined above.

(1) The alleged *instruction to the Informant* to conduct a procedure that she was not eligible to conduct per the protocol did not in itself constitute an inaccurate *representation in the research record*. Instead, the alleged action, if true, would constitute a protocol deviation and possible research impropriety.
(2) Falsely representing that the Respondent conducted a procedure that the Informant actually carried out would likewise constitute possible research impropriety, if proven. However, the Informant did not allege that this falsification resulted in an inaccurate representation of the research record as defined above, i.e., "the record of *data or results* that embody the facts *resulting from scientific inquiry*." Falsification of *who* conducted the procedure by itself would not necessarily result in an inaccurate representation of the "research record." The Informant did not allege that the research record, as defined above, was inaccurately represented.
(3) The possibility that the above alleged improprieties might lead to certain adverse consequences does not in itself constitute research misconduct as defined in VHA Handbook 1058.2.

Based on the Informant's allegations as forwarded by OSC on April 4, 2012, none of which meet the definition of research misconduct, ORO concludes that a research misconduct Inquiry should not be convened according to the procedures set forth in VHA Handbook 1058.2.