DEPARTMENT OF HEALTH & HUMAN SERVICES

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February 15, 2001

Mr. Michael J. Sullivan
Director
Department of Veterans Affairs Medical Center
University and Woodland Avenues
Philadelphia, PA 19104

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1528

Research Projects: Cardiology Clinic Research Activities
Principal Investigator: Dr. W. Bruce Dunkman

Dear Mr. Sullivan:

The Office for Human Research Protections (OHRP), formerly the Office for Protection from Research Risks (OPRR), has reviewed the Philadelphia Veterans Affairs Medical Center (PVAMC) reports dated May 18, 1999 and June 14, 1999 regarding the allegations of possible noncompliance with Department of Health and Human Services (HHS) regulations for protection of human subjects (45 CFR Part 46) involving the above referenced research. OHRP apologizes for the delay in its response.

In reviewing your report dated May 18,1999, OHRP notes the following:

(1) Regarding Ms. Ann Lovell's investigation into the BEST study consent form, your report stated:

(a) "Her investigation concluded that the language of the BEST consent form underestimated the radiation exposure risks and that the Radiation Safety Committee (RSC) had not reviewed the protocol as specified by policy."

(b) "[she] found that the PRAISE-2 study also had not been reviewed or approved by the Radiation Safety Committee."

(c) "Because of these concerns, enrollment of new patients into these two studies was suspended at the Medical Center"

(2) Regarding the issues related to review by the RSC, your report stated:

(a) "PVAMC's failure to have a researcher obtain approval for research from the Radiation Safety Committee was an institutional oversight."

(b) "PVAMC's failure to have the Institutional Review Board (IRB) confirm that RSC approval was obtained was also an institutional oversight."

(3) Regarding reporting of unanticipated problems and suspension of research your report states:

(a) "Our Multiple Project Assurance and Title 45 CFR Part 46 103(b)(5) specifies that "serious or continuing noncompliance" and suspensions of IRB approval be reported to the IRB, the appropriate institutional official and to the Department or Agency head."

(b) "In retrospect, it is clear that despite the suspension of the study, the fact that we failed to follow established IRB and RSC review procedures constituted a condition of "noncompliance" which conceivably produced a potential for "serious" consequences."

Based upon its review of the materials provided with your reports, as well as materials provided by facsimile on January 2, 2001 and February 1, 2001, OHRP makes the following determinations:

(1) Department of Health and Human Services (HHS) regulations at 45 CFR 46.111(a)(1) require, among other things, that an IRB, in order to approve research, determine that risks to subjects are minimized by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk.

OHRP finds, as was stated in your May 18, 1999 report, that the PVAMC IRB failed to minimize risks to subjects by not ensuring that the researcher obtained the approval of the Radiation Safety Committee as was specified in PVAMC policy.

Corrective Actions: OHRP finds that the following corrective actions taken by the PVAMC adequately address the above deficiency:

(a) Modification of the PVAMC's "request to Review Research Proposal" and instructions to researchers.

(b) Adoption of a worksheet for use in the research committees to organize data entry and simplify the process of specifying and monitoring pending actions.

(c) Appointment of a new Radiation Safety Committee Chairperson and an new Radiation Safety Officer.

(d) Inclusion of the Radiation Safety Officer as a member of the Human Studies Committee.

(e) The development of adequate policies and procedures and standard operating procedures for the function of the IRB.

(2) HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5) require reporting to the IRB, appropriate institutional officials, and the Department or Agency head and OHRP of (i) any unanticipated problems involving risks to subjects or others or any serious or continuing noncompliance with 45 CFR Part 46 or the requirements or determinations of the IRB and (ii) any suspension or termination of IRB approval.

OHRP finds, as was stated in your May 18, 1999 report, that PVAMC failed to report the suspension of the BEST and PRAISE-2 studies to OPRR.

(3) HHS regulations at 45 CFR 46.108 require that, except when an expedited review procedure is used, the IRB review proposed research at convened meetings at which a majority of the members of the IRB are present. OHRP finds that the IRB failed to meet this requirement for the following IRB meetings: May 14, 1992 (7 of 17 members present); August 13, 1992 (7 of 17 members present); November 13, 1997 (6 of 14 members present).

OHRP notes that any actions taken at meetings lacking a quorum must be considered invalid. OHRP further notes that the continuing review of the BEST study and approval of modifications to the Valsartan 107 study occurred at the November 13, 1997 meeting. OHRP emphasizes that should the quorum fail during a meeting (e.g., those with conflicts being excused, early departures, loss of a nonscientist), the meeting is terminated from further votes unless the quorum can be restored.

(4) HHS regulations at 45 CFR 46.107(e) stipulate that no IRB member may participate in the IRB's initial or continuing review of a project in which the member has a conflicting interest, except to provide information requested by the IRB. OHRP found instances in which an IRB member inappropriately participated in the initial and continuing review of protocols for which he had a conflicting interest. Specifically, OHRP finds that Dr. Dunkman was present at the IRB meetings for the initial and continued approval for the Valsartan 107 study on December 12, 1996 and December 11, 1997, respectively. Dr. Dunkman did not abstain from voting on this protocol in which he is the principal investigator.

OHRP strongly recommends that IRB members absent themselves from the meeting room when the IRB votes on research in which they have a conflicting interest, and such should be noted in the IRB meeting minutes.

(5) HHS regulations at 45 CFR 46.109(e) require that continuing review of research be conducted by the IRB at intervals appropriate to the degree of risk and not less than once per year. The regulations make no provision for any grace period extending the conduct of the research beyond the expiration date of IRB approval. Additionally, where the convened IRB specifies conditions for approval of a protocol that are to be verified as being satisfied by the IRB Chair or another IRB member designated by the Chair, the approval period must begin on the date the protocol was reviewed by the convened IRB, not on the date the IRB Chair or his or her designee verifies that IRB-specified conditions for approval have been satisfied.

OHRP finds that the PVAMC IRB failed to conduct continuing review of VA project number 0007 (Efficacy and Safety of Felodipine in ER Patients with Heart Failure) at least annually.

If the IRB does not re-approve the research by the specified expiration date, subject accrual should be suspended pending re-approval of the research by the IRB. Enrollment of new subjects cannot ordinarily occur after the expiration of IRB approval. Continuation of research interventions or interactions in already enrolled subjects should only continue when the IRB finds that it is in the best interests of individual subjects to do so. OHRP and IRBs must address on a case-by-case basis those rare instances where failure to enroll would seriously jeopardize the safety or well-being of an individual prospective subject.

Required Action: OHRP requires that PVAMC submit (i) a detailed corrective action plan to address findings (2) through (5) above; and (ii) a detailed plan for ensuring that all IRB members and staff, and all research investigators, are appropriately educated, on an ongoing basis, about the ethical principles and regulatory requirements for the protection of human subjects. These plans must be submitted to OHRP no later than March 20, 2001.

(6) OHRP acknowledges that your report of June 14, 1999 included the decision by Merit Systems Protection Board Administrative Judge Michael T. Rudisill regarding the issue of retaliation against a whistleblower. OHRP would like to note that in addition to the statements provided in your report, Judge Rudisill found that:

> (a) "The appellant also made a protected disclosure in April 1997 when she complained to PVAMC Radiation Safety Officer, Ann Lovell, about the levels of radiation received by research study participants which they were unaware of because said levels were higher than those listed on the informed consent forms previously completed by the study participants."

(b) "[the] only conclusion that I can draw from the evidence presented by both parties is that the agency retaliated against the appellant for her whistleblowing activity both when she was subjected to intolerable working conditions and, ultimately, when it terminated her term appointment prior to its scheduled expiration."

At this time OHRP would like to provide the following additional guidance:

(7) In reviewing the PVAMC IRB standard operating procedures (SOPs), OHRP notes that many of the policies and procedures reference 21 CFR Parts 50 and 56 but may also be subject to regulations at 45 CFR Part 46. In such situations, requirements for both sets of regulations must be met. Additionally, research studies which do not fall under 21 CFR Parts 50 and 56 must still fulfill the requirements required at 45 CFR Part 46. OHRP recommends that PVAMC review and consider revising its SOP's to ensure that all Federal regulations relating to the protection of human subjects are included in its policies and procedures.

(8) Where HHS regulations require specific findings on the part of the IRB, such as (a) approving a procedure which alters or waives the requirements for informed consent [see 45 CFR 46.116(d)]; (b) approving a procedure which waives the requirement for obtaining a signed consent form [see 45 CFR 46.117(c)]; (c) approving research involving prisoners (see 45 CFR 46.305-306); or (d) approving research involving children (see 45 CFR 46.404-407), the IRB should document such findings. OHRP strongly recommends that all required findings be fully documented in the IRB minutes, including protocol-specific information justifying each IRB finding.

(9) In reviewing the PVAMC IRB SOPs OHRP was unable to determine what documents are being provided to the IRB relating to advertisements for recruitment of subjects. OHRP notes that in conducting the initial review of proposed research, IRBs must obtain information in sufficient detail to make the determinations required under HHS regulations at 45 CFR 46.111. Materials should include any advertising intended to be seen or heard by potential subjects.

OHRP appreciates the continued commitment of your institution to the protection of human research subjects. Please do not hesitate to contact me should you have any questions.

Sincerely,

Patrick J. McNeilly, Ph.D.
Compliance Oversight Coordinator
Division of Compliance Oversight

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