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DEPARTMENT OF HEALTH & HUMAN SERVICES
Office of Public Health and Science

Office for Human Research Protections

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June 15, 2006

Robert Williams, Ph.D.
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Eastern Virginia Medical School
721 Fairfax Avenue, Suite 504
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RE: Human Research Subject Protections Under Multiple Project Assurance M-1532 and Federalwide Assurance (FWA) 3956

Research Project: Studies on Control of Insulin-Induced Vasodilation

(1) Nitric Oxide Resistance, Insulin and Endothelin in Peripheral Microvascular Function (IRB # 01-02-FB-0034)

(2) Skin Blood Flow Study Involving Intradermal Injections of Normal Saline, Lidocaine, Insulin, ETA Antagonist (BQ123), ETB Antagonist (BQ788) and L-NAME to Determine Effects On Insulin-Induced Vasodilation in Human Skin

Research Project: Retrospective and Prospective Studies on Neuropathy in an Outpatient Clinical Care and Academic Clinical Research Setting

(3) Retrospective and Prospective Studies of Neuropathy in an Outpatient Clinical Care and Academic Clinical Research Setting (IRB # 01-03-EX-0110)

Research Project: Intraepidermal Nerve Fibers are Indicators of Small Fiber Neuropathy in Both Diabetic and Non-Diabetic Patients

(4) Developing Non-Invasive Tests of Small Fiber Neuropathy (IRB # 12-05-99-0220)

(5) A Comparison of Skin Biopsy and Immunohistochemistry in Newly Diagnosed Diabetics and Non-Diabetics, Non-Neuropathic Subjects (IRB # 02-05-FB-0139)

Research Project: Immune Mediated Neuropathies Improve with IV Ig Therapy: Correlation Between, Before and After Neurologic Symptom Scores, Total Motor Scores and Total Disability Scores, NINA Assay, and Neurosensory Testing

(6) A Double-Blind Placebo Controlled Trial of Intravenous Immunoglobulin (IV Ig) Treatment in Patients with Diabetic Amyothropy and Sensorimotor Neuropathy: A Multi-Center Pilot Study (IRB # 11-09-97-0070)

Research Project: Skin Biopsies in Diabetes and the Metabolic Syndrome: External Validation by Comparison with Other Neurologic Tests and Metabolic Parameters

(7) Retrospective and Prospective Studies of Neuropathy in an Outpatient Clinical Care and Academic Clinical Research Setting (IRB # 01-03-EX-0110)

(8) Developing Non-Invasive Tests of Small Fiber Neuropathy (IRB # 12-05-99-0220)

(9) A Comparison of Skin Biopsy and Immunohistochemistry in Newly Diagnosed Diabetics and Non-Diabetics, Non-Neuropathic Subjects (IRB # 02-05-FB-0139)

Principal Investigator: Aaron Vinik, M.D.

Dear Dr. Williams:

The Office for Human Research Protections (OHRP) has reviewed Eastern Virginia Medical School's (EVMS) March 24, 2004; June 8, 2004; July 26, 2004; September 27, 2004; and March 8, 2005 reports that were submitted in response to OHRP's February 27, 2004 letter to EVMS, regarding allegations of noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human subjects (45 CFR part 46) involving the above-referenced research.

EVMS stated in its June 8, 2004 report that none of the studies linked to the allegations in OHRP's February 27, 2004 letter received funds from any federal department or agency. OHRP notes that the Multiple Project Assurance (M-1532) in effect from March 1984 until January 2003 was applicable to all research involving human subjects, regardless of sponsorship. The Federalwide Assurance (FWA-3956) approved on January 14, 2003 was similarly applicable until March 16, 2005, when the assurance was updated to remove the voluntary election to apply the assurance to all human subjects research regardless of source of support.

Based upon its review of EVMS's reports, OHRP makes the following determinations regarding the above-referenced research:

(1) In accordance with HHS regulations at 45 CFR46.103(b) and 46.109(a), the IRB must review and approve all non-exempt human subject research covered by an assurance. OHRP finds that certain non-exempt human subjects research was conducted without IRB review. OHRP finds that, prior to 2001, research was conducted at the Diabetes Institutes (The Leonard R. Strelitz Diabetes Institutes, a division of the EVMS Department of Internal Medicine) without appropriate IRB review and oversight. Representatives of the Diabetes Institutes were collecting data and specimens (blood and skin biopsies) as part of clinical practice and storing them for future research activities without obtaining IRB approval or informed consent from human subjects.

OHRP acknowledges the following statements include in EVMS's June 8, 2004 report:

> "... in early 2001 the EVMS IRB became aware of possible noncompliant research activities being conducted within the Diabetes Institutes. Representatives from the Office of Research...met with Dr. Aaron Vinik and the research staff of the Diabetes Institutes in February 2001."
>
> "During this meeting the attendees discussed the responsibilities of the Diabetes Institutes to the IRB with regard to review and approval of research activities. It was clear from the discussions that the researchers at the Diabetes Institutes were not aware that some of the activities being conducted at the Diabetes Institutes (such as retrospective chart review, data analyses, and specimen collection and storage) were considered research and required IRB review and approval.

(2) HHS regulations at 45 CFR 45.116 state that, except as provided elsewhere in the regulations, no investigator may involve a human being as a subject in research covered by the regulations unless the investigator has obtained the legally effective informed consent of the subjects or the subject's legally authorized representative. OHRP finds that the investigator initiated the above-referenced human subject research without meeting this requirement.

(3) OHRP finds that the EVMS IRB failed to obtain sufficient information for research study IRB # 01-03-EX-0110 to make the determinations required under HHS regulations at 45 CFR 46.111. In specific, OHRP notes the following:

> (a) OHRP notes the following statements contained in EVMS's June 8, 2004 report:

> "The review of the IRB and Diabetes Institutes records revealed that the IRB was not provided sufficient information to make the determinations required under HHS regulations at 45 CFR 46.111 for...IRB # 01-03-EX-0110."

(b) OHRP notes the following statements in EVMS's June 8, 2004 report regarding the approval of consents in 2001 purported to be associated with an "umbrella protocol":

> "In March 2001 the 'umbrella protocol', consisting of a list of six sub-study titles along with six Informed Consent Forms, were [*sic*] approved by the IRB via expedited review, and this was apparently done without review/approval of a protocol governing the use of those consent forms."
>
> "The records at the IRB and the Diabetes Institutes revealed that communications between the Diabetes Institutes and IRB to submit appropriate 'umbrella protocols' for review and approval by the IRB went unchecked resulting in the Diabetes Institutes utilizing informed consents that had no basis in actual protocols/conduct of research....Furthermore, the IRB continued to approve the Diabetes Institutes' requests to modify the approved Informed Consent Forms without further reviewing relevant information or requesting an appropriate research plan upon which IRB determinations could be made. Similarly, the IRB provided continuing review and approval of the 'umbrella consents' without adequate review of relevant or adequate information about the research."
>
> "The internal investigation/audit in response to your correspondence reveals that this deficiency, resulting in non-compliance, is the result of two major issues:
>
> - lack of understanding by the IRB and the research and IRB staff, as a result of inadequate training and education, regarding what constitutes 'research' and what review/oversight is required by both Principal Investigator and IRB; and
> - inadequate IRB oversight as a result of inadequate staff resources as well as training."

(c) OHRP acknowledges the following statement in EVMS's June 8, 2004 report regarding the content of consents purported to be associated with an "umbrella

protocol":

> "There were multiple versions of the Informed Consent Form for IRB Protocol # 01-02-FB-0034. Three Informed Consent Forms were dated July 7, 2003 and identified as version 3.0. However (*sic*) each version 3.0 included different information including number of site visits, procedures, study contacts and confidentiality information. Some of these documents contained contradictory information, including the number of study visits."

(4) It was alleged that some of the above serious noncompliance was brought to the attention of the IRB in February of 2001, but no reporting actions were taken, in contravention of HHS regulations at 45 CFR 46.103(b)(5). OHRP finds that EVMS failed to report serious or continuing noncompliance to OHRP, in contravention of HHS regulations at 45 CFR 46.103(b)(5).

(a) EVMS's June 8, 2004 report stated the following:

> "The EVMS IRB became aware in early 2001 of the potential for research being conducted at the Diabetes Institutes (The Leonard R. Strelitz Diabetes Institutes, a division of the EVMS Department of Internal Medicine) without appropriate IRB review and oversight. On February 1, 2001, the IRB Manager (Judy Schulz), and I (William Wasilenko, Associate Dean for Research) met with Dr. Aaron Vinik and the research staff of the Diabetes Institutes...to discuss this issue and determine corrective action to assure compliance."
>
> "The meeting between the IRB and the Diabetes Institutes also resulted in the mutual agreement to create a process to enable Dr. Vinik to continue to collect data and samples to be used for future research-related purposes - with the understanding that an 'umbrella protocol' would be developed which would outline this process...At that time, the Diabetes Institutes voluntarily suspended all 'non-IRB approved' research activities and agreed to not use any data or specimens in any future studies from any clinical service patient who did not give permission or who could not be reached for permission."
>
> "At the regularly scheduled meeting of the IRB on February 20, 2001, the

IRB was informed of the discussion between the Diabetes Institutes and the Office of Research....The IRB voted to accept the Diabetes Institutes' voluntary suspension of all non-IRB approved research with the expectation that all research activities be brought into compliance by the creation of an 'umbrella protocol' under which various sub-studies would be conducted - which are to be reviewed and approved by the IRB prior to initiating the research."

"The IRB also voted not to report the Diabetes Institutes' apparent violations to the appropriate regulatory authorities, such as OHRP based on its judgment at the time that the violations did not appear serious enough to warrant the filing of a report."

(b) EVMS's IRB Minutes of February 20, 2001 stated the following:

"On January 16, 2001, the IRB Chair indicated that he would report back to the Board regarding [name of principal investigator]'s unapproved, but finished, IRB study.

"This study involved the collection of demographics from patient charts for subjects identified by initials and date of birth. No subjects were injured, nor was confidentiality breached. After discussion regarding this study, the Board voted *not* (emphasis in original) to report this infraction to either the FDA or OHRP...The Board felt that federal notification was not appropriate because the study involved a chart review, subjects had no extra visits or procedures, no subjects were injured, there was no breach of confidentiality, and [name of principal investigator] assured the Board that 'this would not happen again.' However, the Board requested that a letter be sent to [name of principal investigator] reinforcing that all human subjects research should be submitted to the Board for review."

"[Name of IRB Chair] summarized a situation similar to that of [name of principal investigator] with Dr. Vinik...After discussion regarding this issue, the Board voted *not* (emphasis in original) to report the unapproved studies to either the FDA or OHRP...The Board felt that federal

> notification was not appropriate because the study involved anonymous discarded tissue samples and chart reviews. Subjects had no extra visits or procedures, no subjects were injured, there was no breach of confidentiality, and Dr. Vinik assured the Board that 'this would not happen again.' However, the Board requested that a letter be sent to Dr. Vinik reinforcing that all human subjects research should be submitted to the Board for review."

Corrective Action for Item #4: OHRP notes that the EVMS Standard Operating Procedures, version date March 2003, includes the following statement in the section entitled, "Monitoring of Studies and/or Reporting Noncompliance": "The Institutional Official/Director of Research is responsible for reporting to appropriate officials, the FDA (if appropriate), and OHRP (if appropriate) within 5 working days of his/her receipt of the report of: 1. Any anticipated problems involving risks to human subjects or others; 2. Any instances of serious or continuing noncompliance with regulations or determinations of the IRB; and 3. Any suspensions or terminations of IRB approval other than study terminations due to a lapse in continuing review."

OHRP recommends that the IRB written procedures for reporting serious noncompliance to OHRP note that the following noncompliance is always considered serious and therefore needs to be reported:

- Nonexempt human subjects research conducted without IRB review and approval;
- Research conducted without appropriate informed consent; and
- Substantive changes made to research without prior IRB review and approval (when those changes are not required to eliminate apparent immediate hazards to subjects.)

(5) OHRP finds that IRB members were not advised of a research protocol approved at time of initial or continuing review under an expedited review procedure as required by HHS regulations at 45 CFR 46.110(c).

In particular, OHRP notes the following statements contained in EVMS's June 8, 2004 report:

> "The IRB records do not clearly show how the IRB arrived at the decision to approve Informed Consent Forms relating to the 'umbrella protocol' (IRB Number 01-03-EX-0110). This research and the six corresponding consent forms received expedited approval by the IRB chair in March 2001 (*The IRB Meeting Minutes at that time failed to include documentation that the IRB was informed of this*

action)(emphasis in original). Multiple modifications to the consent forms were later reviewed and approved by expedited review and noted in the IRB meeting minutes."

Corrective Actions for Item #5: OHRP notes that the EVMS Standard Operating Procedures, version date March 2003, includes the following statement in the section entitled, "IRB Evaluation of Expedited Review Studies": "If the study qualifies for Expedited Review and is approved, a notice confirming approval for the study will be sent to the principal investigator and his/her institution is notified via the IRB Minutes...The minutes of the board meeting will reflect the approval of the study through the expedited review process and will include the specific Federal criteria used in making the Expedited Review decision.

Additional Corrective Actions: The following corrective action were described in EVMS's June 8, 2004, July 26, 2004, September 27, 2004 and March 8, 2005 reports.

As a result of OHRP's February 27, 2004, the following corrective actions were taken, as detailed in EVMS's June 8, 2004 report:

- Suspension of Dr. Vinik's investigator-initiated studies;
- Maintain suspension of enrollment of new subjects for all research conducted at Diabetes Institute pending assurance of appropriate IRB review and adequate assurance of integrity in the conduct of the study and in preparation and maintenance of study records;
- Creation and implementation of comprehensive corrective plan, including:
  - Mandatory education/training on research regulations and ethical principles of all research faculty and personnel;
  - Mandatory education/training of IRB members and staff;
  - Review of standard operating procedures for research conducted at Diabetes Institutes;
  - Evaluation of IRB workflow/load and allocation of appropriate technical and personnel resources;
  - Evaluation for compliance of overall research program within EVMS, and
  - Establishment of an ongoing QA/QC program of all research activities to include ongoing education/training activities.

In its July 26, 2004 update to the June 8, 2004 report, EVMS reported that it had lifted the suspension of Dr. Vinik's pharmaceutical-sponsored clinical trials upon completion of required training in good clinical practice by Dr. Vinik. EVMS provided information about the various education/training programs attended by Diabetes Institutes investigators, research coordinators, residents and staff, IRB Office staff and IRB members. EVMS also reported that it has purchased template standard operating procedures (SOPs) for the IRB and IRB Office and would

begin comparing and contrasting those procedures with existing procedures to optimize methods related to protocol review, processing, and compliance within the IRB Office and with the IRB. In its September 27, 2004 update, EVMS indicated that it had a received a complete assessment from an independent consultant regarding IRB workload and staffing issues which was undergoing review and had adopted standard operating procedures for good clinical research practices for EVMS investigators. EVMS indicated that it now requires refresher education in human subjects protections by investigators/staff. EVMS reported that it had developed new SOPs for audits and had begun the recruitment of an additional research compliance coordinator to assist with audits of IRB approved studies. EVMS also indicated that a salary adjustment had been made for key IRB Office personnel to promote retention and recruitment of professional IRB staff.

In its October 8, 2004 update, EVMS reported that Dr. Vinik and his research team had completed refresher courses in human subjects protections, developed standard operating procedures for conducting studies involving humans, and supported the certification process for key investigatory staff. As a result of meeting these IRB requirements and pending re-review by the EVMS IRB of Dr. Vinik's investigator-initiated studies, the suspension of Dr. Vinik's research activities was to be lifted.

In its March 8, 2005 update, EVMS reported that the IRB is now monitoring completion of refresher training by all investigators/staff before granting final approval to protocols. EVMS also reported that, in response to the IRB workload assessment by an independent consultant, it had hired an additional IRB administrator. All IRB administrators have now completed an IRB administrator training course. In addition, EVMS reported that it was in the process of installing a recently purchased IRB database system. An internal auditor has begun working with research compliance coordinators in the Office of Research to audit investigators for good clinical practice and IRB procedural compliance and to monitor IRB activities. To date, the audit group had audited the investigator-initiated studies in the Diabetes Institutes and had begun audits of research in other departments. EVMS also reported that it has created an Office of Research Subjects Protections, which separates the sponsored programs oversight from the human subjects protections program at EVMS and provides administrative support to the IRB.

OHRP has determined that the above corrective actions adequately address the findings noted above and are appropriate under the EVMS Assurance. As a result, there should be no need for further involvement of OHRP in this matter. Of course, OHRP must be notified should new information be identified which might alter this determination.

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

Sincerely,

Karena Cooper, J.D., M.S.W.
Compliance Oversight Coordinator
Office for Human Research Protections

cc: Dr. Gerald Pepe, Interim Dean and Provost, EVMS
Dr. William J. Wasilenko, Associate Dean for Research, EVMS
Dr. Aaron Vinik, EVMS
Dr. Scott Kruger, IRB #1 Chair, EVMS
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