DEPARTMENT OF HEALTH & HUMAN SERVICES

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May 1, 2008

Ronald W. Swinfard, M.D.
Chief Medical Officer
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Cedar Crest & I-78
PO Box 689
Allentown, PA 18104

RE: Human Research Protections Under Federalwide Assurance FWA-624

Research Project: **A Randomized Comparison of Heart Rate Targeted vs. Fixed Dose Beta Blockade in Intermediate and High Risk Patients Undergoing Vascular Surgery**

Principal Investigator: **Martin Matsumura, M.D.**

Dear Dr. Swinfard:

Thank you for your June 26, 2007 report in response to our May 24, 2007 letter regarding research conducted under the above-referenced research project. Based on the information submitted to us, we make the following determination(s):

A. **Determinations Regarding the Above-Referenced Research**

(1) Department of Health and Human Services (HHS) regulations at 45 CFR 46.103(b)(4)(iii) provide that an institutional review board (IRB) shall review and approve all proposed changes in a research activity, during the period for which IRB approval has already been given, prior to initiation of such changes, except when necessary to eliminate apparent immediate hazards to the subjects. It was alleged that the Lehigh Valley Hospital (LVH) IRB did not review and approve the following protocol changes prior to initiation:

(a) Enrolling the complainant's husband into the research even though he was ineligible due to treatment with the antiarrhythmic medication, digoxin.

We have determined that there is no proven violation of HHS regulations at 45 CFR 46.103(b)(4)(iii) regarding this allegation. We base this determination on the following information, which was provided by LVH in response to this allegation:

"1. Digoxin does not possess any of accepted classes of Vaughan-Williams antiarrhythmic propoerties and as such is not traditionally classified as an antiarrhythmic.

"2. The specific purpose of this exclusion criterion was to avoid enrollment of patients taking medications that possess intrinsic beta-blocking properties (i.e., amiodorone and sotalol), which could potentially affect he pharmacodynamic effects of the intervention under study (i.e., perioperative beta blockade). Such exclusion criteria have been used in prior studies of the effect of perioperative beta-blockade for the same reason. (Yang, 2006)."

Based on this explanation, we conclude the use of the drug digoxin was not – and did not need to be – within the scope of the stated exclusion criteria for the protocol. The classic scheme for categorizing antiarrhythmic drugs includes categories I thru IV, none of which includes digoxin. While we acknowledge that in some review articles and text books, digoxin is sometime listed as a category V or miscellaneous antiarrhythmic agent, we note that it generally lacks antiarrhythmic properties. Instead, digoxin is an agent that is used to control the heart rate in patients with atrial flutter or atrial fibrillation without actually targeting the underlying arrhythmia. Of note, patients are frequently treated with both beta blockers and digoxin, so use of digoxin would not have been a contraindication to using beta blockers in the subject population for this research.

(b) Failing to have a cardiologist assess the subject's eligibility for the study, as required by the protocol.

We have determined that there is no proven violation of HHS regulations at 45 CFR 46.103(b)(4)(iii) regarding this allegation. We reviewed the LVH IRB-approved protocol and note that the protocol did not require that the assessment/screening be conducted by a cardiologist; instead, the protocol stated that "Patients will be screened for cardiac risk factors prior to surgery." Notwithstanding the protocol requirements, we acknowledge LVH's statement that the principal investigator confirmed with the subject's primary cardiologist that the subject was a candidate for the study.

(2) HHS regulations at 45 CFR 46.111(a)(1) delineate that the following criterion must be satisfied in order for an IRB to approve research covered by the regulations:

Risks to subjects are minimized: (i) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

It was alleged that the LVH IRB approved the above-referenced research even though the IRB failed to ensure that risks to subjects are minimized, as required by HHS regulations at 45 CFR 46.111(a). In specific, it was alleged that the exclusion criteria of a resting heart rate less than 55 beats per minute or systolic blood pressure less than 90, unless the subject is already being treated with a beta-blocker, did not adequately minimize risks to subjects. It

was also alleged that even in the presence of treatment with beta-blocker, such low heart rate or blood pressure should have been an exclusion criterion.

Based on the following response provided by LVH, we have determined that there is no proven violation of HHS regulations at 45 CFR 46.111(a) regarding this allegation:

- The exclusion criteria only applied when determining whether a patient was a potential study candidate; these criteria were not the parameters by which beta-blocker dosing decisions were made during the study;
- The hemodynamic parameters by which dosing decisions were made were consistent with the American College of Cardiology/American Heart Association 2006 Focused Update on Perioperative Beta-Blocker Therapy and typical clinical practice with LVH;
- Literature supports the practice of targeting a heart rate of 60 bpm or below in the perioperative period to achieve maximum cardioprotection with the use of perioperative beta-blocking agents; and
- Dosing parameters set by the study team are supported by the lack of adverse events related to hypotension or bradycardia for the entire study.

Based on the information submitted to us, we have the following questions and concerns:

B. **Question Regarding the Above-Referenced Research**

[Redacted]

C. **Questions and Concerns Regarding the LVH System for Protecting Human Subjects**

[Redacted]

[Redacted]

D. **Recommendations**

Based on the information submitted to us, we have the following recommendations regarding the document entitled "Research Participant Protection Office Polices and Procedures for the Institutional Review Boards of Lehigh Valley Hospital and Health Network" (hereinafter referred to as LVH IRB Polices and Procedures Document):

(1) We note that various policies within the LVH IRB Polices and Procedures Document distinguish between voting IRB members and non-voting IRB members. See Policy: IRB I.F Conflict of Interest; Policy IRB II.A; Composition of the IRB; Policy II.C.2; Member Responsibilities – Regular Non-voting member; Policy IRB III.B; IRB Meeting Administration. Please note that there is no such entity as a non-voting IRB member under HHS regulations at 45 CFR part 46. Thus, we recommend revising these policies accordingly.

(2) Policy IRB III.B; IRB Meeting Administration. Section 3.5.1 of this policy does not reflect that meeting minutes will include the basis for disapproving research as required by HHS regulations at 45 CFR 46.115(a)(2). We note that LVH equates "tabling of the research" with deferral, not disapproval. See IRB Voting Member Checklist and Summary: Convened IRB Review Form; Section Four. We recommend revising this policy to reflect that LVH IRB meeting minutes will include, among other things, the basis for disapproving research as required by HHS regulations at 45 CFR 46.115(a)(2).

(3) Policy IRB IV.C; Initial Review – Criteria for IRB Approval. This policy provides that "All research proposals that intend to enroll human subjects must meet certain criteria before study related procedures can be initiated." We note that reference to "study related procedures" in this policy may be too narrow. As you may be aware, HHS regulations at 45 CFR 46.109(a) provides that an IRB must review and approve all research activities covered by this policy [45 CFR 46], including all research interventions or interactions with a living individual that result in the collection of data about the individual. According to the definition of 'human subject' at 45 CFR 46.102(f), an intervention "includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes." An interaction includes "communication or interpersonal contact between investigator and subject;" e.g., collecting eligibility information from potential subjects prior to initiating study-related procedures. Thus, an IRB must review and approve all research activities, including all recruitment interactions with a living individual, before study related activities can occur given that these activities result in the collection of data about living individuals

for research purposes. Based on this explanation, we recommend that LVH consider revising this policy to more clearly define the scope of "study related procedures."

(4) Policy IRB IV.I; Categories of Action. We note that this policy states that the LVH IRB calculates the approval date for conditionally approved studies, i.e., studies in which approval is withheld pending minor clarifications, based on the date that the required information or materials are approved by the IRB. HHS regulations at 45 CFR 46.108(b) and .109(e) require, respectively, that (1) except when an expedited review procedure is used, each IRB must review proposed research at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas; and (2) an IRB must conduct continuing review of research at intervals appropriate to the degree of risk, but not less frequently than once per year. According to the Office for Human Research Protections (OHRP) Continuing Review Guidance document, IRBs should focus on the date of the convened meeting at which the IRB "conditional approval" occurred when determining the date by which continuing review must occur, and not the date that the required information or materials are approved by the IRB. See Scenario 2 in the OHRP Guidance on Continuing Review (http://www.hhs.gov/ohrp/humansubjects/guidance/contrev0107.htm).

Please submit your responses to the questions and concerns noted above so that we receive them no later than June 13, 2008. If during your review you identify additional areas of noncompliance with HHS regulations for the protection of human subjects, please provide corrective action plans that have been or will be implemented to address the noncompliance.

We appreciate 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,

Lisa A. Rooney, J.D.
Compliance Oversight Coordinator

cc: Dr. Scott J. Lipkin, Director, Research Participation Protection Office, and Chair, IRB #1, Lehigh Valley Hosp & Hlth Network
Mr. Christopher Morabito, IRB Chair, Lehigh Valley Hosp & Hlth Network IRB #2
Dr. Martin Matsumura, Lehigh Valley Hospital
Dr. Andrew C. von Eschenbach, Commissioner, FDA
Dr. Joanne R. Less, FDA