DEPARTMENT OF HEALTH & HUMAN SERVICES

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April 5, 2004

Jane E. Henney, M.D.
Senior Vice President and Provost
for Health Affairs
University of Cincinnati
Room 250, Health Professions Building
Eden and Albert Sabin Way
Cincinnati, OH 45267-0663

VIA FEDERAL EXPRESS

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1138 and Federalwide Assurance FWA-3152

Research Project: Specialized Center of Research (SCoR) in Heart Failure
Principal Investigator: Lynne E. Wagoner, M.D., F.A.C.C.
Project Number: 93-07-26-01

Dear Dr. Henney:

The Office for Human Research Protections (OHRP) has reviewed the University of Cincinnati's (UC) report dated February 19, 2004, responding to allegations of noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human research subjects (45 CFR part 46) in the above-referenced research.

In its letter of January 6, 2004, OHRP raised the following concerns:

> (1) HHS regulations at 45 CFR 46.116 require that legally effective informed consent be obtained prior to involving human subjects in research. HHS regulations at 45 CFR 46.117 require that consent of the subject be documented. It was alleged that for some research subjects described in the above-referenced protocol, legally effective informed consent was not

obtained or documented.

Based upon UC's report of February 19, 2004, OHRP finds that permission was obtained from all research subjects in the above-referenced protocol. However, OHRP notes that prior to March 1999, the informed consent document used and approved by the UC Institutional Review Board (IRB) failed to adequately address the elements of informed consent required by HHS regulations at 45 CFR 46.116.

Corrective Action: OHRP notes that since March 1999, UC has ceased use of the University of Cincinnati Hospital form entitled, "Consent for Treatment, Releases and Financial Agreement,"and begun use of the form entitled, "Consent to Participate in a Genetics Research Study." OHRP acknowledges that the informed consent document approved by the UC IRB on October 24, 2001 includes the elements required for informed consent as set forth in HHS regulations at 45 CFR 46.116.

OHRP also acknowledges the efforts undertaken at UC to educate and train research teams in the conduct of human subjects research, and the specific measures undertaken by the UC IRB to communicate with the research community on subjects such as obtaining informed consent, correcting exculpatory language, and requesting waivers of informed consent.

(2) HHS regulations at 45 CFR 46.116 require that informed consent information be in language understandable to the subject or the subject's legally authorized representative. The informed consent documents approved by the UC IRB for the substudy entitled "SCoR in Heart Failure: DNA and Exercise in Control Subjects Substudy" (IRB #99-11-15-03-EE), and for the substudy entitled, "SCoR in Heart Failure: DNA" (IRB #93-7-26-1; Study #HL52318-6) appeared to include complex language that would not be understandable to all subjects.

Corrective Action: Based upon UC's February 19, 2004 report, OHRP acknowledges that Protocol #99-11-15-03-EE is no longer enrolling subjects; therefore, the informed consent document is no longer used. In response to OHRP's specific concerns raised in the letter of January 6, 2004, OHRP notes that UC has taken the following corrective actions:

(a) Protocol #93-7-26-1 uses a revised consent form that UC states does not contain complex language.

(b) UC has reviewed all of the related active protocols, and states that complex language does not appear in the informed consent documents currently used.

(3) HHS regulations at 45 CFR 46.109(e) require that continuing review be conducted at intervals appropriate to the degree of risk, and not less than once per year. Continuing IRB review of research must be substantive and meaningful. OHRP finds that the study protocol was reviewed on September 27, 2000 and was next reviewed on October 24, 2001. Thus, the protocol was not reviewed by the UC IRB at least annually, as required by the regulations.

Corrective Action: OHRP acknowledges UC's statement that since the fall of 2001, the UC IRB has required materials to be submitted for reapproval and continuing review at least one month prior to the expiration date. The UC IRB reminds investigators when materials are overdue, and the investigators are informed that if materials are not submitted in a manner permitting timely review, all enrollment must cease until the study has been reviewed. For further guidance, please note that OHRP guidance on continuing review includes a section entitled, "How is the Continuing Review Date Determined?" (http://ohrp.osophs.dhhs.gov/humansubjects/guidance/contrev2002.htm).

(4) OHRP finds that the IRB had insufficient information to make the determinations required under 45 CFR 46.111 for continuing review of this research prior to March 1999. In specific, the progress reports did not include all subjects who participated in blood draws for the research.

Corrective Action: OHRP notes that beginning on March 31, 1999, the UC IRB has required that all subjects enrolled in studies (including those undergoing blood draws only) must be reported to the IRB on the annual progress report form.

(5) HHS regulations at 45 CFR 46.116 prohibit any exculpatory language in informed consent through which the subject is made to waive, or appear to waive, any of the subject's legal rights. OHRP finds the language in the UC IRB-approved informed consent documents for the substudy entitled, "SCoR in Heart Failure: DNA and Exercise in Control Subjects Substudy" (IRB #99-11-15-03-EE) and for the substudy entitled, "SCoR in Heart Failure: DNA" (IRB #93-7-26-1; Study #HL52318-6), stating that "I [the subject] will, unless otherwise agreed by the principal investigator, have no rights to share in any profit...." is exculpatory.

Corrective Action: OHRP acknowledges UC's statement that the UC IRB has revised the informed consent document to comply with HHS requirements, and the newly revised informed consent document has been submitted to the UC IRB for approval. OHRP also acknowledges that the UC IRB provides current information to investigators regarding eliminating exculpatory language from informed consent documents.

OHRP finds that the corrective actions above adequately address OHRP's concerns and findings, and are appropriate under the UC MPA and FWA. As a result of these determinations, there should be no need for further involvement of OHRP in this matter. Of course, OHRP must be notified should new information be identified that might alter this determination.

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

Sincerely,

Rina Hakimian, J.D., M.P.H.
Compliance Oversight Coordinator
Division of Compliance Oversight

cc: Ms. Mary A. Belkis, UC
Dr. Peter T. Frame, Chair, IRB #1A, UC
Dr. Margaret Miller, Chair, IRB #2XM, UC
Dr. James J. Mulchahey, Chair, IRB #1B, UC
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