DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

FOR US POSTAL SERVICE DELIVERY:
Office for Human Research Protections
6100 Executive Boulevard, Suite 3B01
National Institutes of Health (MSC 7507)
Rockville, Maryland 20892-7507

FOR HAND DELIVERY OR EXPRESS MAIL:
Office for Human Research Protections
6100 Executive Boulevard, Suite 3B01
Rockville, Maryland 20852

Telephone: 301-435-0668
FAX: 301-402-2071
E-mail: mcneillp@od.nih.gov

May 10, 2001

Jack O. Burns, Ph.D.
Vice Provost for Research
Office of Research
University of Missouri-Columbia
205 Jesse Hall
Columbia, MO 65211

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1502

Research Activity: Curtis, JJ, *et al.* Continuous Warm Blood Cardioplegia: A Randomized Prospective Clinical Comparison. *International Journal of Angiology.* 5:212-218; 1996.

Dear Dr. Burns:

The Office for Human Research Protections (OHRP) has reviewed you report of February 22, 2001 regarding the above referenced research. Based on the documents provided in you report, OHRP acknowledges the following corrective actions taken by the University of Missouri-Columbia (UMC):

(1) UMC has developed a satisfactory plan to contact all surviving subjects (or relatives of all deceased subjects) of the above referenced research. The text of the draft letters intended to inform the subjects, or survivors thereof, appropriately describes their unwitting participation in the research, the risks associated with the research, and the nature of the investigators noncompliance.

OHRP finds that the proposed procedure for contacting and debriefing subjects which was approved by the UMC IRB is acceptable. OHRP concurs with this procedure.

Required Action: By June 21, 2001, please submit to OHRP a progress report on UMC's implementation of this debriefing procedure. Please include with your report a copy of one of the letters used to debrief both the subjects or surviving relatives of subjects (with redaction of subject name and address).

(2) UMC has conducted a campus-wide audit of all research involving human subjects and has appropriately suspended all research studies which had not had proper Institutional Review Board (IRB) approval. OHRP acknowledges that no suspended research study will be allowed to continue until receiving proper IRB approval.

(3) UMC has developed an adequate plan to educate all research investigators, IRB members, and all IRB staff on an ongoing basis about the ethical principles and regulatory requirements for the protection of human subjects. OHRP notes that UMC has held a series of workshops for faculty and researchers and developed a videotape which is available to faculty and others regarding the protection of human subjects. OHRP acknowledges UMC's efforts in establishing a web site dedicated to IRB education issues and the fact that all UMC IRB compliance officers, IRB chairs and members have undergone appropriate training.

Additionally, UMC has indicated that Dr. Curtis and his staff have been educated regarding HHS regulations for the protection of human subjects

(4) UMC has developed appropriate written standard operating procedures (SOP) for its IRBs and Administrative offices for the following topics:

(a) The procedures which the UMC IRBs will follow for conducting their initial and continuing review of research.

(b) The procedures which the UMC IRBs will follow for reporting their findings and actions regarding initial and continuing review to the institution.

(c) The procedures which the UMC IRBs will follow for determining which projects require review more often than annually.

(d) The procedures which the UMC IRBs will follow for determining which projects need verification from sources other than the investigators that no material changes have occurred since the previous IRB review.

(e) The procedures which the UMC IRBs will follow for ensuring prompt reporting to the IRBs of proposed changes in a research activity, and for ensuring that such changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to the subject.

(f) The procedures which the UMC IRBs will follow for ensuring prompt reporting to the IRBs, appropriate institutional officials, the head of any supporting Federal Department or Agency, and OHRP regarding (i) any unanticipated problems involving risks to subjects or others; (ii) any serious or continuing noncompliance with the requirements of 45 CFR Part 46, or the

requirements or determinations of the IRB; (iii) any suspension or termination of IRB approval of research.

(5) The UMC IRBs have revised their SOPs regarding the taking and archiving of minutes to ensure that IRB meetings document all information required by Department of Health and Human Services (HHS) regulations at 45 CFR 46.115(a)(2).

(6) UMC has developed polices to ensure that continuing IRB review of research is substantive and in compliance with HHS regulations.

(7) UMC has indicated that it has amended procedures that indicate that the Compliance Officer does not have the authority to approve changes to IRB approved protocols or informed consent documents.

OHRP notes that Health Sciences IRB SOP 1.6.2.1 allows for the Compliance Officer to make minor and administrative changes to IRB approved protocols. HHS regulations at 45 CFR 46.110 stipulates that under an expedited review procedure, the review may be carried out by the chairperson or by one or more experienced reviewers designated by the chairperson from among the members of the IRB. Please revise the UMC IRB policies and procedures accordingly.

(8) UMC has presented the Cardiovascular Surgery Patient Data Registry (CVS-PDR) to the IRB for review and approval.

OHRP acknowledges that the CVS-PDR was approved by a joint meeting of the UMC IRBs on February 20, 2001 and that the Chair of the Department of Surgery is listed as its principal investigator.

OHRP finds that the corrective actions (2 - 8) listed above adequately address the issues raised in its November 22, 2000 letter to UMC. Based on this determination, there should be no further involvement of OHRP relating to items (2 - 8) listed above.

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

(9) Regarding the Health Sciences IRB SOPs, OHRP would like to note the following:

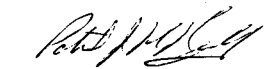
(a) The Health Sciences IRB SOP 1.6.3.1 indicates that adverse events will be reported to and reviewed by the IRB. This SOP does not indicate that the head of any supporting Federal Department or Agency, and OHRP will be notified of any unanticipated problems involving risks to subjects or others. OHRP acknowledges that Health Sciences IRB SOP 1.1.4.1 requires reporting to Federal Agencies and OHRP. OHRP recommends that SOP 1.6.1.1 cross reference SOP 1.1.4.1 to ensure that proper notification occurs as required under HHS regulations.

(b) The Health Sciences IRB SOP 1.7.1.1 describes the emergency use of a test article. OHRP would like to note that nothing in the HHS regulations at 45 CFR Part 46 is intended to limit the authority of a physician to provide emergency medical care, to the extent the physician is permitted to do so under applicable Federal, State, or local law. However, when emergency medical care is initiated without the physician obtaining and documenting the legally effective informed consent of the patient or the patient's legally authorized representative for participation in research (unless the IRB has appropriately waived such requirements), the patient may not be considered a research subject. Such emergency care may not be claimed as research, nor may any data regarding such care be included in any report of a research activity.

(c) UMC has indicated that a prisoner representative has been appointed as a voting member of the IRB for review of research involving prisoners, as required at 45 CFR 46.304(b). Health Sciences IRB SOP 1.10.1.1 indicates that the IRB will "invite a prison representative with the appropriate background who is not a member of the board, to review the proposal and consult on behalf of the prisoner's rights." OHRP would like to reiterate that regulations at 45 CFR 46.304(b) require that the prisoner representative must be a voting member of the IRB. This SOP should be revised accordingly.

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 questions.

Sincerely,



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

cc: Dr. Charles M. Borduin, Chair, IRB-01XM., UMC
Dr. L. Wayne Hess, Chair, IRB-02, UMC
Dr. Jack Curtis, UMC
Commissioner, FDA
Dr. David Lepay, FDA
Dr. James F. McCormack, FDA
Dr. John Mather, ORCA, Department of Veterans Affairs
Dr. Greg Koski, OHRP
Dr. Melody H. Lin, OHRP
Mr. George Gasparis, OHRP

Dr. Jeffrey M. Cohen, OHRP
Ms. Roslyn Edson, OHRP
Mr. Barry Bowman, OHRP