DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
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November 30, 2001

William J. Wasilenko, Ph.D.
Director, Office of Research
Eastern Virginia Medical School
Lewis Hall, Suite 2054
P.O. Box 1980
Norfolk, VA 23501-1980

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1355
Research Project: CRC/Merck Clinical Trial (IRB #13-07-99-0021)
Principal Investigator: Jay. M. Baker, M.D.

Dear Dr. Wasilenko:

The Office for Human Research Protections (OHRP), formerly the Office for Protection from Research Risks (OPRR), has reviewed your letters dated May 19, 2000 and October 30, 2001, responding to allegations of noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human research subjects that were presented in OPRR's March 24, 2000 letter regarding the above-referenced research. OHRP apologizes for the delay in its response.

The allegations involved the following:

(1) A human research subject may have suffered an unexpected problem involving risk to the subject during participation in the above-referenced research at the Clinical Research Center (CRC) of the Eastern Virginia Medical School (EVMS).

(2) Such problem was not promptly reported to the institutional review board (IRB), appropriate institutional officials, and OPRR as required by HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5).

(3) EVMS may have failed to comply with its obligation set forth in informed consent documentation provided to the subject, to provide the reasonable costs of medical treatment for

injury or illness resulting from the study intervention.

Based upon its review of your letters, OHRP finds no evidence to substantiate the above allegations. In particular, OHRP notes the following:

(1) At OHRP's request, EVMS investigated the above allegations. Upon review, including interviews with the investigators and the clinical coordinator, and independent medical records review, EVMS found that the investigators correctly concluded that the subject's unanticipated symptoms had no likely connection to the study drug. OHRP finds no evidence contradicting EVMS' conclusion that the subject's symptoms were not related to participation in the research study and therefore not subject to the reporting requirements of HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5).

(2) According to EVMS' reviewed medical records, the subject presented to a hospital emergency room on November 28, 1999, an outpatient cardiologist on November 29, 1999, and a general practitioner on November 30, 1999. On December 3, 1999, the subject returned to EVMS to discontinue her participation in the study. On January 5, 2000, the subject had an echocardiogram and on January 17, 2000, a follow-up cardiology visit. EVMS states that the study sponsor reimbursed the subject's expenses for non-EVMS medical care and that the subject was not charged for any care she received at EVMS facilities.

As a result of OHRP's findings, there should be no need for further involvement of OHRP in this matter. However, OHRP should be notified if new information is identified which might alter this determination.

At this time, OHRP offers the following additional guidance to EVMS:

(1) EVMS' current procedures for reporting adverse events (April 2001 Standard Operating Procedures, page 30) appear to indicate that investigators need to report to the IRB only "serious unexpected adverse events" which, for example, result in inpatient hospitalization or significant disability or incapacity. HHS regulations do not reference "serious adverse events," but instead refer to "unanticipated problems involving risks to subjects or others." OHRP is concerned that limiting required reporting of unanticipated problems to "serious adverse events" may result in a failure to report under HHS regulations at 45 CFR 46.103(b)(5). OHRP recommends that EVMS clarify in its reporting policies that investigators involved in human subject research should report to the IRB all unanticipated problems involving risks to subjects or others.

OHRP appreciates the continued commitment of your institution to the protection of human research subjects. Please feel free to contact me should you have any questions.

Sincerely,

Carol J. Weil, J.D.
Compliance Oversight Coordinator

cc: Director, OHRP
Dr. Michael A. Carome, OHRP
Dr. Michael Bono, IRB Chair
Dr. David F. Archer, CRC/EVMS
Raymond Gilmartin, Merck & Co.
Therese Babb, R.N., CRC/EVMS
Dr. Jay M. Baker, CRC/EVMS