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: 301-402-5567
FAX: 301-402-2071
E-mail: mc2a@nih.gov

December 20, 2000

William A. Peck, M.D.
Executive Vice Chancellor and Dean for Medical Affairs
Washington University School of Medicine
660 South Euclid, Box 8106
St. Louis, MO 63110

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1123

Research Project: Preventing Depression Recurrence in Diabetes
Principal Investigator: Patrick J. Lustman, Ph.D.
IRB Project Number: HSC# 96-0806
HHS Project Number: R01 DK53060

Dear Dr. Peck:

The Office for Human Research Protections (OHRP) has reviewed Dr. Philip Ludbrook's December 8, 2000 report regarding the above referenced research and the system for protection of human subjects at the Washington University School of Medicine (WU).

Based upon its review of Dr. Ludbrook's report, OHRP makes the following determinations:

(1) Department of Health and Human Services (HHS) regulations at 45 CFR 46.111(a)(1) require that, in order to approve research, the IRB must determine that risks to subjects are minimized by using procedures which are consistent with sound research design and which do not necessarily expose subjects to risk. OHRP finds that this requirement was satisfied by the WU IRB when it conducted its initial and continuing review of the above referenced research project.

(2) HHS regulations at 45 CFR 46.103(b)(4)(iii) require that the IRB 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. OHRP finds that this requirement was satisfied for all protocol changes involving the above referenced research project.

(3) OHRP finds that the revisions to the informed consent document for the above referenced research that were described in Dr. Ludbrook's report adequately address the concerns raised in OHRP's October 11, 2000 letter.

(4) HHS regulations at 45 CFR 46.103(f) require that an institution with an approved assurance shall certify that each *application* for research has been reviewed and approved by the IRB. OHRP finds that the WU IRBs receive and review Federal grant applications proposing human subject research.

(5) Continuing IRB review of research must be substantive and meaningful. In conducting continuing review of research not eligible for expedited review, all IRB members should at least receive and review a protocol summary and a status report on the progress of the research, including (a) the number of subjects accrued; (b) a description of any adverse events or unanticipated problems involving risks to subjects or others and of any withdrawal of subjects from the research or complaints about the research; (c) a summary of any recent literature, findings obtained thus far, amendments or modifications to the research since the last review, reports on multi-center trials and any other relevant information, especially information about risks associated with the research; and (d) a copy of the current informed consent document. Primary reviewer systems may be employed, so long as the full IRB receives the above information. Primary reviewers should also receive a copy of the complete protocol including any modifications previously approved by the IRB. Furthermore, the minutes of IRB meetings should document separate deliberations, actions, and votes for each protocol undergoing continuing review by the convened IRB.

OHRP finds that the WU IRBs' current procedures for conducting continuing review conform to the above guidance.

(6) HHS regulations at 45 CFR 46.115(a)(2) require that the minutes of IRB meetings document the vote on all IRB actions (i.e., actions related to initial review, continuing review, and review of protocol modifications) including the number of members voting for, against, and abstaining. In order to document the continued existence of a quorum, OHRP strongly recommends that votes be recorded in the minutes using the following format: Total = 15; Vote: For-14, Opposed-0, Abstained-1 (NAME). OHRP finds that the minutes of the WU IRB meetings now satisfy this requirement.

Furthermore, OHRP notes that the minutes for the WU IRB meetings clearly document high-quality, detailed, and substantive reviews of research protocols that reflect the IRB's understanding of important ethical issues and regulatory requirements related to the protection of human subjects.

(7) HHS regulations at 45 CFR 46.108 require that, except when an expedited review procedure is used, the IRB review proposed research at convened meetings at which a

majority of the members of the IRB are present. OHRP finds that the WU IRB-02 failed to meet this requirement for the August 13, 1997 meeting (7 voting members present, 8 voting members absent). OHRP acknowledges that this was an isolated event. Furthermore, OHRP finds that WU has taken appropriate corrective actions to ensure that its IRBs will not take any actions unless a majority of IRB members are in attendance at the convened meeting.

(8) OHRP finds that the revised WU written IRB policies and procedures adequately describe each of the procedures referenced under HHS regulations at 45 CFR 46.103(b)(4) and (5).

As a result of the above 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 which might alter these determinations.

At this time OHRP provides the following additional guidance:

(9) OHRP notes that the WU IRBs sometimes approve research contingent upon substantive modifications or clarifications without requiring additional review by the convened IRB. OHRP recommends the following guidelines in such cases: (a) When the convened IRB requests substantive clarifications, protocol modifications, or informed consent document revisions, IRB approval of the proposed research must be **deferred**, pending subsequent review by the convened IRB of responsive material. (b) Only when the convened IRB stipulates specific revisions requiring simple concurrence by the investigator may the IRB Chair or another IRB member designated by the Chair subsequently approve the revised research protocol on behalf of the IRB under an expedited review procedure.

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

Sincerely,

Michael A. Carome, M.D.
Director, Division of Compliance Oversight

cc: Dr. Peter Slavin, President, Barnes-Jewish Hospital
Mr. Ted Fry, President, St. Louis Children's Hospital
Ms. Patricia Scannell, IRB Administrator, WUSM
Dr. William Powderly, Chairman, IRB-01, WUSM
Mr. Lloyd J. Vasquez, Jr., Chairman, IRB-02, WUSM

Dr. Perry Grigsby, Chairman, IRB-03, WUSM
Dr. Philip Ludbrook, Associate Dean and Chairman, IRB-04 and -05, WUSM
Commissioner, FDA
Dr. David Lepay, FDA
Dr. James F. McCormack, FDA
Dr. John Mather, Director, Office of Research Compliance and Assurance, Veterans Health Administration
Dr. Greg Koski, OHRP
Dr. Melody H. Lin, OHRP
Dr. J. Thomas Puglisi, OHRP
Dr. Jeffrey M. Cohen, OHRP
Dr. Clifford C. Scharke, OHRP
Dr. Katherine Duncan, OHRP
Mr. George Gasparis, OHRP
Mr. Barry Bowman, OHRP