DEPARTMENT OF HEALTH & HUMAN SERVICES

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December 18, 2000

Lee E. Limbird, Ph.D.
Associate Vice Chancellor for Research
Vanderbilt University
D-3300 Medical Center North
Nashville, Tennessee 37232-2104

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1363

Research Project: Thapa PB, Gideon P, Cost TW, Milam AB, Ray WA. Antidepressants and the risk of falls among nursing home residents. N Engl J Med 1998;339:875-82.
HHS Project numbers: R49/CCR410144 and FD-U-000073
Principal Investigator: Wayne A. Ray, Ph.D.

Dear Dr. Limbird:

The Office for Human Research Protections (OHRP), formerly the Office for Protection from Research Risks (OPRR), has reviewed the following documents submitted by Vanderbilt University (VU) in response to OHRP's July 22, 1999 letter regarding the above referenced research:

(1) Your October 15, 1999 report regarding the above referenced research and VU's system for protection of human subjects.

(2) The list of all active protocols approved by the VU Institutional Review Boards (IRBs) that was submitted under Ms. Leona Marx's October 29, 1999 cover letter.

(3) The minutes of three meetings of each of the VU IRBs that were submitted under Ms. Marx's December 17, 1999 cover letter.

(4) The written IRB Policies and Procedures and the Manual for Investigators Engaged in Research with Human Subjects that were submitted under your September 21, 2000 cover letter.

Based upon its review of the above documents, OHRP makes the following determinations:

(1) HHS regulations at 45 CFR 46.116(d) require that the IRB make and document four specific findings when approving a waiver of the requirements to obtain informed consent from human research subjects. OHRP finds that the VU IRB failed to satisfy these requirements when reviewing and approving Dr. Ray's research protocol referenced above.

Corrective Action: OHRP acknowledges that (a) the VU IRB members and investigators have been educated about the HHS regulatory requirements at 45 CFR 46.116(d) regarding waiver of informed consent; and (b) the revised VU IRB Policy and Procedures stipulate that the findings required under HHS regulations at 45 CFR 46.116(d) are to be fully documented in the IRB minutes, including protocol-specific information justifying each IRB finding. OHRP has determined that these corrective actions are appropriate under the VU MPA.

(2) VU has taken appropriate corrective actions to address all other concerns raised by OHRP in its July 22, 1999 letter. In particular, OHRP notes the following:

(a) The VU IRBs have implemented administrative procedures to ensure that (i) all research undergoes continuing review not less than once per year, as required by HHS regulations at 45 CFR 46.109(e); and (ii) research is suspended whenever IRB approval expires prior to such continuing review occurring.

(b) VU has implemented procedures to ensure that all VU-affiliated institutions engaged in HHS-supported human subject research that is conducted under the auspices of VU hold an OHRP-approved Assurance prior to their involvement in the conduct of the research, as required by HHS regulations at 45 CFR 46.103(a) and the VU MPA.

(c) The minutes of the VU IRB meetings now document all information required by HHS regulations at 45 CFR 46.115(a)(2).

(d) The VU IRBs receive and review complete copies of Federal grant applications, as required by HHS regulations at 45 CFR 46.103(f).

(e) VU has prepared detailed written IRB Polices and Procedures.

(f) VU has implemented education programs to ensure that all investigators and all IRB members are educated on an on-going basis about the ethical principles and regulatory requirements for the protection of human subjects.

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:

(1) Regarding the discussion of "Pilot Activities" (section 5.i of the policy entitled "Activities Subject to IRB Jurisdiction"), please note the following:

(a) HHS regulations at 45 CFR 46.102(d) define research as a systematic investigation, including *research development*, testing and evaluation, designed to develop or contribute to generalizable knowledge.

(b) Pilot studies (or pilot activities) under which an investigator obtains (i) data through intervention or interaction with living individuals, or (ii) identifiable private information about living individuals should be considered human subject research, regardless of whether the investigator intends to publish or present the data obtained during the pilot study (or pilot activity).

(2) The IRB Policies and Procedures should be expanded to include additional operational details for each of the following activities:

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

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

(c) The procedures for ensuring prompt reporting to OHRP and the head of any Department or Agency head of (i) any unanticipated problems involving risks to subjects or others; (ii) any serious or continuing noncompliance with the requirements of the HHS regulations for protection of human subjects or the requirements or determinations of the IRB; and (iii) any suspension or termination of IRB approval. Please note that under the VU MPA, these reporting requirements apply to all research, regardless of sponsorship. Furthermore, the VU IRB Policies and Procedures should specifically identify OHRP as a recipient of these reports.

(3) For research requiring review by the convened IRB, continuing review must occur within one year of the date of the IRB meeting at which the research was approved (with or without specific revisions), not within one year of the date final approval is issued to the investigator.

(4) Regarding the discussion of "Surrogate Consent" (section 2.b of the policy entitled "Legally Effective and Prospectively Obtained Informed Consent"), please note that with respect to the individuals identified as being able to give "surrogate consent" on behalf of another individual, this is permissible under the HHS regulations only if such "surrogates" are legally authorized representatives of the prospective subjects, in accordance with HHS regulations at 45 CFR 46.102(c) and 46.116.

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 any questions.

Sincerely,

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

cc: Mr. William A. Mountcastle, Director, Nashville Veterans Affairs Medical Center
Dr. Alastair J. J. Wood, Assistant Vice Chancellor for Research, VU School of Medicine
Dr. Gordon Bernard, Medical Director, IRB, VU Medical Center
Dr. Margaret G. Rush, Chairperson, IRB-01, VU
Dr. William O. Cooper, Chairperson, IRB-02, VU
Dr. Dr. Leonard Bickman, Chairperson, IRB-03, VU
Commissioner, FDA
Dr. David Lepay, FDA
Dr. James F. McCormack, FDA
Dr. John Mather, Director, Office of Research Compliance and Assurance, Department of Veterans Affairs
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Mr. Barry Bowman, OHRP