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

June 11, 2001

Fawwaz T. Ulaby, Ph.D.
Vice President for Research
University of Michigan
4080 Fleming Building
503 Thompson Street
Ann Arbor, Michigan 48109-1340

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1184

Research Project:	**Depression, Peptides and Steroids in Cushing's Syndrome**
Protocol Number:	**IRB MED 87-155**
Investigators:	**Dr. Monica N. Starkman, Dr. David E. Schteingart, Dr. Stanley Berent, Dr. J.E. Shipley, Dr. O.G. Cameron, Dr. Ziad Kronfol, Dr. Stephen Gebarski, Dr. Alan Douglass, Dr. Bruno Giordani**

Dear Dr. Ulaby:

The Office for Human Research Protections (OHRP), formerly the Office for Protection from Research Risks (OPRR), has reviewed your report of April 10, 2001, regarding the above referenced research.

In reviewing documents provided with your report, as well as other documents provided by UM and the complainant, OHRP notes the following:

(1) The complainant alleged that, Dr. David Schteingart recommended that the complainant undergo a one-year post surgical brain MRI for clinical purposes in order to check for pituitary tumor recurrence. The complainant further alleged that at the same time Dr. Schteingart (a) invited the complainant to undergo additional imaging during this MRI procedure for research purposes in order to assess the effect of Cushing's

disease on the hippocampus and memory; (b) told the complainant that by including the additional imaging, the complainant would not have to pay for the MRI procedure; and (c) invited the complainant to also undergo four-hour long neuropsychological testing for research purposes.

(2) The complainant was hospitalized at the University of Michigan (UM) General Clinical Research Center (GCRC) as a "B" category patient and was expected by the staff to be undergoing, at least in part, research procedures. During this hospitalization, the complainant underwent multiple procedures including the following:

(a) A pituitary-focused brain MRI without and with contrast, as well as additional specially tailored images for volumetric measurement of the hippocampus.

(b) Neuropsychological testing.

(3) The above referenced research project included the MRI imaging for volumetric measurement of the hippocampus and neuropsychological testing procedures for research purposes that were performed on the complainant.

(4) The Diagnostic Service procedure order for the complainant's MRI scan listing Dr. Schteingart as the Attending Staff and included the following hand written notation:

"Cushing's syndrome; question pituitary adenoma. *Please add Gebarski hippocampus research protocol*" [italics added for emphasis].

(5) A UM Hospitals Department of Radiology report (signed by Dr. Stephen Gebarski, a co-investigator on the above referenced research project) for the complainant's MRI procedure stated the following:

(a) "PROCEDURE: Pituitary-focused brain MRI without and with intravenous contrast material. *Additional specially tailored images were acquired for research volumetrics.*" [italics added for emphasis]

(b) "*Brain volumetrics will be available on a research basis.*" [italics added for emphasis]

(6) In a hand-written letter to the complainant, a radiology file room clerk (first name Llody, last name not legible) stated the following:

"Enclosed are your MRI films ... I talked to Dr. Gebarski's secretary (Pam) and they were hoping that you could return these MRI films within 30 days of receipt. *They were using it for long-term research purposes.*" [italics added for emphasis]

(7) A copy of a printout of research subjects enrolled in one of Dr. Gebarski's research projects included the complainant. Page 7 of your April 10, 2001 report stated, "We

agree that the name of the complainant on such a preliminary list appears to signal a problem of insufficient careful systems of separation of research from clinical care. In this instance the clinically-relevant work requested by Dr. Schteingart became confounded with the research logistics on IRBMED 1987-155."

(8) Your April 10, 2001 report stated:

(a) "Dr. Starkman has noted that the actual requests to do the measurement are issues later only after a separate determination is made that the individual meets the inclusion criteria of having active Cushing's Disease." (Page 6)

(b) "Had [Dr. Schteingart] prompted radiology for the results, he would have found the volumetrics on the images had been held up by the research procedures. As mentioned above Dr. Gebarski required a directive from Dr. Starkman to do the volumetric measurements on the basis of a finding of active Cushing's Disease." (Page 8)

(c) "The complainant did indeed have the extra images taken, but it is not the case that the complainant underwent volumetric measurement of her hippocampus for any purpose." (Page 9)

(d) "Notwithstanding the above, we agree that the complainant underwent interventions, if not the measurements, currently in use as research procedures in IRBMED 1987-155." (Page 9)

(9) Regarding protocol IRB MED 87-155, your April 10, 2001 report provided the following information:

(a) An additional 51 subjects enrolled in IRB MED 87-155 were found to have Cushing's disease.

(b) An additional 39 subjects enrolled in IRB MED 87-155 were not found to have Cushing's disease. The subjects listed were consented and were to have undergone the same procedures as the complainant.

(10) Regarding protocol IRB MED 87-128 and its successor project IRB MED 00-575, your April 10, 2001 report stated:

(a) "[we] found that the file was incomplete, with the earliest documents going back to only 1994."

(b) "We also found that the material the file now included was not minimally adequate for an IRB file and did not document all required determinations."

OHRP makes the following determinations regarding the above referenced research:

(1) OHRP finds no evidence that the complainant was admitted solely for clinical purposes. To the contrary, the available information points to the position that complainant was to be a research subject. All references to the complainant indicated that the researchers and staff of the UM GCRC understood the complainant to be included in research activities and, in fact, the complainant underwent procedures as part of protocol IRB MED 87-155. The complainant was included on a list of subjects with an assigned subject number which leads OHRP to conclude that the complainant was indistinguishable from other subjects enrolled in IRB MED 87-155, particularly those included on the list of 39 subjects who were enrolled but found not to have Cushing's disease. Additionally, the sequence of events involving hippocampal volumetrics measurements were being dictated by the protocol.

OHRP finds that the complainant underwent research interventions, including extra MRI scans and neuropsychological tests, as part of protocol IRB MED 87-155, while admitted to the UM GCRC. Furthermore, the investigators failed to obtain legally effective informed consent from the complainant prior to performing the procedures as required by HHS regulations at 45 CFR 46.116.

Corrective Action: OHRP acknowledges the corrective actions being taken by UM to address the issues raised as a result of the present complaint including the following:

(a) Suspension and re-review of IRB MED 87-155.

(b) Removal of all clinical information relating to the complainant from any location where it might be available for research.

(c) Counseling of the investigators regarding the boundaries between clinical care and research.

(d) Establishment of an Ombudsman within the UM GCRC.

(e) Development of clearer policies and procedures for investigators to follow regarding when utilizing GCRC facilities.

(f) Enhancement of the UM IRB system by increasing the number of IRBs and increasing the administrative capacity of the IRB office.

(g) Providing better educational program on the protection of human subjects for IRB members as well as a web-based curriculum for investigators.

Action 1- Required: By July 29, 2001 the UM must submit to OHRP a status report regarding the IRB's re-review of protocol IRB MED 87-155. This report should include: (i) the IRB assessment of the adequacy of the informed consent procedures; (ii) an

assessment of the investigator's maintenance of research records, to ensure that the investigators meet the requirements for the protection of human subjects as provided under HHS regulations at 45 CFR Part 46; and (iii) a description of any additional corrective actions taken by the UM IRB to address any additional areas of noncompliance.

(2) HHS regulations at 45 CFR 46.115 require that the IRB shall prepare and maintain adequate documentation of IRB activities and that records relating to research be retained for at least three years after the completion of the research. OHRP finds that the UM IRB records for protocols IRB MED 87-128 and IRB MED 2000-575 failed to include all the information stipulated by 45 CFR 46.115.
OHRP acknowledges UM's closure of IRB MED 2000-575 and its intent to initiate a new protocol.

Action 2 - Required: By July 29, 2001, the UM must provide OHRP with a detailed corrective action plan to address the above finding.

OHRP has the following additional comments:

(3) Regarding the use of 4-C-14 cortisol, OHRP acknowledges the UM's review of the use of this material and the preliminary determination from the Food and Drug Administration (FDA) regarding the necessity of obtaining an Investigational New Drug (IND) application. OHRP also acknowledges the efforts made by UM in strengthening the coordination between the IRB and the Radioactive Drug Research Committee/Subcommittee on the Human Use of Radioisotopes (RDRC/SHUR) as well as a review of the RDRC/SHUR policies and procedures.

OHRP requests that UM provide a copy of any final determination by the FDA on the use of 4-C-14 cortisol be provided to this office along with a description of any actions taken on the part of UM regarding any such determination.

OHRP appreciates the continued commitment of your institution to the protection of human research subjects.

Please do not hesitate to contact me if you have questions

Sincerely,

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

cc: Ms. Judith A. Nowack, U. Michigan
Dr. David C. Smith, U. Michigan, IRB MED Chair
Dr. Charles J. Kowalski, U. Michigan, IRB HLTH Chair
Dr. Eugene Burnstein, U. Michigan, IRB BEHAVSCI Chair
Dr. Gerald T. Gardner, U. Michigan, IRB DRBN Chair
Dr. Suzanne M. Selig, U. Michigan, IRB FLINT Chair
Commissioner, FDA
Dr. David Lepay, FDA
Dr. James F. McCormack, FDA
Dr. Raymond Farkas, FDA
Ms. Nancy N. Mundo, FDA Detroit District
Dr. John Mather, ORCA, Department of Veterans Affairs
Dr. Greg Koski, OHRP
Dr. Melody Lin, OHRP
Dr. Michael Carome, OHRP
Dr. Jeffrey Cohen, OHRP
Mr. George Gasparis, OHRP
Ms. Roslyn Edson, OHRP
Mr. Barry Bowman, OHRP