DEPARTMENT OF HEALTH & HUMAN SERVICES
Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
The Tower Building
1101 Wootton Parkway, Suite 200
Rockville, Maryland 20852
Telephone: 240-453-8120
FAX: 240-453-6909
E-mail: Lisa.Rooney@hhs.gov

December 4, 2008

Jonathan J. Oviatt, J.D.
General Counsel
Mayo Clinic
Siebens 9
200 First Street SW
Rochester, MN 55905

RE: Human Research Subject Protections Under Federalwide Assurance – 5001

Dear Mr. Oviatt:

Thank you for your September 3, 2008 letter in response to our July 23, 2008 letter regarding research conducted under the above-referenced Federalwide Assurance (FWA).

A. In our July 23, 2008 letter we made the following determinations:

(1) We determined that the Mayo Clinic institutional review board (IRB) did not conduct continuing review of research at least once per year as required by Department of Health and Human Services (HHS) regulations at 45 CFR 46.109(e) and that investigators continued to conduct research activities beyond the expiration date of IRB approval.

Corrective Action: The Mayo Clinic provided us with a final version of the IRB's Procedure for Continuing Review as well as the IRB's Procedure for Expired IRB Approval. These procedures satisfactorily address our prior determination, and are appropriate under the terms of the Mayo Clinic FWA.

(2) We determined that the Mayo Clinic IRBs did not maintain minutes of IRB meetings in the detail required by HHS regulations at 45 CFR 46.115(a)(2). In specific, we found that (a) some minutes were written before the IRB meeting took place; (b) in some instances pre-written meeting minutes only included "approval" options, i.e., an IRB staff member deleted the options of deferral or disapproval prior to the IRB meeting; and (c) both pre- and post-meeting written minutes did not include the basis for requiring changes in or

disapproving research or a written summary of the discussion of controverted issues and their resolution.

Corrective Action: We acknowledge that the following corrective actions have been taken to address this finding:

(a) The Mayo Clinic drafted a final IRB procedure for documenting full committee IRB determinations/motions (including the basis for the IRB requiring changes in or disapproving research);
(b) The Mayo Clinic IRB drafted three separate checklists to guide IRB staff in capturing all IRB discussions in a systematic fashion so that key items are not inadvertently omitted from the minutes; and
(c) The Mayo Clinic has made changes to its electronic IRB system to allow for efficient input of relevant information.

These corrective actions satisfactorily address our prior determination and are appropriate under the terms of the Mayo Clinic FWA.

(3) We determined that the Mayo Clinic did not have written IRB procedures that adequately describe certain activities, as required by HHS regulations at 45 CFR 46.103(b)(4).

Corrective Action: The Mayo Clinic provided us with final versions of the following written IRB procedures:

(a) IRB Committee Determinations/Motions – Full Committee Procedure;
(b) IRB Committee Determinations/Motions – Expedited Review Procedure;
(c) IRB Approval of Research Policy;
(d) Procedure for Continuing Review; and
(e) Procedure for Modifications to Previously Approved Research.

These procedures satisfactorily address our prior determination, and are appropriate under the terms of the Mayo Clinic FWA.

B. We make the following additional determinations:

(1) HHS regulations at 45 CFR 46.115(a) require that the institution prepare and maintain adequate documentation of IRB activities. In numerous instances among the 11 IRB files that were examined, it was difficult to reconstruct a complete history of all IRB actions related to the review and approval of the protocol. In some instances, we could not determine what the IRB actually approved. For example,

(a) IRB file for 06-008853 reflects that the IRB reviewed and unanimously (9-0) approved this study during its March 1, 2007 IRB meeting; noting receipt of a protocol dated August 21, 2006. We could not locate the protocol dated August 21, 2006 in the IRB file that was initially submitted to our office. Instead, we could only locate a subject diary for the study, dated September 25, 2006; an undated document

entitled "Study Monitoring;" and two identical protocols dated as follows: "Date: 25 September 2006; Amendment 1: 20 March 2007."

(b) IRB file for 1717-05 reflects that the study was modified a total of 5 times, however the IRB file only contains the following four versions of the study: an undated PHS grant application (pages 86 – 125) reflecting a 7/13/2006 scan date; two undated PHS grant applications (pages 86 – 126) reflecting a 7/13/2006 scan date; an undated PHS grant application (pages 86 – 127) reflecting an 10/3/2006 scan date; and an undated PHS grant application (pages 86 – 126) reflecting no scan date. Moreover, we could not locate in the file a protocol dated July 26, 2007 which is referenced in 2 electronic IRB report documents and appears to be the current IRB approved protocol for the study.

(c) IRB file for 06-002246 reflects that the IRB reviewed a protocol dated March 1, 2006 (approved by IRB on 3/23/2006) as well as LS Addendum 1 (approved by IRB on 10/26/2006) and LS Addendum 2 (approved by IRB on 08/2/2007), however, these protocols could not be located in the IRB file that was initially submitted to our office.

Given the above, we determine that the Mayo Clinic for some research protocols failed to prepare and maintain adequate documentation of IRB activities as required by HHS regulations at 45 CFR 46.115(a).

Required Action: Please provide us with a corrective action ensuring that the Mayo Clinic will prepare and maintain adequate documentation of IRB activities in accordance with HHS regulations at 45 CFR 46.115(a).

(2) HHS regulations at 45 CFR 46.116(a)(6) provides that when research involves more than minimal risk, each subject shall be provided with an explanation as to whether any compensation and any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained. Moreover, HHS regulations at 45 CFR 46.103(b)(4)(iii) provide that an IRB must 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. A complainant alleged that the Mayo Clinic investigator for IRB 133-05 00 did not provide a subject free medical services for side effects from research, as indicated in the informed consent document. Given these allegations, we are concerned that the investigator may not have provided a subject with free medical services, as indicated in the informed consent form, without first obtaining IRB review and approval of this change in the research as required by HHS regulations at 45 CFR 46.103(b)(4)(iii).

We acknowledge Mayo Clinic's response that the IRB Compliance Coordinator investigated this allegation (prior to our office raising this allegation in its July 23, 2008 letter) and concluded that the complainant's condition was not cause by the research, i.e., it was determined not to be a research-related injury, but rather a recurrence of a pre-

existing condition, which coincidentally occurred shortly after the study. We note further that prior to rendering this conclusion, the IRB Compliance Coordinator held meetings with the complainant, corresponded with the complainant via email, thoroughly reviewed the subject's medical records, and consulted with the principal investigator, co-investigator, and an endocrinologist unrelated to the study. Based on the information provided, we have determined that this allegation of noncompliance is unproven. No evidence was presented to us indicating that the subject's condition was caused by the research.

C. Additional Questions and Concerns:

[Redacted]

We acknowledge all of the remaining responses provided by the Mayo Clinic in its September 3, 2008 letter that are not specifically addressed above.

Please submit your response to the additional determination (B)(1) above and the additional concern above so that we receive them no later than January 6, 2009. If during your review you identify additional areas of noncompliance with HHS regulations for the protection of human subjects, please provide corrective action plans that have been or will be implemented to address the noncompliance.

We appreciate your institution's continued commitment to the protection of human research subjects. Please contact me if you should have any questions regarding this matter.

Sincerely,

Lisa A. Rooney, J.D.
Compliance Oversight Coordinator

cc: Ms. Marcia Andresen-Reid, Administrator, IRBs, Mayo Clinic
Dr. Bart L. Clarke, Chair, Mayo Foundation IRB #1 and #5
Dr. Joseph K. Lobl, Chair, Mayo Foundation IRB #2

Dr. Randall K. Pearson, Chair, Mayo Foundation IRB #3
Dr. Joseph Rubin, Chair, Mayo Foundation IRB #4
Dr. R. Scott Wright, Chair, Mayo Foundation IRB #6
Dr. Andrew C. von Eschenbach, Food and Drug Administration (FDA) Commissioner
Dr. Joanne R. Less, FDA
Dr. Sherry Mills, Office of Extramural Research (OER), National Institutes of Health (NIH)
Mr. Joe Ellis, OER, NIH