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Office of the Secretary
Office of Public Health and Science

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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 26, 2007 letter in response to our August 8, 2007 request that the Mayo Clinic evaluate allegations of noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human research subjects (45 CFR part 46). Based on the information submitted, we make the following determinations:

A. Determinations regarding the Mayo Clinic's system for protecting human subjects:

(1) We determine that the Mayo Clinic institutional review board (IRB) did not conduct continuing review of research at least once per year as required by HHS regulations at 45 CFR 46.109(e) and that investigators continued to conduct research activities beyond the expiration date of IRB approval. The September 26, 2007 Mayo Clinic continuing review report of HHS-supported, IRB-approved studies (the September 26, 2007 continuing review report) reveals that approximately 140 of 1060 listed HHS-funded active protocols had one or more lapses in continuing review, e.g., IRB 1026-98 experienced 4 consecutive instances in which the IRB failed to conduct continuing review of the research at least once per year. See page 1 of September 26, 2007 continuing review report. Moreover, we acknowledge that the Mayo Clinic investigation found instances where investigators had not stopped their research activities upon the expiration date of IRB approval. The protocols that experienced such lapses consisted of research involving no more than minimal risk as well as research involving greater than minimal risk, and lapses ranged in time from more than 30 days to 20 years.

We note that in an August 2, 2007 letter the Mayo Clinic self-reported its discovery regarding the failure of the Mayo Clinic IRBs to conduct continuing review of research at least once per year as required by HHS regulations at 45 CFR 46.109(e). Please note that the allegations of noncompliance addressed here (and throughout this letter with the exception of item (C) below) pre-date our receipt of the Mayo Clinic's August 2, 2007 letter: the August 2, 2007 letter was received in our office on August 14, 2007; one week after we sent our initial inquiry letter. In specific, the August 2, 2007 report provided the following:

> "We recently learned that the [electronic IRB] system (which was implemented in January 2007) was not properly recognizing situations in which IRB approval expired, and that appropriate action was therefore not taken to prevent further study activities."

We acknowledge that the Mayo Clinic took certain corrective actions in response to this recent discovery regarding the failure of the electronic IRB system. The Mayo Clinic continued that "If we discover any serious or continuing non-compliance during the review described in item (iii), these matters will be reported separately to OHRP."

We note that the August 2, 2007 self report was limited in scope, in that the report only identified continuing review noncompliance associated with implementation of the electronic IRB system, which was implemented in January 2007. The September 26, 2007 continuing review report, which was submitted in response to our August 8, 2007 inquiry letter, identified continuing review issues that predated the implementation of the electronic IRB system. Of note, this September 26, 2007 continuing review report reveals that the Mayo Clinic has had continuing review noncompliance issues as early as 1986.

Corrective Action: We acknowledge that the Mayo Clinic IRBs have taken the following corrective actions to address the continuing review noncompliance noted in the August 2, 2007 letter: (i) notification to all investigators with expired studies to promptly submit a continuing review or final progress report; (ii) asking investigators with expired studies whether any study activity occurred during the period of expiration; and (iii) referring those studies with activity after expiration to the IRB Compliance Coordinator for review and appropriate action. In addition, we note that the Mayo Clinic has identified the DRAFT Procedure for Continuing Review – the procedures the Mayo Clinic IRB will take to ensure that continuing review noncompliance does not occur in the first place. See Tab 2 of the Mayo Clinic September 26, 2007 response.

Required Action: Please provide us with the final version of the DRAFT Procedure for Continuing Review.

(2) We determine that the Mayo Clinic IRBs do not maintain minutes of IRB meetings in the detail required by HHS regulations at 45 CFR 46.115(a)(2). In specific, we find that some minutes have been written before the IRB meeting takes place and that both pre- and post-meeting written minutes do not include the basis for requiring changes in or

disapproving research or a written summary of the discussion of controverted issues and their resolution. We base this determination on our review of various meeting minutes as well as on the following information, which was provided by Mayo Clinic in response to this allegation:

> "We have become aware of limited circumstances in which an IRB staff member has deleted the options of deferral or disapproval prior to the meeting, so it appears that approval is the only possible outcome. … We also recognize the importance of including a written summary of the discussion of controverted issues and their resolution. IRB members and staff have been educated about the importance of this requirement, but we acknowledge that some minutes fail to include an adequate summary. …"

Corrective Action: We acknowledge the corrective actions that Mayo Clinic has implemented to address this determination, in specific, that the Mayo Clinic has held training sessions with IRB members/staff to ensure that draft minutes list all three possible final outcomes and that final minutes include a written summary of the discussion of controverted issues and their resolution.

Required Action: Please provide us with a corrective action plan that will ensure that the Mayo Clinic IRB meeting minutes satisfy all requirements outlined in HHS regulations at 45 CFR 46.115(a)(2) including the requirement that minutes include the basis for requiring changes in or disapproving research. We note that the proposed corrective action only addresses the requirement that minutes include a written summary of controverted issues and their resolution.

(3**)** We determine that the Mayo Clinic does not have written IRB procedures that adequately describe the following activities, as required by HHS regulations at 45 CFR 46.103(b)(4). We base this determination on our review of the 2006 IRB Policy and Procedures Manual (Tab 16 of the September 2007 Mayo report) – the manual that contained the procedures that were in effect at the time that the compliance oversight investigation was opened.

(a) The procedures which the IRB will follow for reporting its findings and actions to investigators and the institution.

(b) The procedures which the IRB will follow for determining which projects require review more often than annually.

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

(d) The procedures which the IRB will follow for ensuring prompt reporting to the IRB of proposed changes in a research activity, and for ensuring that such changes in approved research, during the period for which IRB approval has already been given,

may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to the subject

We reviewed this manual and found that many of the above-referenced procedures were inadequate or absent. For example, Section 12.1 - Continuing Review Procedures provides limited details regarding the procedures the IRB will follow for determining which projects require review more often than annually. In another example, Section 12.2 – Protocol Revisions - is silent regarding the reporting of proposed changes that are necessary to eliminate apparent immediate hazards to subjects. Lastly, we note that this manual does not include the procedures the IRBs will follow for (i) determining which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review and (ii) reporting its findings and actions to investigators and the institution. We note, however, that the Mayo Clinic has provided us with DRAFT written IRB procedures that appear to address items (a), (b) and (d) above.

Required Action: Please provide us with final written IRB procedures that adequately describe the activities outlined above. Please refer to OHRP's Guidance on Written IRB Procedures, available at http://www.hhs.gov/ohrp/humansubjects/guidance/irbgd107.htm, when drafting the procedures.

B. Additional questions and concerns regarding the Mayo Clinic's system for protecting human subjects:

(1) [Redacted]

[Redacted]

(2) [Redacted]

[Redacted]

(3) [Redacted]

(4) [Redacted]

(5) [Redacted]

[Redacted]

[Redacted]

(7) [Redacted]

[Redacted]

(8) [Redacted]

[Redacted]

C. [Redacted]

Please submit your response to the findings, questions and concerns and additional allegation noted above so that we receive them no later than September 4, 2008. 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, FDA Commissioner
Dr. Joanne R. Less, FDA
Dr. Sherry Mills, Office of Extramural Research, National Institutes of Health
Mr. Joe Ellis, OER, NIH