DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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Robert Glickman, M.D.
Dean
New York University School of Medicine
Office of the Dean
550 First Avenue
New York, New York 10016

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1177

Dear Dr. Glickman:

The Office for Human Research Protections (OHRP) has reviewed New York University School of Medicine's (NYUSM's) June 15, 2000, November 16, 2000, and June 30, 2001 reports and letters regarding allegations of non-compliance with Department of Health and Human Services (HHS) regulations for the protection of human subjects that were described in OHRP's February 25, 2000 letter.

Based on its review, OHRP makes the following determinations:

(1) HHS regulations at 45 CFR 46.115(a)(2) require that the minutes of Institutional Review Board (IRB) meetings be in sufficient detail to show attendance at the meetings; the vote on these actions including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolution. In its February 25, 2000 letter, OHRP presented a complaint alleging that the NYUSM IRB failed to ensure that the requirements were satisfied.

Based upon its review of IRB minutes for the period covering February 22, 1999 to February 28, 2000 submitted in NYUSM's June 15, 2000 report, OHRP finds that minutes of the NYUSM IRB meetings comply with the requirements of HHS regulations at 45 CFR 46.115(a)(2). OHRP acknowledges NYUSM's statement in its June 15, 2000 report that

NYUSM initiated a formal compliance program in 1999 and subsequently engaged in quality improvement of its documentation of IRB meetings, with the format of the minutes subsequent to May 17, 1999 providing more detail than found in previous minutes. In addition, OHRP acknowledges that NYUSM revised its research Policies and Procedures in October 2000 such that the minutes include a summary of protocol-related issues, actions taken by the IRB and the basis for those actions including documentation of any required findings, and that the format of minutes have been revised such that all information on a particular protocol is contained in the same section, including the issues considered and the rationale for each decision.

(2) HHS regulations at 45 CFR 46.108(b) require that except when an expedited review procedure is used, the IRB shall review proposed research at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in a nonscientific area. In its February 25, 2000 letter, OHRP presented a complaint alleging that the NYUSM IRB failed to ensure that this requirement was satisfied. Based upon its review of the minutes of IRB meetings for the period covering February 22, 1999 to February 28, 2000 submitted with NYUSM's June 15, 2000 report, OHRP finds that the NYUSM IRB has complied with these requirements.

(3) When an IRB utilizes a primary reviewer system for the initial or continuing review of a research protocol, OHRP recommends that the primary reviewer is present at the IRB meeting during its deliberations on that protocol. In its February 25, 2000 letter, OHRP presented a complaint alleging that IRB review of protocols may have occurred in the absence of the primary reviewer assigned to that protocol.

Based upon its review of IRB minutes covering the period February 22, 1999 to February 28, 2000 submitted in NYUSM's June 15, 2000 report, OHRP finds that NYUSM has adequately responded to this allegation. In a June 15, 2000 letter to OHRP, NYUSM noted that its internal review of IRB activities found "[a] few instances of less than optimal performance" regarding its primary reviewer system and that previous "NYUSM policy [had] permitted consideration of a protocol by the convened committee if the Primary Reviewer was present or had submitted written comments." OHRP acknowledges that the NYUSM IRB's revised Policies and Procedures now require that all materials submitted for each protocol be assigned to two primary reviewers and that at least one primary reviewer be present at the IRB meeting for deliberations on that protocol.

(4) When some or all of the subjects participating in a research study are likely to be vulnerable to coercion or undue influence, such as children, prisoners, mentally disabled persons or economically or educationally disadvantaged persons, HHS regulations at 45 CFR 46.111(b) require the IRB to ensure that additional safeguards have been included in the study to protect the rights and welfare of such subjects. In its February 25, 2000 letter, OHRP presented a complaint alleging that the NYUSM IRB failed to ensure that this requirement was satisfied.

Based upon its review of the minutes of IRB meetings covering the period from February 22, 1999 to February 28, 2000 submitted in NYUSM's June 15, 2000 report, OHRP finds that the NYUSM IRB appears to comply with this requirement.

(5) HHS regulations at 45 CFR 46.110(b)(1) limit the use of expedited review procedures to specific research categories published in the Federal Register at 63 FR 600364-60367. OHRP acknowledges NYUSM's statement in its June 15, 2000 letter that continuing review of some research that was not eligible for an expedited review procedure under HHS regulations occasionally was conducted by an expedited review procedure.

OHRP finds that NYUSM has adequately responded to this deficiency. OHRP notes that NYUSM IRB's revised Policies and Procedures of October 2000 include specific guidance on review using expedited procedures, including the eligibility requirements for expedited review and a specific form to be filled out by the expedited reviewer.

(6) OHRP notes that the City of New York Office of the Comptroller conducted an audit of Bellevue Hospital's compliance with the Health and Hospitals Corporation's medical research approval regulations, reviewing clinical studies which were active in 1996-1997. Bellevue Hospital Center is affiliated with the NYUSM and is covered under NYUSM's MPA. On June 30, 2001, NYUSM submitted to OHRP the final audit report (hereafter "NYC audit report") dated July 25, 2001 and NYUSM's response. OHRP acknowledges the NYC audit report's findings and response by NYUSM. In particular, OHRP notes the following:

> (a) HHS regulations at 45 CFR 46.103(b)(5) require that unanticipated problems involving risks to subjects or others be reported to the IRB, institutional officials, and the appropriate Federal Department or Agency. The NYC audit found some instances in which investigators failed to provide the IRB with information on adverse events and unanticipated problems involving risks to subjects.
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> OHRP finds that NYUSM has adequately addressed this finding. OHRP notes that in its response to the NYC audit report, NYUSM acknowledged that "NYU IRB's self assessment revealed imprecise instructions to Investigators regarding adverse event reporting requirements which have been clarified in the IRB's recently revised Policies and Procedures and Guidelines for Investigators."
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> (b) HHS regulations at 45 CFR 46.109(e) require that continuing review of research be conducted by the IRB at intervals appropriate to the degree of risk and not less than once per year. The regulations make no provision for any grace period extending conduct of the research beyond the expiration date of IRB approval. According the NYC audit report, "the NYU IRB...did not ensure compliance with regulations on the annual renewal of approvals for research protocols."

OHRP finds that NYUSM has adequately addressed this finding. Specifically, OHRP notes that the NYUSM IRB has changed its guidelines in an effort to ensure that principal investigators provide renewal applications in a timely manner, including a reminder to the principal investigator requesting completion of a "Request for Preapproval" or "Study Closure Form" prior to the required review date. In addition, the NYUSM IRB's revised Policies and Procedures clearly indicate that all research activity not authorized by the IRB beyond the approval period must cease.

As a result of the above findings, 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 findings.

At this time, OHRP provides the following additional guidance:

(7) Based on its review of IRB minutes provided with NYUSM's June 15, 2000 report, NYUSM should assess whether two IRBs are sufficient to ensure substantive and meaningful review given the volume of active protocols.

(8) OHRP recommends that written IRB polices and procedures provide a step-by-step description with key operational details for each of the procedures required at 45 CFR 46.103(b)(4) and (5). Specifically, OHRP recommends that the NYUSM IRB's Policies and Procedures be revised to include the following:

(a) A specific procedure for how the IRB determines which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review, including specific criteria used to make these determinations (e.g., such criteria could include some or all of the following: (i) randomly selected projects; (ii) complex projects involving unusual levels or types of risk to subjects; (iii) projects conducted by investigators who previously have failed to comply with the requirements of the HHS regulations or the requirements or determinations of the IRB; and (iv) projects in which concerns about possible material changes occurring without IRB approval have been raised based upon information provided in continuing review reports or from other sources).

(b) A procedure for ensuring prompt reporting by the IRB of unanticipated problems involving risks to subjects or others which mentions the specific office(s) or institutional official(s) within NYUSM to be notified, and OHRP.

OHRP appreciates NYUSM's continued commitment to the protection of human subjects. Please feel free to contact me if you have any questions.

Sincerely,

Leslie K. Ball, M.D.
Compliance Oversight Coordinator
Division of Compliance Oversight

cc: Ms. Kay Ryan, NYUSM
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