DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
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July 8, 2004

Mr. William New
Vice President for Research
Tufts-New England Medical Center
750 Washington Street
Box 817
Boston, MA 02111

RE: Human Research Subject Protections Under Former Multiple Project Assurance (MPA) M -1439 and Federalwide Assurance (FWA) 00004449

Research Project: A Pilot Study of a Reduced Intensity Conditioning Regimen for Allogeneic Bone Marrow Transplants for the Treatment of Malignancies (Alternative Title: A Pilot Study of Nonablative Allogeneic Bone Marrow Transplants for the Treatment of Malignancies)
Principal Investigator: Kenneth B. Miller, M.D.

Dear Mr. New:

The Office for Human Research Protections (OHRP) has reviewed the Tufts-New England Medical Center's (TNEMC) reports of June 13, July 26, August 12, August 15, and October 29, 2002 and November 7, 2003, submitted in response to OHRP's June 12, 2002 letter regarding allegations of noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human subjects (45 CFR part 46) involving the above-referenced research.

Based upon its review, OHRP makes the following findings regarding the above-referenced research:

(1) Under HHS regulations at 45 CFR 46.103(a), 46.103(b)(5), and 46.113, institutions holding an applicable assurance of compliance with HHS regulations for the protection of human research subjects must ensure prompt reporting to the institutional review board (IRB), appropriate institutional officials, any supporting department or agency head (or designee), and OHRP of any suspension or termination of IRB approval.

OHRP finds that the TNEMC IRB Chair terminated the IRB's approval of the above-referenced research effective January 14, 2002, based upon an institutional determination

that the protocol constituted an evolving standard of care rather than research. OHRP further finds that this termination of IRB approval was not reported promptly. Specifically, this termination was not reported to OHRP until June 13, 2002.

Corrective Action: OHRP acknowledges that in July 2002, TNEMC implemented a Policy on Suspensions/Involuntary Terminations and Reporting Suspensions/Involuntary Terminations (revised October 2003). This Policy clarifies that: (a) IRB suspensions/involuntary terminations are to occur by vote of the membership at regularly scheduled meetings, except in cases of emergency in order to protect the safety of study subjects; and (b) the IRB Chair or Vice Chair must report suspensions/terminations to the FWA Institutional Official immediately and to OHRP by telephone within five business days. OHRP finds that this corrective action adequately addresses the above finding and is appropriate under the TNEMC FWA.

(2) HHS regulations at 45 CFR 46.103(b)(4) require that the IRB 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. OHRP finds that although the subject accrual goal in the IRB-approved protocol for the above research was 25, TNEMC investigators enrolled 37 subjects in the study before August 14, 2001 without seeking IRB approval for an amendment increasing enrollment.

Corrective Action: OHRP acknowledges that TNEMC's Policy on Investigating and Reporting Research Non-Compliance (implemented in November 2002) clarifies that subject enrollment exceeding the IRB-approved accrual goal constitutes research noncompliance. OHRP finds that this corrective action adequately addresses the above finding and is appropriate under the TNEMC FWA.

OHRP has the following additional comment:

(3) OHRP acknowledges TNEMC's report that the investigators did not promptly forward to the IRB serious adverse events, as required by TNEMC's reporting policy then set forth in section XI(A) of the TNEMC IRB Operations Manual (revised 11/9/01).

OHRP further acknowledges that TNEMC took the following corrective actions regarding the failure by investigators to report serious adverse events: (a) in November 2002, TNEMC implemented its Policy on Investigating and Reporting Research Non-Compliance (current version dated May 17, 2004), which sets forth procedures for handling investigator delinquency in reporting serious and/or unexpected adverse events; (b) all TNEMC investigators were required to complete a lecture on reporting adverse events by June 30, 2004, as part of TNEMC's revised mandatory education requirements for research personnel; (c) TNEMC required each investigator with active IRB-approved research protocols to perform a self-audit of the protocols, and to certify to the IRB that all serious adverse events had been reported to the IRB in a timely manner; and (d) TNEMC

revised its continuing review form to request independent documentation of serious adverse events and/or unanticipated problems from external sites.

OHRP also acknowledges that the principal investigator conducting the above-referenced research is no longer affiliated with TNEMC.

OHRP has the following additional concerns about the above-referenced research:

(4) [Redacted]

(5) [Redacted]

[Redacted]

(6) [Redacted]

(7) [Redacted]

Please reply to OHRP's questions and concerns by July 30, 2004. If you identify additional instances of noncompliance in preparing your response to the above concerns, please include in your response a description of any additional corrective actions that have been or will be taken by TNEMC to address the noncompliance.

OHRP appreciates TNEMC's continued commitment to the protection of human research subjects. Feel free to contact me should you have any questions.

Sincerely,

Carol J. Weil, J.D.
Compliance Oversight Coordinator
Office for Human Research Protections

cc: Ms. Margaret Newell, TNEMC
Ms. Kate Gottfried, TNEMC
Ms. Jennifer Graf, TNEMC
Dr. Steven D. Schwaitzberg, TNEMC
Dr. Edward L. Decker, TNEMC
Dr. Bernard Schwetz, OHRP
Dr. Melody H. Lin, OHRP
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Ms. Janice Walden, OHRP
Ms. Pat El-Hinnawy, OHRP
Ms. Melinda Hill, OHRP