DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
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August 19, 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) July 23, 2004 report, submitted in response to OHRP's July 8, 2004 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) HHS regulations at 45 CFR 46.116 require that informed consent information be in language understandable to the subject or the subject's legally authorized representative. OHRP finds that the informed consent document approved by the TNEMC IRB for the above research study included complex language that would not be understandable to all subjects, such as in the following excerpts:

(a) "Specifically, the experimental part of this study is the use of photopheresis and continuous infusion Pentostatin prior to allogeneic transplant to suppress the

immune system so that a reduced amount of total body irradiation (half the usual dose) can be used."

(b) "Photopheresis is a form of therapy which consists of injecting UVADEX (liquid methoxsalen) into a portion of your blood (the white blood cells) and exposing those cells to ultraviolet light. These white cells are obtained by inserting an intravenous needle into the vein in your arm. Through the needle, blood is removed and enters the photopheresis machine by an intravenous tube. Here within the machine, the blood is separated by a centrifuge into red blood cells, white blood cells and plasma. The white blood cells and a portion of your plasma are then given the UVADEX and exposed to ultraviolet light (similar to sunlight) which crosslinks the DNA."

Corrective Action: OHRP acknowledges the following changes to the TNEMC IRB as of November, 2003: (a) IRB coordinators now pay particular attention to language in the informed consent form and to proposed consent modifications prior to review by the IRB; (b) IRB primary reviewers scrutinize informed consent forms for readability and reading level, and pay greater attention to this aspect of their review than previously; and (c) a secondary reviewer system implemented in October 2003 places particular emphasis on ensuring that informed consent forms are readable and understandable.

(2) Under HHS regulations at 45 CFR 46.110(c), IRBs which use expedited review procedures must adopt a method for keeping IRB members advised of research proposals approved under an expedited review procedure. OHRP finds that TNEMC IRB members were not informed about the Chair's November 29, 2001 approval of an amendment increasing enrollment in the above research from 50-80 subjects.

Corrective Action: OHRP acknowledges that the TNEMC IRB Operations Manual requires that a list of all IRB actions taken in accordance with expedited review procedures is provided to the full Board at the next convened meeting of the IRB, and is disseminated with IRB meeting minutes.

(3) OHRP had expressed concern that actions taken with respect to the above research study suggested that the TNEMC IRB Chair lacked a detailed understanding of the specific requirements of the HHS regulations for the protection of human subjects. OHRP acknowledges that when the Chair reviewed and approved amendments involving the above research in 2001, he had recently been appointed and was operating under IRB policies and procedures that have since been updated. OHRP also acknowledges that since 2003, TNEMC has sponsored multiple mandatory educational sessions attended by all researchers, including the Chair.

OHRP makes the following recommendation to TNEMC concerning its human subject protection program:

(4) OHRP previously expressed concern that the TNEMC IRB conducted expedited review and approval of proposed amendments to increase enrollment in the above study from 25 to 50 subjects, and again from 50 to 80 subjects, apparently without obtaining information in sufficient detail to make the determinations of risk versus benefit required under HHS regulations at 45 CFR 46.111. OHRP recommends that any amendment to a protocol should be requested in writing, with the justification for the amendment documented. OHRP notes that the primary investigator submitted requests to increase enrollment from 25 to 50 subjects on October 1, 2001, and from 50 to 60 subjects on October 15, 2001, without any outcomes data to support these requests. OHRP further notes that the IRB Chair approved an increase in enrollment to 50 patients on October 3, 2001, without reviewing any written documentation of study outcomes data, and approved an increase in enrollment to 80 on November 29, 2001, despite raising questions about the mortality data and the adequacy of the control population. OHRP suggests that the requested amendments increasing enrollment could potentially change the nature of this study from the initially approved pilot to a phase I or phase II clinical trial of non-ablative allogeneic bone marrow transplantation, which might constitute more than a minor change in previously approved research under 45 CFR 46.110(b)(2), requiring review by the convened IRB. OHRP recommends that when an investigator submits requests for substantial increases in enrollment, even when those requests are made serially but within a short period of time, the IRB should consider whether these changes significantly affect the purpose and/or the design of the study, and therefore require review by the convened IRB.

OHRP finds that the corrective actions described above adequately address OHRP's findings and are appropriate under the TNEMC FWA. In addition, TNEMC has adequately addressed the concerns raised in OHRP's July 8, 2004 letter. As a result, there should be no need for further involvement of OHRP in this matter.

OHRP appreciates TNEMC's continued commitment to the protection of human research subjects.

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
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