DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
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January 10, 2005

Michael Gottesman, M.D.
Deputy Director for Intramural Research
National Institutes of Health
Building 1, Room 160
1 Center Drive
Bethesda, MD 20892

RE: Human Research Subject Protections under Federalwide Assurance FWA-5897

Dear Dr. Gottesman:

The Office for Human Research Protections (OHRP) has reviewed the November 29, 2004 report submitted by the National Institute of Allergy and Infectious Diseases (NIAID) in response to determinations of noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human research subjects (45 CFR Part 46).

In its October 15, 2004 letter, OHRP made the following determinations:

> (1) OHRP found that the NIAID Institutional Review Board (IRB) inappropriately utilized expedited review procedures in approving an amendment to the protocol entitled "A Randomized, Open-Label, Phase III, International Study of Recombinant IL-2 (Proleukin) in Patients With HIV-1 Infection and CD4 Cell Counts Greater Than or Equal to 300 Cells/mm^3: Evaluation of Subcutaneous Proleukin in a Randomized International Trial" (#00-I-0071). The NIAID IRB Chair approved this amendment, using expedited review procedures, to add the following study purpose: "To determine if it is safe to give IL-2 for several years to people who are infected with HIV." NIAID's November 29, 2004 report to OHRP clarified that the modification reflected only the addition of a secondary study purpose, and not additional research activities which would change the risk/benefit ratio in human subjects. Therefore, the use of expedited review procedures for this amendment was permitted according to HHS regulations at 45 CFR 46.110, and no further corrective actions are necessary.

(2) 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. OHRP notes that the continuing review of the above-referenced research protocol was to occur by July 14, 2004. OHRP found in its October 15, 2004 letter that since the investigator for the study entitled "A Comparative Study of Ethical Issues in Multinational Clinical Research: Research Subject Perspective" (#00-CC-0179) did not respond to the request of the IRB to provide additional information, NIAID IRB approval of that protocol expired. HHS regulations make no provision for any grace period extending the conduct of the research beyond the expiration date of IRB approval.

OHRP notes that according to your November 29, 2004 report, it is the practice of NIAID and the NIH to "suspend protocols within two working days after the protocol annual review expiration date. This suspension is entered in to the Clinical Center MIS patient data system. This action prevents the entry of new patients on to a suspended protocol. Fifteen days after the Continuing Review due date, an overdue memo is sent to the principal investigator and IRB Chair. After 30 days, if the review status remains unchanged, the protocol is subject to administrative termination at the discretion of the OPS Director."

Please note that once IRB approval expires for a protocol, all human subjects activities must cease (including but not limited to enrollment of new subjects), unless the IRB finds that it is in the best interest of individual subjects already enrolled in the research to continue participating in the research interventions or interactions. For further information, see http://www.hhs.gov/ohrp/humansubjects/guidance/contrev2002.htm.

Required Action: By February 21, 2005, please submit to OHRP a corrective action plan to ensure that continuing review of research is conducted not less than once per year, and that research is suspended if it is not reviewed and approved by the IRB by the date on which IRB approval expires, in accordance with HHS regulations and OHRP guidance.

In addition, OHRP makes the following recommendation:

(3) NIAID's November 29, 2004 report states that it was "confirmed" that Protocol #00-CC-0179 was suspended on July 16, 2004, and that no subjects were enrolled after that date until November 12, 2004, when the Office of Protocol Services removed the suspension. However, there was no documentation in the IRB file reviewed by OHRP that showed expiration of IRB approval on July 14, 2004; the suspension of the protocol on July 16, 2004 (by the Clinical Center Office of Protocol Services); or the administrative termination of the study on August 15, 2004 (30 days later, as set forth in NIH standard operating procedures).

HHS regulations at 45 CFR 46.115(a) require that the institution prepare and maintain adequate documentation of IRB activities. Therefore, OHRP recommends that NIAID take steps to ensure that documentation of IRB decisions and actions is adequate.

OHRP appreciates the continued commitment of NIAID and NIH to the protection of human research subjects. Please do not hesitate to contact me should you have any questions.

Sincerely,

Rina Hakimian, J.D., M.P.H.
Compliance Oversight Coordinator
Division of Compliance Oversight

cc: Dr. Peter Mannon, NIAID
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