DEPARTMENT OF HEALTH & HUMAN SERVICES

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Office of Public Health and Science

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October 15, 2004

Michael Gottesman, M.D.
Deputy Director for Intramural Research
National Institutes of Health
Building 1, Room 103
9000 Rockville Pike
Bethesda, MD 20892

RE: Human Research Subject Protections under Federalwide Assurance (FWA) #5897

Dear Dr. Gottesman:

As you know, the Office for Human Research Protections (OHRP) conducted an on-site evaluation of human subject protection procedures at the National Institute of Allergy and Infectious Diseases (NIAID) on September 21-23, 2004. The evaluation was conducted by three OHRP staff members with the assistance of two expert consultants, and included meetings with the signatory official on the National Institutes of Health (NIH) Federalwide Assurance, the NIAID Institutional Review Board (IRB) Chair, the director of the NIH Office of Human Subjects Research, the director of the NIAID Office of Clinical Affairs, members of the NIAID IRB, administrative staff of the NIAID Regulatory Compliance and Human Subjects Protection Branch, and several investigators who submit protocols to the IRB. OHRP reviewed IRB files for approximately twelve open protocols, ten exempt protocols, the minutes of the IRB meetings held during July and August 2004, and IRB minutes from selected open protocols from 1988 to the present.

In the course of the OHRP review, the NIAID IRB Chair, IRB members, and the staff of the NIAID Regulatory Compliance and Human Subjects Protection Branch displayed understanding, enthusiasm, and commitment to the protection of human subjects. The NIAID IRB's review of research appears to be substantive and meaningful, and the NIAID IRB office and facility appear to be well organized. OHRP notes that the reorganization of NIAID's regulatory compliance and human subjects protection functions into a branch was widely acknowledged as being useful, and was accompanied by sufficient allocation of resources and expertise to this important area.

OHRP Findings Relative to Systemic Protections for Human Subjects

Based on its evaluation, OHRP makes the following findings:

(1) Department of Health and Human Services (HHS) regulations for the protection of human subjects at 45 CFR 46.110(b)(1) and (2) limit the use of expedited review procedures to specific research categories and minor changes in previously approved research during the period (of one year or less) for which approval is authorized. OHRP notes that the NIAID request form for expedited review states: "Amendments that do not increase participant risk or reduce potential benefits, and involve only minor changes to an IRB approved protocol, may be eligible for expedited review."

OHRP finds the NIAID IRB inappropriately utilized expedited review procedures in approving the 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." Since the safety of the study drug might change the risk/benefit ratio in human subjects, it does not appear to be appropriate to characterize this addition as a minor change and to review this amendment using expedited review.

Corrective Action Required: By November 29, 2004, please submit to OHRP a corrective action plan to ensure that expedited review procedures are used appropriately for protocol amendments.

(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. Continuing review of research must be substantive and meaningful regarding risks, potential benefits, informed consent, and safeguards for human subjects. HHS regulations at 45 CFR 46.111 set forth the criteria that must be satisfied in order for the IRB to approve research. The IRB must ensure that these criteria are satisfied at the time of both initial and continuing review. For the protocol entitled "A Comparative Study of Ethical Issues in Multinational Clinical Research: Research Subject Perspective" (#00-CC-0179), continuing review by the NIAID IRB was required by July 14, 2004 in order to meet the regulatory requirements of 45 CFR 46.109(e). The NIAID IRB reviewed this protocol on June 7, 2004, requesting certain changes. No response from the principal investigator was filed, and a second notice was sent on August 31, 2004. This was the last entry in the file that was reviewed by OHRP.

OHRP finds that the NIAID IRB did not conduct appropriate continuing review of protocol #00-CC-0179. If an investigator has failed to provide continuing review

information to the IRB or the IRB has not reviewed and approved a research study by the continuing review date specified by the IRB, the research should be suspended, unless the IRB finds that it is in the best interests of individual subjects to continue participating in the research interventions or interactions. Enrollment of new subjects should not occur after the expiration of IRB approval.

Corrective Action Required: By November 29, 2004, please submit to OHRP an appropriate corrective action plan to address the finding in paragraph (2) above.

OHRP makes the following additional recommendations to NIAID:

(3) HHS regulations at 45 CFR 46.115(a) require that the institution prepare and maintain adequate documentation of IRB activities. While examining the NIAID IRB records, OHRP sometimes found it difficult to reconstruct a complete history and sequence of all IRB actions related to the review and approval of protocols. OHRP notes, however, that this concern pertains only to the paper files examined by OHRP. In contrast, it appears that there is an evolving effort to promote and maintain a system of electronic filing, notification, and recordkeeping that seems highly organized and efficient.

OHRP recommends that the NIAID IRB office conduct an internal audit of all open protocols and take appropriate steps to ensure that the documentation requirements of HHS regulations at 45 CFR 46.115(a) are satisfied for all such protocols.

(4) HHS regulations at 45 CFR 46.107(a) require that "the IRB … be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects." OHRP notes that while the location of the research site is Bethesda, Maryland, the research portfolio includes research involving HIV and AIDS patients, and subjects with infectious diseases coming from international communities.

OHRP recommends that NIAID give consideration to improving the diversity of the IRB membership through inclusion of community members and other nonscientists, such as patient advocates, members of vulnerable populations, or experts in multicultural affairs, to complement the extensive scientific expertise already available to it.

(5) HHS regulations at 45 CFR 46.103(b)(4) and (5) require that an institution have written IRB policies and procedures. OHRP notes that some written procedures used by

the NIAID IRB provide minimal operational details. In specific, we note the following provisions of the NIAID Standard Operating Procedures (SOPS):

(a) Chapter 5, "The IRB's Adherence to Regulatory Requirements and NIH Procedures," (Letter D: Reporting Unanticipated Problems) states that the PI is responsible for reporting promptly to the IRB (i) any unanticipated problems involving risks to subjects or others or (ii) any unexpected serious harm.

OHRP recommends that NIAID provide further written information as to what constitutes an "unanticipated problem involving risks to subjects or others," as well as a more comprehensive description of "unexpected serious harm."

(b) Chapter 5, "The IRB's Adherence to Regulatory Requirements and NIH Procedures," (Attachment 5-13: "Protocol Approval letter and Charge to Investigator") states in the third sentence of the second paragraph: "In addition, *substantive* [emphasis added] changes in research activities, during the period for which IRB approval has been given, may not be initiated by you without prior review and approval by your IRB, except where necessary to eliminate apparent immediate hazard to subjects."

Please note that HHS regulations at 45 CFR 46.103(b)(4) specify that the IRB must review *all* changes in research activities, not only substantive changes.

(c) Chapter 9, "IRB Actions," (Letter H: "Reporting Noncompliance or IRB Suspensions of Approved Protocols") states that the IRB Chair will notify specified individuals and offices of protocol violations and "serious and continuing noncompliance with federal regulations."

OHRP recommends that NIAID describe what circumstances constitute "serious and continuing noncompliance" that would require reporting by the IRB chair.

OHRP also notes that information regarding IRB policies and procedures is available in multiple locations. OHRP recommends that efforts be taken to ensure that the information available on the NIAID Web site, in the NIAID IRB written procedures (SOPS), and in NIAID's guidance to investigators is both consistent and clear.

(6) OHRP was impressed with the high level of review offered by the IRB members and the IRB chair, the depth of IRB members' scientific expertise, and the obvious concern for the safety and welfare of human subjects. However, it was not clear to OHRP that all

members of the NIAID IRB were sufficiently familiar with specific regulatory requirements, such as the need for documentation of certain findings, and the use of terms such as "vulnerable populations" and "expedited review." The NIAID IRB clearly devotes extensive attention to analysis of risks and benefits and to discussion of controverted issues. Nevertheless, OHRP recommends that all individuals involved in the support, review, and conduct of human subjects research at NIAID receive continuing education in the specific regulatory provisions of 45 CFR part 46.

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
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