DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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March 23, 2004

Dr. Robert A. Figlin
Chairman, Medical Institutional Review Board
Office for Protection of Research Subjects
University of California at Los Angeles
405 Hilgard Avenue
Los Angeles, CA 90095-1694

Subject: Secretary's Determination under Department of Health and Human Services Regulations at 45 CFR 46.407 on the Research Protocol Entitled "HIV Replication and Thymopoiesis in Adolescents" (1 R01 AI051996-01A1); Principal Investigator Dr. Paul Krogstad

Dear Dr. Figlin:

This letter is written on behalf of the Assistant Secretary for Health (ASH), Department of Health and Human Services (HHS). In July 2002, the University of California at Los Angeles (UCLA) institutional review board (IRB) forwarded the above-referenced protocol to the Office for Human Research Protections (OHRP) for consideration pursuant to requirements of the HHS regulations at 45 CFR 46.407 (i.e., research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children). The proposed research protocol would be funded by the National Institute of Allergy and Infectious Diseases (NIAID) grant number 1R01 AI051996-01A1.

In accordance with the requirements of 45 CFR 46.407, HHS solicited opinions regarding the proposed study from experts in relevant disciplines in June 2003. On July 16, 2003, a Federal Register Notice was published soliciting public review and comment, pursuant to the requirements of 45 CFR 46.407, for a period of 45 days. Documents related to the protocol were made available on the OHRP website, including the grant proposal, IRB protocol application, assent/permission documents, IRB deliberations on the proposed protocol, and IRB response to questions from panel assembled under 45 CFR 46.407. No comments were received in response to the Federal Register Notice.

Following consideration of the research protocol, recommendations by the experts, and the report of the NIAID Center for Scientific Review Special Emphasis Report, the ASH found that the research may be approved under 45 CFR 46.407, and recommended that HHS support the proposed research protocol, contingent upon specific modifications to the proposed research protocol as outlined below. The proposed research protocol, if so modified, would be in conformance with 45 CFR 46, subpart A; as well as 45 CFR 46, subpart D, sections 46.407 and 46.408 which require that the research (i) present a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; (ii) be conducted in accordance with sound ethical principles; and (iii) have adequate provisions for soliciting the assent of children and the permission of their parents or guardians. For your reference, the ASH's decision memorandum is enclosed with this correspondence.

The required modifications are as follows:

(1) the consent forms must include a better description of the procedures and associated risks, and, specifically, a fuller description of the risks of 24-hour exposure to an IV, to include the current language, plus, a statement that more clearly describes the risk of thrombophlebitis, such as the following: "Rarely, having a needle placed in your vein can cause thrombophlebitis. This condition occurs when the vein develops severe painful inflammation and a clot forms inside the vein";

(2) timing and use of HIV confirmatory testing should be discussed, as appropriate;

(3) the consent documents must be expanded to include a fuller disclosure of confidentiality risks (including methods to protect it, and its durability);

(4) the consent documents must include a broader discussion on the issue of no-cost treatment provided to participants for research-related injury as a condition of participating in the study;

(5) description of implications for females who are/may become pregnant (in terms of possible exclusion, confidentiality risks, and/or increased risks of procedures (even if there are none));

(6) consent documents must clarify the nature of information that can and will be provided back to subjects (including use of examples and how they will be provided to subjects);

(7) consent documents must provide more clarifying language to convey that participation in the sub-study at issue is distinct from participation in the main study;

(8) consent documents must include a broader, more explicit description regarding the handling, storing, and future disposition of blood samples obtained during the course of the study;

(9) the protocol must clearly indicate that glucose-intolerant individuals will be excluded from the study, and that confirmatory sequential serum testing will be done throughout the study;

(10) the consent documents must be changed to reflect the exclusion of glucose-intolerant subjects from the study and the use of sequential serum testing; and,

(11) the IRB must seek assurance from the investigator that the compounds used in this study are prepared in accordance with the Food and Drug Administration's Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients (http://www.fda.gov/cder/guidance/4286fnl.pdf), and that the protocol includes a calculation of the grams per kilogram of deuterium to be administered in each aspect of the sub-study and assurances that no subject would exceed the dose limit.

These stipulations must be incorporated into the research protocol, permission/assent forms, and other documents as appropriate, approved by the reviewing IRB, and confirmed by OHRP, prior to HHS funding of the research protocol and the enrollment of human subjects. Once the required stipulations have been incorporated into the protocol and related documents and approved by the IRB, the IRB should then forward the approved protocol to OHRP. Upon confirmation that the required changes have been made, OHRP will send a letter to the IRB and principal investigator indicating that enrollment may begin.

In addition, OHRP suggests that the UCLA IRB provide additional consideration to the following issues:

(1) clarification of information provided regarding compensation for participation;

(2) omitting any language that may tend to conflate the respective physician and investigator roles;

(3) expanding consent forms to include CT scan information in "Procedures" section; and,

(4) expanding consent documents to indicate that a CT scan is associated with more radiation exposure than a chest X-ray and to describe the specific amount of radiation to which the subject will be exposed.

Please do not hesitate to contact us with any questions. Thank you for your continuing commitment to the protection of human subjects.

Sincerely,

/s/ Bernard A. Schwetz

Bernard A. Schwetz, D.V.M., Ph.D.
Acting Director
Office for Human Research Protections

Enclosures

cc: Dr. Paul Krogstad, UCLA
Ms. Judith Brookshire, UCLA
Mr. Steven Peckman, UCLA
Dr. Lana Skirboll, NIH
Dr. Susan Plaeger, NIAID
Dr. Melody Lin, OHRP
Dr. Michael Carome, OHRP
Dr. Irene Stith-Coleman, OHRP
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