



# MEMORANDUM

OFFICE FOR PROTECTION OF RESEARCH SUBJECTS  
2107 Ueberroth Building  
169407

December 12, 2001

PAUL A. KROGSTAD, M.D.

**RE: Request for Additional Information - Response To Be Reviewed by the Full Committee**

UCLA IRB #01-11-064-01

HIV Replication and Thymopoiesis in Adolescents

The Medical Institutional Review Board (M-IRB) wishes to thank you for your recent submission. Your above referenced study was reviewed by the M-IRB during the meeting of December 05, 2001. After careful consideration, the Committee found that more information is required before a decision on whether to approve the study can be reached. As a result, your response to the posed questions on the following pages must be returned to the full Committee for review and discussion during a convened meeting.

**PLEASE NOTE:** No subjects may be contacted, recruited, or enrolled into this study until an Approval Notice and approved informed consent form(s) have been issued.

If your response is received by the office on or prior to January 09, 2001, it will be reviewed by the Committee at the meeting scheduled for January 16, 2001. Please note that it is the UCLA IRB policy that unless a response is received from you within 30 days of the date of this letter, we will withdraw this submission from the approval process. Therefore, should there be reasons which make it impossible for you to respond before 30 days, please advise as soon as possible. If you have any questions, please contact

Sincerely,

Robert A. Figlin, M.D.

Chair

On behalf of the Medical Institutional Review Board

**Please return two copies of your response to:**

Office for Protection of Research Subjects  
Medical Institutional Review Board  
2107 Ueberroth Building

Campus Mail Code 169407

- A. Please respond to the following, and make the necessary changes to the informed consent form(s) where appropriate; if you disagree with the Committee's requests for changes, please explain. **(Respond separately to each numbered item in sequence, employing the same number to identify your response.)**

1. UCLA's Multiple Project Assurance with the National Institutes of Health, Office for Protection from Research Risks (NIH/OPRR) stipulates that the Committee is responsible for assessing the risks vs. anticipated benefits of research performed under the auspices of UCLA. The Committee expressed concern that though the risk/benefit ratio of the main portion of this study is appropriate, the risk/benefit ratio for the substudy, as currently proposed, cannot be approved, according to the 45 CFR 46, subpart B, as described in The NIH/Office for Protection from Risks (NIH/OPRR), Institutional Review Board Guidebook:

*"The federal regulations require IRBs to classify research involving children into one of four categories and to document their discussions of the risks and benefits of the research study. The four categories of research involving children that may be approved by IRBs, based on degree of risk and benefit to individual subjects, are as follows:*

*1. Research not involving greater than minimal risk [45 CFR 46.404].*

*2. Research involving greater than minimal risk, but presenting the prospect of direct benefit to an individual subject. Research in this category is approvable provided: (a) the risk is justified by the anticipated benefit to the subject; and (b) the relationship of risk to benefit is at least as favorable as any available alternative approach [45 CFR 46.405].*

*3. Research involving greater than minimal risk with no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition. Research in this category is approvable provided: (a) the risk represents a minor increase over minimal risk; (b) the intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational settings; and (c) the intervention or procedure is likely to yield generalizable knowledge about the subject's disorder or condition that is of vital importance for the understanding or amelioration of the subject's disorder or condition [45 CFR 46.406].*

*4. Research that is not otherwise approvable, but which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children. Research that is not approvable under 45 CFR 46.404, 46.405, or 46.406 may be conducted or funded by DHHS provided that the IRB, and the Secretary, after consultation*

*with a panel of experts, finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a significant problem affecting the health and welfare of children. The panel of experts must also find that the research will be conducted in accordance with sound ethical principles [45 CFR 46.407].”*

Since the substudy proposes to administer deuterium labeled glucose over a 24 hour period in healthy children, the substudy does not appear to qualify for approval under the aforementioned categories for research with children. In order for the substudy to qualify for possible UCLA IRB approval, the Committee requests that you review the above categories and consider whether the substudy could be modified in order to conform to either 45 CFR 46.404, 46.405 or 46.406. All proposed revisions to the substudy should be detailed in your response to this correspondence as well as in the protocol summary and consent forms.

- a. If you wish to omit the substudy at this time and withdraw it from further IRB consideration, please explain how that might impact the scientific validity of the main portion of the study.
- b. If you do not wish to conduct the substudy as currently proposed, it will be forwarded to the Secretary of the DHHS for review, according to 45 CFR 407.

**Please also address the following questions as they relate to the main study and substudy. Based upon your response to the above, some of the following questions may not be relevant:**

2. The protocol indicates that subjects would be enrolled into two groups: 1) individuals who were infected perinatally, and 2) individuals who were infected by “adult behavior.” Please clarify for the Committee and detail in the protocol summary how the method or duration of HIV infection will be ascertained for the two groups of infected adolescents/young adults.
3. Please clarify for the Committee the source of the deuterium labeled glucose for intravenous infusion, as well as the deuterium labeled for oral administration.
  - a. Please indicate the purity of the deuterium labeled glucose and water to be used in this study.
  - b. Please clarify how the aliquot of water will be determined, and indicate the interval between aliquots administered both in the General Clinical Research Center (GCRC) and at the subject’s home.
  - c. Please verify for the Committee that the isotopically labeled materials that will be employed in this study are approved for use in humans.

4. Please clarify for the Committee and indicate in the consent form whether subjects must be willing to allow the researchers to review their medical records in order to participate in the study. If so, please indicate in the “Procedures” section of the consent form that subjects will be asked to sign a separate medical records release form in order for the researchers to access their medical records.
  - a. If medical record review is not a requirement for study participation, please include the following statement in the “Procedures” section of the consent form: *“On the checklist at the end of this consent form, you will be asked to indicate if you would permit the researchers to access your medical records.”*
    - i. Please provide check boxes before the “Subject’s Signature” block for subjects to accept or decline to allow the researchers to access his or her medical records for research purposes:

*“Please check the appropriate box below and initial:*

*I agree to allow the researchers to review my medical records for research purposes.*

*I do not agree to allow the researchers to review my medical records for research purposes.*
5. Please clarify for the Committee and indicate in the protocol summary and substudy consent form the number of subjects that will be enrolled into the substudy.
6. Please clarify for the Committee and indicate in the protocol summary how subjects will be selected and contacted regarding possible participation in the substudy.
7. The “Payment for Participation” section of the substudy consent form indicates that subjects will receive \$75 for the overnight stay, \$25 for day 14 visit and \$50 for day 28 visit. Since the procedures for day 14 and day 28 appear identical, the Committee requests that subjects be provided the same payment for each visit.
8. The consent forms indicate in the section entitled “Sample Remaining at the End of the Study” that samples will be shared with other researchers. However, the protocol does not describe the sharing of samples. Please clarify whether you intend to share the samples with other researchers, and if so, please describe the reason for sharing the samples.
9. Your response to question 4 of the Summary Information (Section III of the IRB application) indicates that the study will also be conducted at Children’s Hospital, Los Angeles. Please detail their role in this study and, if appropriate, forward to the Committee a copy of the Approval

Notice and approved consent documents for this study from the Institutional Review Board (IRB) of the Children's Hospital, Los Angeles.

10. This study may fall under the purview of the Medical Radiation Safety Committee (MRSC), because CT scans will be undertaken as part of the study activities. Please forward to the Committee the determinations of the MRSC for this study or documentation from the MRSC that they wish to exempt this study from their review.

**Please Note:** If the M-IRB approves the research, an approval notice will only be issued for administrative purposes (no subjects may be contacted or recruited) and the related consent form held on file until the MRSC approval or letter of exemption is received by the M-IRB.

11. The Form 740 ("Investigators' Statements of Financial Interest Related to Sponsored Projects") does not indicate whether the other co-investigators have financial interests related to the project (please see attached copy). Please submit a revised Form 740 with the appropriate information included, along with your response to this correspondence.

B. Please make the following modifications to the informed consent and assent forms: **(Please provide bold typeface or underline changes on one of each copy for the reviewers and provide two clean copies of each to be used as the official version of the documents.)**

1. Please indicate in each consent form the number of subjects expected to enroll in this study at UCLA and in total.
2. Please describe in the beginning of each consent form and assent form the expected duration of the subject's participation in the research study.
3. Please identify the sponsor of the study within the first paragraph of each consent form (e.g., "This study is sponsored by a grant of the National Institutes of Health (NIH).").
4. Please clarify in each of the consent forms the types of blood tests that may be performed on the samples collected during the study.
5. Please modify the consent and assent forms as indicated by the markings on the enclosed copies.