

June 27, 2003

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**RE: Expert Review of Research under 45 CFR § 46.407 of Protocol, “HIV Replication and Thymopoiesis in Adolescents”**

Dear Doctor Schwetz:

Thank you for inviting me to review this sub-study investigating HIV infection and thymopoiesis involving intravenous infusion with an overnight hospital stay. Of particular interest, of course, is the enrollment of adolescents who are not infected with HIV, thus qualifying as “healthy” participants in this research. Because I agree with the UCLA Institutional Review Board (IRB) that this sub-study poses more than minimal risk to these participants and because these participants should not be construed as having a condition the treatment of which will be aided by this research, this portion of the protocol is not approvable under 45 CFR § 46.404, § 46.405, or § 46.606. I believe the research is approvable under 45 CFR § 46.407, with some modification of the protocol and informed consent. My discussion addresses why I perceive these protocols to entail more than minimal risk and why this research is nonetheless of sufficient importance that it should be allowed to be pursued pursuant to optimal ethical standards.

**I. Research not approvable under 45 CFR § 46.404, § 46.405, or § 46.406.**

This protocol offers no prospect of direct benefit to these seronegative research participants. The study involves a CT scan at the outset and, if the research participant opts for participation, administration of an intravenous deuterium-labeled glucose product over 24 hours in the sub-study. The report from the Medical Radiation Safety Committee group indicates that the radiation exposure required for the CT scan is equivalent to the background radiation that a child would encounter in normal, daily life over 16 months. Given this quantification, I believe that this component of the trial is of minimal risk. The method being utilized for garnering data on in vivo labeling of lymphocyte turnover has been demonstrated successful in trials involving healthy adults and affected children. This 24-hour intravenous infusion with a glucose concentration containing deuterium markers (a stable isotope) represents risk that is distinct risk from that “ordinarily encountered [by adolescents] in daily life.” § 46.102(i). I would judge the risk of this intervention to be greater than minimal because it is a lengthy period of venous access. This assessment places the study outside the auspices of § 46.404.

The discussions surrounding this protocol raised an important question of interpretation regarding the federal rules as they apply to assessment of minimal risk when a study involves more than one procedure posing the potential for harm to the research participant. While it may be helpful to evaluate the degree of risk involved with each intervention, I agree with the UCLA IRB that the final assessment of whether a study involves more than minimal risk can be a cumulative evaluation, taking into account all the interventions required by the protocol. However, it should not be possible to conclude that a protocol does not involve more than minimal risk overall if any component part of the study itself poses

more than minimal risk. In the case of this HIV protocol, the fact that the intravenous infusion alone poses a greater than minimal risk to research participants places the research as a whole in this category unapprovable under § 46.404.

Because these are healthy research participants, the sub-study offers no possibility of therapeutic benefit that justifies the greater than minimal risk and the intervention cannot be approved under § 46.405. Likewise, given the volunteers' normal status, the research is not approvable under § 46.606 as "[r]esearch involving greater than minimal risk and no prospect of direct benefit to the individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition." Enrollment of the seropositive research subjects is appropriate under § 46.606, as I would deem the interventions involved only a minor increase over minimal risk, but the seronegative participants cannot be approved under the generalizable knowledge provision.

It is interesting to at least pause though, and consider why these normal, healthy participants do not have a condition that might make their enrollment permissible under this last provision. It has not obvious that these are healthy participants, who are supposed to be exposed to ordinary risks, when it is clear from the protocol that the controls in this study are not normal adolescents. Indeed, they have been classified as "at-risk" based on a pattern of behaviors that would place them at risk for HIV infection, such as sexual activity and intravenous drug use. In the world of these research volunteers, the greater than minimal risk supposed by an assessment of the protocol components may not be so great given the nature of their daily lives. It is also quite likely that some of these adolescents, while they are receiving treatment for their hazardous tendencies, are likely to acquire HIV and subsequently be among those potentially benefiting from these research results. Nevertheless, these control research participants should not be regarded as having a condition that allows them to be exposed to a greater than minimal risk given the uncertainty of them reaping benefit from this research down the road. It would be unjust to place adolescents in this category simply because they lead more precarious lives. These participants should not be exposed to greater scientific risks based on their familiarity with more acute social risks.

## **II. Research approvable under 45 CFR § 46.407, with protocol/informed consent modifications**

This research truly involves only a minor increase over minimal risk for the control research participants. The research design is quite sound, involving the comparison of prenatally infected HIV-positive adolescents, those infected with HIV in adolescents, and unaffected adolescents. In the scientific discussion of this protocol, I was convinced that the age-matched groups for this trial were a necessity to investigating parameters of thymopoiesis and T cell turnover in adolescence depending upon the category of HIV infection and administration of antiretroviral therapy. It is particularly impressive that these investigators have the infrastructure of relationships with adolescent patients to recruit appropriate risk-matched uninfected individuals into this study.

### **A. The research presents a reasonable opportunity to further understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children.**

While the trial has proceeded in young adult patients who are not HIV-positive, these are not optimal scientific controls for the earlier adolescent age group given the substantial changes noticed in the function of the thymus during adolescence. It is expected that this research will assist in answering important questions that can lead to better control of HIV infection in adolescents, as well as in all patients who are prenatally infected. This is certainly a unique opportunity for access to an optimally designated study population by which better understanding of effective therapies can be derived. Likewise, HIV infection in childhood and

adolescence is certainly a serious health problem, even more so when considered on a global basis rather than only the incidence of affected patients in this country.

**B. With some modification, this research can be conducted in accordance with ethical principles.**

While the IRB has done a good job noting several issues that will enhance the quality of the informed consent in this sub-study, I have a few additional concerns about the conduct of the trial as it is currently presented. Most of these recommendations go to amendment of the consent/assent forms.

- The investigators for this trial should be enrolling trial participants, not personal physicians. Even in those cases where an investigator may also be a research candidate's personal physician, another member of the research team who does not have clinical responsibilities to the patient should administer the consent for trial participation to optimize voluntariness of participation. I note that the language of the consent form, probably boilerplate, states: "Your health care provider may be an investigator of this research protocol, and as an investigator, is interested in both your clinical welfare and in the conduct of the study." If it were possible, I would recommend omitting this language, as it conflates the role of the physician-investigator, the mission of this essentially observational trial, and greatly increases the possibility that research participation may in some way be in the therapeutic interest of these patients. Adolescents should especially be protected from misconceiving the option of research participation versus the obligations of clinical care.
- Because of the unique problems of imbedding consent for research within consent for research, it is particularly important to convey that the opportunity for participation in the sub-study is absolutely distinct from participation in the study overall. The fact that a separate consent form and compensation scheme are involved is helpful to this end. However, adolescents especially may have a difficult time of conceiving of their right to say no to a subsequent sub-study once they have assented to participation in the general study. As such, it may be worth laying out the distinct nature of the study more explicitly or in greater detail in the initial consent form.
- Given the at-risk status of the uninfected controls in this study, I was curious that confirmatory HIV testing did not seem to be part of the protocol, unless of course this test is being performed as part of the scheduled blood draws. If it is the case that these trial participants will be tested for HIV in the course of the study, this should be made clear in the consent forms. This population in particular may have their own preferences about knowing their HIV status. Even if an HIV test result were not necessarily provided to the participant, the fact that such a test might be run would still be of significance in obtaining their informed assent/consent to the collection of trial data. In the event that this complexity exists and has not been thought through, the investigators should provide language about the potential for HIV testing as part of the informed consent process and documentation.
- The consent form is currently completely inadequate on the point of storage of tissue samples, in this case retention of blood. Acknowledging that the University of California will own the research samples is one component of informed consent for retention. The possible nature of other research that may be performed with the sample should be clarified, along with the duration of retention of the sample. Options for refusing follow-up in other research and withdrawing the sample should be clearer. The next section, "Information

About Your Sample,” which might rather be called “Provision of Study Results,” makes the section on “Sample Remaining at the End of the Study” more confusing. Please consult the standards articulated in the National Bioethics Advisory Commission Report, *Research Involving Human Biological Materials: Ethical Issues and Policy Guidance*, at <http://www.georgetown.edu/research/nrcbl/nbac/hbm.pdf>.

- I support the investigators commitment to provide treatment in the event of research injury wholeheartedly. The IRB has made appropriate alterations in the compensation mechanism. One point to clarify is who will be in receipt of the compensation in the event that a parent gives permission for enrollment and an adolescent assents. A compensation amount appears on both forms and I assume the sole recipient of compensation is the adolescent, but perhaps this should be clarified in the parents’ form.

Other than these recommendations to shore up the ethical conduct of this trial, I believe that the provisions for soliciting the assent of the seronegative adolescent participants and soliciting the parental permission are adequate. The sub-study of this research protocol should be approved under § 46.407.

### **III. Conclusion**

I regard this research as an innovative effort to obtain optimal scientific information in the era of HIV/AIDS. While I was initially concerned about the control study population here, as they may be perceived as being less stable than other healthy adolescent research subjects, alternatively they may be the best participants for this research given their similar social markers and the possible benefits that may inhere by exposure to the disciplined and altruistic aspects of research participation. The sub-study poses greater than minimal risk when its component requirements are taken together, but I believe with appropriate clarification in the consent documents and consideration of other enrollment safeguards to optimize consent/assent, this important research should be approved under 45 CFR § 46.407.

Sincerely,

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