

1 July, 2003

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Doctor Schwetz:

I appreciate the opportunity to review the protocol for the study "HIV Replication and Thymopoiesis in Adolescents."

In addition to attending the panel review of 17 June, 2003, I have carefully reviewed the investigator's application to involve human subjects in research, protocol, informed consent documents and considered the scientific discussion. I conclude that the research described therein is not approvable within the guidelines established in 45 CFR 46.404, 46.405, or 46.406.

My comments address why I perceive this protocol generates more than minimal risk to the participant without adequate corresponding prospect of benefit, which excludes the protocol from approval under 45 CFR 46.404, 46.405 and 46.406.

I believe the research is approvable within the guidelines established in 45 CFR 46.407, with modifications to the informed consent and assent forms.

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

Because this protocol involves more than minimal risk with no direct benefit to healthy volunteer children (one-third of the study participants), and will not yield knowledge about their condition or disorder (because they don't have one), I do not find that it meets the provisions for approval under the federal rules except under 45 CFR 46.407. I believe the probability and/or magnitude of harm or discomfort, though relatively minor, are nonetheless greater risks than those encountered in a healthy child's daily life or during the performance of routine physical or psychological examinations or tests. I understand that the radiation exposure of the CT scan represents approximately 16 months of background radiation which is greater than a non-participant would receive and some subjects may have as many as three CTs within about 30 months.

It is reasonable to expect that the I.V. placement with duration of up to 24 hours and/or drinking of water solution will cause discomfort as well. I find that the age of the adolescent participants to be recruited for this study, however, mitigates the risk because they are able to understand, assent, cooperate and tolerate these "risks" in a manner that an infant or young child might not be able to do.

II. Research approvable under 45 CFR 46.407, with protocol/informed consent modifications:

In my opinion, the research presents a reasonable opportunity to further understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children. The study appears to be very promising and scientifically sound. My comments and recommendations are chiefly administrative.

III. Comments:

PREGNANCY (Risk not addressed):

Since pregnancy will not exclude women from the study, this information should be included in the guardian consent and the youth assent forms. A statement such as, "Pregnancy does not warrant exclusion or withdrawal from this study," would also be helpful in the Withdrawal of Participation by the Investigator section of the forms. A confidentiality plan should be in place and described to protect the adolescent's privacy regarding discussion and dissemination of this information. The risks to an adolescent who is/becomes pregnant and to the baby should be addressed, even if there are no risks. Female adolescents in

this study may be/become pregnant during the course of this potential 30 month study. The risks (physicals, blood tests, CT exposure, I.V. infusion of labeled glucose or drinking the special water solution) to pregnant females and/or their child should be included. The very nature of this protocol is likely to draw recruits who could be involved in high-risk adult behaviors which may result in pregnancy.

CT SCAN:

The statement included in the consent forms' POTENTIAL RISKS AND DISCOMFORTS section which reads, "The amount of radiation to which you will be exposed for each CT scan is the same as a chest x-ray" is vague and should be omitted. Both the consent and assent forms should describe, specifically, the amount of radiation to which the subject will be exposed. I understand the organ dose estimate as follows: thymus (20 mGy), esophagus (20mGy), breasts (7 mGy), and thyroid (4.5 mGy), as well as the estimated radiation dose equivalent of 1.3 years of background radiation for youths of this age group participating in this study. I believe this clear statement should be included in the consent/assent forms along with the existing statement that healthcare workers are permitted to receive twelve times more than this during a year of work which is a helpful reference to the layman.

PROCEDURES:

The consent forms do not include information about the infusion of sugar solution or drinking of water solution in the PROCEDURES section. This should be added to the consent form for both HIV+ and control subjects to prevent confusion and include this important data.

The assent forms do not include information about the CT scan(s) in the PROCEDURES section. This should be added to the assent form for both HIV+ and control subjects to prevent confusion and include this important data.

The timelines in the HIV+ consent and assent forms PROCEDURES section are displayed very differently. The manner in which they are drafted could lead the guardian and/or subject to misunderstand what is expected of the subject on certain dates, as the following roadmaps differ in content as well as the timeline construction:

HIV+ Group:

Consent Form Procedure Timeline: Month 0, Month 6, Months 12 and 18, Months 24 and 30

Assent Form Procedure Timeline: Month 6

Control Group:

Consent Form Procedure Timeline: Month 0, Month 6, Months 12 and 18

Assent Form Procedure Timeline: Month 6

The descriptions contained in the consent and assent forms for each group should be combined. Identical descriptions and timelines should be listed in both consent and assent forms. The language of the youth assent forms is no more challenging to comprehend than the consent forms, so there seems no value to having different descriptions.

POTENTIAL RISKS AND DISCOMFORTS:

The assent forms do not have CT scan listed in the POTENTIAL RISKS AND DISCOMFORTS section although it is listed in the corresponding consent form. This information should be added to the assent forms for both HIV+ and control subjects to prevent confusion and include this important data.

The consent forms do not have Infusion of sugar solution or Drinking of water solution listed in the POTENTIAL RISKS AND DISCOMFORTS section, although these risks are listed in the corresponding assent forms. This information should be added to the consent forms for both HIV+ and control subjects to prevent confusion and include this important data.

PAYMENT FOR PARTICIPATION:

Adding a statement similar to the following underlined sentence would add clarity and prevent subject misunderstanding by explaining the purpose of the compensation:

If you choose to participate in this study, you will be paid \$XX for each visit during this study, or a total of \$XX if you complete the visits. These payments are to compensate you for accepting the risks and/or inconveniences described herein and participating in this research protocol.

SAMPLE REMAINING AT THE END OF THE STUDY:

The details regarding what will happen with the sample remaining at the end of the study described in the consent and assent forms should be more informative. The statement, “The researcher is not required to store your sample(s) indefinitely,” does not describe how long the sample *will* be stored or the purpose(s) for which it may be used. This section should also include information about the sample/patient confidentiality plan. The purposes for which “other researchers” may pursue specific studies with the sample should be more descriptive, (i.e. who may use the sample, how long the sample will be stored/available to “other researchers” and how the sample may be used), so that the subject may make a truly informed consent in donating their sample.

The participant may be willing to allow the sample to be used for some types of research, but not others. As the consent/assent forms are currently drafted, subjects/guardians must choose either an implicit waiver of all authority over purposes for which the sample may be used or a total declination to share their sample. They should have the right to limit the extent of their sample(s) use. There may be research with which they are ethically opposed, for example, such as controversial use fetal tissue or in support of human cloning, and for which they should be permitted to decline participation.

It is reasonable to assume that many, if not most, of the subjects/guardians in the study will be motivated to contribute toward improved understanding of HIV for personal reasons since two-thirds of them will be HIV+. They should not be made to feel obligated to share their sample with other researchers for reasons that are not described, may not be related to HIV or with which they may be morally opposed. Physically and/or emotionally vulnerable subjects often feel burdened to contribute to the benefit of research, especially if they believe it will further the knowledge about their child’s disease or their own. To avoid the potential injustice of coercing this population, adding a third option such as the following to the SHARING OF SAMPLES section of the consent/assent form would be beneficial:

“_____ I agree to have my tissue/fluid sample shared with other researches, except under the following conditions or for the following purposes _____.”

INFORMATION ABOUT YOUR SAMPLE:

The section of the assent form which asks the participant if they want to receive “specific information about what the study found about me” is vague. This could lead a participant to believe they might learn more about their individual health status or benefit more from participation than is reasonable. The form would be less ambiguous if it stated specific examples of what they could expect to receive, such as copies of labs, etc..

In order to receive either “general information about what the study found” or “specific information about what the study found about me,” the process for maintaining confidentiality should be described. The participant should be specifically told if they will receive a copy of this study when it is published if they so desire. If confidentiality causes this to be a burdensome challenge, providing the participants with an internet website where the study will be posted and the anticipated release date could be a simple solution.

PRIVACY AND CONFIDENTIALITY:

Should the subject permit their samples to be shared with other researchers, the confidentiality associated with this process should be stated. The obligation and plan to provide confidentiality to female subjects who are/become pregnant and the confidential manner in which general or specific information drawn from the study will be provided to subjects who have requested it should be described.

PARTICIPATION AND WITHDRAWAL:

Again, since pregnancy will not exclude women from the study, a statement such as, “Pregnancy does not warrant exclusion or withdrawal from this study,” would be helpful in the Withdrawal of Participation by the Investigator section of the forms.

IDENTIFICATION OF INVESTIGATORS:

This section lists five investigators with their current contact information for the purpose of research related injury, adverse reaction or emergency related to this study. It should not serve a dual use as contact information for subjects who desire “general information about what the study found” or “specific information about what the study found out about me” per the Information about My Sample section of the consent and assent forms.

The consent/assent forms state the participant is responsible for contacting “the investigator” to provide address and/or telephone number changes if they desire to receive information about their sample. Subjects are directed to the Identification of Investigators section of their consent/assent form for contact information. It is not evident that either a confidential process is in place that will permit any of the five investigators to field a phone message from an (unknown) adolescent providing their phone or address change, or those investigators are administratively prepared to follow-up with the record update. The process whereby subjects/guardians may provide update contact information in order to receive requested general or specific information and the confidentiality associated with this should be more clearly described.

I appreciate the opportunity to review and comment on this most interesting research protocol and hope that my comments and recommendations are helpful. Thank you for the invitation to participate in the public discussion of this study.

Respectfully,

Colleen M. O’Brien