Sound-bite version: This appears to be in part a mistake, but is still appropriate to review. UCLA referred this because a sub-study involving the administration of radioactive materials was included; 45 CFR §46.406 might be invoked for the HIV-infected subjects, but not for the controls. From the letter forwarding the protocol for HHS special panel review:

> **"The IRB also found that the administration of radioactive materials to seronegative adolescents did not address a particular disorder or condition of that specific subject population, as required under 45 CFR 46.406, since they are healthy control subjects."**

The problem with that finding is that the isotope being used is a stable isotope, not a radioactive one. There is no administration of radioactive materials to anyone in this protocol. An argument may thus be made that the substudy qualifies under 45 CFR §46.404, research involving no greater than minimal risk. I do not believe that there is sufficient information before us to make that finding, however. I do think that it is eligible for approval under 45 CFR §46.407, and I would conditionally recommend its approval. The conditions primarily pertain to information we do not have—concerns that may already have been addressed satisfactorily; there is also some room for refinement of the consent process and its documentation.

Exposition:

A. Does the research involve greater than minimal risk?

At a second pass, it seems still appropriate to review this matter, though a non-trivial argument may now be made for approvability under §46.404. In order to make the finding of approvability under §46.404, however, one would have to conclude that all of the risks in the study meet the "no greater than minimal risk" standard:

- Volumetric CT of mediastinum
- Venipuncture for various tests of T-cell number, function and phenotype
- Deuterium-label T-cell turnover study
- Informational risks and confidentiality/privacy risks associated with the study

I don't think we can make those findings confidently on the basis of the information in front of us; before the panel met, I had concerns in three areas:

- Confidentiality provisions are only described in sweeping generalities, so we didn't know what the information-related risks actually are or how long they persist.
  - *What sort of samples/data are being retained with traceable identifiers?*
  - *How secure is the code used for the identifiers?*
  - *How long are the samples or data being retained with identifiers?*
  - *To what other uses might identifiable information or samples be put?*
  - *Is fuller exposition on informational risk necessary in the consent process?*
  - *How is the consent transition being planned for (many of the subjects will be adolescents at study entry, but will reach majority during the study and become their own consent authorities)?*
- We are not told in the IRB application if the CT involves the use of contrast, or what the radiation exposure actually is. This concern was addressed during the panel

meeting and in information faxed to panel members after the meeting. With respect to a finding of "no greater than minimal risk," the problem now becomes deciding whether a non-contrast CT in an unsedated, co-operative adolescent poses risks that are greater in likelihood and probability of harm than are the risks of everyday life (45 CFR §46.102[i]).

Careful reading of the grant application revealed a single use of the phrase "non-contrast spiral CT," so the risk of contrast is apparently not an issue. The radiation dose is variously described as about as much as a chest x-ray (which would by the newest techniques under 5 mRem, and would not exceed 25 mRem unless very old equipment were used), equivalent to 16 months of ordinary background radiation (national average background radiation is 365 mRem per annum*, so 16 months would be about 485 mRem), or about 1/12 the allowable annual occupational exposure (Allowable annual exposure is 5 rem; 5/12 of 5 rem is a bit over 400 mRem). Most published data concerning limited-field spiral CT by modern techniques indicate a dose that is within the range encountered in other diagnostic radiographs, but considerably greater than that of a chest film. Information faxed to the panel confirmed that the calculated exposure was about 400 mRem (using a method that corrects for radiosensitivity of the exposed organs). There is uncertainty about the risk of exposure in this range, because most of the assumptions involve extrapolations from information obtained at higher exposures. The risk, in any event, is low enough to be difficult to measure adequately, and it is relatively common in everyday life to have occasion to require diagnostic radiographs yielding exposure of this magnitude within a year.*

- Although we are provided with an undated FDA letter, date-stamped 1997, saying that an IND would not be required for an isotopically labeled tracer glucose preparation, and we are provided with a copy of an e-mail confirming that this opinion would still apply to the study under review, we were originally provided with no information assuring us that it is being prepared to ordinary pharmaceutical standards of sterility, purity, non-pyrogenicity and stability. Thus, the risks of the tracer sub-study were uncertain.

During the panel meeting, we requested and received documentation that the isotope powder had been submitted for sterility and pyrogenicity testing, which it passed. We were also advised that this sterile, pyrogen-free powder was being prepared for intravenous infusion by the research pharmacist(s) in the GCRC. Therefore, if there is no failure of process in the GCRC pharmacy, the intravenous preparation should carry very little risk. One then must consider the risk of a GCRC stay and the presence of an intravenous infusion needle for a day. This is a risk I think should be considered by age. That is, a small child would likely find the experience frightening—both physically and in terms of separation anxiety, and may have difficulty co-operating completely. For such a child, the risk is greater than it is for an older child who can understand and give assent and co-operate, and who may enjoy rather than be frightened by a night away from home and parents. Because this study only involves subjects age 13 and over, I believe that the risks of the sub-study fall within "minimal risk."

I think the argument for allowability of the substudy in the normal controls under §46.404 might have merit, even if we cannot really make that finding:

- A non-contrast CT could be argued to be no greater than minimal risk in a consenting, co-operative adolescent requiring no sedation.
- The glucose tracer study involves a stable isotope, not a radioactive isotope, and the venipunctures can be accepted as minimal risk in older children, able to assent and co-operate. So if the tracer is prepared to pharmaceutical standards, the study could be of very low risk, indeed.
- The information being collected on the normal subjects is not sensitive, so the prospect of harm with inadvertent release is very small and the chances that anyone would actively seek it are also very small. If we had a fuller description of robust privacy/confidentiality provisions, we could very possibly also find the information-related risks to be no greater than minimal risk.

Thus, although it is *possible* that this could qualify under §46.404, we do not have the information to exclude the possibility that it poses greater than minimal risk without offsetting benefit, in which case it does become problematic for a local IRB to approve it for normal control subjects who are children.

Conclusion: This *may be* of greater than minimal risk, and we should review it as such rather than delay the process to pursue the possibility that a minimal-risk categorization may be defensible.

B. Does the research pose a realistic prospect of direct benefit to individual study participants?

There is no claim of benefit, and there is no prospect I can see beyond a remote actuarial possibility that some of the research information could turn out to be clinically useful. Even that claim is not available for the control subjects.

Conclusion: There is no realistic prospect of direct benefit to individual study participants, so this study is not approvable under 45 CFR §46.405.

C. How great is the increment in risk over the "minimal risk" standard?

As mentioned in the exposition under "A," some of the risk information is incomplete. That being said, I think the spectrum of likely risk is from an extreme at which the "minimal risk" criteria would actually be met, to the opposite extreme at which serious risks would be delivered. Unless there are serious problems with confidentiality provisions, this should produce only a slight increase in risk beyond the "minimal risk" standard.

Conclusion: With some reservations, it appears that the increment in risk is mild to moderate, so approval under 45 CFR §46.406 is not automatically excluded by virtue of the risk level.

D. Does the study provide the opportunity to learn important information in understanding or ameliorating the subjects' disorder or condition?

The work seems to be well designed, and addresses important questions about an infection of great public health impact. It would therefore seem to meet this criterion, with one disclaimer: the obvious exception is the normal control subjects, for whom

the substudy provides additional risk without providing information about any disorder or condition that affects them.

Conclusion: With the exception of the control subjects, it appears that the criterion is met, so approval under 45 CFR §46.406 is (a) not automatically excluded for the HIV-infected subjects and is (b) not clearly possible for the controls.

Here of course the discussion branches: for HIV-infected subjects, the experiences of participating in the study, including the substudy, will be reasonably commensurate with the experiences of being treated and monitored for HIV disease, so I believe it is eligible for approval under 45 CFR §46.406. For the normal subjects, the substudy presents experiences that are different from those of their lives, and they do not clearly have a disorder or condition about which important information is being gathered..

Intermediate Conclusion: If the confidentiality/informational risks are adequately contained *and* one accepts the CT as being within minimal risk *and* if one accepts the 24-hour i.v. as being within minimal risk for older children, one *could* find the study—including the sub-study and including the uninfected control subjects—to be of minimal risk. If any of these is held to be greater than minimal risk, neither 45 CFR §46.405 nor §45 CFR 46.406 would apply to the uninfected control subjects, and review under 45 CFR §46.407 would be required. I am personally comfortable considering the CT to be no greater than minimal risk, and I personally believe that the subjects are old enough that the deuterium-glucose infusion would be of no greater than minimal risk if the preparation were made to customary pharmaceutical standards. Therefore, in the presence of robust confidentiality protections, I would have been willing to approve this protocol in its entirety under 45 CFR §47.404. It remains appropriate to consider the "407" criteria nonetheless, both because the confidentiality provisions might *not* allow the informational risks to be "no greater than minimal risk" and because others might not share my comfort with the CT and the infusion as "minimal risk" procedures.

Does this study meet the requirements for approval under 45 CFR §46.407?

Although I believe there are some wrinkles that would have to be ironed out before actual final approval could be given, I believe this protocol may be approved under §46.407, because:

- The research presents a reasonable opportunity to further the understanding, prevention or alleviation of a serious problem affecting the health or welfare of children. *HIV infection is a large public health problem in children; the control data are needed to interpret the patient data in the study; the study has reasonably good prospects of yielding important information helpful in understanding HIV infection in adolescents. I.e., I agree with this finding by the IRB, required under §46.407(a) and §46.407(b)(2)(i).*
- The research will be conducted in accordance with sound ethical principles (45 CFR §46.407(b)(2)(ii):
  - Risks are minimized, to the point that they flirt with the "minimal risk" threshold. *Note, however, that this assertion could fail scrutiny if the confidentiality provisions are not robust.*
  - The need to study adolescents is well established, in that the scientific question addresses the consequences of neonatal infection and events in the pubertal and immediately post-pubertal period.
  - The lack of direct benefit to subjects is a potential concern, but the amount of incremental risk is so slight that I think it is allowable in normal subjects; it's well within the range of excess risk allowable under 45 CFR §46.406.

- There may be an opportunity to lower risk further by using MRI rather than CT, but it is recognized that MRI may be less available, more expensive, more time-consuming and less well standardized than (and thus might be scientifically problematic compared to) CT.

- Appropriate provisions have been made for consent, permission and assent. *That being said, they could be improved. I think that a fuller exposition of the confidentiality provisions may have been helpful to the UCLA IRB, as it would be to me; fuller disclosure of the confidentiality risks would be appropriate for the subjects. If I were a member of a reviewing IRB, I'd be asking for more. I would urge the UCLA IRB and the investigator to improve this part of the protocol and process. Although it is not as great a concern, I also think that "respect for persons" would be more honored by explaining why some tests are being done. Telling people they might get a sugar infusion is all very nice, but would it not be even nicer to tell them that it's being done to look at how well the body is making certain kinds of cells and how long they're lasting? Finally, it is problematic for risks to be borne by adult subjects on the strength of research permission granted by their parents when they were still minors. There should be a provision for assuring the continued presence of consent as majority is reached.*

Proposed recommendation to the Secretary:

Enable the local IRB to grant approval under 45 CFR §46.407, advising them before granting final approval to give additional scrutiny to:

(a) the adequacy of the confidentiality provisions and the durability of any confidentiality risk
(b) the adequacy of the disclosure of the confidentiality risks in the consent process and form
(c) the adequacy of the description of the purpose of the research in the consent process and form
(d) why the IRB application asks approval for genetic testing, but this is not mentioned in the consent form

my original list had two additional items, which I feel were adequately addressed during the panel meeting:

(e) the adequacy of the pharmaceutical preparation of the tracer isotope
(f) the actual radiation exposure for the specific CT technique as it will actually be performed in this group of subjects, including marrow absorbed dose and total body exposure dose in mRem

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