May 19, 2003

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Acting Director
Office for Human Research Protections
Department of Health and Human Services
The Tower Building
1101 Wooten Parkway, Suite 200
Rockville, MD 20852

RE: Subpart D Panel Review, "Sleep Mechanisms in Children: Role of Metabolism"

Dear Doctor Schwetz:

It has been very interesting to consider this proposed protocol studying the biochemical underpinnings of sleep in adolescence. In this trial involving healthy research participants, the potential risks imposed by the protocol make the research difficult to approve outside the setting of a § 46.407 panel. Given that this research is not directed at potential therapy for any condition that the research participants suffer, and given the fact that the interventions pose more than a minor increase over minimal risk in the life of an ordinary adolescent, I conclude that this trial is not approvable under 45 C.F.R. § 46.404, 46.405, or 46.406 (also 21 C.F.R. § 50.51, 50.52, or 50.53). However, answers to the research questions here may be very helpful in providing baseline data about sleep in this age group, in which health problems related to sleep can take hold. As such, I find the research approvable under 45 C.F.R. § 46.407 (and the corresponding 21 C.F.R. § 50.54), with some modification of the enrollment procedures and the consent document.

I. The protocol is not approvable under 45 C.F.R. § 46.404, 46.405, or 46.406 (also 21 C.F.R. § 50.51, 50.52, or 50.53)

The multiple clinical components of this trial clearly place it outside the category of minimal risk as it pertains to healthy adolescents. Minimal risk encompasses those interventions commensurate with the risks the child would face in the ordinary course of daily life. Being subject to some of the protocol elements in isolation may meet the test of minimal risk, such as a simple MRI, but bundled with other interventions such as sleep deprivation and placement of an intravenous line, the protocol certainly exceeds minimal risk. Thus, the protocol is not approvable under § 46.404.

Given a finding of more than minimal risk, a protocol may also be approved if it offers "the prospect of direct benefit to the individual subjects." § 46.405 In this case, there is no prospect of direct medical benefit to the research participants, as they do not have a health need that is being addressed by the protocol. While the adolescents may benefit intellectually, experientially or economically from research participation, these are not the positive effects intended by the federal rule. The protocol is not approvable under this prong.

The research is also not approvable under § 46.406 because while it does involve greater than minimal risk without the prospect of direct benefit, the healthy participants do not have a "disorder or condition." If these were patients with a neurocognitive, behavioral

or cardiovascular condition related to a sleep disorder, this would be a study likely to yield generalizable knowledge about their condition, with arguably a minor increase over minimal risk. However, when we conduct research on healthy volunteers we set the bar higher in terms of the risks we allow the pediatric population to incur. Under this regulatory scheme, this research must go to an expert panel review for consideration of approval.

II. The protocol should be approved under 45 C.F.R. § 46.407 (and 21 C.F.R. § 50.54), with some changes to the enrollment procedure.

This research does represent one necessary aspect of efforts to "understand, prevent or alleviate a serious problem affecting the health or welfare of children." § 46.407 The relation of sleep to health problems is increasingly investigated and changes in disease and sleep patterns in adolescence makes this population an especially fertile group for research. Fundamental understanding of sleep issues in children will no doubt offer important clues for specific health problems, as well as general wellness among adolescents.

In assessing whether this protocol will be conducted according to sound ethical principles, there are several questions that can reasonably be raised. First, is this research protocol even scientifically feasible? I will defer to my clinical colleagues on this point, however I was persuaded that studying the cellular mechanisms of sleep could be an important to research in this field and the investigators backing this protocol appear to have experience that leads them to reasonably conclude that this research protocol will produce valid and helpful data.

Next, is this the appropriate population to be studying in the first instance? I regard this issue as the most critical question in my review of the protocol. This research proposal obtained NIH funding pursuant to a Request for Applications specifying the study of sleep in adolescents. A like protocol has not been conducted in adults, either with or without sleep disorders, nor has the research been conducted in affected children or adolescents. Arguably, this research should be conducted in adults first, given the particular concerns of subjecting children to greater than minimal risk when they do not have the authority or capacity to consent. This is especially true where the research could reasonably be conducted in young adults only 3-5 years older than these research participants. The population chosen for this study seems to have been established on the basis of a funding opportunity. However, this does not absolutely lead to a conclusion that conducting the study here is not ethically appropriate. While having an initial adult study may be preferable, it is hard to imagine how having an adult study would make this protocol in adolescents any safer.

Garnering data from the normal adolescent population will be necessary at some point and this study is a reasonable first step. The protocol has built in the safeguard of running the study intervention in five adults prior to enrolling the adolescents, presumably to work out any safety concerns associated with running an EKG in a Tesla 4 MRI. The investigators have taken precautions to limit the number of wire leads in the MRI and to prevent injury by exposure to coils. Still, I would recommend that the investigators establish an independent DSMB to assess the safety of this part of the trial during the initial adult phase and throughout the enrollment of adolescents. This final step will ensure that all efforts are being made to minimize the risk to this study population.

The actual age of those being recruited to this protocol is reassuring, as the adolescent participants will likely be able to appreciate the risks of the research protocol, thus making informed assent decisions. The investigators seem to be taking actions to screen the participants for susceptibility to anxiety and claustrophobia related to the MRI, as well as any physical conditions that could be exacerbated by the sleep deprivation component of the trial. I would suggest that the challenge and discomfort of sleep deprivation be emphasized in the consent process. Many adolescents would misinterpret the opportunity to stay up all night playing video games as a chance for enjoyment, when ultimately some of these individuals would find the task prescribed by the protocol to be excruciating. The management of withdrawing from the study due to intolerance of sleep deprivation should be laid out in the consent information.

Regarding the enrollment mechanism, the investigators should undertake separate consent for trial evaluation and enrollment. At present, the investigators have created a consent document that can serve as permission for both evaluation and enrollment. These should be entirely separate decisions, though a thorough description of the research protocol should be provided at the evaluation stage. After viewing the MRI and going under physical assessment and blood tests, potential participants have much more information about the protocol and can make a more informed choice about consent/assent to enrollment at this point.

The consent form as it stands has several problems that need to be rectified for this protocol to proceed.

- I agree with the IRB that the description of the various components of this research (blood draws, fluid administration, timing of sleep deprivation, duration of MRI, etc.) are not precisely described in the consent form. It is almost impossible to appreciate the overall time commitment involved in the protocol based on the description in the consent form. A model timeline for the component parts of the study might be helpful to develop and include in the consent document.
- The consent form should state that the pregnancy test will be administered to all female research candidates, so as not to raise suspicion among parents about particular research candidates. Otherwise, in screening the adolescents for risk of pregnancy their confidentiality regarding their sexual activity may be violated. It is also necessary to think through how a candidate will be discretely discharged from study eligibility if a pregnancy test comes back positive and the adolescent does not want this information to be shared with the parents at that time.
- Compensation levels seem appropriate for this research protocol, though if it were possible I might suggest that the adolescent receive a larger portion of the payment. Still, the compensation is probably commensurate to the adults versus the adolescents in terms of limiting its coercive effect.
- In the section outlining "Costs to You," the participant, the consent form currently states that there are no costs. In my reading of the protocol, participants may need time away from school or other social activities to complete participation in this study and that should be noted in this section of the consent form.

If modifications are made to the consent form and enrollment process to meet the concerns enumerated in this discussion, **I conclude that this valuable research should be approved under § 46.407**. It will be important for the investigators to take seriously the concerns expressed about how the research will be presented to the potential participants, especially in

terms of advising the adolescents of time commitment and potential discomfort. In allowing this protocol to proceed in this population of trial participants, monitoring to ensure the safety of the MRI evaluation is also critical. I thank OHRP for giving me the opportunity to review this protocol and trust that the information this study garners will advance understanding of sleep disorders in the unique adolescent population.

Sincerely,

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