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Doctor Schwetz:

I appreciate the opportunity to review the protocol for the study of "Sleep Mechanisms in Children: Role of the Metabolism."

In addition to attending the panel review of 6 May, 2003, I have reviewed RFA HL-01-006, the protocol, informed consent documents and considered the scientific discussion. I conclude that the research described therein is not approvable under 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 46.404, 46.405 and 46.406.

I do not believe the research is approvable under 45 CFR 46.407 with modification of the both the protocol and informed consent.

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

A. More than minimal risk:
Because this protocol involves more than minimal risk with no direct benefit to healthy volunteer children, I do not find that it meets any of these provisions for approval under the federal rules. This protocol clearly and realistically involves the prospect of complications more serious "than those ordinarily encountered [by children] in daily life." 46.102(i).

B. Risks and inconveniences not addressed:
I do not believe that the risks associated with participation in this trial are life threatening but I feel they are certainly greater than those encountered in a child's daily life. I am particularly concerned about the behavior and risks this age group (13-17 yrs) might encounter after release from the clinical environment while still in a significant sleep-deprived state. The obligation to extend supervision or guarantee physical protection—at least until the child returns to their home --seems a reasonable one, for example. Attaining both the guardian and participant's agreement that they will not drive or operate machinery for a period of time could minimize this risk. Provision for the journey home (taxi voucher, etc.), would be a welcome addition to the protocol, especially since financial compensation will not take place until the conclusion of the child's role.

C. Symptoms of sleep deprivation not clearly described:
It is to be expected that trial participants will temporarily suffer the typical symptoms of sleep deprivation such as irritability, edginess, inability to tolerate stress, problems with concentration and memory, behavioral or social problems, blurred vision, alterations in appetite and activity intolerance. The risk associated with the sleep deprivation state is greater than a child of this age group would normally encounter. The symptoms are likely to cause both physical and emotional discomfort and frustration which qualifies this protocol as one which would cause more than minimal risk. I do not find the study accurately describes the symptoms in the risks section of the consent.

D. Timeline not clearly described in the consent:
The wording of the "procedures" section of the consent is vague and does not clearly indicate the length of time the child will need to be at the institution or the wakeful hours in total.

E. Risk to Others:
The protocol should also be seen as posing more than minimal risk because individuals other than the trial participants may suffer harm due to the behavior and decisions made by the adolescent after they depart the clinical setting. There is no guarantee that the minors involved in the study will be under the direct supervision of a responsible adult until they have totally recuperated from their sleep-deprived state. Therefore, it would be prudent to realize the subjects could cause harm to another person, perhaps unwittingly, such as in driving an automobile or using machinery in an impaired state. Merely identifying sleep deprivation as a risk falls short.

F. Adult vs. Child study:
It is acknowledged that there is a paucity of information known about the role of metabolism in children during sleep. A great deal could certainly be learned from the data this study would potentially generate. The fact, however, that this methodology has not been tested in the adult population yet, is a cause for concern. It seems reasonable that the safety of the techniques proposed in the study should be evaluated in the adult population prior to proceeding with study of the juvenile population. (One questions the extent of the adolescent's ability to understand what the effects of 52+ hours of sleep deprivation will feel like, and if they can indeed make an informed consent decision.)

G. Financial Incentive:
The pressure of economic incentive to metropolitan children could be great enough to cause the candidate or their guardians to accept participation notwithstanding the risks. Additionally, the family's financial gain seems inordinately large in comparison to the participant's. Ascent of the minor should be taken privately and after showing the child the magnet, giving them the opportunity to decline for any reason citing anxiety associated with the device to protect their confidentiality, if necessary.

H. Adverse Academic Situation:
Although this study is focused on children in an age group that ordinarily attends school, the study did not address school or plans for the student to maintain their academic progress. The risk statement, "You also should not be tested the night before school," implies the adolescent might plan attend school following sleep deprivation, which is not likely. Unless the study is accomplished during a long break from school, such as summer, it is reasonable to expect the study's two 52+ hour visits will interfere with the student's academic pursuits, unless they are home instructed and adjust their schedule appropriately.

I. Recruitment Method and Mechanism:
The recruitment documentation was not available to review. In an effort to reach all strata of socioeconomic population, I recommended that internet recruitment be included and home instructed students be made aware of the opportunity to participate. If there is any indirect benefit to be derived from a child's participation in this study, it could be argued that a home instructed student with an interest in science might be the best candidate for several reasons implied above.

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

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

To my lay understanding, the research presents an *opportunity* to further understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; however I do not believe it is a *reasonable* one. The concepts are scientifically valid, but the timeliness of the test durations and the feasibility of maintaining a child in a sleep deprived state for 52+ hours

are questionable. The protocol information states, "None of the studies proposed have been done in adults or children." This fact causes concern about the feasibility of analyzing the data and ethics of beginning with children rather than consenting adults. The approach of the protocol which aims to, "…study children of various ages, from the very young infant to the adult," calls into question the ethical approach of starting with the 13-17 year old group for, "simplicity and for practical and safety reasons." It is unlikely that there would be logical support for conducting this study on a healthy infant; therefore I also question the argument for selecting the 13-17 year old group.

III. Other Comments:

1. Possibly reconsider the monetary compensation amounts and/or division of funds between child and guardian. The guardian's portion may be coercive to individuals, especially those from less advantaged income groups.

2. It seems inappropriate to place the "Payment for Joining the Study," section in the informed consent before the risks and benefits section. I recommend it be moved to the "Costs to You" section near the end of the consent.

3. The statement, "There are no costs to you," should be removed from the "Costs to You" section because the family may incur unforeseen costs such as tutoring or loss of the child's or guardian's income during transportation or appointments.

4. If this study goes forward, recommend internet recruitment be considered. This would be especially helpful to provide exposure of the study to gifted and talented program students, home instructed children and students who have attended community college "medical school" type of summer programs. These children would be less likely to be academically set back and more prepared to understand the medical process and derive some indirect benefit from their participation, which is a goal.

In conclusion, I support the pursuit of research to study the role of metabolism in sleep of children and adults. However I find the length sleep deprivation proposed in this study, when considered with the inclusive clinical hours and transportation to the center to be problematic and ultimately unacceptable. If research *is* to be conducted on children that requires extensive sleep deprivation, (>24 hours), however, it should be limited to the smallest number of subjects required to obtain sufficient data.

I appreciate the opportunity to comment on this interesting research protocol and hope that these comments are helpful. Thank you for the chance to participate in the public discussion of this study.

Respectfully,

Colleen M. O'Brien