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Panel Review of Research Involving Children under Subpart D: "Sleep Mechanisms in Children: Role of Metabolism"

Consultative Review—Attn: Dr. Bernard Schwetz, Dr. Irene Stith-Coleman & Dr. Leslie Ball, Office for Human Research Protections, Department of Health and Human Services

General Remarks:

The first questions to address in research involving children are "Why children" and "Why children now?" The answers to these queries establish the importance of the scientific question(s) at hand, and should also speak to (1) the competence of the investigators and (2) the integrity of their methodology. Inherent in these questions is also an assessment of the potential risks of the study to individual subjects relative to any possible individual subject benefits, as well as to the importance of the general knowledge gained.

The investigators propose to study metabolic processes in sleep; specifically, they will non-invasively measure glycogen, glutamate turnover rate and glutamate-glutamine cycling in wakefulness and sleep in adolescent children ages 13-17. A subset of adolescents will be studied in the same way post-sleep deprivation. Five adults will be studied prior to the adolescents. The investigators' hypotheses are:

1. Stage IV sleep, as compared to wakefulness, has a lower brain metabolic activity in children; this is reflected by a reduced glutamate turnover rate and this reduction is prevented by sleep deprivation;
2. Control mechanisms of glial glucose oxidation play an important role in glutamate/glutamine cycling and represent and important checkpoint in mechanisms of sleep deprivation; and
3. Brain glycogen content increases during the course of sleep in children and sleep deprivation markedly lowers glycogen content.

The proposed study will involve three visits to the Children's Clinical Research Center (CCRC) at the Yale-New Haven Hospital. Visit #1 involves a screening Specialty Clinic visit (approximately 1 hour) for a physical examination and history (including blood tests [15cc] to test for exclusion criteria such as elevated serum glucose or liver function tests, low hematocrit, and impaired renal function). Visits #2 and #3 will include visits to the CCRC and Nuclear Magnetic Resonance (NMR) Center. Subjects will be randomly assigned to one of four groups; ^{13}C-

acetate infusion with (1) normal activities and with (2) sleep deprivation of an entire night – and the following day, and ^{13}C-glucose infusion with (1) normal activities and with (2) sleep deprivation of an entire night and the following day. Wake and sleep stages will be monitored in the 4-tesla Neuroscan NMR magnet during the 90 minute infusion period, with blood samples taken every 15 minutes (total 15cc). Sleep stages in the magnet will also be assessed using EEG and EOG monitoring.

The study is conceptually very interesting. The maleffects of sleep deprivation, while important during development (negative impacts on school performance and achievement), are also (as outlined by the investigators) important in adults (negative effects such as vehicle and other accidents and poor work performance). Studies are also important in both the adult and pediatric populations because of physiological differences that occur during early development and at varying ages.

This reviewer believes that, given the relatively novel techniques employed in this proposed research, tests in young adults/children should be preceded by thorough safety testing in adults. There are engaging reasons to employ the tools in this investigation in subjects of any age. However, this reviewer is not convinced that testing only five adults prior to undertaking the study in children/young adults justifies the inclusion of children at this time. Also, 13-17 year old children are not a physiologically heterogenous group; they will be both pre-and post-pubertal.

The investigators have a solid history of sleep research in children, especially in relation to control of respiration and obstructive sleep apnea. They acknowledge that none of the studies proposed in this protocol has been tested in adults or children, and that "only a small part of what is proposed here has been done in animals with the use of invasive techniques." The investigators' long-term goals include the study of children of various ages, from the very young infant to the adult. They have chosen the adolescent population to study for "simplicity and for practical and safety reasons." They state in the protocol that "In the future, we intend to study other age groups such as infants and adults."

45 CFR §46.404 Research not involving greater than minimal risk.

The study is not approvable under this category. This reviewer agrees with the local IRB that one night (plus one day) of sleep deprivation, infusion of ^{13}C acetate and ^{13}C glucose, and extended periods of study (90 minutes) by nuclear magnetic resonance spectroscopy (the temporal element is the risk here, not the radiation itself, which at 4 Tesla is less risky than x-ray or CT scan because it does not involve ionizing

radiation) are greater than minimal risk. To this she would add placement of an intravenous infusion catheter for up to 12 hours, multiple blood draws, and possible psychological sequelae of withdrawal from the study.

§ 46. 102 (i) Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

The Report from NHRPAC: Clarifying Specific Portion of 45 CFR 46 Subpart D that Governs Children's Research (2002) addresses the interpretation of minimal risk under the Common Rule. The report is under review by DHHS, and has not been adopted as guidance by OHRP/DHHS. However, this reviewer (an author of the report) finds it useful in considering and evaluating risk in children's research. The report states:

"We interpret the definition of minimal risk to be that level of risk associated with the daily activities of a normal, healthy, average child. Risks include all harms, discomforts, indignities, embarrassments, and potential breaches of privacy and confidentiality associated with the research. Conceptually, the minimal risk standard defines a permissible level of risk in research as the socially allowable risks which parents generally permit their children to be exposed to in non-research situations. Healthy children, ranging from newborns to teens, experience differing levels of risk in their daily lives. Indexing the definition of minimal risk to the socially allowable risks to which normal, average children are exposed routinely should take into account the differing risks experience by children of different ages…The interpretation of whether the level of risk is minimal should be one of 'equivalence of risk.' A test or procedure which entails minimal risk is one for which the probability and magnitude of harm associated with the test or procedure is equivalent to and no greater than the risk of events ordinarily encountered in the daily life of a normal healthy, average child, or the socially allowable risks parents permit their normal, healthy, average children to be exposed to in their ordinary lives."

45 CFR §46.405 Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.

The reviewer agrees with the local IRB that the proposed research is not approvable under this category. The prospective subjects in this study are normal, healthy volunteers with no prospect of direct benefit. The investigators acknowledge as much in their protocol and state in the written consent documents that "you will not benefit from joining this study."

45 CFR §46.406 Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.

This reviewer agrees with the local IRB that "as healthy children, the knowledge to be gained would not relate to the 'understanding or amelioration' of the subject's disorder or condition." The proposed research population comprises normal, healthy volunteers.

The Report from NHRPAC: Clarifying Specific Portion of 45 CFR 46 Subpart D that Governs Children's Research (2002) also addresses the interpretation of "minor increase over minimal risk," and "disorder or condition" under the Common Rule. The report is under review by DHHS, and has not been adopted as guidance by OHRP/DHHS. The report states:

"Minor Increase Over Minimal Risk: IRBs are responsible for determining what level of risk constitutes a minor increment over minimal. In making the determination, IRBs should only permit risks that are a little more than minimal and pose no significant threat to the child's health or well-being. While the definition of minimal risk is indexed to the risks encountered to in the daily lives of normal, healthy, average children, the permissible level of risk associated with a minor increase over minimal should be just a bit more than that level and also commensurate with the risks of interventions or procedures having been experienced or expected to be experienced in the lives of children with a specific disorder or condition. The concept of commensurability is important to allow the child and parents to have a basis upon which to make thoughtful judgements about assent and permission. The fact that children may experience invasive procedures with considerable risk and discomfort during the care and treatment of a disease does not justify risks greater than a minor increase over minimal in a research study that provides no prospect of direct benefit to the individual subjects."

"Disorder or Condition: "A controversial issue in permitting research based on this section of the regulations is interpretation of the definition of 'disorder or condition.' The National Commission used the word 'condition' to refer to situations that may 'jeopardize the health of children, interfere with optimal development, or adversely affect well-being in later years.' The phrase 'disorder or condition' refers to a characteristic of the group of potential research subjects, and implies that this characteristic can be understood more broadly than simply a specific disease or diagnostic category."

"We interpret the concept of disorder or condition as relating to a specific characteristic which describes a group of children, a physical, social, psychological, or neuro-developmental condition affecting children, or the risk of certain children developing a disease in the future based on diagnostic testing or physical examination. Thus, for example, prematurity, infancy, adolescence, poverty, living in a compromised physical

environment, institutionalization, or having a genetic predisposition to future illness are some of the disorders or conditions of children that can, under the appropriate circumstances, warrant permissible research that presents levels of risk that are a minor increase over minimal without the prospect of direct benefit."

45 CFR §46.407 Research not otherwise approvable which represents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

This reviewer cannot recommend approval of the protocol, "Sleep Mechanisms in Children: Role of Metabolism" under 45 CFR §46.407 at this time. The study should be preceded by significant adult safety data. An independent pediatric data and safety monitoring board (with experts in statistics and methodology) should determine when sufficient adult data exist (are five adult subjects enough?) to ensure the relative safety of applying study techniques to a group of healthy adolescents.

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

While the research questions are important, the opportunity to study them is not reasonable given the lack of adult safety data. Although important physiological differences between adolescents (and younger children) and adults argue justifiably for research in the pediatric as well as the adult population, the problem under study does not warrant proceeding with a pediatric investigation absent relevant adult safety data.

2. **The research will be conducted in accordance with sound ethical principles;**

• Distributive Justice: Fair distribution of potential risks and benefits among potential study populations is a justice issue that inheres in any study. The potential for abuse or exploitation increases when subjects cannot make their own assessments of the relative risks and benefits of the proposed research, or when those assessment-making capabilities are not fully developed. Such potential subjects are, in effect, vulnerable to abuse by others. Thus, the standard practice, when feasible, of performing animal studies prior to human studies (although one could argue the biological or philosophical underpinnings of this approach), of studying adults prior to children, older children prior to younger children, and those with full decisional capacity prior to those with impaired or no decisional capacity. The study population at hand, adolescent children, is, by definition, a vulnerable population.

• Compensatory Justice: The reviewer highly commends the investigators and their institution for their commitment to supply "immediate, essential, short-term medical treatment" for research-related injury at no cost to the research subject. Although compensation for research injury is not required by regulation, virtually all federal human research advisory committees have recognized it as a moral duty owed by the sponsors of the research. The study sponsors (National Institutes of Health), investigators, and research institutions should consider mechanisms for compensation for research injuries. [Institute of Medicine report, Responsible Research: A Systems Approach to Protecting Research Participants (2002); Recommendation 6.8: Compensate any research participant who is injured as a direct result of participating in research, without regard to fault. "Because the contributions of science benefit society as a whole, it seems indisputable that society is obligated to assure that the few who are harmed in government-sponsored scientific research are appropriately compensated for study-related injuries…the same argument applies to privately funded research." pg. 188. See also: Advisory Committee on Human Radiation Experiments, 1995; Department of Health, Education and Welfare, 1977, National Bioethics Advisory Commission, 2001a,b; President's Commission, 1982).

• Amelioration of Risk: There is a small, but potential risk of undiagnosed epilepsy in the healthy volunteer population; prospective subjects should be screened for a family history of epilepsy or seizure disorder.

3. Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians.

• Evaluation of prospective subjects will include pregnancy testing. No provision is explicated in the protocol for how this testing will be managed in a way that protects the privacy of girls who may refuse consent because of the pregnancy test, or who may test positive. The procedural safeguards to protect prospective subjects' privacy and confidentiality in this context should be clearly enumerated in the protocol. The written consent document merely states, "If appropriate, you will be given a pregnancy test before this study begins."

• The compensation scheme outlined in the protocol and the written consent document may be coercive. Given the locale from which the subject population will most likely be drawn, paying the adolescent's parents up to $350 for their child's participation in a study may lead to undue pressure on the adolescent to enroll in, or not withdraw from the study. A separate issue is raised by paying the parents significantly more money than the adolescent will receive (total

possible = $100), as the adolescent is the one who will undergo the risks, discomforts, and major inconveniences occasioned by participation in the study.

Written Consent Document:

• Language in the consent document frequently conveys the message that inability to participate in the study, per exclusion criteria, is an individual or personal failing. For example:

> "Before you can be part of the study…you will come for a physical examination to see if you are able to join the study."
> "If you are allergic to this cream [EMLA] you will not be able to join the study."
> "If you do not pass the screening test, you will not be able to join the study."
>
> The exclusion criteria should be conveyed in a more positive and sensitive manner. As written, the document may be coercive, in that a subject who wishes to withdraw from the study may not do so given the perceived exclusivity of being "able to join the study."

• All consent and any educational materials should be available to non-English speaking parents in their languages, and translators should be available during the consent process, and at each visit required under the protocol.

Other:

• The IRB of record should be commended for its excellent minutes and record-keeping; this greatly facilitated review of the study under consideration. One shortcoming of the local IRB review is that it did not speak to the relative risk of each procedure.

• The investigators state, under "Conveyance of Information Back to Subjects," that "since the studies we are proposing are novel and we do not have any such data in the literature, most likely we will not be able to provide information for use to the parents." The reviewer would suggest that when the data are published, the subjects and their parents receive reprints of the study, so that they can fully appreciate the meaning of their (or their child's) participation in research.

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