I. Brief Summary of Rationale for Protocol

The investigators propose to use NMR spectroscopy to measure certain aspects of cellular brain metabolism in four groups of adolescent children (ages 13 – 17 years) during wakefulness, sleep and after sleep deprivation. Apparently, the pattern and processes of sleep differ between children, adolescents and adults. One can then speculate, in the absence of studies, that the underlying brain processes and metabolic activity in children and adolescents are different from that of adults. The study is likely to yield generalizable knowledge about the normal physiologic processes associated with sleep as a basis for studying abnormal sleep and sleep-related disorders. It should be pointed out that this grant proposal was written in response to a Request for Applications from NIH that stipulated the inclusion of adolescent subjects (SLEEP AND SLEEP DISORDERS IN CHILDREN; Release Date: June 6, 2001; RFA-HL-01-006.)

The investigators state (appropriately) that none of these studies have been performed before in either children or adults. Throughout the proposal, an argument is consistently made in favor of the research given that the metabolic measurements have not been performed previously in either adolescents or during sleep. The question as to whether adults should be studied before adolescents is discussed below.

II. Procedures included in the Protocol (along with a discussion of feasibility and risks)

A. Magnetic Resonance Imaging (4 tesla):

MRI involves three different fields: static magnetic fields, radio-frequency (RF) fields, and gradient fields. The physical limits of human exposure during MRI are related to the type of field, with switched gradient fields leading to peripheral nerve stimulation, and RF fields leading to tissue heating. The limits of human exposure to static magnetic fields are unknown. According to the relevant chapters in *Magnetic Resonance Procedures: Health Effects and Safety* (ed. F. G. Shellock, CRC Press: New York, N.Y., 2001), the use of a 4 tesla machine has not been associated with any physical risks other than the risks of bringing ferromagnetic materials (either internal or external to the subject) into the MRI magnet. The protocol discusses the screening procedures used to assure that this does not happen.

The FDA considers a 4 tesla MRI to be a non-significant risk device, assuming it also meets several criteria. The FDA criteria (updated October 3, 1997) for significant risk investigations (requiring an IDE) involving MRI devices are: (1) main static magnetic field greater than 4 tesla; (2) specific absorption rate (SAR) greater than 4 W/kg averaged over the whole body for any period of 15 minutes; or 3.2 W/kg averaged over the head for any period of 10 minutes; or 8 W/kg in any gram of tissue in the head or torso, or 12 W/kg in any gram of tissue in the extremities, for any period of 5 minutes; (3) time rate of change of gradient fields (dB/dt) sufficient to produce severe discomfort or painful nerve stimulation; or (4) peak unweighted sound pressure level greater than 140 dB or A-weighted r.m.s. sound pressure level greater than 99 dBA with hearing protection in place (http://www.fda.gov/cdrh/ode/magdev.html). Recently, this reviewer was informed that the FDA recently revised the significant risk levels of MRI scanners to be above 8 tesla. As the FDA determined that this protocol did not require an IDE, this reviewer assumes (in the absence of evidence to the contrary) that the MRI scanner and techniques

described in the protocol qualify as a non-significant risk device. The investigators also state in the protocol that they will operate the MRI scanner within these safety limits.

There are other known risks that can be characterized as psychological distress, including anxiety and claustrophobia. There are few studies in pediatrics, and estimates range widely (from less than 1% up to 20%) of the number of patients who experience some form of psychological distress. The use of relaxation techniques and MRI simulation prior to the actual MRI scan are demonstrated effective in reducing anxiety. Those adolescents who may suffer anxiety or claustrophobia are excluded, through a screening process which includes a trial MRI scan. *The investigators have included MRI simulation in the protocol, however this process is not adequately described in the protocol. For example, it is unclear is this screening MRI scan involves acclimatization in a "mock" magnet, as needed, or a real MRI scan.* A nurse is present at all times in the room, and the adolescent can request that the study be stopped at any time. A physician is present at all times in the immediate vicinity. The protocol also includes a description of screening for, and safety procedures in response to the unlikely event of an injury from an internal or external ferromagnetic object.

This reviewer determines that the MRI scan presents no more than minimal risk, defined as "…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." (45 CFR §46.102(i))

B. Polysomnography (including EEG and other Physiologic Recordings)

Polysomnography is performed as a screening test to exclude undiagnosed sleep disorders, and also performed as part of the MRI scanning. The risks of this procedure are minimal, assuming that the safety of the procedure has been adequately tested in adults. For example, the use of wires (i.e., electrodes) for the recording of physiologic measurements in the MRI scanner is difficult, and has risks. The wires, if coiled, can serve as a source of heat and possibly burn the skin. With appropriate precautions and use, these risks are minimal. In addition, the ability to measure physiologic signals that result from electrical (i.e., brain) activity while in the magnet needs to be demonstrated. For this reason, the investigators propose to study up to 5 adults to determine the feasibility and scientific accuracy of the measurements before turning to the study of adolescents.

A sample of 5 adults may be insufficient to determine the safety and feasibility of the scientific methods. *An independent data monitoring committee (DMC) should be appointed to review the data from the adult pilot study, and make a determination that the study is both safe and feasible before studying adolescents. Given the financial benefit of the grant to the institution, this DMC should be composed of a majority of members from outside of the institution.*

With adequate safety testing in adults, as determined by an independent DMC, this reviewer considers the risks of polysomnography both inside and outside of the MRI scanner to be no more than minimal risk.

C. ^{13}C-glucose and ^{13}C-acetate IV infusions.

^{13}C is a naturally occurring, non-radioactive, stable isotope. As such, it poses no risk above and beyond that associated with the infusion of either acetate or glucose. The protocol involves a 90 minute ^{13}C-acetate IV infusion, and either a 90 minute or 12 hour ^{13}C-glucose IV infusion. The protocol uses a glucose clamp technique with a 20% glucose infusion, targeting serum glucose levels at either the euglycemic (5 mM), or hyperglycemic (7 – 10 mM) range. To minimize risks, glucose samples are to be collected every 15 - 20 minutes, and acetate levels every 10 – 15 minutes. Although the authors provide no data in support of the statement, they claim that the hyperglycemia presents "no danger of hypoglycemia at the end" of the infusion. *The protocol should state an appropriate period of observation in the research facility after the glucose infusion has ended.* Also, the amount of sodium and acetate are less than that infused during the administration of Lactated Ringers, a standard intravenous solution for intravenous rehydration. Nevertheless, the infusion of the solutions increases the risks of extravasation, given the hyperosmolality of the 20% dextrose solution and the acidity of the acetate solution.

Intravenous catheters (2) will be in place anywhere from 90 minutes to 12 hours, and will also be used for frequent blood sampling. *Local anesthesia will be used for IV placement, although the documents reviewed are ambiguous as to whether EMLA Cream or a lidocaine injection will be used.* The impression is that EMLA cream will be used exclusively.

Given the length of time that the catheters are in place, and the solutions that will be infused through the catheters, this reviewer considers these procedures to present more than minimal risk, although the risk is no more than a minor increase over minimal risk.

D. History and Physical Examination, Blood Draws, and Urine Testing.

There is a discrepancy between the protocol and the assent/permission form, with the protocol indicating that the volume of blood will be limited to a maximum of 40 ml over 9 days, and the assent/permission form mentioning 60 ml for each infusion study. *This discrepancy needs to be clarified.* The volume of blood presents no more than minimal risk. The blood will be used for screening eligibility laboratory values to exclude pancreatic, hematologic, liver or renal disease. Although HIV, hepatitis and drug abuse are exclusions from the study, there is no mention in the procedures about how these conditions will be ascertained. *This needs to be clarified, for the method used will impact significantly on the necessary measures to protect the adolescents' confidentiality.*

There is no mention in the protocol about what tests will be performed on the urine. Since pregnancy is an exclusion from having the MRI scan performed, one may presume that a urine pregnancy test will be performed, although it is not mentioned in either the protocol or the assent/permission form. *One is left in doubt whether urine drug testing will be performed, as drug abuse is mentioned as an exclusion but there is no mention of any drug testing in the protocol. Both these issues need to be clarified.* With appropriate measures to protect the confidentiality of the adolescent subjects, the history, physical examination and urine testing present no more than minimal risk.

E. Sleep Deprivation

The amount of sleep deprivation included in this study does not appear to present more than a minimal risk. This conclusion is supported by the lack of significant adverse events reported in the study of 82 children and adolescents by Fallone and colleagues (Fallone G., Acebo C., Arnedt JT., Seifer R., Carskadon MA. Effects of acute sleep restriction on behavior, sustained attention, and response inhibition in children. *Perceptual & Motor Skills. 93(1):213-29, 2001 Aug.*). There is the remote possibility that previously undiagnosed epilepsy may be uncovered by the sleep deprivation test. *However, there is no discussion in the assent and permission form of the risks of operating machinery and performing other important tasks the day after the sleep deprivation procedure. For example, who is responsible for supervision after sleep deprivation? How are the subjects getting home? This needs to be added, and highlighted.*

There is also the real possibility that an adolescent will be unable to stay awake during the MRI performed on the day after the sleep deprivation, in spite of his or her best efforts. *Procedures should be outlined that will minimize any distress, such as an opportunity to participate again or providing the stipend regardless of whether the adolescent did or did not stay awake.*

F. Admission to the Clinical Research Center (CRC)

The amount of time spent in the CRC will ranging from one day and night (24 hours), to two to three days and two night (perhaps up to 56 hours). *With appropriate activities available to the adolescent, and isolation from any patients and/or subjects with illnesses, the length of time spent in the CRC presents no more than minimal risk.*

III. Comments on Permission and Assent Process (Undue Influence and Coercion)

The description of the screening process in the assent/permission form is unclear. This reviewer understands that the screening process will include a history and physical examination, including blood and urine testing, a screening MRI study ("mock" magnet), and polysomnography. *The order of the screening process should be as follows.* Since the MRI scanning is the central aspect of the study, the trial run though the "mock" MRI scanner to determine the adolescent's level of comfort should come first. There is no reason to potentially compromise the adolescent's confidentiality if he or she cannot tolerate being in the MRI scanner. The screening history, physical examination and laboratory testing should then be performed, followed by screening polysomnography (at visit 2). *The screening process, as well as the tests that will be performed, and how the adolescent's confidentiality will be protected should be better described in the assent form.*

The proposed payment schedule is for the adolescent to receive $100 and for the parent(s) to receive $350, which appears to be the policy of the IRB at AECOM. In this reviewer's opinion, the distribution of financial compensation for time and effort is backwards. The adolescent is the one undergoing the procedures, and the presence of the parent (who is likely sleeping as well) may actually hinder the ability of the adolescent to withdraw from the study if the parent stands to gain financially. *It is reasonable to compensate the adolescent for the time spent in the study at the minimum wage of $5.15 an hour. The parent should only*

receive reimbursement for expenses. The schedule for compensation as outlined in the current protocol has the potential for creating undue parental pressure on the adolescent to enroll in the study. It should be mentioned that any advertisements and other recruitment materials to be used were not included in the packet of materials reviewed.

The language in the assent form about failing to "pass the screening test" should be altered. An adolescent may be sensitive to "passing tests" and thus unduly distressed by failing to pass these initial tests.

IV. Additional Concerns

The consent form indicates that treatment for a physical injury resulting from this research will be billed to the subject or the subject's insurance company. This is not appropriate. *Although the possibility of injury in this study is remote, necessary treatment as a result of an injury related to this research study should be provided by the institution free of charge.* In this reviewer's opinion, this should be one of the "sound ethical principles" required for consideration under §46.407.

There is no discussion in the protocol of how the confidentiality of the adolescent will be protected, especially when the investigator may exclude an otherwise eligible adolescent for being pregnant, HIV or hepatitis infected, or abusing drugs. For example, multiple tests should be performed so that an exclusion cannot be traced to the results of one test. The adolescent who is to be excluded based on testing that should remain confidential should be "coached" on possible reasons for not wanting to do the study.

There needs to be a discussion of an *appropriate referral* for the diagnosis of previously unrecognized sleep disorders, along with any results obtained during the screening process (such as pregnancy, HIV, hepatitis, and so forth).

The assent form is inappropriately labeled a "young adult assent" rather than an "adolescent assent." Young adult usually refers to the 18- 21 year old age group.

The assent form (and the protocol) has an insufficient discussion of how the impact of the study on school performance will be minimized.

V. Should these studies be performed in adults prior to adolescents?

There are two general reasons why studies should be performed in adults prior to being performed in children, whenever possible. The first is to determine the safety of the experimental procedures; the second is to answer the scientific question if it is unnecessary to study children to obtain the answer. The research proposal argues (convincingly in this reviewer's opinion) that studying adults will not answer the scientific questions about adolescent sleep architecture and metabolic activity. However, it remains necessary to determine the safety and feasibility of the research procedures using adult subjects prior to performing these procedures on adolescent subjects. *This reviewer considers the enrollment of adolescent subjects in this protocol scientifically appropriate, provided that the safety and feasibility of the technical procedures to be performed in this protocol are established first in adults.*

VI. Application of the Criteria for IRB Approval

A. Apply the general criteria of 45 CFR 46.111.

Provided that changes in the protocol are made in accord with the italicized recommendations (above), the risks to subjects are minimized by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk. Since the subjects enrolled are healthy normal adolescents, it is not appropriate to use procedures already being performed on the subjects for diagnostic or treatment purposes (§46.111(a)(1)). If the safety and feasibility of the procedures are established first in adult subjects, the selection of subjects is equitable, taking into account the purposes of the research and the setting in which the research will be conducted (§46.111(a)(3)). The risks to subjects are reasonable in relation to the importance of the knowledge that may reasonably be expected to result, as there are no direct benefits to the subjects. There may be the indirect benefit of participating in the advancement of knowledge (§46.111(a)(2)). Nevertheless, when some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, ... additional safeguards have been included in the study to protect the rights and welfare of these subjects (§46.111(b)), requiring us to apply the additional protections found in 45 CFR 46, Subpart D.

B. Assess the risk presented by each intervention or procedure in the proposed research.

As discussed above, and after further steps are taken to minimize risks, all of the procedures except for the ^{13}C-glucose and ^{13}C-acetate IV infusions present no more than minimal risk (§46.404/50.51). The ^{13}C-glucose and ^{13}C-acetate IV infusions present greater than minimal risk (§46.405/50.52 or §46.406/50.53), and thus require us to evaluate the possibility of direct benefit to the adolescent child. By all accounts, there is no prospect of direct benefit (§46.406/50.53) for any of the procedures or interventions included in the research. The ^{13}C-glucose and ^{13}C-acetate IV infusions present no more than a minor increase over minimal risk (§46.406(a)/50.53(a)); however, they do not result in any knowledge to ameliorate a disorder or condition (§46.406(c)/50.53(c)), as the adolescents included in the research do not have any disorder or condition. Finally, based on the review and discussion of the protocol, this reviewer believes that the research does present a "reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children." (§46.407(a); 50.54(a)). This criteria does not require that the adolescents included in the research have such a "serious problem," only that the knowledge that may reasonably result would further our understanding of such a problem.

C. For all categories, consider the requirements for parental permission and child assent (§46.408;50.55).

With the modification outlined above, this reviewer determines that informed consent (that is, parental permission and adolescent assent) will be sought (and appropriately documented) from each prospective subject and/or the subject's legally authorized representative, in accordance with, and to the extent required by §46.116 and §46.117. (§46.111(a)(4,5))

D. When appropriate, there are adequate provisions for monitoring the data collected to ensure the safety of subjects. (§46.111(a)(6))

E. When appropriate, there are adequate provisions to protect subject privacy and to maintain data confidentiality. (§46.111(a)(7))

With the changes outlined above, this reviewer determines that these two criteria for IRB approval are met.

Final Recommendation:

This reviewer finds that the research under consideration does not satisfy the conditions of §46.404, §46.405, or §46.406. However, after the recommended modifications, the research "presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; (ii) …will be conducted in accordance with sound ethical principles; and (iii) adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians, as set forth in §46.408."

Consistent with sound ethical principles guiding pediatric research, and assuming that the modifications recommended above are in fact made, the use of normal adolescent children in the proposed research is scientifically appropriate and necessary. The adolescent subjects will be chosen to minimize the likelihood of individual harm and maximize the likelihood of gaining knowledge that furthers the understanding, prevention, or alleviation of a serious problem specifically affecting the health or welfare of other children. The risks of the research to the adolescent subjects are balanced by the importance of the knowledge gained. After some modifications, the research optimizes an adolescent's capacity to give assent, and to understand the anticipated experience and risks of the research.