DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
The Tower Building
1101 Wootton Parkway, Suite 200
Rockville, Maryland 20852

[March 5, 2004]

TO: Cristina V. Beato, M.D.
Acting Assistant Secretary for Health

FROM: Acting Director, Office for Human Research Protections

SUBJECT: Recommend Disapproval of HHS Support for Research–ACTION

ISSUE

Recommendation by the Office for Human Research Protections (OHRP) that the Department of Health and Human Services (HHS) should not support the proposed research protocol entitled *Sleep Mechanisms in Children: Role of Metabolism* which would involve the enrollment of 13- to 17-year-old subjects. In making this recommendation, OHRP has reviewed the proposed research and considered the opinions of experts, and provided an opportunity for public review and comment, via a *Federal Register* Notice in accordance with 45 CFR 46.407 (see Summary attached at Tab A). No public comments were received on the proposed research during the 45-day solicitation period.

OHRP staff is scheduled to brief you on this issue on Monday, March 8 at 11:15 am.

DISCUSSION

Background: All studies conducted or supported by HHS that are not otherwise exempt and that propose to involve children as research subjects require institutional review board (IRB) review in accordance with the provisions of HHS regulations at 45 CFR part 46, subpart D. Pursuant to HHS regulations at 45 CFR 46.407, if an IRB reviewing a protocol to be conducted or supported by HHS does not believe that the proposed research involving children as subjects meets the requirements of HHS regulations at 45 CFR 46.404 (research not involving greater than minimal risk), 46.405 (research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects), or 46.406 (research involving a minor increase over minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition), and was suitable for review under the procedure provided in 45 CFR 46.407 (research not otherwise approvable which presents an opportunity to understand, prevent or alleviate a serious problem affecting the health or welfare of children), the proposed research may proceed only if the following conditions are met: (a) the IRB finds and documents that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem

affecting the health or welfare of children; and (b) the Secretary, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) and following opportunity for public review and comment, determines either: (1) that the research in fact satisfies the conditions of 45 CFR 46.404, 46.405, or 46.406, or (2) that the following conditions are met: (i) 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) the research 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 45 CFR 46.408.

In November 2002, OHRP received a request from the Committee on Clinical Investigations -- the Institutional Review Board for Yeshiva University, including the Albert Einstein College of Medicine -- to review the above-cited protocol pursuant to requirements of HHS regulations for the protection of human subjects at 45 CFR 46.407. The proposed research would be supported by National Institutes of Health (NIH) grant RO1 HL070919-01, awarded by the National Heart, Lung, and Blood Institute (NHLBI). This grant proposal was written in response to a June 6, 2001, NIH Request for Applications (RFA) designed to stimulate basic and clinical research which would advance understanding of the following: (1) the biological, age-specific and ontogenic requirements for sleep in healthy children; (2) pathophysiological mechanisms underlying the onset and progression of childhood sleep disorders; and (3) the effects of sleep disorders and sleep deprivation on the cardiopulmonary, immunological, hematological and behavioral health of children (see http://grants.nih.gov/grants/guide/notice-files/not98-024.html). NIH noted under the "Special Requirements" section of this RFA the following:

> In order to be considered responsive to this announcement, applications must propose hypothesis-driven studies that focus on biological requirements for sleep or the mechanisms linking sleep disturbances to cardiopulmonary, immunological, hematological, mental, or behavioral abnormalities in school-age children. For the purpose of this RFA, studies must focus on school-age children 4 to 18 years of age. If studies of the inter-relationship between chronic disorders and sleep are proposed, the focus must be on mechanisms underlying sleep disturbance. Studies of the circadian system, if proposed, must also be tightly coupled to mechanisms of sleep control. Studies proposing the use of nonmammalian species or in vitro preparations should clearly establish the relationship of these models to the goals set forth in this RFA.

After reviewing the proposed research, the Albert Einstein Committee on Clinical Investigations (CCI) determined this research could not be approved under 45 CFR 46.404, 46.405, or 46.406, but found the research presented a reasonable opportunity to further the understanding, prevention or alleviation of a serious problem affecting the health or welfare of children and was suitable for review under 45 CFR 46.407.

The principal investigator, Dr. Gabriel Haddad, proposes to study brain metabolism in adolescents ages

13 to 17 years by using Nuclear Magnetic Resonance (NMR) spectroscopy to measure glycogen, glutamate turnover rate, and glutamate-glutamine cycling in wakefulness and sleep, and to study a subset of children in the same manner following sleep deprivation. It was noted in the IRB Protocol Application that investigators would *perform studies on 5 adult subjects before focusing on adolescents.* According to the PI, none of the proposed studies have been done in adults or children and only a few have been done in animals. The general hypothesis for the proposed studies is that: understanding sleep mechanisms depends on detailed understanding of metabolic processes involving the functional coupling between glia and neurons; and, the overall down regulation of synaptic activity during sleep allows for restoration of glial energy stores. The specific hypotheses are:

- Stage III-IV sleep (deep sleep) has a lower metabolic requirement and a lower glutamate turnover rate (tricarboxylic acid cycle rate) in both neurons and glia, as compared to wakefulness.

- As compared to wakefulness, sleep stage III-IV is characterized by a lower rate of brain neuronal glutamate release and glial glutamate uptake in children; this reduced glutamate/glutamine cycling during sleep stage III-IV in the brain of children is prevented by sleep deprivation.

- Brain glycogen content increases during the course of sleep in children and sleep deprivation markedly lowers glycogen content.

The long term aims of the study are: (a) to better understand sleep; and to be able to better understand (b) the diseases afflicting children and adults that impact on their sleep; and (c) sleep-related diseases that impact on neurocognitive, cardiovascular, behavioral, and other functions. A clinical trial outline is attached at Tab B.

Review by HHS Panel of Experts: In May 2003, OHRP assembled a panel of five experts in accordance with the provisions of HHS regulations at 45 CFR 46.407, and each provided her/his recommendation to the Secretary (See Tab B - Tabular Summary of Expert Recommendations). The experts' areas of expertise included ethics, pediatrics, neurology, health policy and law. A summary of the experts' recommendations is attached at Tab C.

None of the experts recommended that the protocol as currently proposed be approved. All of them expressed concerns about the lack of data from adult subjects. One expert found that she could not recommend approval under 45 CFR 46.407 at this time given that (i) the techniques employed in the proposed research are relatively novel and should be preceded by thorough safety testing in adults before being used in young adults/children; and (ii) an independent pediatric data and safety monitoring board (with experts in statistics and methodology) should determine when sufficient adult data exist. Two experts recommended that a number of modifications should be made in the research protocol before it would be approvable under 45 CFR 46.407, including determining safety and feasibility of,

and fully studying, the procedures in adult subjects before proceeding to adolescents.

Similarly, one expert noted that the fact that none of the proposed studies have been done in adults or children causes concern about the feasibility of analyzing the data and ethics of beginning with children rather than consenting adults. Nevertheless, this expert found that the proposed research was approvable under 46.407, with protocol/informed consent modifications, including removing the statement, "There are no costs to you,...." from the "Costs to You" section because the family may incur unforseen costs, e.g., tutoring or loss of the child's or guardian's income during transportation or appointments.

Another expert found it arguable that the proposed 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," but concluded that the study should be approved under 46.407 provided that stipulated modifications were made. Specifically, the expert states (in her report to OHRP) that, "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." The modifications identified included the following: provide a statement that the pregnancy test would be administered to all female research candidates; precisely describe the various components of the research (e.g., blood draws, fluid administration, timing of sleep deprivation, duration of MRI); and the investigators should undertake separate consent for trial evaluation and enrollment.

Two experts concluded that the C-13 Acetate infusion and the C-13 Glucose infusion procedures in the proposed study – in which two intravenous catheters would be in place for up to 90 minutes (acetate infusion) or up to 12 hours (glucose infusion) – represent a minor increase over minimal risk. Several experts questioned the proportion of compensation paid to each parent or guardian (up to $350) compared to that paid to the child (up to $100) at the completion of the study, and indicated that the higher amount paid to parents or guardians seems inordinately large; and may lead to undue pressure on the adolescent to enroll in, or not withdraw from, the study. One expert suggested that it was reasonable to compensate the adolescent for time spent in the study at the minimum wage of $5.15 an hour and the parent should only receive reimbursement for expenses.

Two experts recommended that an independent Data Safety Monitoring Board (DSMB) should be established to assess safety associated with electrocardiogram (EKG) monitoring in the 4 Tesla MRI during the adult phase of the study and throughout enrollment of adolescents.

All of the experts recommended that specific modifications be made to the permission/assent documents, which included the following:

(1) better describe the screening process and tests that will be performed and how confidentiality will be protected;

(2) better describe the various components of the research protocol (blood draws, fluid

administration, timing of sleep deprivation, duration of MRI, etc.);

(3) discuss the procedure for electrophysiological (polysomnography) monitoring while in the magnet MRI and incorporate this procedure in the permission/assent document;

(4) clarify language in the "Procedures" section of the permission/assent document and the length of time the child will need to be at the Clinical Research Center or the wakeful hours in total;

(5) change language to be more neutral. For example, the following statements should be changed: "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;" and "If you do not pass the screening test, you will not be able to join the study;"

(6) emphasize the challenge and discomfort of sleep deprivation in the consent process; and, accurately describe the symptoms of sleep deprivation in the "Risks" section of the permission/assent document;

(7) lay out in the permission/assent document the management of withdrawing from the study due to intolerance of sleep deprivation;

(8) include information related to risks of working after a night of sleep deprivation, similar to the information warning about the use of machinery and driving;

(9) include sufficient information on how the impact of the study on school performance will be minimized.

NHLBI Special Emphasis Panel: During the review under 46.407 of the proposed research, OHRP considered the report of the NHLBI Special Emphasis Panel, the peer-review committee which convened in February 2002 to review the original grant application. The Panel's report states that no protection of human subjects concerns were identified with the protocol.

OHRP RECOMMENDATION

OHRP has reviewed the research protocol and considered the recommendations provided by the experts. OHRP recommends that HHS not support the proposed research protocol involving the enrollment of 13- to 17-year-old subjects.

OHRP bases its recommendation on the reports of experts who have reviewed this research protocol under 45 CFR 46.407 the comments of the NHLBI Special Emphasis Panel, which reviewed the original grant application, and the relevant requirements under 45 CFR 46, subpart A. OHRP finds that the research is not approvable under 45 CFR 46.404 because the research involves two

intravenous cathethers that will be in place from up to 90 minutes to up to 12 hours in minor subjects, which constitutes greater than minimal risk to the subjects. OHRP finds that the research may not be approved under 45 CFR 45.405 because the proposed research involves healthy children, who will not directly benefit from the procedures or interventions included in the research. Because the subjects to be enrolled in this study would be healthy children who do not have a disorder or condition, OHRP finds that this research may not be approved under 45 CFR 46.406.

OHRP has determined that the research protocol does not reach the threshold required for approval under the provision set forth in HHS regulation at 45 CFR 46.407, which requires that the research (i) presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; (ii) be conducted in accordance with sound ethical principles; and (iii) have adequate provisions for soliciting the assent of children and the permission of their parents or guardians, as set forth in 45 CFR 46.408.

The principal investigator acknowledged that none of the proposed studies have been done in adults or children and only a few have been done in animals. However, he indicated that they would start with five adults to perform some studies and then focus on adolescents. Most of the experts that OHRP assembled recommended that the proposed research should be conducted in adults and that analysis and review of the adult data should be performed before conducting the research in adolescents.

In determining whether the research would be conducted in accordance with sound ethical principles, OHRP has considered the relevant requirements set forth in 45 CFR 46, subpart A. For example, under HHS regulations at 45 CFR 46.111(a)(1)(i), the IRB must ensure that risks to subjects are minimized by using procedures which are consistent with sound research design and do not unnecessarily expose subjects to risk; and, HHS regulations at 45 CFR 46.111(a)(2) require the IRB to determine that risks are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of knowledge that may reasonably be expected to result.

OHRP finds that the research proposed under grant RO1 HL070919-01 addresses a fundamentally important topic, the role of brain metabolism in sleep. However, OHRP is recommending that HHS not support the proposed research involving the enrollment of 13- to 17-year-old subjects in this protocol, at this time, because there is a lack of data regarding the safety and feasibility of the proposed study procedures in adults or children. Although the study proposes to perform the protocol procedures on five adults before enrolling adolescents, OHRP believes data from five adults could be inadequate to determine the safety or feasibility of performing these procedures on adolescents. Furthermore, the findings from the adult study may lead to changes in the protocol involving adolescents, which would need to be considered before determining whether the study is approvable under 45 CFR 46.407. If data from the adult studies, indicate that the protocol procedures are feasible and safe, then the Institution may consider resubmitting this study involving 13-17 year old subjects, after making any necessary changes in the protocol based on results from the adult studies.

RECOMMENDATIONS

1. Determine that HHS should not support the proposed research protocol, involving the enrollment of 13- to 17-year-old subjects, at this time.

2. Make this decision available to the public via appropriate methods, such as placement on the OHRP web site.

DECISION

1. Determine that HHS should not support the proposed research protocol, involving the enrollment of 13- to 17-year-old subjects, at this time.

Approved /s/ Cristina V. Beato, M.D. Disapproved _____ Date March 15, 2004

2. Make this decision available to the public via appropriate methods, such as placement on the OHRP web site.

Approved /s/ Cristina V. Beato, M.D. Disapproved _____ Date March 15, 2004

/s/ Bernard A. Schwetz

Bernard A. Schwetz, D.V.M., Ph.D.

3 Attachments:
Tab A - Summary
Tab B - Clinical Trial Outline
Tab C -Tabular Summary of Experts' Recommendations