1 Committee No. 1130-01: Title: Alcohol, Sleep, and Circadian Rhythms in Young Humans
Principal Investigator: Mary Carskadon, PhD
Reviewed by Ms, Dr. and Ms.

Comments and Revisions Requested by the IRB:

- A reviewer noted that the 8 consents for this project are well written and clear.
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- Study 2, Adult-parent consent, typo in Section 1
- Study 2, Child consent, Section 2, page 3, paragraph 3, revise to explain that participants receive different doses on different nights.
- A reviewer objected to the classification of the lower dose as "small". Dr. Acebo explained that several drops are floated on top of the tonic water
- A reviewer noted that the protocol describes safeguards to protect participants who consume alcohol during the study
- Dr. Carskadon confirmed that children ages 9-10 will not be included in the alcohol consumption portion of this project (study 2)
- A reviewer noted that there is no scientific data that can be used to determine the appropriate alcohol doses for children. Dr. Carskadon agreed and noted that data from adult studies has been extrapolated to calculate dose, expected response , and potential risks.
- A reviewer noted that page 18 of the protocol specifies that participants will consume alcohol on an empty stomach. Dr. Carskadon offered to include a standard meal at an interval before alcohol is consumed. If a meal is added to the protocol, it must be included in the consent form in the description of procedures section.
- Study 2 consents, include a statement that it may take up to six hours for participants to return to baseline after consuming alcohol (blood alcohol levels return to 0)
- Dr. Carskadon provided relevant excerpts from the NIAAA Recommended Council Guidelines on Ethyl Alcohol Administration in Human Experimentation
- The reviewers expressed difficulty in determining the appropriate pediatric risk category. The reviewers did not agree with Dr. Carskadon's assessment that these experiments qualified for pediatric risk category B because in the reviewer's opinion, no direct benefit is provided. Dr. Carskadon responded that participants would benefit from the motivational interviews.
- A reviewer expressed concern that some adolescents may learn that they can consume alcohol without impairment. Dr. Carskadon explained that the motivational interviews will provide generalized information and will not provide direct feedback about individual results. The reviewer noted that since individual results will not be disclosed, then the motivational interview does not present direct benefit. Dr. Carskadon asked the IRB to consider other benefits that are not directly gained by participants.

- Ms. reminded the Committee that pediatric risk category D allows for research that may not otherwise be approved under subpart D. The pediatric review sheets have been revised to include consideration of category D.
- Dr. Carskadon informed the IRB that this application has been reviewed by NIAAA and found to be of high scientific merit.
- Dr. Carskadon requested a determination of the specific risks involved in this research. A reviewer noted that there are many studies in the literature describing the ill effects of alcohol consumption. Dr. Carskadon noted that a number of studies have shown that moderate drinking may be beneficial and also noted that this study does not propose to provide excessive amounts of alcohol. A reviewer noted that any alcohol consumption includes risks, especially to inexperienced drinkers. It was noted that the State of R.I. recently lowered the legal blood alcohol limit to .08 because of scientific studies of the effects of alcohol consumption.
- A reviewer noted that a literature search did not reveal any data regarding the provision of alcohol to minors in a controlled study. Dr. Carskadon explained that there is no data because this research is on the cutting edge and the results have yet to be published.
- Dr. Carskadon provided documentation from the NIAAA website concerning the benefits of moderate alcohol consumption. This information is based upon studies in adults.
- Dr. requested that the IRB consider if the administration of alcohol as described in the protocol present immediate dangers to participants and whether participation in the study promotes alcohol use that is problematic.
- A reviewer noted that the protocol specifies that parents will not be told of their child's alcohol and drug use without the child's permission. Include this information in the consent form.
- Consent, describe procedure for obtaining saliva samples
- A reviewer noted that the risks to providing alcohol to children are not all known. The reviewer expressed concern over providing alcohol to individuals with a family history of alcohol abuse. Dr. Acebo noted that there are unknown risks associated with most study drugs. The known risks have been included in the consent form.
- Written comments from one reviewer were read to the committee. The reviewer did not find any benefit to participants and did not recommend approval of this study.
- A reviewer requested an explanation of the recruitment process. Dr. Carskadon explained that different techniques would be used for each study and age group. Study 1 does not involve providing alcohol to participants. Flyers and brochures will be posted at alcohol treatment centers in hopes that parents visiting these treatment facilities will be interested and enroll their children. Dr. Carskadon confirmed that only parental alcohol use will be examined and consent to collect that information is obtained from the parents.
- A reviewer requested that Adolescent Assent forms be created.
- A reviewer asked what is known about the added risks associated with providing alcohol to individuals with a family history of alcohol abuse. Dr. Carskadon responded that there is limited data and none involves the provision of alcohol in controlled settings as proposed in this study. Dr. Carskadon agreed that there is probably an increased risk in individuals with a positive alcohol family history. Dr. Carskadon hopes that all participants will benefit from the summary interview at the end of the study.
- Study 2, (Consent) Section 3, include a statement that it is unclear whether drinking alcohol represents more of a risk to individuals with a positive family history of alcohol abuse

- The consent is not consistent with regards to the federal certificate of confidentiality, some portions state that one has been obtained and other sections state that an application will be submitted. Correct all references to be consistent. Dr. Carskadon explained that a certificate has not been obtained and an application will be submitted.
- Protocol , page 23, correct reference to "adults with minimal alcohol experience", this should read "adults with moderate alcohol experience"
- A reviewer requested copies of the Ethic Committee review letter and also the letter from the Attorney General's office. Dr. Carskadon provided copies of these documents for the file.
- It was noted that these letters concerned the proposed pilot study. The IRB discussed whether the revised protocol should be submitted for review by the Ethics Committee and the Attorney General. Dr. Carskadon explained that after IRB approval is granted, the researchers will meet again with the Attorney General to develop specific details for the waivers from prosecution for subjects and research staff that are described in the letter. It was noted that the waiver is not required for Study 1.

Dr. arrived at 12:00 p.m., during the presentation
Dr. and Dr. arrived at 12:25 p.m., during the presentation

Dr. and Dr. recused themselves and left the room. Quorum was maintained

Committee Action: Members commented that the study is very well written. The Committee conducted a discussion of the risks and benefits of participation in this study. Several reviewers noted that they had done extensive research on the topic and found evidence in the literature supporting the premise that children with positive family alcohol history are at an increased risk from developing a problem with alcohol. The IRB did not find that adolescents would be more likely to drink as a result of participating in this study. The IRB discussed the Pediatric Risk categories. The IRB agreed that Study 2 presents greater than minimal risk in the provision of alcohol, as described on pages 27-29 of the protocol, Section 3 of the consent forms , and also on the Human Subjects Protection form. The IRB discussed whether the project presents an intervention or procedure that holds out the prospect of direct benefit for the individual subject. Some members did not believe that the motivational interview would present direct benefit because only generalized information would be provided and individual results on performance under the influence of alcohol would not be shared. The IRB discussed whether the research is likely to yield generalizable knowledge about the subject's disorder or condition. Members noted that these are healthy subjects, as defined on page 26 of the protocol, and do not have a condition or disorder. Other members questioned whether under-age alcohol use could be considered to be a condition. Some members noted that this study presents an important opportunity to understand specific effects of alcohol in adolescents. A member noted that as written, the federal regulations do not provide a means to approve this protocol under either pediatric risk categories A , B or C. The IRB agreed that the research presents an opportunity to further the understanding of the effects of alcohol use in adolescents. The IRB decided to conduct separate, confidential votes for approval and child risk category.

A motion was made to request individual votes for pediatric risk categories for each study.

Study 2 & 3: 1 vote for Category C, 2 votes for Category B, 9 votes for Category D

A motion was made to approve the study with the requested revisions.
10 approved 2 opposed
The motion passed

Application, study 1, was approved in accordance with Pediatric Risk Category A per 45CFR46.404 pending receipt of requested revisions.

Application, Study 2 and Study 3 were approved in accordance with Pediatric Risk Category D per 45CFR46.407 pending receipt of requested revisions. The application will be sent to the Secretary of DHHS for public review and comment.