Official Title: A SMART Design to Improve Sleep Disturbance in Adolescents with Neurodevelopmental Disorders

NCT Number: NCT03730194

Most recent approved updates to IRB protocol: 9/23/2021

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Pediatric Biomedical Research
SECTION I

1. Status:
New Submission
♦ Revised electronic IRB Application; IRB# 775-18-FB
Initial electronic submission of an existing expedited IRB approved protocol; IRB#

2. Title of Protocol:
A SMART Design to Improve Sleep Disturbance in Adolescents with Neurodevelopmental Disorders

3. Responsible Personnel:
A. Principal Investigator (PI):
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B. Secondary Investigator (SI):

C. Participating Personnel:
Cordts, Katrina M - Psychiatry - 402-552-6002 - katrina.cordts@unmc.edu - alt #: 402-836-9910 - degree: PhD - address: DRC2 4002 UNMC Midtown (Zip 5920) - phone: 9-4749

Ellis, Cynthia Retelsdorf - MMI Developmental Medicine - 402-559-4985 - cellis@unmc.edu - alt #: 402-559-4985 - degree: MD - address: CHMC-IHW 8200 Dodge Street, IHW5 (Zip 2155) - phone: 402-955-7182

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Mathews, Therese (Terri) Lynn - CON-Omaha Division - 402-559-6633 - tmathews@unmc.edu - alt #: 402-559-4985 - degree: Ph.D., APRN - address: CNS 40112 UNMC Midtown (Zip 5330) - phone: 9-6633

D. Lead Coordinator:

E. Coordinator(s):
Klein, Abbey Jo - CON-Omaha Division - 402-559-6549 - abbey.klein@unmc.edu - alt #: 402-559-6731 - degree: BSN - address: CNS 50105 (Zip 5330) - phone: 402-559-6549

F. Data/Administrative Personnel:
Berger, Ann Malone - CON-Omaha Division - 402-559-4957 - aberger@unmc.edu - alt #: 402-669-7685 - degree: PhD, APRN, AOCN, FAAN - address: CNS 5092 UNMC Midtown (Zip 5330) - phone: 9-4957

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Kupzyk, Kevin A - CON-Omaha Division - 402-552-7262 - kevin.kupzyk@unmc.edu - alt #: 402-552-7262 - degree: PhD - address: CNS 5091 UNMC Midtown (Zip 5330) - phone: 2-7262

Smith, Makenzie Jacqueline - Student - Nursing (BSN) - Omaha - 402-289-1049 - makenzie.smith@unmc.edu - alt #: 402-559-6731 - degree: BSN student

Stappert, Danielle Jaquelyn - - 402-860-1292 - - alt #: 402-559-6731 - degree: BSN

G. Are you a student or house officer?
No

4. Funding Source:
Check all that apply and provide the source of the funding.
Cooperative Group:
♦ Grant - Provide Source: National Institutes of Health, 1K01NR017465-01A1
Commercial - Provide company name:
Department of Defense
Other - Provide Source:
Center for Clinical and Translations Research (CCTR)

5. Contract:
Is there a contract or agreement associated with this study?
No

6. Funding Agency Deadline for IRB Approval:
♦ Yes 12/01/2018
No

7. Study Sites:
A. Provide the names and locations of all study sites where this research will be conducted under the oversight of the Joint Pediatric IRB.
University of Nebraska Medical Center, Munroe-Meyer Institute (including satellite clinics), 985450 Nebraska Medical Center

University of Nebraska Medical Center, Center for Nursing Science & College of Nursing 985330 Nebraska Medical Center

Children's Hospital & Medical Center (including satellite clinics)
8200 Dodge Street

B. Is this a multi-site study?
No

C. Does this study involve any international sites where the PI will either conduct or supervise the study?
No

8. Principal Investigator Assurance
The PI understands and accepts the following obligations to protect the rights and welfare of research subjects in this study:

- **I certify that I have carefully reviewed this application and all supporting documents. I have determined that the application is accurate, complete and ready for submission to the IRB.**
- **I certify that I, and all listed research personnel, have the necessary qualifications, expertise, and hospital credentials to conduct this study in a manner which fully protects the rights and welfare of research subjects.**
- **I certify that all listed research personnel will be given a copy of the final IRB**

approved application and any other relevant study-related documents in accordance with their defined responsibilities.

- I recognize that, as the PI, it is my responsibility to ensure that this research and the actions of all research personnel involved in conducting the study will comply fully with the IRB-approved protocol, all applicable federal regulations, state laws, and HRPP policies.

- I recognize that it is my responsibility to ensure that valid informed consent/assent has been obtained, as appropriate, from all research subjects or their legally authorized representative (LARs). I will ensure that all research personnel involved in the process of consent/assent are properly trained and are fully aware of their responsibilities relative to the obtainment of informed consent/assent according to federal regulations, state laws, and HRPP policies.

- I certify that the minimum amount of protected health information (PHI) or other identifiers necessary will be used and disclosed to conduct this research study (if applicable). I will implement reasonable safeguards to protect the PH/identifiers at all times.

- I will promptly inform the IRB of internal adverse events, as well as any unanticipated problems involving risk to the subjects or to others, as required within the time frame defined by HRPP policies. I will analyze each internal adverse event/reported problem to determine if it impacts the risk-benefit relationship of the study, the safety of the subjects, or informed consent.

- I will analyze each MedWatch/safety report to determine if it impacts the risk/benefit relationship of the study, the safety of the subjects, or informed consent. I will promptly submit external adverse event reports in accordance with HRPP policies.

- I will promptly inform the IRB if I become aware of: 1) any complaints from research subjects, LARs, or others about research participation, 2) violations of federal regulations or state law, 3) violations of the HIPAA Rule, or 4) violations of HRPP policies.

- I will promptly inform the IRB of the results of external audits performed by sponsors, Contract Review Organizations (CROs), cooperative groups, FDA, or other external groups.

- **I will not initiate any change in protocol without IRB approval except when it is necessary to reduce or eliminate a risk to the subject, in which case the IRB will be notified as soon as possible.**

- **I certify that there are, or will be, adequate resources and facilities to safely initiate, carry out and complete this research at the study sites specified in Section I.7. This includes sufficient staff, funding, space, record keeping capability, and resources necessary to address adverse events and any unanticipated problems involving risk to the subject or others. If the necessary resources become unavailable I will promptly notify the IRB.**

- **I will promptly inform the IRB of any significant negative change in the risk/benefit relationship of the research as originally presented in the protocol and approved by the IRB.**

- **I understand that continuing review by the IRB is required at least annually in order to maintain approval status. I will maintain IRB approval as long as this study is active.**

- **I understand that I am responsible for appropriate research billing in accordance with UNMC Clinical Trial Professional and Technical Fee Billing Policy #8008 or applicable Children s Hospital & Medical Center policy.**

- **I certify that I and all other personnel listed in Section I.3A-E of the IRB Application have disclosed all potential financial conflicts of interest as required and are in full compliance with the UNMC Conflict of Interest Policy #8010 and HRPP Policy. I further certify that all potential financial conflicts of interest are appropriately managed in order to ensure protection of the rights and welfare of subjects.**

- **I will maintain all required research records on file and I recognize that representatives from the IRB, OHRP, HHS, FDA, and other Federal Departments or Agencies may inspect these records in accordance with granted authority.**

- **I understand that failure to comply with the Common Rule, applicable Subparts B, C, and D of HHS regulations at 45 CFR 46, applicable FDA regulations, the HIPAA Rule, applicable state law, HRPP policies, and the provisions of the IRB-approved protocol may result in suspension or termination of IRB Approval of my research project and/or other administrative or legal actions.**

Hanish, Alyson E - 2021-09-22 11:01:13.316

9. Principal Investigator Financial Interest Disclosure
A. As the PI, I declare:
♦ I have no financial interest in this research.
I have a financial interest in this research.

B. As the PI,
♦ I understand I must disclose any change in my financial interest during the course of this research within five (5) business days from the time the change becomes known.

C. As the PI who is ultimately responsible for the proper conduct of this research, I also certify that:
♦ No Responsible Personnel have a financial interest in this research.
The Responsible Personnel listed below have informed me that they have a financial interest in this research.

D. I have informed all Responsible Personnel that if there is any change in their financial interests during the course of this study it must be disclosed within five (5) business days from the time the change becomes known.
Hanish, Alyson E - 2021-09-22 11:01:13.316

11. Scientific/Scholarly Merit and Resource Review Certification
A. Scientific Reviewer:
Dickinson, Kristin A - CON-Omaha Division - 402-559-5358 - kristin.dickinson@unmc.edu - alt #: 402-559-5358 - degree: PhD, RN, OCN - address: CNS 50107 UNMC Midtown (Zip 5330) - phone: 9-5358

As the Scientific Reviewer,
♦ I do not have a financial conflict of interest associated with this study.

My signature certifies that this application has been reviewed for scientific/scholarly merit and available resources. I have determined that the application merits consideration by the IRB based upon the following:

- **1) The proposal has an acceptable level of scientific/scholarly merit which justifies the use of human subjects.**

- **2) The proposal has a sound research design in consideration of the stated objectives,**
- **3) The PI has the necessary qualifications, experience and credentials to conduct this research.**
- **4) The PI has or will have the necessary funding to support this research.**
- **5) There is or will be adequate physical space required for the research interventions at all study sites specified in Section 1.7. In addition, there is or will be adequate laboratory and clerical support, data storage capability, and any other resources necessary to complete this research.**
- **6) At all study sites specified in Section 1.7, there is emergency equipment, personnel, or services necessary to respond promptly to adverse events or unanticipated problems involving risk to the subject or others.**
- **7) I will promptly notify the IRB if the necessary resources to support this research become unavailable.**
- **8) I am not listed as study personnel in Section I of this application.**

Dickinson, Kristin A - 2018-10-31 11:11:00.000

Do you have any additional comments that you wish the IRB to consider during the review of this application?
No

SECTION II

PROTOCOL ABSTRACT

1. Provide a brief (less than 400 words) abstract of the research protocol. This summary should include: 1) the title of the protocol, 2) a *brief* description of the purpose of the study, 3) eligibility criteria, 4) interventions and evaluations and 5) follow-up.

A SMART Design to Improve Sleep Disturbance in Adolescents with Neurodevelopmental Disorders

The objective of this study is to pilot a sequential, multiple assignment, randomized trial (SMART) design to compare the impact of a sequence of sleep interventions, based on participant treatment response, to optimize sleep health in older children (defined hereafter as adolescents 10-18 years of age) with neurodevelopmental disorders (NDDs). Inclusion criteria for the study are as follows: 1) Participant must be 10-18 years of age and consistently living with parental (or legal guardian) supervision; 2) Participant must have diagnostic report of confirmed NDD diagnosis [ASD or ADHD]; 3) There must be documentation of participating adolescent being classified as non-intellectually impaired [e.g. IQ>70]; 4) There must be parent report of the adolescent spending less than or equal to 8 hours in bed per night on 3 or more nights per week in the past month or composite score greater than 41 on Children's Sleep Habits Questionnaire; and 5) The adolescent must be medication-free or on a stable dose of medications [no changes within 30 days prior to enrollment] with parental agreement to avoid changes in current medications [unless provider directed] during study participation. At baseline, endogenous melatonin will be measured in the adolescents. This study will utilize exogenous melatonin, a novel behavioral sleep intervention, *The Bedtime Bank,* and a combination of those interventions in an attempt to increase total sleep time while decreasing sleep disturbances and sleep-related impairments through objective evaluation using actigraphy and subjective evaluation using the Cleveland Adolescent Sleepiness Questionnaire and PROMIS Sleep Disturbance and Sleep Related Impairment questionnaires. At the end of the 8 week evaluation period, data will be analyzed by the PI, an on-site statistician, and consultants with expertise in SMARTs to address feasibility and acceptability to prepare for a full-scale SMART.

Research has shown that, when compared to parents of typically developing children, parents of children with NDDs may have an increased risk of sleep problems. For this reason, parents will be invited to participate in a voluntary sub-study to monitor their own sleep patterns in concordance with their child's.

PURPOSE OF THE STUDY AND BACKGROUND

2. Purpose of the Study

What are the specific scientific objectives of the research?

The overall objective of this study is to pilot a sequential, multiple assignment, randomized trial (SMART) design to compare the impact of a sequence of sleep interventions, based on participant treatment response, to optimize sleep health in adolescents (10-18 years of age) with NDDs.

We plan to test our central hypothesis and accomplish our overall objective for this pilot by pursuing the following three specific aims with a sample of 40 adolescents, ages 10-18 years old:

1. Determine the extent to which melatonin or The Bedtime Bank increases total sleep time (TST) in adolescents with NDDs.

H_0: The Bedtime Bank will be more effective than exogenous melatonin at increasing TST from baseline.

2. Determine the extent to which melatonin and The Bedtime Bank increase TST in adolescents who do not respond to melatonin or a behavioral sleep intervention.

H_0: Melatonin and The Bedtime Bank will be more effective at increasing TST from baseline than melatonin or The Bedtime Bank.

3. Investigate associations among endogenous melatonin levels at baseline with participant response to treatment.

H_0: Participants with low baseline nocturnal melatonin will respond at higher rates to a melatonin-only treatment compared to participants with typical baseline nocturnal melatonin levels.

3. Background and Rationale

Describe the background of the study. Include a critical evaluation of existing knowledge, and specifically identify the information gaps that the project is intended to fill.

Sleep disturbances are common in children with neurodevelopmental disorders (NDDs), with an estimated prevalence of 50-80%.[1-5] Sleep disturbances in children with NDDs include long sleep onset latency, frequent awakenings, bedtime resistance, poor sleep efficiency, and less than optimal total sleep time.[6,7] Abnormalities in melatonin physiology, a neurohormone involved in circadian regulation, have been reported in children with NDDs.[8,9] Exogenous melatonin and behavioral sleep interventions show promise in treating sleep disturbances in children with NDDs; however, there is a paucity of empirical data and a need for rigorously-designed studies.[10-15] The high prevalence of sleep disturbances in children with NDDs and the negative long-term consequences of sleep disturbance create a *critical need* for a personalized approach to determine effective sleep interventions and the optimal treatment for sleep disturbances in children with NDDs.

The proposed study targets the biological (e.g. endogenous and exogenous melatonin) and behavioral (e.g. *The Bedtime Bank,* a novel sleep intervention) characteristics of sleep disturbance in adolescents with NDDs and aims to optimize innovative research methods by using the sequential, multiple assignment, randomization trial (SMART) design, which is important to advancing nursing science.[16]

According to the Academy of Sleep Medicine, adolescents physiologically require 8 to 12 hours of sleep per 24 hours[17]; however, over the past two decades, researchers, teachers, parents, and adolescents have consistently reported inadequate sleep throughout adolescence.[18] Healthy People 2020 includes sleep health as an important topic area for public health, with one of the objectives specifically addressing the need to increase the proportion of adolescents who get a sufficient amount of sleep.[19] The NIH Sleep Disorders Research Plan specifically addresses the scientific opportunity and need for research in sleep deficiency.[20] It is important to note that there is no standard age range for defining adolescence; however, the World Health Organization defines adolescents as young people between the age of 10 and 19 years.[21,22]

Sleep deficiency in adolescents is associated with both physical and mental health problems, including obesity, depression, anxiety, delinquent behavior, and alcohol use, as well as suicidal behavior.[20,23-26] There is also an association between lower academic performance and shorter sleep duration.[27] Sleep deficiency has safety-related consequences, with sleepiness at the wheel significantly increasing the risk of automobile accidents in adolescents.[28-30] The American Academy of Pediatrics has even recommended delaying school start times, and, overall, the evidence supports delayed school start times to combat the growing concern of adolescent sleep deprivation.[31,32] Monitoring bedtimes in adolescents is also important, and research is needed for interventional strategies that target bedtimes in an effort to reduce associated functional impairments and improve academic and emotional outcomes.[33] Insufficient sleep in adolescents is an important public health issue, and many sleep disturbances begin in adolescence and subsequently persist throughout adulthood.[34]

The Sleep Research Society and the NIH partnered to organize a workshop focused on the translation of evidence-based interventions for sleep and circadian disorders into practice strategies that benefit population health and patient outcomes. Adolescent sleep health, the lack of sleep intervention studies, and the need for effective interventions that can reduce chronic sleep loss and circadian misalignment in adolescents were all identified as essential next steps for research.[35] Furthermore, the recommendations specifically address the need for inclusion of vulnerable adolescent populations (e.g. adolescents with NDDs) into intervention efforts, as they are at risk for sleep-disturbances and poor neurological and psychological outcomes.[35]

NDDs are a group of conditions with onset in the developmental period that result in deficits primarily associated with the function of the brain and central nervous system. Sleep disturbances are common in children and adolescents with NDDs, with an estimated prevalence of 50-80%.[1-5] Sleep disturbances include long sleep onset latency, frequent awakenings, bedtime resistance, poor sleep efficiency, and less than optimal total sleep time.[6,7,36] Sleep disturbances are an important issue in NDDs, as sleep problems can exacerbate and worsen repetitive and stereotypic behavior, inattention, and hyperactivity, as well as interfere with learning and cognition.[37-41] Sleep problems in children and adolescents with NDDs can also adversely affect parental sleep and family functioning.[42-45] The current sleep literature primarily focuses on the two most prevalent NDDs, autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD). ASD is characterized by deficits in social communication and social interaction, as well as the presence of repetitive and restrictive behaviors,[46] with an estimated prevalence of 1% in the United States.[47] ADHD is characterized by a persistent pattern of inattention and/or hyperactivity-impulsivity,[46] with an estimated prevalence of 11% of children 4-17 years of age in the United States.[48] Both ASD and ADHD are characterized by a range of deficits that produce impairments of personal, social, academic, or occupational functioning.[46]

Across NDDs, it appears that sleep disturbance is the result of a combination of biological, psychosocial, environmental, and behavioral factors, and the *biopsychosocial model of common sleep problems* was used for the proposed research (**Figure 1**).[49] Although the model incorporates the core behaviors of ASD, the authors specifically address applicability to additional NDDs. The proposed research targets the abnormal melatonin levels and secretion (e.g. endogenous and exogenous melatonin) and disordered sleep (e.g. *The Bedtime Bank,* a novel sleep intervention) characteristics of sleep in adolescents with NDDs.

Although it is known that sleep problems persist throughout childhood, into adolescence, and even into adulthood in persons with NDDs, little is known about sleep problems during the period of adolescence.[50-53] Insufficient sleep in adolescence is common and may be magnified and exacerbate underlying conditions in children with NDDs. The high prevalence of sleep problems in children with NDDs, and the potential negative consequences of sleep disturbance, make appropriate intervention an urgent priority for many families.[54]

Melatonin: Abnormalities in melatonin physiology, a neurohormone involved in circadian regulation, have been reported consistently in children with NDDs.[8,9,55-57] However, two studies have found no differences in endogenous melatonin production in children with ASD compared to typically developing peers.[58,59] Exogenous melatonin has shown promise in increasing total sleep time (TST) and improving sleep latency in children and adolescents

with NDDs with minimal side effects[13,60,61] and has been reported as evidence-based after a review of twenty studies.[8] However, the mechanism of action is still uncertain.[8,62] In the United States, melatonin is sold as an over-the-counter supplement. One study surveyed parents of children with ASD regarding the use and perceived effectiveness of complementary and alternative medicine (CAM) to manage ASD-related symptoms. Exogenous melatonin use for their child was reported by 45% of parents and received one of the highest ratings of effectiveness of all the CAM therapies.[63] Parents report value to naturalness of melatonin, and, in one study, parents favored melatonin over other medications for sleep in their children.[64]

Behavioral Sleep Interventions: A recent systematic review and meta-analysis found behavioral treatments for young, typically developing children (birth to 5 years) with sleep disturbances result in significant improvements in sleep-onset latency, night waking frequency, and night waking duration.[65] However, there is currently very low-quality evidence for behavioral treatments in adolescents, as well as children/adolescents with NDDs.[65] A few studies have shown that interventions predominantly aimed at parent education in pediatric sleep hygiene improve sleep disturbances in young children with NDDs,[66-71] as well as older children and adolescents with DDs.[72] Currently, behavioral sleep interventions for children with NDDs are sparse and limited by methodological concerns (e.g. small sample sizes, wide age ranges, & lack of objective measures).[6,12,65,73] To our knowledge, no studies have reported behavioral sleep interventions specific to adolescents with NDDs. Behavioral interventions and exogenous melatonin show promise in treating sleep problems in adolescents with NDDs.[74]

CHARACTERISTICS OF THE SUBJECT POPULATION

4. Accrual

Is this study conducted solely at sites under the oversight of the Joint Pediatric IRB (e.g. UNMC, TNMC, CH&MC, UNO)?

Yes

A. What is the total number of subjects (per group, as applicable) needed to complete the research in order to achieve the scientific objectives of the research?

A convenience sample of 40 adolescents diagnosed with ASD and/or ADHD and 40 parents (or legal guardians) of adolescents (1 parent per adolescent) will be recruited through the UNMC MMI, all MMI outreach clinics, CHMC, and CHMC clinics. A focused plan will be in place to oversample females (e.g. clinicians and study team will be encouraged to invite non-white and female adolescents to participate), given the approximate 4:1 male to female ratio of NDDs. Our anticipated ratio is 3:1 male to female participants. Adolescents and their parent will be identified by a doctoral-prepared nurse as meeting the inclusion criteria.

B. What is the statistical or other justification for the <u>total</u> number of subjects needed to complete the research in order to achieve the scientific objectives of the research?
The sample of 40 was chosen following a sample size calculator, specific to pilot SMARTs,[75] assuming 85% probability, an estimated early non-response rate of 50%, and a minimum of 3 participants falling into the non-responder groups.

C. Based on the anticipated number of screen failures and/or subject withdrawals, what is the maximum number of subjects that will need to be consented in order to achieve the scientific objectives of the research?
The maximum number of adolescent study participants with ASD and/or ADHD that will be consented is 40. In addition, a maximum of 40 parents of the adolescent participants will also be consented, for a total maximum number of 80 participants. Dr. Hanish (PI) will meet participants in-person at baseline, week 4, and week 8. In addition, endogenous melatonin samples will be collected from participants by the end of the first week of baseline data collection. Dr. Hanish will conduct weekly telephone check-ins to discuss daily adherence to the Bedtime Bank (e.g consistent bedtimes and tracker completion) and wearing the actigraph. Technical problems will be triaged quickly and may result in additional telephone calls or in home visits when necessary to further help with participant retention. Participants will also be compensated for their time.

5. Gender of the Subjects
A. Are there any enrollment restrictions based on gender?
No

6. Age Range of Subjects
A. What is the justification for inclusion of children in this research?
Adolescents (10-18 years of age) with neurodevelopmental disorders (NDDs) are included in this study. Adolescents with NDDs are vulnerable to sleep disturbances, and there is a critical need for evidence-based sleep interventions that target this population. The PI, mentoring team, and staff at the facilities in which the participants will be recruited all have expertise in accommodating for adolescents with NDDs. The proposed study will pilot a sequential, multiple assignment, randomized trial (SMART) design utilizing exogenous melatonin, The Bedtime Bank, and their combination for the management of sleep disturbance in adolescents with NDDs. Knowledge gained from this study will contribute to future full-scale SMARTs and our long-term goal of developing evidence-based guidelines for sleep interventions for children and adolescents currently experiencing or at-risk for sleep disturbances.

B. What is the age range for the child subjects, and what is the justification for selecting this age range?

Among the pediatric population, adolescents carry the largest sleep debt. Although it is known that sleep problems persist throughout childhood and into adolescents, little is known about sleep problems during the period of adolescence. A recent systematic review and meta-analysis found behavioral treatments for young children with insomnia result insignificant improvements in sleep-onset latency, night waking frequency, and night waking duration; however, there is currently very low-quality evidence for the treatment of insomnia in older children/adolescence, as well as children with neurodevelopmental disorders.[65] There is no standard age range for adolescence; however adolescence is generally defined somewhere between ten to twenty years of age. For this study, parental participation is required, and adolescents between the ages of 10 and 18 years will be recruited. The clinical trial runs a total of 9 weeks, and the PI will ensure (DOB on demographics) that enrolled adolescent participants will not meet the age of 19 years during the trial.

C. Will this study enroll wards of the state?
No

D. Will adults (19 years of age or older) be included in this research?
Yes

1) What is the justification for including adults in research?
The adults included in this research are to be the parent (or legal guardian) of the participating adolescents. It is required that the parents complete a demographic questionnaire regarding their child, in addition to participating in training on the use of actigraphy and melatonin collection related to the study with their adolescent. The parents will also complete questionnaires used to indicate minimal treatment acceptability and be present during semi-structured interviews during weeks 4 and 8 of the study to discuss treatment acceptability.

Research has shown that, when compared to parents of typically developing children, parents of children with autism have more sleep problems.[42] For this reason, parents may be asked to participate in a voluntary sub-study to monitor their own sleep patterns in concordance with their child's. Participation in the sub-study will consist of daily parental actigraphy monitoring and completion of a daily sleep diary throughout the duration of the trial. Parents will also be asked to complete sleep questionnaires at each of the three study visits.

2) What is the age range of the adult subjects to be included in the research?
The adult subjects will be the parent of an adolescent participant. Parents will likely be between the ages of 25 to 65 years.

3) What is the rationale for the age range of the subjects?
The adult subjects will be the parent of an adolescent participant (10 to 18 years of age). Parents of children in this age range are likely to be between 25 and 65 years of age.

7. Race and Ethnicity
Are there any subject enrollment restrictions based upon race or ethnic origin?
No

8. Vulnerable Subjects
A. Will any of the following vulnerable populations be allowed to participate in this research? Check all that apply.
Pregnant individuals, fetuses or neonates (non-viable or of uncertain viability)
Prisoners
♦ None

B. Will any of the following vulnerable populations (Critically ill patients, Students of the investigator, Socially or economically disadvantaged individuals, Individuals with a stigmatizing illness or condition, Other) be specifically recruited for enrollment in this research?
Yes

1) Check all that apply.
Critically ill patients
Students of the investigator
Employees of the investigator
Educationally disadvantaged individuals
Socially or economically disadvantaged individuals
Individuals with a stigmatizing illness or condition
♦ Other. Explain. Adolescents diagnosed with ASD and/or ADHD

2) Describe the additional safeguards to protect the rights and welfare of these subjects?
In order to protect the rights and welfare of the adolescent participants, consent will be obtained from the parents of the adolescents, while the adolescents will be required to sign assent forms. The participating parents will also be present during all training and interviews conducted with the adolescent, which may be face-to-face, over the phone, or using Zoom video conferencing. The participants will be informed that they may withdraw from the study at any time.

9. Inclusion Criteria

What are the specific inclusion criteria?

Adolescent Inclusion Criteria:

1) Age 10-18 years and consistently living with parental (or legal guardian) supervision
2) Diagnostic report of confirmed NDD diagnosis (ASD or ADHD)
3) Documentation of adolescent being classified as non-intellectually impaired (e.g. IQ>70)
4) Parent report of adolescent spending ≤ 8 hours in bed per night on 3 or more nights per week in the past month or composite score >41 on Children's Sleep Habits Questionnaire
5) Medication-free or on a stable dose of medications (no changes within 30 days prior to enrollment) with parental agreement to avoid changes in current medications (unless provider directed) during study participation

Adult Inclusion Criteria:

1) Parent/guardian of an adolescent participant
2) Age 25-65 years and consistently living with the participating adolescent

10. Exclusion Criteria

What are the specific exclusion criteria?

Adolescent Exclusion Criteria:

1) Unwillingness to stop melatonin 2 months prior to enrollment in the study
2) Parent report of adolescent with a known sleep disorder (e.g. sleep apnea)
3) Adolescents who are not able to take oral medication
4) Adolescents who are visually impaired with known inability to detect light
5) Adolescents with an NDD with known genetic etiology (e.g. Angelman syndrome)
6) Unwillingness to wear actigraph daily and complete daily sleep diary throughout the 9-week trial

Adult Exclusion Criteria:

1) Unwillingness to wear actigraph daily and complete daily sleep diary throughout the 9-week trial

11. Pregnancy and Contraception Requirements

A. Are non-pregnant females of childbearing potential included in this research?

Yes

1) Are there any specific contraception requirements?

No

1) Provide justification.

No interventions are likely to be of risk to a fetus (including Category A drugs)

♦ Other. Explain. It is currently not known if there is any risk to the fetus from exogenous melatonin.

B. Are pregnant females included in this research?
No

1) Provide justification for excluding pregnant females.
Intervention includes a Category B, C, D or X drug
Intervention includes a procedure expected to be of risk to the fetus (e.g. exposure to ionizing radiation, maximal exercise test)
Research is not relevant to pregnant females (e.g. disease or condition rarely encountered in pregnant females)
Knowledge being sought in the research is already available for pregnant females or will be obtained from another ongoing study
A separate study in pregnant females is warranted and preferable
Physiology of pregnancy precludes generalization to other populations
♦ Other. Explain. Pregnant females may have different sleep patterns potentially confounding the study interventions.

2) Describe how pregnancy status will be assessed.
♦ Self-report
Blood pregnancy test
Urine pregnancy test
N/A study includes males only

C. Are breast feeding females excluded from participation?
No

METHODS AND PROCEDURES

12. Methods and Procedures Applied to Human Subjects
A. Are there any evaluations or tests that will be performed for the purpose of determining subject eligibility which would not be routinely conducted as part of standard clinical care of the prospective subject?
No

B. Describe sequentially all procedures, interventions, evaluations and tests.
Recruitment
Upon approval from the UNMC IRB and the DSMB, we will begin recruitment. Flyers will be

posted within the MMI (Appendix H), as well as Childrens Hospital and Medical Center. A Facebook post (Appendix G) will be published by the UNMC CONs Facebook page, as well as the MMI Facebook page. This post will include a link to the study webpage (Appendix I), where further information can be found: https://www.unmc.edu/nursing/research/current-research-grants/sleep-smart.html.

Table 1: Measurement Timeline		
Baseline	**Week 4**	**Week 8**
Demographic Questionnaire (~2-3 minutes)	AARP (~5-7 minutes)	AARP (~5-7 minutes)
CASQ & PROMIS (~7-11 minutes)	CASQ & PROMIS (~7-11 minutes)	CASQ & PROMIS (~7-11 minutes)
DLMO (~3 hours) Urinary Melatonin (~5 minutes) (optional)	Semi-structured interview (~10-12 minutes)	Semi-structured interview (~10-12 minutes)
Actigraphy/Sleep Diary (daily for 1 week)	Actigraphy/Sleep Diary (daily for 4 weeks)	Actigraphy/Sleep Diary (daily for 4 weeks)
Sexual maturation self-assessment tool (~1-3 minutes)		

BASELINE: First Stage Treatment Decision (see **Figure 2 & Table 1**)

The adult consent(s) and adolescent assent materials will be read and consent(s) signed during the first meeting, which may be face-to-face, over the phone, or using Zoom video conferencing.

Parent(s) Complete:

1. Demographic Questionnaire of adolescent: Gender, date of birth, race/ethnicity, and adolescent's list of current medications. (Appendix A).
2. Demographic Questionnaire of parent (if participating in sub-study): Gender, date of birth, race/ethnicity, marital status, and list of current medications (Appendix A).
3. PROMIS Sleep Disturbance (short form v. 1.0, 8b): An eight-item questionnaire used to measure self-reported perceptions of sleep quality, depth, and restoration. This includes perceived difficulties getting to sleep and staying asleep, as well as sleep satisfaction (Appendix B).[76]
4. PROMIS Sleep Related Impairment (short form v 1.0, 8a): An eight-item questionnaire used to measure self-reported alertness, sleepiness, tiredness, and functional impairments associated with sleep problems during waking hours (Appendix B).[76]

Adolescents Complete:

1. Cleveland Adolescent Sleepiness Questionnaire (CASQ): The CASQ is a sixteen-item instrument used to measure daytime sleepiness in adolescents 11-17 years of age. Adolescents rate the frequency of each item using a 5-point Likert scale: never (0 times per month), rarely (less than 3 times per month), sometimes (12 times per week), often (34 times per week) and almost every day (5 or more times per week), with higher scores indicating increased daytime sleepiness (Appendix B).[77]

2. PROMIS Pediatric Item Bank Sleep Disturbance (v. 1.0): A fifteen-item questionnaire used to measure self-reported perceptions of sleep quality, depth, and restoration. This includes perceived difficulties getting to sleep and staying asleep, as well as sleep satisfaction (Appendix B).[76]
3. PROMIS Pediatric Item Bank Sleep Related Impairment (v. 1.0): A thirteen-item questionnaire used to measure self-reported alertness, sleepiness, tiredness, and functional impairments associated with sleep problems during waking hours (Appendix B).[76]
4. Self-assessed pubertal staging: The sexual maturation self-assessment tool (Appendix O) will be completed by the adolescent, with the parent aiding if necessary. This participant will report sexual maturation[78], as pubertal status may have an impact on sleep[79].

Parent and Adolescent Training

1. Dim Light Melatonin Onset (DLMO): The Salimetrics Salivary Melatonin Assay Kit (Carlsbad, CA) will determine DLMO.[80] At baseline, adolescents and parent(s) will be given the saliva collection kit and instructed on how to collect the adolescent's saliva, including written instructions (Appendices J & K) and a return demonstration of sample collection by the adolescent.[80,81] The PI has received salivary assay training. At baseline (single evening), the adolescent (with parent(s) help) will begin saliva collection three hours prior to habitual bedtime, every thirty minutes, for a total of 7 samples. DLMO samples will be obtained in dim lighting (< 30 lux) according to the Journal of Clinical Sleep Medicine.[82] We will also use the Burgess et al. home sampling procedures that demonstrated a good agreement between home and laboratory DLMOs.[81] These procedures include objective measures of compliance for the requirement of dim lighting (e.g. Actiwatch Spectrum pinned to outer most clothing as a light measure) and accurate sampling times (participants will be provided a timer with preset alarms).[81] Goldman et al. also demonstrated feasibility of at home DLMO sampling in adolescents and adults with a NDD.[59] Participants' names and identifying information will be removed from all data collected and codes will be assigned. The key to the code will be kept in a separate, secure area in the UNMC campus. The pre-labeled and de-identified salivary samples will be collected from participants by responsible personnel prior to the implementation of the first stage intervention. Specimens will then be stored in a locked and secured freezer (at the UNMC Biospecimen Bank) until they can be shipped directly to the Salimetrics laboratory for analysis. Salivary samples will only be used for the study described in the consent form.
2. Urinary Melatonin (optional): The Genway Biotech Melatonin ELISA Kits (San Diego, CA) will allow for the analysis and quantification of urinary melatonin in study participants.[83] Serum melatonin quanitification is the gold standard for accurate assessment of circadian phase,[84] but 6-sulfatoxymelatonin, the primary melatonin

metabolite in urine, correlates well with the total level of melatonin in the blood during the collection period.[85] At baseline, adolescents and parent(s) will be given the urine collection kit and instructed on how to collect the adolescents urine (first morning void and evening), including written instructions (Appendix L) and a mock return demonstration. The pre-labeled and de-identified urine samples will be collected from participants by responsible personnel prior to the implementation of the first stage intervention. Specimens will then be stored in a locked and secured freezer (at the UNMC Biospecimen Bank) until they can be run by the UNMC Biospecimen Bank staff for analysis. Urinary creatinine will also be measured as melatonin sulfate is referenced as ng/mg creatinine to control for dilution of urine. Urine samples will only be used for the study described in the consent form.

3. Actigraphy: Objective measure of sleep patterns based on the correlation between sleep-wake state and motor activity. Adolescents wear the Actiwatch Spectrum (Philips Respironics, Bend, OR) on their wrist for 7-days (24 hrs/day) to establish baseline sleep patterns, as well as for 4 weeks (24 hrs/day) for the first stage treatment. TST will be used as the primary tailoring variable to determine responder status. A minimum of 4 weekday nights (Mon-Thurs) and 1 weekend (Fri-Sat) night is required. Participans will be provided with information regarding the care and use of the Actiwatch (Appendix M).
4. Sleep Diary: During the time adolescents are wearing the actigraph, adolescents will record an approximate time of sleep and wake to aid in data analyses.[86] Participants will also be asked to write down any times the device is removed, prolonged quiet activities, and atypical sleep (Appendix C). Reliability in completing the diaries will be established via weekly telephone checks by the study's investigators.
5. MEMs Button: Medication adherence will be monitored using MEMs Buttons. This button is attached to the melatonin bottle. When a dose is administered, the adolescent or parent will press the button to record the dose. Data from the MEMs Button will be downloaded from the device to a computer to ensure dose fidelity.
6. First Stage Treatment (see **Figure 2**): Adolescents will be randomly assigned to 4 weeks melatonin OR 4 weeks of *The Bedtime Bank*. Randomization will follow the real-time randomization for SMART designs.[75]

WEEK 4: Second Stage Treatment Decision (see **Figure 2 & Table 1**)

1. Abbreviated Acceptability Rating Profile (AARP): A parent-completed form to measure overall satisfaction with the treatment protocol (Appendix D). Research has found that the AARP possesses acceptable internal consistency, reliability, and validity.[87] The modified AARP includes 8 items regarding treatment acceptability rated on a Likert-type scale (1 = strongly disagree to 6 = strongly agree). Parents are asked whether they agree that the intervention was acceptable and effective, whether they would keep using it and recommend it to others, and whether they felt it was a good way to solve their child's sleep problems. The AARP yields a total

score that ranges from 8-48, with a score above the midpoint (28+) indicating minimal treatment acceptability.
2. Parent(s) repeat PROMIS sleep measures.
3. Adolescents repeat sleep questionnaires (CASQ and PROMIS sleep measures).
4. Parent(s) and adolescent complete semi-structured interview to discuss treatment acceptability (Appendix E). Semi-structured interviews will be audio recorded for later transcription.
5. Actigraphy: Data will be downloaded and analyzed (automated algorithm Respironics Actiware 6, Philips Respironics, Bend, OR) to determine responders from non-responders to determine Second Stage Treatment Decision. **Responder** = ≥18 minute nightly increase in TST.
6. MEMs Button: Data will be dowloaded and analyzed to assess medication adherence.
7. Second Stage Treatment (see **Figure 2**): Participants who respond remain on the assigned treatment. Participants who are nonresponsive are re-randomized to a different treatment option. Participants who do not complete the assigned treatment remain on the assigned treatment or withdraw from the study. Randomization will occur based on responder status and will follow the real-time randomization for SMART designs.[75] Adolescents will wear the actigraph on their wrist for an additional 4 weeks (24 hrs/day) for a study total of 9 weeks.

<u>WEEK 8: Study Conclusion</u>

1. Parent(s) complete AARP and PROMIS, adolescents repeat sleep questionnaires (CASQ and PROMIS), and parent(s) and adolescent complete semi-structured interview to discuss treatment acceptability. Semi-structured interviews will be audio recorded for later transcription.
2. Actigraphy Data will be downloaded and analyzed to determine response status.
3. MEMs Button: Data will be dowloaded and analyzed to assess medication adherence.

Interventions

1. Melatonin (liquid, immediate release, 3 mg) 30 minutes before bedtime (Appendix N).[58] Reported dosages of melatonin have ranged from 0.75 mg to 15 mg.[5] A 3 mg dose was chosen as Malow et al. found the greatest satisfactory dose response at 3mg.[79]
2. *The Bedtime Bank* protocol (Appendix F).
3. Melatonin+ *The Bedtime Bank* (or The Bedtime Bank+ Melatonin) is a potential treatment option for the Second Stage Treatment Decision (see **Figure 2**).

C. Identify all procedures, interventions, evaluations and tests that are
1) Performed <u>solely</u> for research purposes.

All procedures described above will be performed solely for research purposes.

2) Performed more frequently than they would be if the subject was not participating in the research.
All procedures described above will be performed solely for research purposes.

3) Performed on the subjects in the course of their normal clinical care (i.e. for diagnostic or treatment purposes) where the data are used for research.
N/A

D. Does this research involve genetic testing?
No

E. Will any un-used human biological material (HBM) be used to create a tissue bank for future research?
No

F. Describe briefly the statistical methods used to analyze the data.
Data will be analyzed by the PI, an on-site statistician, and consultants with expertise in SMARTs, with a portion of the PIs training plan devoted to analysis of SMARTs. The pilot will address feasibility (e.g. recruitment/retention, protocol adherence, suitability of primary tailoring variable, other potential tailoring variables, protocol fidelity, and missing data) and acceptability (AARP and semi-structured interview) to prepare the PI for a full-scale SMART.[75,]Pilot SMARTs provide preliminary knowledge about the direction of the effect,[75] and the aims focus on preliminary knowledge; however, conducting formal tests of outcomes or effect size estimation is not justified.[75] We cannot statistically control for age, sex, and race in a pilot SMART, however in the subsequent full-scale SMART, outcomes will be assessed using regression techniques described by Almirall et al.,[88]which will control for age, race, and sex.
Descriptive Statistics: Statistical analyses will be performed using SPSS version 25.0 (IBM Corp., Armonk, NY). Descriptive statistical analyses (mean, median, standard deviation, frequency, and range) will be used to describe demographics, questionnaires (CASQ, PROMIS, & AARP), and *The Bedtime Bank* tracker.
Response: Actigraphy data will be downloaded to a computer and TST will be calculated using an automated algorithm (Respironics Actiware 6, Philips Respironics, Bend, OR) to determine response status of ≥18 minute nightly increase in TST.
For Aim 1 & 2: Analysis of these aims will be the proportion of treatment responders within each subgroup.
For Aim 3: Salimetrics laboratory (Carlsbad, CA) will perform DLMO analysis and provide the PI with results, including baseline melatonin concentration (pg/mL). The relationship of baseline melatonin and response rate to the melatonin-only, as well as treatment acceptability (AARP & interview) will be assessed.

G. Indicate the study design/phase by checking the appropriate box(s).
Phase I
Phase I/II
Phase II
Phase II/III
Phase III
Phase IV
♦ Other: Sequential, multiple assignment, randomized trial
Case-Control
Cohort
Cross-sectional
Randomized, parallel group
Randomized, cross-over
Placebo-Controlled
Single Blind
Double Blind
Triple Blind

DRUGS, BIOLOGIC DRUGS AND DEVICES

13. Drugs and Biologic Drugs
A. Does this study involve an investigational drug or biologic drug?
Yes

B. Does this research involve an FDA-approved and marketed drug or biologic drug?
No

14. Devices
A. Does this research involve an investigational device?
No

B. Does this research involve an FDA-approved and marketed device?
No

CONFIDENTIALITY AND PRIVACY

15. Confidentiality and Privacy
A. Will research data be stored:
1) On a secure server at UNMC/TNMC/CH&MC/UNO?

Yes

2) On a local hard drive?
No

3) On a portable computer?
Yes

a) Is the portable computer encrypted and password protected?
Yes

4) On a flash drive?
No

5) In a database accessible through the internet?
No

6) In hard copy?
Yes

a) Will the hard copies be stored at UNMC/TNMC/CH&MC/UNO during the conduct of the study (i.e. not the long term storage location)?
Yes

b) Will the hard copies be stored off campus during the conduct of the study (i.e. not the long term storage location)?
No

c) Describe the physical methods to protect the hard copies (e.g. locked file cabinet or locked briefcase).
Participant consents; demographics; AARP, CASQ, and PROMIS questionnaires; sleep diaries; and actigraphy data reports will be completed using a hard copy. These copies will be stored in the primary investigator's office in a locked file cabinet. When transporting documents (e.g. MMI to UNMC) a locked briefcase will be used.

d) Will hard copies ever be transported from one site to another site (on or off campus)?
Yes

i) Describe how the data will be secured during transport.
The primary investigator or study coordinators will directly transport data from the site of data collection to the primary investigator's office where the copies will be stored in a locked file cabinet.

7) Other?
No

B. Will any of the following subject identifiers be recorded (at any time) in association with the research data?
Yes

1) Indicate the subject identifiers that will be recorded:
♦ Name
♦ Postal address information: street address, city, county, precinct, ZIP code
♦ DATES (e.g. date of study visit, date of sample collection, birth, admission, discharge)
♦ Telephone numbers
Fax numbers
♦ Electronic mail addresses
Social Security numbers
Medical Record numbers
Health plan beneficiary numbers
Account numbers
Certificate/license numbers
Vehicle identifiers and serial numbers, including license plate numbers
Device identifiers and serial numbers
Web Universal Resource Locators (URLs)
Internet Protocol (IP) address numbers
♦ Biometric identifiers, including finger and voice prints
Full face photographic images [and any comparable images]
No identifiers will be maintained

2) Will a unique subject identifying number, characteristic or code be used to protect the confidentiality of the data? This includes codes assigned by the investigator to link data to other identifiers like the subject s name or medical record number.
Yes

a) Where will the key, that links the unique subject identification code to the subject s name or other identifier, be stored?

Research data will be linked to patients by ID code only. Each subject will be assigned an ID code for use on all study materials. The only link between a subjects name and ID code will be the consent form. A copy of the consent form will be kept in the PIs research office in a locked file separate from other study materials. All data collected using subject identification numbers and paper forms will be stored in a locked filing cabinet in a locked research office used only by study personnel. Data collected at UNMC will use data encryption technology and the secure firewalls at both sites to ensure privacy during electronic transmission.

3) What is the justification for recording the specific identifiers listed above?

♦ Schedule appointments

Collect continuous clinical information from the medical records

♦ Follow-up with subjects

Link stored tissue with subject identification for it to be withdrawn in the future if requested

♦ Other. Explain. Date of birth is needed for inclusion criteria. Telephone number and/or email address is also needed to follow-up with subjects during participation in the intervention. Semi-structured interviews will be recorded and transcribed.

4) How long will the subject identifiers be maintained in association with the research data?

Participants will be assigned a unique subject identification code in order to ensure that any demographic information obtained will not compromise confidentiality. Data will be retained for up to 7 years after the study. This pilot SMART will provide preliminary knowledge for use in a subsequent full-scale SMART.

5) How will the research data be archived or destroyed when the data is no longer required?

Data will be retained for up to 7 years after the study, as this pilot SMART will provide preliminary knowledge for use in a subsequent full-scale SMART. After 7 years, the research data will be destroyed (e.g. hard copies will be shredded and ITS will remove research data from the investigator's computer).

6) Will research data that contain subject identifiers be disclosed to any other investigators at UNMC, TNMC, UNO or CH&MC who are <u>not</u> listed in Section I of this application?

No

7) Will research data that contain subject identifiers be disclosed to any investigators <u>outside</u> of UNMC, TNMC, UNO or CH&MC?

No

8) Will research data that contain subject identifiers be disclosed to any commercial sponsor, contract research organization (CRO) or Data and Safety Monitoring Board (DSMB)?
No

9) Will research data that contain subject identifiers be disclosed to any other external organization or entity (e.g., NCI cooperative groups)?
No

10) Will research data be shared with third party payers?
No

C. What provisions will be in place to protect the subject's privacy? Check all that apply.
♦ Obtaining consent in a private conference room or area
♦ Ensuring that only personnel listed on the IRB application Section I.3(A-E) are present during the consent process
♦ Ensuring that the fewest number of individuals possible are aware of the subject's participation in the research.
♦ Ensuring that the research activities are performed in as private of a place as possible
Other. Explain.

D. Does this research involve data banking at UNMC, TNMC, UNO or CH&MC for future research that is not related to this study?
No

E. Does this research involve data banking by an outside organization (e.g. NCI Cooperative Group, pharmaceutical company) for future, unspecified research that are not integral to the current research?
No

RISK/BENEFIT ASSESSMENT

16. Potential Risks
What are the potential risks associated with each research procedure, intervention, evaluation and/or test? If data are available, estimate the probability that a given harm may occur and its potential reversibility.
There are minimal risks associated with this study. Patients will be informed during enrollment that salivary testing is used for research purposes only.

Risk for collecting saliva: The risk of collection of saliva for melatonin analysis is minimal. To avoid any psychological stress regarding salivary specimen collection, participants will be provided with in-person instructions with return demonstration and written instructions, as well as the investigator's contact information if any questions should arise during sample collection.

Risk for collecting urine: The risk of urine collection for melatonin analysis is minimal. To avoid any psychological stress regarding urinary specimen collection, participants will be provided with in-person instructions with mock return demonstration and written instructions, as well as the investigator's contact information if any questions should arise during sample collection.

Risk for completing questionnaires: There is the potential for psychological risk in that the adolescent and the adolescent participants parents will be asked to identify concerns and answer questions regarding the adolescents sleep characteristics that may make the person feel uncomfortable. However, this risk should be no greater than the discomfort parents are normally exposed to due to their adolescents sleep-related problems. Questionnaires were pilot tested and required 7-10 minutes to complete. At each visit, it is estimated it will take the participant about 7-10 minutes to complete the questionnaires. We have private consultation rooms in the clinics that will be used by participants during completion of the questionnaires, and the participants can take breaks if needed.

Risk for wearing research device: Generally, the risk of wearing research devices is minimal. There is no contraindication to wearing an actigraph. It is possible that participants may find the actigraph uncomfortable to wear. If the research participants feel uncomfortable wearing the research device, they have the right to withdraw from the research at any time.

Risk for sleep interventions:
The Bedtime Bank: In a feasibility study (181-16-EP), the UNMC IRB deemed our behavioral sleep intervention, The Bedtime Bank, minimal risk. There is the potential for psychological risk in that the adolescent and the adolescent participants parents will be asked to track the adolescents' sleep characteristics that may make the person feel uncomfortable.
Melatonin: Generally, the risk of administering 3 mg of melatonin, 30 minutes before bedtime is minimal. A recent review of twenty clinical studies that used exogenous melatonin found that most studies specifically reported that exogenous melatonin was not associated with any side effects.[8,60] Although of low incidence, side effects of melatonin in children may include: daytime sleepiness, headaches, dizziness, increased enuresis,

irritability, abdominal pain, and diarrhea.[8,60]

17. Risk Classification
What is the overall risk classification of the research?
♦ Minimal risk
Greater than minimal risk
Significant risk

18. Minimization of Risk
A. Will the research utilize procedures already being performed on the subjects for diagnostic or treatment purposes?
No

B. Describe how the subjects of the research will be monitored by the investigators and other research personnel to ensure their safety.
Monitoring study safety will occur from the initial screening, throughout the informed consent process, and through study completion. Weekly monitoring of participants (telephone check-in) and internal monthly quality audits of protocol fidelity will occur. Any adverse events will be reviewed in real time according to University policy. Follow-up visits to analyze and discuss treatment acceptability will be scheduled every four weeks throughout the eight-week study, for a total of three visits. During this time, any stress or discomfort encountered as a result of the study will be discussed. The PI and study coordinators will also be available to the study participants via phone or email should the participants or their parents have any questions or concerns regarding the study.

C. Describe the process by which the PI will be informed and how the PI, in turn, will inform other research staff about events concerning subject safety (including (a) interim results; (b) adverse events; (c) unanticipated problems involving risks to subjects or others; (d) noncompliance; (e) complaints).
1) At UNMC/TNMC/CH&MC and/or UNO (check all that apply).
Not applicable. The PI is the only person listed in Section I of the IRB Application.
♦ By email or campus mail (for events which do not constitute immediate subject safety hazards)
♦ By phone
♦ By in-person meeting
By scheduled submission of case report forms
Other. Explain.

2) At external study sites under the oversight of the Joint Pediatric IRB as applicable

(check all that apply).
By email or mail (for events which do not constitute immediate subject safety hazards)
By phone
By in-person meeting or teleconference
By scheduled submission of case report forms
♦ Other. Explain. N/A

D. Describe the auditing plan for research conducted:
1) Within the Organization (UNMC, TNMC, UNO or CH&MC), identify who will conduct the audits and specify the audit frequency.
Prior to the accrual of human subjects, a detailed data and safety monitoring plan will be submitted to the UNMC IRB and to the funding agency for approval (See final DSMP plan dated 12/31/18).The monitoring of compliance for the proposed procedure will be done by the UNMC IRB, the mentoring team (Drs. Ellis, Berger, Kuhn, and Mathews), and a Data Safety Monitoring Board (DSMB). UNMC has two standing DSMBs. One is for any cancer related study, and one is for non-cancer studies. The non-cancer DSMB includes several members experienced with clinical research and clinical trials, including biostatistics expertise and a research subject advocate. The principal investigator Dr. Hanish has identified a content expert (Dr. Bunny Pozehl) for this DSMB who is independent of the study team. The PI will provide written reports of progress and compliance every 6 months to the DSMB. The DSMB will set up meetings and prepare minutes and responses to the study team for the duration of the study. Each report will include monitoring of: compliance with informed consent and eligibility requirements, recruitment plan according to protocol, follow-up data collection according to protocol, expected and actual accrual, protocol violations, and patient withdrawals from the study. Adverse events encountered by the research team will be reported to the PI immediately. Per University policy, all serious adverse events (AE) will be reported to the UNMC IRB within two business days after the PI is notified of the AE. Any fatal adverse events will be reported immediately according to institutional policies. Results of the monitors reports will be provided in writing to the PI and discussed as needed within 1 month (or less if the situation requires). All deviations from protocol and adverse events will be reviewed by the PI, co-investigators, and senior nurse scientists to identify if follow-up action is need (e.g., protocol tightening or consequent IRB changes).

2) At external study sites under the oversight of the Joint Pediatric IRB, identify who will conduct the audits and specify the audit frequency.
N/A

E. Is there is an independent DSMB for this study?
Yes

Will you be submitting the DSMB charter?
Yes

F. Describe the specific criteria by which the investigator would withdraw individual subjects from the research (for example, medical criteria, such as specific toxicity or lack of efficacy or non-medical criteria, such as non-compliance).
The investigators will withdraw individual subjects from the research if they no longer meet inclusion/exclusion criteria. Individual subjects will also be withdrawn from the research by investigators if the participating adolescent or his/her parent(s) withdraws consent to participate at any time.

G. Describe the specific criteria for halting or early termination of the study (for example statistical evidence of unacceptable toxicity or early demonstration of efficacy or lack of efficacy).
Monitoring study safety will occur from the initial screening, throughout the informed consent process, and through study completion. Weekly monitoring of participants (telephone check-in) and internal monthly quality audits of protocol fidelity will occur. Any adverse events will be reviewed in real time according to University policy. The research will be terminated if, for any reason, it appears that the participants are at risk. The research will also be terminated if the parent of the participant (or the participant him/herself) expresses desire to discontinue to the investigator.

H. Describe plans and resources available to promptly address any subject injury.
Dr. Hanish (PI) will be responsible for ensuring that all adverse events and unanticipated problems are reported to the senior nursing scientist assigned as co-mentor (Dr. Ann Berger), the University of Nebraska Medical Center Institutional Review Board, and the NIH. Per University policy, all serious adverse events (AE) will be reported to the UNMC IRB within two business days after the PI is notified of the AE. Any fatal adverse events will be reported immediately according to institutional policies.

19. Potential Benefits to the Subject
Are there potential benefits to the subjects that may reasonably be expected from participation in the research?
Yes

Describe.
This study has the potential to increase total sleep time in adolescent participants. This study could have positive effects on the adolescent's sleep habits, as well as his or her family's quality of life.

20. Potential Benefits to Society

What are the anticipated benefits (i.e., value) to society that may reasonably be expected to result from this research?

The high prevalence of sleep disturbances in children and adolescents with neurodevelopmental disorders and the negative long-term consequences of sleep disturbance create a critical need for a personalized approach to determine effective sleep interventions and the optimal treatment for sleep disturbances. Knowledge gained from this study will contribute our long-term goal of developing evidence-based guidelines for sleep interventions for children and adolescents currently experiencing or at-risk for sleep disturbances.

21. Alternatives to Participation

A. How do the study procedures or courses of treatment differ from the care that the subject might receive were he/she not to participate in the research?

The research is different from standard care in that the participants will be required (if applicable) to discontinue their usual dose of melatonin for at least 2 months prior to enrollment in the study. It is also required that participants be either medication-free or on a stable dose of medications (no changes within 30 days prior to enrollment) with parental agreement to avoid changes in current medications (unless provider directed) during study participation. The participants will also wear their actigraph for 24 hours/day for a total of 9 weeks during the conduction of the study.

B. Are there any reasonably available alternatives in the non-research context which would have the potential for providing the same benefits (treatment or other) to subjects?

Not applicable. There are no direct benefits to subjects; the alternative is to not participate in the research.

♦ Yes. Describe: Participants could choose to take melatonin outside of the research study, as it is readily available over-the-counter.

No. Explain:

C. Would any of the study procedures or courses of treatment in the protocol be available to the prospective subject if they elected not to participate?

Yes

Explain.

Given that melatonin can be obtained over-the-counter at many retail locations and that many other behavioral models pertaining to sleep exist, study subjects could reasonably attempt the study interventions on their own should they choose not to participate. In spite of this, subjects would lack the actigraphs and corresponding software used in this study to

objectively analyze the effects of these interventions on sleep. Endogenous melatonin levels are not readily available clinically.

D. How do the risks of the research compare with the risks of alternative procedures or courses of treatment described above?
Generally, the risk of administering 3 mg of melatonin, 30 minutes before bedtime is minimal. A recent review of twenty clinical studies that used exogenous melatonin found that most studies specifically reported that exogenous melatonin was not associated with any side effects.[8,60] Although of low incidence, side effects of melatonin in children may include: daytime sleepiness, headaches, dizziness, increased enuresis, irritability, abdominal pain, and diarrhea.[8,60]

E. How do the anticipated benefits of the research compare with the benefit of alternative procedures or courses of treatment described above?
Due to potential concerns of reported variability in reported melatonin dosage[89], confirmation of laboratory assayed melatonin dosage will be obtained. Participants may benefit from the consistent dose and quality of the melatonin provided during the study, when compared to traditional over-the-counter melatonin.

FINANCIAL OBLIGATIONS AND COMPENSATION

22. Financial Obligations of the Parent(s)/Guardian(s) of the Subject
A. Who will pay for procedures and treatments performed solely for research purposes?
Sponsor
♦ Grant
CRC, CCTR
Costs or fees waived by TNMC, UNMC- P, CH&MC or CSP
Subject's health insurance
Medicare/Medicaid
Department/Section funds
Other. Explain.
Parent(s)/guardian(s).

B. Are there any other financial obligations that the parent(s)/guardians of the subject will incur as a result of participating in the study (e.g. travel expenses, meals, supplies)?
No

23. Compensation to the Subject for Participation

Will the subject and/or their parent(s)/guardian(s) receive any compensation for participation?
Yes

Describe the form of compensation, dollar amount (if applicable) and the prorated compensation plan (if applicable).
Compensation will be provided in the form of gift cards. Subjects will receive $40 for each outcome, data collection (baseline, 4 weeks, & 8 weeks) for a total of $120. Subjects will receive an additional $30 for participating in the baseline salivary melatonin measurement. If participants choose to participate in urinary melatonin collection, they will be compensated an additional $10. If parents choose to participate in parental actigraphy monitoring and resulting questionnaires and sleep diary completion, they will be compensated an additional $20 for each outcome (baseline, 4 weeks, & 8 weeks) for a total of $60. Subjects will receive total possible compensation for SMART feasibility trial of $220. Compensation will occur at each visit (following baseline, first stage, and second stage).

PRIOR REVIEW

24. Prior IRB Review
A. Has this study (or one substantially similar) been previously submitted to the Joint Pediatric IRB (or the UNMC IRB) and then withdrawn by the investigator for any reason?
No

B. To the best of your knowledge, has this study (or one substantially similar) been considered by another IRB and not granted approval?
No

SUBJECT IDENTIFICATION & RECRUITMENT

25. Method of Subject Identification and Recruitment
A. Will prospective subjects be identified through initial contact by the investigator?
Yes

1) Identified through (check all that apply):
♦ Clinic
Hospital inpatient units
Previous research participants
Investigator, clinic or hospital-maintained databases or registries

♦ Other. Explain. A Facebook post will be uploaded through UNMC and MMI's Facebook page as a means to advertise the study and recruit participants. The advertisement will target Nebraska and Iowa men and women who are parents of pre-teens and teens.

2) Describe how the research staff has ethical access to the potential subjects.
A convenience sample of 40 adolescents diagnosed with NDDs and 40 parents (or legal guardians) of adolescents (1 parent per adolescent) will be recruited through UNMC MMI, MMI satellite clinics, CHMC, and CHMC clinics, in addition to social media. A flier will be distributed with study contact information at or near the clinic check-in desks or an approved location for study fliers. Participants may contact the investigators directly if inquiring through a posted flier. Potentially eligible participants will be identified in clinic by Dr. Ellis, Dr. Mathews, Dr. Hanish or UNMC MMI/CHMC staff who have ethical access to the population and obtain permission for the researcher to contact them. Dr. Hanish (PI) will contact potential participants in-person at regularly scheduled clinic visits or over the telephone. The research staff may provide study-related information to potential subjects during clinic; however, subjects will initiate subsequent contact with the investigators if interested in additional study-related information.

B. Will prospective subjects make the initial contact with the research personnel to inquire about the study?
Yes

1) Identified through (check all that apply):
♦ Referral by clinician or other parties specifically for the research
♦ Flier
Newspaper advertisement
Television spot
Radio announcement
♦ Word of mouth
Public UNMC study database
♦ Other. Explain. A Facebook post will be uploaded through UNMC and Munroe Meyer's Facebook page as a means to advertise the study and recruit participants. The advertisement will target Nebraska and Iowa men and women who are parents of pre-teens and teens.

C. Will this study be listed in the clinical trial registry at www.clinicaltrials.gov?
Yes

Provide the NCT number.

NCT03730194

OBTAINMENT OF INFORMED CONSENT

26. Waiver or Alteration of Informed Consent
Is a waiver or alteration of consent requested for either 1) all of the subjects or 2) a subset of subjects?
No

27. Waiver of a Signed Consent Form
Is a waiver of the requirement to obtain a signed consent form requested?
No

28. Process of Permission (Informed Consent) for Parent(s)/Guardian(s)
A. When will the parent(s)/guardian(s) of the prospective subject be approached relative to their child's actual participation in the study?
Parent(s) of the children will be approached first to determine their interest. If the parent expresses further interest in participating in the study, the investigator will set up a date and time convenient to the parent to meet one-on-one at UNMC, MMI, CH&MC, or to converse over the phone to further explain the study.

B. Where will informed consent be obtained, and how will the environment be conducive to discussion and thoughtful consideration by the parent(s)/guardian(s)?
Informed consent will be obtained in a private room located in the UNMC Center for Nursing Science (4th or 5th floor) or MMI (located on the 3rd floor of the psychology department), via a telephone call, or through Zoom video conferencing technology. The UNMC Center for Nursing Science and MMI are convenient locations and will provide parent(s) the opportunity to ask questions in a private setting. A telephone call or Zoom video conferencing technology will provide the same level of privacy for parent(s) and participants, and will allow for participation if in-person visits are not possible (in the case of a state of emergency) or if the participant resides in a geographic location, such as a rural community, that is not within feasible driving distance to UNMC.

C. Who will be involved in the process of consenting the parent(s)/guardian(s) about their child's participation in the study and what are their responsibilities?
The principal investigator (Dr. Alyson Hanish) or study coordinators (Abbey Klein and Danielle Stappert) will be involved in the consent process, including explanation of the research, training procedures, and participant question/concerns.

D. How much time will be allotted to the process of consent?

The parent(s) will be scheduled for a meeting within two weeks of their expressed interest in study participation. The consent process is anticipated to take approximately 10 minutes, but an additional 20 minutes will be allotted to allow time for participant questions (total of 30 minutes allotted).

E. How will the process of consent be structured for parent(s)/guardian(s) who are likely to be more vulnerable to coercion or undue influence?
Both the primary investigator and study coordinators have completed CITI training and are aware of the ethical considerations in obtaining informed consent. Additional protections during the consent process may include a subject advocate, involvement of subject's family or friends,use of teaching aids, and allotment of ample time for questions or concerns.

F. Will non-English speaking subjects be enrolled in this research and/or will non-English speaking parent(s)/guardians be consenting for the prospective subject?
No

Provide justification for why non-English speaking subjects will be excluded.
Non-English speaking subjects will not be recruited at this time because the sleep questionnaires and the Bedtime Bank are available only in English.

G. How will it be determined that the parent(s)/guardian(s) understood the information presented?
Parents will be given a flier along with the consent form, and they will have an opportunity to meet with the principal investigator or study coordinators, either face-to-face or using telephone/video conferencing technology, to further review the study information. Parents will also be provided with contact phone numbers should they have any further questions or concerns. Parents will be asked to paraphrase the nature of the research, methods, and study risks and benefits, as well as that participation is voluntary.

H. Will there be a formal process of on-going re-consent (over and above re-consent associated with changes in protocol)?
No

29. Process of Obtaining Assent From the Child
A. Will the investigator ask children and adolescents to assent to participate in the research?
Yes

B. How will it be determined that the child understood the information presented?
Adolescents will be given a flier along with the consent form, and they will have an

opportunity to meet with the principal investigator or study coordinators, either face-to-face or using telephone/video conferencing technology, to further review the study information. Adolescents will also be provided with contact phone numbers should they have any further questions or concerns. Adolescents will be asked to paraphrase the nature of the research, methods, and study risks and benefits, as well as that participation is voluntary.

C. Will children reach the age of majority (i.e., 19 years old) during the course of the study?
No

30. Consent Forms and study information sheets
Indicate the type of consent forms and study information sheets to be used in this research:
♦ Parental/Guardian consent form
♦ Youth Study Information Sheet
Child Study Information Sheet
Screening consent form
Addendum consent form
Adult consent form
Other:

31. Documentation of Consent and Assent
List who will sign the consent form as the "Person Obtaining Consent".
Hanish, Alyson E

Klein, Abbey Jo

32. Information Purposely Withheld
Will any information be purposely withheld from the parent(s)/guardian(s) of the subject or the subject during the research or after completion of the research?
No

RESOURCES

33. Describe the resources available to safely conduct this study at <u>each</u> study site specified in Section I.7.
All necessary equipment has been secured prior to IRB submission. All actigraphs are being stored in the office of the PI, and a computer that has the necessary actigraphy data

analysis software is available for use on the 5th Floor of the Center for Nursing Science at UNMC.

Informed consent will take place in a private room at either UNMC or MMI.

Both the primary investigator and the study coordinators have the ability to promptly respond to unanticipated problems.

LITERATURE REVIEW

34. References

Provide a full listing of the key references cited in the background (Section II.3). The references should clearly support the stated purpose of the study.

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SECTION III

SUBMISSION DEADLINE

A. Full Board Review:
The IRB meets monthly, on the fourth Tuesday of the month. No more than 15 applications (i.e., initial review of a new study, re-review of a tabled study) will be reviewed at each meeting. All reviews are performed on a first-come first-served basis. The IRB meeting schedule and deadline dates can be found on the IRB website at www.unmc.edu/irb**.**

B. Expedited Review
Applications that qualify for expedited review have no submission deadline and can be reviewed independent of the IRB meeting schedule. Please call the Office of Regulatory Affairs for assistance in determining if your study meets the requirements for expedited review.

SUBMISSION CHECKLIST

Check all that apply.
♦ Subject recruitment material
♦ Pharmacy and Therapeutics (P&T) Committee Investigational Drug Study Registry and/or Marketed Drug Form
Investigational Device Review Committee (IDRC):): Review by the IDRC is required for all protocols involving the use of investigational or marketed devices.
For studies conducted at CH&MC: Performance site approval for all non-UNMC, TNMC, UNO and CH&MC sites
For studies conducted at CH&MC: Copy of all questionnaires, surveys, assessment tools, and other relevant materials
For studies conducted at CH&MC: Clinical Trial Master Matrix as required by UNMC and TNMC.
For studies conducted at CH&MC: Detailed protocol
For studies conducted at CH&MC: Investigator's brochure
For studies conducted at CH&MC: Grant Application
For studies conducted at CH&MC: IRB Review Fee Form for all commercially sponsored research projects.
For studies conducted at CH&MC: UNMC Disclosure of Potential Conflict of Interest Form for the Principal Investigator if a financial interest has been declared in Section I.10.
For studies conducted at CH&MC: UNMC Disclosure of Potential Conflict of Interest Form for any responsible personnel with a financial interest declared in Section I.10.

♦ Other Appendix G, I, K, L, P, C, E, J, M, N,O
No attachments

ADDITIONAL REVIEW REQUIREMENTS

Final IRB approval and release of studies is contingent upon approval by the following UNMC committees or departments. Check the appropriate boxes:
Pharmacy and Therapeutics (P&T) Committee: Review by the P&T Committee is required for all protocols involving the use of investigational or marketed drugs.
UNMC Eppley Cancer Center Scientific Review Committee (SRC): Review by the SRC is required for all protocols involving cancer patients.
Institutional Biosafety Committee (IBC): Review by the IBC is required for all protocols involving the use of gene transfer and vaccines.
Radioactive Drug Research Committee (RDRC): Review by the RDRC is required for all protocols involving the use of a radio-labeled drug for which the investigator or the institution holds the IND.
Sponsored Programs Administration (SPA)/Office of Regulatory Affairs: For commercial sponsored studies, the consent form and contract will be compared for consistency by the ORA. Final IRB approval and release is contingent upon completion of a signed contract, verified by SPA, for all commercially sponsored research.
Conflict of Interest Committee (COIC): All responsible personnel listed in I.3A-E of the IRB application (i.e., PI, Secondary Investigator, Participating Personnel, and Coordinator(s)) must disclose **any** financial interest in the research (see Section I.10 of this application). Data and Administrative Personnel are exempt. The COIC will review any financial interest which is classified as significant.
Investigational Device Review Committee (IDRC): Review by the IDRC is required for all protocols involving the use of investigational or marketed devices.
Other Review
♦ **No Additional Reviews Required**

ADDENDUM Q
Investigational New Drugs or Biologic Drugs

Title of Protocol

A SMART Design to Improve Sleep Disturbance in Adolescents with Neurodevelopmental Disorders

Principal Investigator

Hanish, Alyson E - CON-Omaha Division - 402-559-6731 - alyson.hanish@unmc.edu

A. Investigational New Drugs and Biologic Drugs

1. Does this research involve an investigational drug or biologic drug?

No

B. Investigations Using FDA-Approved and Marketed Drugs or Biologic Drugs

1. Does this research involve an investigational use of an FDA-approved and marketed drug or biologic drug?

No

ADDENDUM Y

Research Involving Adults as Subjects Participating in a Pediatric Trial

Title of Protocol

A SMART Design to Improve Sleep Disturbance in Adolescents with Neurodevelopmental Disorders

Principal Investigator

Hanish, Alyson E - CON-Omaha Division - 402-559-6731 - alyson.hanish@unmc.edu

Waiver of Alteration of Informed Consent

Is a waiver of alteration of consent requested?

No

1. Capacity to Consent

a. At the time of initial consent, will all subjects have the capacity to give informed consent?

Yes

b. Is there a reasonable likelihood that some subjects may lose the capacity to continue to provide informed consent during the course of the study?

No

2. Process of Informed Consent for Competent Adult Subjects

a. When will the prospective subject be approached relative to their actual participation in the study?

Parent(s) of the children will be approached first to determine their interest. If the parent expresses further interest in participating in the study, the investigator will set up a date and time convenient to the parent to meet one-on-one at UNMC, MMI, CHMC, or to converse over the phone to further explain the study.

b. What is the location where informed consent will be obtained, and how will the environment be conducive to discussion and thoughtful consideration?

Informed consent will be obtained in a private room located XXX. This is a convenient location and will provide parent(s) the opportunity to ask questions in a private setting.

c. Who will be involved in the process of consent and what are their responsibilities?

The principal investigator (Dr. Alyson Hanish) or study coordinators (Abbey Klein and Danielle Stappert) will be involved in the consent process, including explanation of the

research, training procedures, and participant question/concerns.

d. How much time will be allotted to the process of consent?
The parent(s) will be scheduled for a meeting within two weeks of their expressed interest in study participation. The consent process is anticipated to take approximately 10 minutes,but an additional 20 minutes will be allotted to allow time for participant questions (total of 30minutes allotted).

e. How will the process of consent be structured for subjects who are likely to be more vulnerable to coercion or undue influence?
Both the primary investigator and study coordinators have completed CITI training and are aware of the ethical considerations in obtaining informed consent. Additional protections during the consent process may include a subject advocate, involvement of subject's family or friends,use of teaching aids, and allotment of ample time for questions or concerns.

f. Will non-English speaking subjects be enrolled in this research?
No

Provide justification for why non-English speaking subjects will be excluded.
Non-English speaking subjects will not be recruited at this time because the Bedtime Bank is currently developed in English.

g. How will it be determined that the subject understood the information presented?
Parents will be given a flier along with the consent form, and they will have an opportunity to meet with the principal investigator or study coordinators to further review the study information. Parents will also be provided with contact phone numbers should they have any further questions or concerns. Parents will be asked to paraphrase the nature of the research, methods, and study risks and benefits, as well as that participation is voluntary.

h. Will there be a formal process of *on-going* re-consent (over and above re-consent associated with changes in protocol)?
No

3. Consent and Assent Forms
Indicate the type of consent forms and/or study information sheets to be used in this research:
♦ Adult consent form
Legally authorized representative (LAR) consent form
Adult study information sheet

Screening consent form
Addendum consent form
♦ Other. Explain. Adolescent Assent Form