Title: A Feasibility Study to Determine the Effects of a Novel Mattress Support for Treatment of Positional Obstructive Sleep Apnea at Home

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Not applicable

IDE: non-significant risk (NSR) investigational device that meets the abbreviated Investigational Device Exemptions (IDE) requirements at 21 CFR 812.2(b)

SPONSORING ORGANIZATION: Hill-Rom Co., Inc.

I. Objectives

1) Determine the effects of a mattress support (Wave 4.3) that promotes the avoidance of supine airway position at home on the apnea-hypopnea index (AHI) in patients with positional obstructive sleep apnea (OSA).
2) Determine the effects of Wave 4.3 on subjective measures of sleepiness and daytime function in patients with positional OSA.
3) Determine the effects of Wave 4.3 on subjective measures of sleep quality in patients with positional OSA.

The risks associated with this study are minimal compared to the potential benefits. Knowledge about the effects of a simple mattress support that promotes the avoidance of supine position at home would be an important advance in the care of these patients, since currently established treatments such as continuous positive airway pressure (CPAP) and mandibular advancement device (MAD) have limitations in terms of treatment adherence.

II. Background and Rationale

Obstructive sleep apnea (OSA) is a major public health problem that affects millions of Americans.[1] The condition is characterized by repetitive upper airway obstructions during sleep causing oxyhemoglobin desaturations, hypercapnia, arousals and increases in sympathetic tone.[2] OSA causes daytime sleepiness and impairs daytime function.[3-5] OSA is associated with a variety of adverse health, economic, and safety consequences that includes hypertension, stroke, cardiovascular disease, diabetes, motor vehicle crashes, reduced work performance, and increased healthcare utilization.[6-11] The first line treatment for OSA is CPAP.[12] However, patient adherence to CPAP is a major problem. An estimated 50% of patients do not use the device at least 4 hours per night (the recommended minimum hours of nightly use).[13] Mandibular advance devices (MAD) are also utilized for OSA treatment, but this form of therapy is limited by patient suitability, adherence, and efficacy.[14] Therefore, alternative treatments are needed in the treatment of OSA.

As an alternative to CPAP and MAD, patients with positional obstructive sleep apnea (POSA) may be candidates for therapies that are designed to prevent the supine posture during sleep, ie, positional therapy.[15] POSA is said to be present when there is a reduction in the AHI during non-supine sleep compared to supine sleep.[16] Approximately 30% of patients referred to sleep medicine clinic have positional OSA.[17] We, and others, have shown that positional OSA is very common in those with mild to moderate disease as defined by an AHI < 30 events/hr based on polysomnography (PSG).[16,17] Frank and colleagues proposed a new classification system for individuals with POSA called the Amsterdam Positional OSA Classification (APOC) in an attempt to have a universal definition of the condition.[18,19] POSA include patients who have a total AHI >5/hr and spend >10% time in the supine and non-supine positions, and are classified as: APOC I if the AHI is <5/hr in the nonsupine position, APOC II if the total AHI is 5-40/hr and the non-supine AHI is reduced by 50% but remains >5/hr, and APOC III if the total AHI is >40/hr and the non-supine AHI is reduced by 25-50%.[18]

Currently, there are several strategies that are used to avoid the supine position during sleep. These include simple instructions to avoid the supine position, use of tennis ball sewn on a pajama top, and devices that are worn during sleep that vibrates whenever the supine posture is detected.[15,20-22] These techniques are limited by poor compliance (tennis ball technique), concerns about sleep disruption due to the vibrations, and absence of long-term efficacy data.[20,21,23] Therefore, investigation of other treatment options is needed for the treatment of POSA.

Wave 4.3 is a novel device that has been developed by the Hill-Rom Early Innovation team (Hill-Rom, Batesville, IN) for treatment of OSA that occurs in the supine position. The investigational device in the proposed study is a non-significant risk (NSR) device that is designed to be used as a mattress support at home and with any combinations of sleep pillows, bed linens, and bed clothes. Hill-Rom performed initial testing on this device, and Hill-Rom's Executive Director of Medical Safety believes this device poses minimal to no risk to patient safety.

III. Procedures

A. Research Design

This is a feasibility study of sleeping at home with and without the novel mattress support (Wave 4.3) for two consecutive weeks in patients with POSA. Informed consent will be obtained from all participants.

B. Subject Selection:

1. Inclusion/Exclusion Criteria

A. Key Inclusion Criteria

We will recruit subjects who are:

- 18-75 years of age
- Willing and able to give informed consent
- Able to speak and understand English
- Previous sleep study prior to enrollment done based on previous clinical evaluation by the subject's treating physician in the course of usual clinical care:
    a. overall AHI 5-40 events/hr.
    b. at least 10% time spent in the supine and 10% time in the non-supine positions.
    c. APOC I and APOC II
    d. central respiratory events < 50% of the total number of apneas and hypopneas
- Using at least a queen-sized mattress when sleeping at home

- Patients who meet the above criteria who have been prescribed CPAP or dental device but are non-adherent to treatment will be enrolled in the study. CPAP non-adherence will be defined as average nightly use < 4hrs/night

based on a download of the CPAP machine, or self- acknowledged discontinuation or non-regular of CPAP use.

- Patients who meet the above criteria who have been prescribed CPAP or dental device but are adherent to treatment will be enrolled in the study provided that: a) they are willing to use the Wave device instead of their CPAP or dental device for the duration of the study, and b) they do not have severe OSA defined as an AHI > 30 events/hr in their clinical sleep study.

B. Key Exclusion Criteria

- Incapable of giving informed consent
- Under the age of 18
- Active titration of medication
- Pregnancy, lactation (will be screened with urine pregnancy test)
- Self-reported Substance abuse (current)
- Excessive alcohol consumption
    - Excessive alcohol use is defined as:
    - More than 3 glasses of wine a day
    - More than 3 beers a day
    - More than 60 mL of hard liquor a day
- Use of home oxygen
- Presence of severe daytime sleepiness defined as an Epworth sleepiness scale score ≥ 16 or a prior history of falling asleep while driving
- Presence of cardiac pacemaker or automatic implantable cardioverter-defibrillator (AICD).
- Unstable medical problem such as uncontrolled hypertension.
- Body Mass Index (BMI) >45 kg/m^2
- Any other clinically significant condition that, in the opinion of the investigators, might put the subject at risk of harm during the study or might adversely affect the interpretation of the study data.

2. Screening Procedures

A screening visit will be scheduled to determine eligibility. A separate informed consent for the purpose of screening potential candidates will be obtained. Female patients of childbearing potential will be required to have a negative pregnancy test result at screening.

After their study participation has ended, those with an AHI ≥5/hour based on the HSAT will be referred to their primary care physician or the sleep medicine clinic for treatment discussion using established therapies

3. Vulnerable Populations

- Children, fetuses, neonates, or prisoners are not included in this research study.

4. Populations vulnerable to undue influence or coercion

Cognitively impaired persons are not included in this research study, since the potential subject has to be able to give informed consent. Should an OSU employee or student be approached, they will be given the opportunity and time to consider participation and will be reassured that declining to participate will not jeopardize or hinder their standard of care at the OSU Sleep Disorders Center, nor will it have any bearing on either their student status or employment.

5. Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this study.

C. Study Plan

This is a preliminary single-arm study. The study will last up to 4 weeks including the screening period. Subjects will sleep using the mattress support at home for two consecutive weeks.

Outcome measures will include: AHI derived from HSAT (primary outcome), oxygen desaturation index (ODI), Epworth Sleepiness Scale (ESS) score, Functional Outcomes of Sleep Questionnaire (FOSQ), Visual Analog Scale (VAS) and questionnaire assessments of sleep quality, and actigraphic sleep measures. Subjects will also keep a sleep diary every night for the duration of the study. Subjects will be asked about their bed partners' report on snoring and witnessed apneas.

Visit 1: Screening Visit and Procedures

A separate informed consent for the purpose of screening potential candidates will be obtained.

Instead of an in-person visit, the participant consent for the purpose of screening will be conducted using a REDCap-based electronic consent form for those who are willing and able to do this. The consent form will be developed in REDCap, a secure, web-based, HIPAA-compliant, data collection platform with a user management system allowing project owners to grant and control varying levels of access to data collection instruments and data (e.g. read only, de-identified-only data views) for other users. Potential participants will participate in the consent process by:

- Being approached in-person at The Ohio State University and accessing the REDCap survey via iPad or other portable electronic device and/or
- Self-initiated access of consent forms on personal portable electronic devices using posted QR codes or web-links on study posters, brochures, or websites. Self-initiated accessing of consent forms may occur at The Ohio State University campus or at home.
- Participant signatures will be obtained using a typed name. Upon completion of the consent encounter, participants will be provided with a copy of the consent document by printing a pdf copy of the consent form.
- During the in-person consent process, consent will be obtained by a member of the study team. For self-initiated consent, contact information will be provided (email and phone) for prospective participants to contact a member of the study team with questions, prior to consent.

- After the screening consent has been signed, female patients of childbearing potential will be required to have a negative pregnancy test result.
- During this visit, the following will also be obtained:
    a. Sleep Questionnaire and Medical History
    b. Medication list
    c. Body Mass Index, neck circumference (NC), blood pressure (BP), resting pulse oximetry, pulse rate
    d. Collect results of the previous clinical sleep study
    e. CPAP adherence, if applicable
    f. Epworth Sleepiness Scale (ESS) score
    g. Instructions on how to use the HSAT equipment at home for one night to obtain the baseline research HSAT study. Those with technically inadequate HSAT will have the study repeated.

- The following are the reasons why subjects may not proceed with the study after screening:

a) No POSA or POSA with APOC III based on the previous clinical sleep study.
b) No POSA or POSA with APOC III based on the baseline research HSAT study.
c) Meets one of the exclusion criteria.
d) Does not meet inclusion criteria.

- **Expected visit length: 60 minutes**
- Participants will be requested to return the HSAT device either in-person or via mail in a pre-paid envelope.

Visit 2

- Those who remain eligible will then sign a separate informed consent for the remainder of the study. REDCap will not be used for the consent process to the main study. The following will be obtained during this visit:

    a. FOSQ
    b. Assessment of sleep quality: VAS and Questionnaire
    c. Actigraphy for duration of the study
    d. Medications changes

- Participants will be given instructions on how to use Wave 4.3 mattress support at home and a phone number to call for the research coordinator for questions. The mattress support will be delivered at the subject's home by professional staff of the sponsor (Hill-Rom) in the presence of the research coordinator or investigator.
- **Expected visit length: 30 minutes**

Visit 3.

- This will occur on the 14th day of sleeping with the mattress support (that is, after night 13). The purpose of this visit is to provide the HSAT device to be used while sleeping with the mattress support.
- Medication changes
- **Expected visit length: 20 minutes**

Visit 4.

- Return HSAT equipment.
- The following will be obtained during this visit:
    a. ESS
    b. FOSQ
    c. Assessment of sleep quality: VAS and Questionnaire
    d. Medication changes
- **Expected visit length: 30 minutes**
- It may be necessary to repeat the home sleep study for another night if data after sleeping with the Wave mattress support is not adequate.

Phone Calls: Phone calls will be made by an investigator or research staff to answer any questions that participants may have (will occur between Visits 2 and 3): after the second night (third day) and seventh night of sleeping on the Wave 4.3 surface.

Mattress support pick-up: The mattress support will be picked up by professional staff of the sponsor (Hill-Rom) in the presence of the research coordinator or investigator at a mutually agreed time.

Visit Schedule

Procedures				
	Visit #			
	1	2	3	4
Screening consent	x			
Study consent		x		
Pregnancy test, if applicable	x			
Clinical Sleep Study Results*	x			
CPAP adherence, if applicable	x			
Sleep Questionnaire and Medical History	x			
Medication list	x			
Medication changes		x	x	x
Height and weight	x			
Neck Circumference	x			
BP, Pulse rate, SpO_2	x			
Provide HSAT Equipment	x		x	
ESS	x			x
FOSQ		x		x

Sleep quality	x		x
Wave instructions	x		
Actigraphy**	x	x	x
Sleep diary**	x	x	x

BP= blood pressure
SpO_2= oxygen saturation by pulse oximetry
HSAT= home sleep apnea test
ESS= Epworth Sleepiness Scale
FOSQ= Functional Outcomes of Sleep Questionnaire
VAS= Visual Analog Scale
*Clinical sleep study is completed per standard clinical care.
** Done while sleeping with Wave Mattress support for 14 days

D. Detailed Procedures

1. Clinical Sleep Study:

Subjects will undergo diagnostic sleep study according to the evaluation of their physician. This is the sleep study performed within the context of usual clinical care that will determine whether subjects meet the criteria for POSA.

2. OSU Sleep Questionnaire and Medical History (15 minutes)

Sleep Questionnaire (Visit 1 only; No need to complete if previously completed the OSU Sleep Disorders Center Questionnaire in sleep clinic)

3. Medication List (5 minutes)

For all subjects we will obtain information about medications they are currently taking, including supplements.

4. BMI, neck circumference, blood pressure, pulse rate, SpO_2 (10 minutes)

Blood Pressure, weight and height measurements (to calculate BMI) will be done during visit 1. We measure the neck circumference at a point just below the larynx (Adam's Apple) and perpendicular to the long axis of the neck. Blood pressure measurement will be done according to the usual standard protocol.

5. CPAP treatment adherence (5 minutes)

CPAP adherence will be obtained from the medical record or downloaded from the subject's machine if they are on CPAP therapy but will not be performed if they self- acknowledged discontinuation or non-regular of CPAP use.

6. Questionnaires (15 minutes)

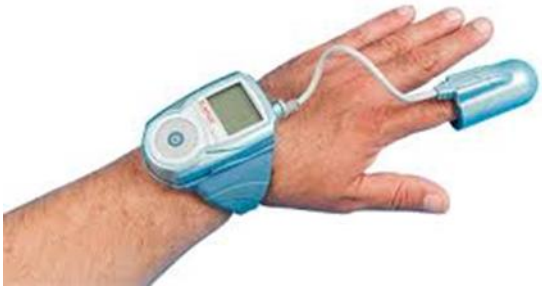
a. Epworth Sleepiness Scale (ESS) score
b. Functional Outcomes of Sleep Questionnaire (FOSQ)
c. Assessment of sleep quality: VAS and Questionnaire

7. Actigraphy

This device is the size of a small wristwatch that measures activity and is a non-invasive method of monitoring human rest/activity cycle. The instructions for the

device use will be provided. The data is then downloaded into a computer. A sleep diary is routinely administered with actigraphy.

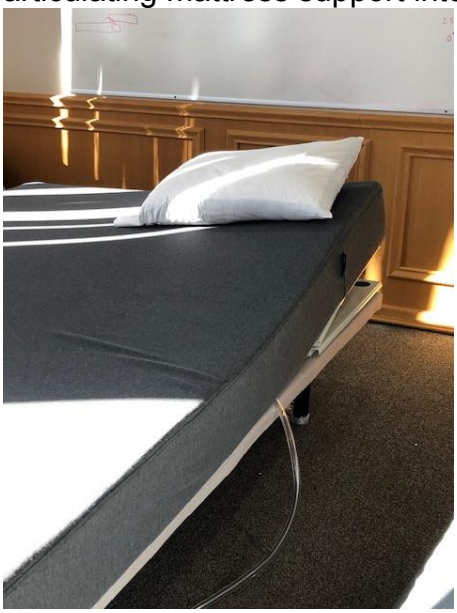
8. HSAT



The home sleep study will be done using the WatchPAT HSAT device (Itamar Medical). The WatchPAT (see Figure) is non-invasive, FDA-approved, has extensive validation, easy to use, with a low rate of study failure.[24] The device monitors peripheral arterial tone as an index of sympathetic activity changes, pulse oximetry, actigraphy, sleep position and snoring. The WatchPAT report includes the AHI (events with 4% desaturation), Respiratory Disturbance Index (RDI) which includes respiratory events associated with 4% desaturations or arousals, ODI, sleep staging identification, snoring level and body position. Data from the WatchPAT will be reviewed for artifacts. Subjects will be instructed on its use at home, shown a video for proper use (https://www.youtube.com/watch?v=VhFd88QM0Io), and provided written instructions.

9. Wave mattress support

The Hill-Rom Early Innovation team has developed a device ("Wave 4.3"), an articulating mattress support intended to treat POSA.



As above, the investigational device is an NSR device that follows the abbreviated Investigational Device Exemptions (IDE) requirements at 21 CFR 812.2(b) addressing labeling, IRB approval, informed consent, monitoring, records, reports, and prohibition against promotion for an NSR device study.

The Wave 4.3 mattress support is an insert, placed underneath the user's existing mattress, that when inflated increases the longitudinal incline of the mattress support, increasing in inclination in the direction of the head of the bed. The resulting mattress contours are such that the mattress has a lateral inclination of approximately 15 degrees in the head section and 10 degrees in the torso section. In addition to the features allowing the user to activate and deactivate creation of this Graduated Lateral Rotation™ orientation, this device has sensors and monitoring system allowing for remotely monitoring the status of the system, including confirming that the supports are achieving the prescribed support angles, and that the system is working as planned.

The Wave 4.3 mattress support has been designed and prototyped by Hill-Rom, using a number of components from its commercial medical bed mattresses, including the air bladders, air supply system. A detailed design of the device is attached. The device will be delivered and installed by Hill-Rom personnel in the presence of the research coordinator who will instruct the subject on its use.

IV. Data Analysis

Sample size

The primary endpoint for the study is the change in the AHI from baseline to the 14th night of sleeping with the surface. From prior data, we estimate the standard deviation of the paired differences to be 11.4. Using a one-sided paired t-test with type I error rate of 0.05, we will have 80% power to detect a 6 point reduction in AHI with 24 evaluable patients. We assume a loss to follow-up rate of 20% and a screen failure rate of another 20%; thus will enroll 40 patients.

Statistical methods

The primary analysis will assess the change in AHI from baseline to the 14th night of sleeping on the surface. We will use a one-sided paired t-test to assess the reduction in AHI. If the study is not stopped early for either efficacy or futility, the final analysis will conclude a significant reduction in AHI if the p-value is less than 0.048. Secondary endpoints will be assessed similarly using paired t-tests or appropriate non-parametric tests for paired data. We may also explore longitudinal changes in actigraphy measures using mixed effects models.

Interim Analysis:

Interim analyses for efficacy and non-binding futility will be conducted when 50% of the evaluable patients have reached the primary endpoint after 14 days of using the device. That is, it will be conducted after 12 patients have an evaluable primary endpoint. The analysis will assess the primary endpoint using the error spending approach described by Lan and Demets.[25,27] The study will be stopped early for efficacy if the p-value is less than 0.006 and stopped for futility if the p-value is greater than 0.37. If neither boundary is reached, the trial will not be stopped early and will enroll the full planned number of participants.

V. Event Reporting

(a) Adverse Events

The ICH Guideline for Good Clinical Practice E6(R1) defines an adverse event (AE) as:

> Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

As this is a study that does not include a pharmaceutical product intervention, this definition would include AEs that occur as a result of protocol procedures and protocol treatment.

A serious adverse event (SAE) is any AE that:

- Results in death
- Is immediately life-threatening
  This term refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that may have led to death.
- Requires inpatient hospitalization or prolongation of existing hospitalization
  In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in an outpatient setting.
- Results in persistent or significant disability/incapacity
  The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

  Medical or scientific judgment should be exercised in deciding whether expedited reporting is appropriate in this situation. Examples of medically important events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalizations; or development of drug dependency or drug abuse.

1. Collecting and reporting adverse events:
All AEs occurring after subject has signed consent and up to the study completion visit must be recorded on specific data collection forms.

2. Collecting and reporting Serious Adverse Events:
The OSU Event Reporting Form should be used to report untoward events that may affect participants in research approved by an OSU IRB. Events requiring prompt reporting include adverse events, protocol deviations, and other unforeseen problems or findings that suggest participants, research staff, or others are placed at greater risk by the research than previously expected. These events, classified broadly as unanticipated problems involving risks to participants or others, must be reported promptly to the

IRB. Unanticipated problems can occur in any type of research and may involve physical, psychological, social, legal, or economic harms.

Events Requiring Prompt Reporting

Events that may represent unanticipated problems involving risks to participants or others and therefore require prompt reporting include the following:

- Adverse events or injuries that are serious, unexpected, and related;
- Events requiring prompt reporting according to the protocol or sponsor;
- Reports, interim analyses, or other oversight committee/monitoring reports altering the risk/benefit profile;

These events should be promptly reported (see below), regardless of whether they occur during the study, after study completion, or to a participant who has withdrawn from or completed study participation.

Timeframe for Reporting

All internal events (those occurring in research at OSU or at a site under an OSU IRB's jurisdiction) as described above should be reported **within 10 days** of the Investigator's or research staff member's learning of the event. Events resulting in temporary or permanent interruption of study activities by the Investigator or sponsor to avoid potential harm to participants should be reported **immediately (within 48 hours)** whenever possible.

Additional Information

Related adverse events and other problems involving risk that do not meet the reporting requirements and do not represent potential unanticipated problems involving risks to participants or others should be reported in summary form at the time of continuing IRB review. However, any problem or adverse event that an investigator believes could influence the safe conduct of the research should be reported promptly.

(b) Protocol Deviations

Protocol deviations are accidental or unintentional changes to the protocol or procedures. In the event that the protocol deviation involves risk to the subject or potential risk to future participants, or with the potential to recur or significantly impacts the integrity of the research data, the event should be reported to the IRB in a timely manner, in accordance with their reporting guidelines.

VI. Ethical Considerations

The study will be conducted in accordance with the ICH guidelines on GCP, the GCPs applicable to any region where the study is conducted, and the ethical principles set forth in the Declaration of Helsinki. Good clinical practice is defined as a standard for the design, conduct, performance, recording, analysis, and reporting of clinical studies in a way that provides assurance that the data and reported results are credible and accurate, and that the rights, safety, and well-being of study participants are protected.

Per GCP, the protocol will be reviewed and approved by the IRB or IEC of each participating center prior to study initiation. The investigator will keep the IRB/IEC informed as to the progress of the study.

(a) Consent procedures

The investigator/study personnel will explain the nature of the study, and will be available to answer questions regarding procedures, risks and alternatives to participation. The consenter will inform the subject that participation is voluntary and that the subject can withdraw or be withdrawn from the study at any time. The principal investigator or his/her entitled designee will obtain written informed consent from each subject. Documentation of the informed consent process along with the original consent form will be maintained in the subject's research folder. A copy of the signed informed consent will be provided to the subject for their records.

(b) Subject compensation

Participants who qualify for the study will receive up to $400 compensation for participating in the study in the form of a ClinCard or by direct deposit (optional for OSU employees who may elect to receive payment by check). They will receive $200 at Visit 3 and $200 after Visit 4. If the participant is unable to complete all the visits, compensation will be prorated for the visits that are completed. All subject payments are taxable income.

VII. Data Handling and Record Keeping

The investigator shall maintain the records of the study e.g.: subject research charts, regulatory documents and all other study specific documentation for a minimum of 15 years or in accordance with currently OSU-IRB regulations.

1. *Confidentiality*
    - Confidentiality of all records will be maintained and data will be kept in a locked filing cabinet and only research staff and authorized members of the IRB will have access.
    - Electronic data is protected by codes to which only research staff and authorized members of the IRB, Office of Responsible Research Practices, and Data Safety Monitoring Committee will have access
    - The PHI to be collected; who will use the information within the institution and why; who may disclose the information and to whom; the subjects rights to access research information and their right to withdraw authorization (approval) for any future use of personal health information are all listed in the HIPAA form specific to the research
    - The names of subjects and any other identifying information will be kept in a secure location.
    - Should publications result from this study all PHI will be removed*.*

2. *Research and/or Development Agreement with Hill-Rom*

This research will be performed under a fully executed agreement between The Ohio State University and Hill-Rom (see attachment).

VIII. Data Safety Monitoring Plan

The risks involved with sleeping with the Wave mattress support, completion of questionnaires, HSAT, and actigraphy are minimal.

This study will be monitored to ensure participant safety and data integrity. The monitoring for this study will be conducted by the Principal Investigator and the study team. The information that will be evaluated will be the incidence and severity of adverse reactions related to the study procedures, enrollment and efficiency of data capturing. The adverse events will be assessed on a case by case basis at the time the study team is aware of the event.

Overall study monitoring will take place on an ongoing basis with study review meetings taking place at least every 4 months. In the event the side effects suggest the risk outweighs the benefit, the study will be stopped and the IRB notified in order to evaluate possible solutions to the risk problem.

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