Glasses for Adolescent Delayed Sleep-Wake Phase Disorder (GLAD)

NCT04378933

August 24, 2021

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General Study Information

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Study Title: Glasses for Adolescent Delayed Sleep-Wake Phase Disorder (GLAD)

IRB#: 18-003036
Protocol version number and date: Version 18; August 12, 2021 IRB approved 8/24/2021

Research Question and Aims

Hypothesis 1: Among adolescents with delayed sleep-wake phase disorder (DSWPD), those using evening amber glasses and employing prescribed stable wake times will show an increase in total sleep time (TST), and sleep onset times will advance (shift earlier) as compared to the control group.
Hypothesis 2: Dim light melatonin onset (DLMO) will advance (shift earlier) in the amber glasses + stable wake time group, but not in the control group. If DLMO does not advance (as has been reported in other circadian rhythm sleep-wake disorder (CRSWD) interventions with successful sleep-related outcomes [reviewed in [6]]) this aim will still provide data on the clinical utility of the DLMO.

Specific Aims: The aims of this study will address *at least* two goals to address gaps in the research domain of CRSWDs. We propose a 3-week **field study** that examines the efficacy, acceptance, and compliance of using evening amber glasses to block evening light **combined** with a stable wake time in adolescents (14-17 years) with DSWPD (International Classification of Sleep Disorders [**ICSD-3] criteria).**[3] After 1 week of baseline measurements, subjects will be instructed to wear glasses (which allow 14% entry of ambient light exposure) starting 7 h before individually calculated midsleep time measured during the preceding week. This corresponds to the time when adolescents are most sensitive to phase delaying light according to Co-I Crowley's recently published phase response curve (PRC) to light in adolescents (Figure 1).[22] This "amber glasses + stable wake time" group will be compared to a control group: adolescent DSWPD patients who will wear clear-lensed glasses (which allow 100% of ambient light to reach the eyes, otherwise identical in appearance) in the evening at the same times as the alternate group, but without scheduled wake times. Outcome measures will include TST and sleep onset time derived from wrist actigraphy, daytime subjective sleepiness, salivary DLMO, and assessments of acceptance and compliance.

Aim 1: Examine actigraphic sleep outcomes in adolescents with DSWPD before and after a 2-week intervention of evening amber glasses + stable wake times compared to evening clear glasses + no wake time instructions.

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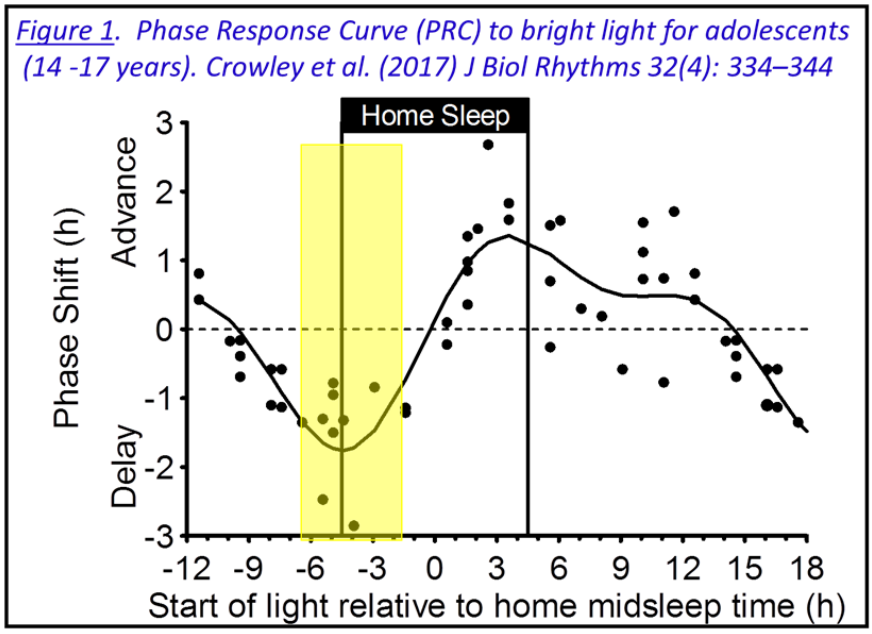
Aim 2: Examine circadian phase DLMO in adolescents with DSWPD before and after a 2-week intervention of evening amber glasses + stable wake times.

Background:
DSWPD is common among adolescents[3] and further increases their susceptibility to chronic sleep restriction and associated deleterious outcomes.[2,27,39,47] In a series investigating 22 adolescents with DSWPD, 59% demonstrated poor scholastic performance, and 45% displayed a variety of behavioral problems.[47] In a prospective study involving 14 patients (5 adolescents) followed over a period of 5 years in a clinical setting, all subjects reported severe disability as a result of failure of timely morning awakenings. Accordingly, those with DSWPD demonstrate significantly worse quality of life scores compared to age- and gender-adjusted norms.[39] Despite its prevalence, the CRSWD Practice Guidelines[6] contain only 4 DSWPD treatment studies that specifically address the pediatric/adolescent population.[30,43,49,50] The sole study that utilized post-awakening light therapy[30] did not provide compliance data, which is generally described as poor.[10] Oral melatonin was utilized in the remaining reviewed studies.[43,49,50] Adolescent patients are frequently reluctant recipients of this supplement, due to concerns related to adverse effects on reproductive function and the regulation of growth hormone.[17,33,35,45,48] Sleep/wake scheduling instructions used in isolation also demonstrate limited success. While Iwamitsu and colleagues demonstrated uniform sleep-related improvements utilizing such interventions among hospitalized DSWPD patients (a cost-prohibitive option for most), only 57% showed persistent improvement subsequent to discharge.[32] **Alternative, cost-effective, home-based, readily implemented evidence-based outpatient treatments for young patients are clearly needed.**

Co-Investigator (Co-I) Crowley recently published the first PRC to light for healthy adolescents aged 14 to 17 years[22] and found that maximum phase delay shifts are produced when light begins during the ~3 h before to ~3 h after habitual bedtime (see yellow highlight in Figure 1). Aoki and colleagues reported hypersensitivity to nocturnal light among select DSWPD patients compared to unaffected counterparts, as assessed by the degree of melatonin suppression with 2000 lux-hours of light exposure,[4] which may indicate that evening light around habitual bedtime results in even larger shifts than what was observed in healthy adolescents. Published relevant "eyewear" studies dovetail on data from bench research that demonstrate particular circadian sensitivity to short wavelengths that look blue.[11,46] In an open-label study, *adult subjects with DSWPD* wore amber glasses that blocked wavelengths ≤ 530 nm for a minimum of 3 evening hours, and for a period of 2 weeks, in conjunction with other behavioral directives. Outcomes were compared to a weeklong baseline period.



As determined by the Pittsburgh Sleep Quality Index (PSQI),[13] significant improvements in TST, initial sleep latency, and sleep quality were noted.[26] A more recent open-label study[25] of 9 DSWPD patients (mean age 18.11±3.18 years) tested 3 weeks of similar evening eyewear (21:00 to bedtime) and found a non-significant DLMO advance (>1 h) and an actigraphic sleep onset time advance >2 h compared to a baseline week. These small studies provide some preliminary evidence that amber glasses may be beneficial for DSWPD patients. *However, the studies were small (under-powered), uncontrolled, did not focus solely on adolescent patients, and did not assess compliance and feasibility. Moreover, these studies did not utilize the PRC to light for adolescents to time eyewear use in the evening (Figure 1).*

Abstract:
Thus, a more rigorously designed, appropriately-powered randomized placebo-controlled study is needed. Additional novel aspects of our protocol include use of eyewear that can fit over prescription glasses and that minimally interfere with media viewing. Finally, we will use knowledge of the adolescent light PRC (Figure 1) to time eyewear use based on each individual's habitual sleep pattern (further details below). Data from the proposed protocol therefore have the potential to introduce a safe, non-pharmacological, readily implemented economical treatment intervention, and may provide data for larger clinical trials to further identify optimal interventions. **The identification of a successful treatment for adolescent DSWPD is an essential "first step" in establishing whether improvement of sleep complaints can directly address associated adverse outcomes. Due to discussed deficiencies in the present literature, results from the proposed trial will be informative regardless of outcome.**

Time Line for the Conduct of the Study: We will enroll up to a total of 70 adolescents to participate in a 3-week study over 3 years at 2 sites (Mayo Clinic and Rush University). When possible, we will run participants in groups of 2.

Year 1 (2018): the first ~3 months will be dedicated to buying study equipment, hiring and training staff, and writing detailed instructions to be followed at both sites. Recruitment and screening will be ongoing. In the remaining school months, a minimum of 10 and a maximum of 16 participants will be enrolled (5-8 participants per site).

Year 2 (2019): A total of 20 participants (minimum of 16) will be enrolled during school months (8-10 per site). Interim data analysis will occur during the summer months.

Year 3 (2020): 18 total participants (minimum of 16) will be enrolled during school months (8-9 per site). Final data analysis and manuscript preparation will occur during the grant's final months.

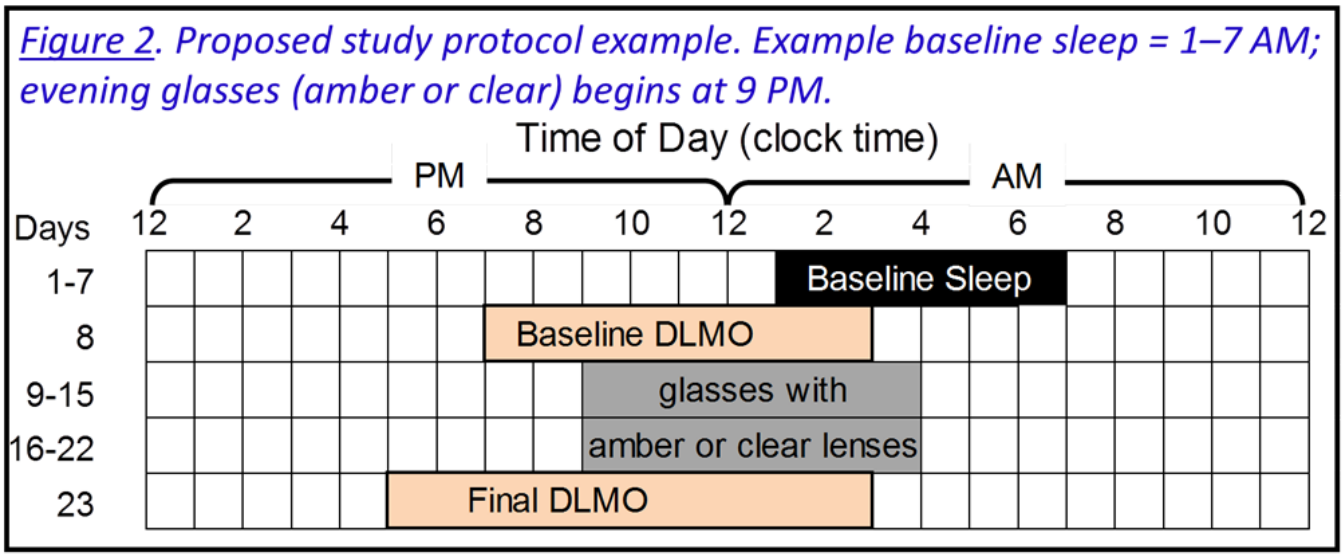
Study Design and Methods

Recruitment. Study participants will be patients seen by the principal investigator and colleagues at Mayo Clinic Sleep Medicine. Additional recruitment activities includes posting approved IRB fliers in schools, public locations, etc., with the approval of the location. Fliers will also be posted at Mayo Clinic in approved areas and in Mayo Classified ads.

The PI may make arrangements with public schools to attend classrooms to give an oversight of the research and hand out IRB approved fliers.

Study team members may send out the Mayo Clinic IRB approved advertisement/flier information through Peachjar which is a communication process used by many school districts, including those outside of the Rochester community.
School officials may email IRB approved flier content from within school systems, targeting the subject population.

3.1 Experimental Protocol. Subjects will complete the 3-week protocol pictured in Figure 2. Sleep will be measured with wrist actigraphy and sleep logs throughout the study (see section 3.2). For the first 7 days, subjects will sleep at home on their usual sleep schedule ("baseline"). Figure 2 shows an example average sleep schedule of 1-7 a.m.



Sleep measured during this baseline week will dictate timing of evening glasses use for both groups and wakeup time in the experimental group. After this baseline week, participants will be randomized to one of two groups. One group (amber glasses + fixed wake) will wear glasses with amber lenses (see section 3.3) beginning 7 h before average baseline midsleep time (e.g., starting at 9 pm in the example in Figure 2 because average midsleep time is 4 am) until the time of intended sleep onset or until a duration of 7 hours of use is reached. Wearing glasses at this time will block phase delaying light according to the adolescent PRC published by Co-I Crowley[22] (Figure 1), regardless of the time at which the adolescent initiates sleep. Participants will also be required to wake up at the same time (±30 mins), including on weekends. Fixed wake-up time will be based on average school-morning wake time. An optional 0.5 h nap zone will be timed 12 h after the midpoint of baseline sleep, as dark during this time should have minimal effects on circadian phase[12] and sleep duration should be sufficiently short such that sleep onset difficulties are not exacerbated. The second group (clear glasses + free wake) will wear identically appearing glasses with clear lenses (see section 3.3) and with the same timing. This group will act as the control group and will not be given any instructions with respect to sleep schedule. Reminder text messages will encourage compliance. These will be sent every afternoon, via a free text messaging service (such as "Remind," used within the Rochester Public School District). Since we wish to gauge compliance in a "real world" setting, we will not drop any subjects after baseline, and will incorporate all into compliance assessments. The DLMO (see section 3.4) will be measured after the baseline week on day 8 and after the 2-week intervention on day 23 to measure circadian phase shifts.

3.2 Sleep and Ambient Light Monitoring. Participants will wear an actigraph wrist monitor (AW-L or Actiwatch Spectrum, Philips Respironics) throughout the study to quantify sleep variables and, when applicable, monitor compliance to assigned sleep/wake times. Actigraphs have been extensively reviewed by various American Academy of Sleep Medicine Task Forces and are endorsed for the longitudinal assessment of circadian rhythm sleep disorders.[36,37] Participants will additionally complete daily sleep diaries which will include documentation of caffeine intake. They will call a time-stamped voice mail at bed and wake times. Data will be downloaded and daily sleep diaries entered into RedCap (paper diaries will be available as a back-up) will be reviewed with the participant during weekly visits. Motivational interviewing techniques will be

employed during these visits if subjects express difficulties with respect to eyewear use (both groups) or if they have difficulties awakening at prescribed times (amber + fixed wake group). Ambient light exposure to the eye will be monitored by another actigraph with a light sensor (AW-L or Actiwatch Spectrum, Philips Respironics) (without the wristband) that has been attached to a lanyard. Participants will wear the lanyard with photosensor around their neck throughout the study like a necklace so that the light sensor is sitting on their chest. Participants will wear the light sensor necklace at all times throughout the study, except when trying to sleep. During sleep episodes, participants will be instructed to place the light sensor face-up on a night stand (or something of similar height) next to their bed. A light sensor at chest level will measure light getting to the eyes more accurately than if the sensor is worn on the wrist. Participants will be instructed to wear the light sensor necklace on the outer layer of their clothes (e.g., remove the light sensor from sweaters and coats). Co-I Crowley has used this method with adolescents for many years. Specific instances may preclude wearing the actigraph devices for circumscribed periods of time (e.g., during contact sports).

3.3 Reducing Evening Light with Amber Glasses. Participants in the "amber glasses + fixed wake" group will use amber lenses (Cocoons®, Live Eyewear, San Luis Obispo, California) starting 7 h before baseline midsleep time until self-selected bedtime or for a duration of 7 hours (Figures 1-2). This eyewear transmits only 14% of light and absorbs most short wavelength (blue) light waves. Indoor house light levels are typically less than 100 lux. Therefore, light transmission will be reduced by 86% and only ~14 lux will transmit to the eye. The frame is designed to block light from all angles. We chose these glasses instead of those used in previous studies,[25,26] as the latter only partially attenuate light-induced phase shifts,[8] and distort colors, which may make electronic viewing more difficult (a particularly relevant adolescent consideration). Moreover, the frames come in 7 different sizes to fit well with or without prescription glasses. Participants in the control group will wear the same frame with clear lenses made by the same company. Compliance (defined as use >75% of the prescribed time for at least 10 days of the 2-week intervention) will be monitored by parent and participant self-report, as well as with a small temperature monitor (iButton, iButtonLink Technology,Whitewater WI) affixed to the inside of the temple of the glasses frame. The iButton will make contact with the skin on the side of the participant's face near the temple when the glasses are on. The change in temperature will allow us to determine when the glasses are on (higher temperature) and when they are off (lower temperature). Each participant will be fitted for glasses size and for location of iButton placement. The ability to objectively monitor use is *a major strength in comparison to previous studies*.[25,26] Our definition of compliance accounts for the fact that some participants may be engaged in activities during some of the prescribed wearing times that either present potential safety concerns (e.g., driving, riding a bike) or are otherwise impractical (working, social activities). Estimating an earliest "glasses on" time of 20:00, these considerations alone should not significantly hamper compliance.

3.4 Dim Light Melatonin Onset (DLMO) Phase Assessments. Saliva sampling for baseline circadian phase assessment (Day 8) will begin 6 h before and end 2 h after baseline bedtime to capture the rise of endogenous melatonin. The final circadian phase assessment will begin 8 h before baseline bedtime to capture the rise of melatonin after a phase advance shift and will end 2 h after baseline bedtime (See Figure 2). All sampling will take place in the inpatient Clinical Research Unit (SMH), and participants may elect to stay overnight if desired or required due to transport or other logistical considerations. The procedures for collecting salivary melatonin are routine. Participants are seated in dim light (<5 lux) and remain awake watching age-appropriate movies or the like. When necessary, participants walk to the adjoining restroom (also <5 lux). Saliva samples are collected

every 30 mins using Salivettes. The samples are immediately centrifuged and frozen, and later shipped on dry ice to SolidPhase, Inc (Portland, ME), where they are analyzed for melatonin using direct radioimmunoassay. All samples from an individual participant will be analyzed in the same assay. The reported sensitivity of the assay is 0.7 pg/mL. Intra-assay and inter-assay variations are 12.1% and 13.2%. We will compute DLMO, the most common and reliable[9,34] circadian phase marker in humans, using these assayed values. Importantly, prior studies performed by Co-I Crowley (and others) have demonstrated the feasibility of procuring samples among young people in the setting proposed.[18,19,28]

3.5 Subjective Sleepiness Measures. Daytime sleepiness will be assessed before and after the 2-week intervention using the Pediatric Daytime Sleepiness[24] scale. Daytime sleepiness will also be assessed daily using visual analogue scales[7] on daily sleep logs.

3.6 Acceptability and Expectation Ratings. A structured interview and a subjective questionnaire (Intervention Acceptability Questionnaire, developed by Co-I Crowley (unpublished)) will be used to assess overall acceptability of wearing glasses in the evening (amber and clear lenses) and maintenance of a stable wake time (in the amber glasses + fixed wake group only). Pre-treatment expectation ratings will be obtained immediately after participants receive the equipment using the Credibility Expectancy Questionnaire (CEQ)[23] to account for differences in treatment expectations/placebo effects.

Resources: *Describe the available resources to conduct the research (personnel, time, facilities, mentor commitment, etc.)*:

☒ (1a) This is a multisite study involving Mayo Clinic and non Mayo Clinic sites. *Please see Study Design and Methods for Mayo Clinic site.*

☐ (1b) Mayo Clinic study staff will be engaged in research activity at a non Mayo Clinic site. *When checked, provide a detailed description of the activity that will be conducted by Mayo Clinic study staff.*

Subject Information

3.7 Participants. Adolescent subjects (14-17 years, inclusive) will be enrolled (n=45) at Mayo Clinic.We restrict the age range to control for stage of puberty since light sensitivity differs between pre- and post-pubertal adolescents.[20] This age range also corresponds to the period when school start times are earliest and adolescents need the most help shifting their sleep schedules. Finally, the optimal times to block out ambient light in the evening are known for this age group (Figure 1).[22]

Inclusion Criteria:

1. Regular school attendance in the setting of a fixed start time
2. Adherence to ICSD-3 DSWPD diagnostic criteria[3]
3. Average spontaneous weekend wake time ≥1 hour than school day wake time and
4. Initiation of school-night sleep at 12 a.m. or later, ≥50% of the time, during a 14-day period (items 3-4 to be determined by sleep logs and actigraphy). As there are no discrete clock times associated with the

ICSD-3 DSWPD description, this cutoff is based on data obtained from the 2006 Sleep in America Poll[40] and experiences gleaned from prior recruitment.[5]

After the initial contact, subjects will be scheduled for consent/assent and subsequent screening. Eveningness tendencies will be further verified with age-appropriate circadian preference questionnaires.[15,31,42] Subjects will complete a self-rated measure of puberty stage.[14] Female participants will complete the For Girls Only questionnaire that provides information on menstrual cycle regularity, use of contraceptive hormones, and symptoms of premenstrual dysphoric disorder (PMDD). Female participants will also report when their menstrual cycle starts on the daily sleep logs. Phase of the menstrual cycle does not impact circadian phase shifts to light, but can influence sleep and melatonin (two of our primary outcomes).

If the screened participants are deemed eligible to participate in the study, they will sign the main research study consent/assent if they agree to be in the study.

To eliminate the confounding effect of psychiatric disturbances, further screening will take place with the Mood Disorder Questionnaire-Adolescent Version and the Children's Depression Inventory.[29,51]

Exclusion Criteria:

1. A positive urine drug abuse screen will disqualify the individual from further participation.
2. Subjects will be withdrawn from the study if the sleep log and wrist monitor activity does not correspond with the sleep schedule identified with the pre-study sleep log.
3.
4. Alcohol and nicotine use will also be screened to qualify for the study. We will also screen for alcohol immediately before each DLMO assessment because alcohol acutely suppresses melatonin.
5. Patients receiving medications that might contribute to sleep disturbances and/or affect treatment responses will be considered ineligible (e.g., hypnotics, antidepressants, stimulants, non-steroidal anti-inflammatory drugs (NSAIDs), beta blockers).[38,44]
6. All subjects will be asked to refrain from caffeine use on the days of phase assessments, and to cease ingestion at least 6 hours prior to nightly bedtime.
7. The Ishihara Color Blindness Test will be done and patients who are color blind/deficient will be disqualified from participating in the study.

3.8 Depression Management Plan

In the instance of an affirmative response to the study participants' screening utilizing the Mood Disorder Questionnaire-Adolescent Version and the Children's Depression Inventory questionnaires, an urgent discussion with the study psychiatrist will take place for evaluation, and appropriate referral for treatment will be made. Study consent form includes participant's consent for permission to interface with his/her primary provider should clinical concerns arise. If emergent concerns arise regarding risk of harm to self or others, the patient will be referred for emergency care.

Research Activity

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Check all that apply and complete the appropriate sections as instructed.

1. ☐ **Drug & Device**: Drugs for which an investigational new drug application is not required. Device for which (i) an investigational device exemption application is not required; or the medical device is cleared/approved for marketing and being used in accordance with its cleared/approved labeling. (Specify in the Methods section)

2. ☐ **Blood**: Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture.

3. ☒ **Biological specimens other than blood**: Prospective collection of human biological specimens by noninvasive means that may include: urine, sweat, saliva, buccal scraping, oral/anal/vaginal swab, sputum, hair and nail clippings, etc.

4. ☒ **Tests & Procedures:** Collection of data through noninvasive tests and procedures routinely employed in clinical practice that may include: MRI, surface EEG, echo, ultrasound, moderate exercise, muscular strength & flexibility testing, biometrics, cognition testing, eye exam, etc. (Specify in the Methods section)

5. ☒ **Data** (medical record, images, or specimens): Research involving use of existing and/or prospectively collected data.

6. ☒ **Digital Record**: Collection of electronic data from voice, video, digital, or image recording. (Specify in the Methods section)

7. ☐ **Survey, Interview, Focus Group:** Research on individual or group characteristics or behavior, survey, interview, oral history, focus group, program evaluation, etc. (Specify in the Methods section)

☐ NIH has issued a *Certificate of Confidentiality* (COC). *When checked, provide the institution and investigator named on the COC and explain why one was requested*. _____

Biospecimens – Categories 2 and 3

(2) Collection of blood samples. When multiple groups are involved copy and paste the appropriate section below for example repeat section b when drawing blood from children and adults with cancer.

a. **From healthy, non-pregnant, adult subjects who weigh at least 110 pounds**. For a minimal risk application, the amount of blood drawn from these subjects may not exceed 550ml in an 8 week period and collection may not occur more frequently than 2 times per week.

Volume per blood draw: _____ml

Frequency of blood draw (e.g. single draw, time(s) per week, per year, etc.) _____

b. **From other adults and children considering age, weight, and health of subject.** For a minimal risk application, the amount of blood drawn from these subjects may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period, and collection may not occur more frequently than 2 times per week.
Volume per blood draw: _____ml
Frequency of blood draw (e.g. single draw, time(s) per week, per year, etc.) _____

(3) Prospective collection of biological specimens other than blood: Saliva samples

Review of medical records, images, specimens – Category 5

For review of existing data: provide a date range or an end date for when the data was generated. The end date can be the date this application was submitted to the IRB. Example: *01/01/1999 to 12/31/2015* or all records through *mm/dd/yyyy*.

Date Range:

Check all that apply (data includes medical records, images, specimens).

☐ (5a) Only data that exists before the IRB submission date will be collected.

☐ (5b) The study involves data that exist at the time of IRB submission **and** data that will be generated after IRB submission. Include this activity in the Methods section.
Examples
- The study plans to conduct a retrospective chart review and ask subjects to complete a questionnaire.
- The study plans to include subjects previously diagnosed with a specific disease and add newly diagnosed subjects in the future.

☐ (5c) The study will use data that have been collected under another IRB protocol. Include in the Methods section and enter the IRB number from which the research material will be obtained. *When appropriate, note when subjects have provided consent for future use of their data and/or specimens as described in this protocol*.
Enter one IRB number per line, add more lines as needed

☐ Data ☐ Specimens ☐ Data & Specimens _____

☐ Data ☐ Specimens ☐ Data & Specimens _____

☐ Data ☐ Specimens ☐ Data & Specimens _____

☐ (5d) This study will obtain data generated from other sources. Examples may include receiving data from participating sites or an external collaborator, accessing an external database or registry, etc. Explain the source and how the data will be used in the Methods section.

☐ (6) Video audio recording: *Describe the plan to maintain subject privacy and data confidentiality, transcription, store or destroy, etc.*

HIPAA Identifiers and Protected Health Information (PHI)

Protected health information is medical data that can be linked to the subject directly or through a combination of indirect identifiers.

Recording identifiers (including a code) during the conduct of the study allows you to return to the medical record or data source to delete duplicate subjects, check a missing or questionable entry, add new data points, etc. De-identified data is medical information that has been stripped of all HIPAA identifiers so that it cannot be linked back to the subject. De-identified data is **rarely** used in the conduct of a research study involving a chart review.

Review the list of subject identifiers below and, if applicable, check the box next to each HIPAA identifier being recorded at the time of data collection or abstraction. Identifiers apply to any subject enrolled in the study including Mayo Clinic staff, patients and their relatives and household members.

Internal refers to the subject's identifier that will be recorded at Mayo Clinic by the study staff.
External refers to the subject's identifier that will be shared outside of Mayo Clinic.

Check all that apply:	INTERNAL	EXTERNAL
Name	X	
Mayo Clinic medical record or patient registration number, lab accession, specimen or radiologic image number	X	
Subject ID, subject code or any other person-specific unique identifying number, characteristic or code that can link the subject to their medical data	X	X
Dates: All elements of dates [month, day, and year] directly related to an individual, their birth date, date of death, date of diagnosis, etc. **Note:** Recording a year only is not a unique identifier.	X	
Social Security number		
Medical device identifiers and serial numbers		
Biometric identifiers, including finger and voice prints, full face photographic images and any comparable images		
Web Universal Resource Locators (URLs), Internet Protocol (IP) address numbers, email address	X	X
Street address, city, county, precinct, zip code, and their equivalent geocodes		
Phone or fax numbers		
Account, member, certificate or professional license numbers, health beneficiary numbers		
Vehicle identifiers and serial numbers, including license plate numbers		

Check 'None' when none of the identifiers listed above will be recorded, maintained, or shared during the conduct of this study. (exempt category 4)	☐ None	☐ None

Data Analysis

3.9 Sample Size. A power analysis assumes a between-subjects design with an alpha level of .05 and power of .80. Based on these assumptions and previous studies that assessed actigraphic and subjective sleep changes after 2[26] or 3 weeks[25] of an amber glasses intervention for (predominantly adult) DSWPD subjects, a minimum of 11 to 17 participants per group are needed to address Hypothesis 1. Both the latter study[25] and a separate relevant investigation [that tested advancement of darkness exposure (sleep opportunity) among young adults with subclinical DSWPD[41]] assessed DLMO changes in relation to the respective interventions, with observed shifts >1 h. Computed effect sizes (d=0.92) predict that 10-20 patients are needed per group to address Hypothesis 2. Accounting for approximately 20% attrition, we therefore aim to enroll up to 70 participants between Mayo Clinic and Rush University.

3.10 Data Analysis Plan. DLMO: We will use a DLMO threshold of 4 pg/mL, which is recommended for children and adolescents.[16,21] Sample times and melatonin values above and below the threshold will be used to compute the DLMO (in clock time) using linear interpolation. DLMO phase shifts will be defined as baseline – final phase assessments. Sleep: Actigraphy data will be analyzed using the Actiware-6 software (Philips Respironics) to estimate sleep/wake. Each nocturnal and nap sleep episode will be inspected within a specific "scoring interval," spanning from 15-min before participants report trying to initiate asleep to 15-min after they report awakening on their daily sleep diaries. Within these scoring intervals, sleep parameters will be computed according to the procedures outlined by Acebo and colleagues.[1]

3.11Statistical Approach. Analyses will be run using SPSS (version 19). A two-tailed 0.05 alpha level will be used for all statistical tests. Data analysts will be blinded to group assignment. From previous research, we expect sleep, sleepiness, and DLMO phase shifts to have roughly normal distributions; however, skew and kurtosis will be assessed to determine statistical normality. Covariates of sex, age, and self-assessed puberty stage will be considered in each analysis. Primary outcomes measures: TST, sleep onset time, subjective daytime sleepiness, and DLMO. For each outcome variable, a 2 (between subjects factor, GROUP: amber glasses + fixed wake vs. clear glasses + free wake)-by-2 (within subjects factor, TIME: baseline week vs. final week of intervention) analysis of variance will examine whether wearing amber glasses in the evening in combination with a stable wake time changes each outcome as predicted compared to the control group.

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