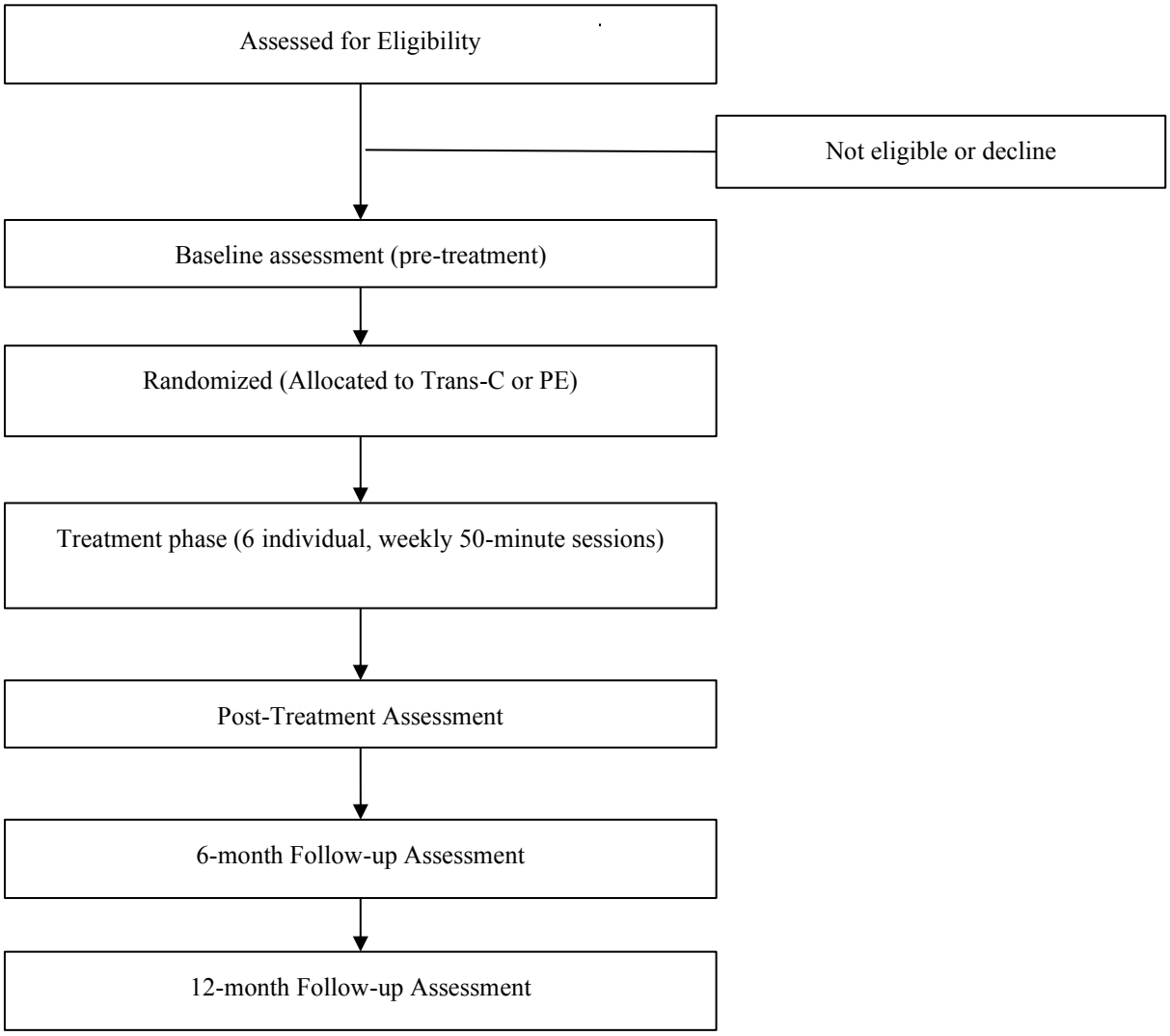
Title:	**Triple Vulnerability? Circadian Tendency, Sleep Deprivation and Adolescence**
CPHS Number:	2012-02-4007 (Date of 1st approval: March, 14 2012)
Clinicaltrials.gov Number:	NCT01828320 (Date of 1st release: April, 02 2013)
Amendment 1 Date: 04/09/2013	Amendment 3 Date: 12/16/2014
Amendment 3 Date: 12/15/2015	Amendment 4 Date: 04/04/2016
Amendment 5 Date: 05/13/2016	Amendment 6 Date: 06/21/2016
Amendment 7 Date: 10/25/2016	Amendment 8 Date: 10/05/2017
Amendment 9 Date: 06/08/2018	Amendment 10 Date: 04/16/2019

Sponsor Eunice Kennedy Shriver National Institute of Child Health and Human Developmer
1 Center Drive, Bethesda, MD 20892 USA

Study Principal Investigator
Allison G. Harvey, Ph.D. Psychology Department, 2121 Berkeley Way, 3rd floor. University c
California, Berkeley, CA 94720-1650. USA. email: aharvey@berkeley.edu

TABLE OF CONTENTS

FIGURE 1: STUDY DIAGRAM



1. PURPOSE

Adolescence is a health paradox: it is the healthiest time of life, yet a time of great risk and vulnerability with potential for devastating long term consequences, including poorer health, school failure and academic underperformance, engagement in risky impulsive behaviors, abuse of substances, increased risk of accidents, relationship difficulties with peers and parents, and the development of emotional and behavioral disorders. Hence, there is an urgent need to identify novel modifiable mechanisms contributing to risk and vulnerability among teens.

The modifiable mechanism targeted in this study is 'eveningness'. Teens who exhibit an evening circadian tendency ('night-owls') follow a delayed sleep schedule, increasing activity later in the day and both going to sleep and getting up later, compared to morning types ('larks'). The circadian tendency toward eveningness during adolescence arises from a confluence of psychosocial, behavioral and biological factors and is an important contributor to, and maybe even cause of, vicious cycles that escalate vulnerability and risk for poor health and major forms of psychopathology. Indeed, eveningness is associated with an extremely wide-range of adverse outcomes including poorer academic performance, poorer self-regulation, greater use of substances, greater tendency for impulsivity and more depression and anxiety. While the basic biological shift toward eveningness during puberty may be difficult to modify, the psychosocial and behavioral contributors are modifiable. Moreover, modifying the psychosocial and behavioral contributors will eliminate key factors that exacerbate the pubertal biological shift.

This conceptualization derives from evidence that biological changes in the circadian system at puberty lead to a shift in sleep timing preferences toward a delayed sleep phase. This effect is compounded by psychosocial changes including less parental control, increased access to stimulating social activities (movies, music, internet, texting, cell phones) and intake of alcohol and substances that contribute to sleep disruption. The social influences are synergistic with biological tendencies toward phase delay and can spiral quickly into a pattern of extremely delayed bedtimes. Yet, school or work usually requires a fixed early wake-up time. These forces converge to constrain the time available for sleep, resulting in high rates of insufficient sleep among youth. Compounding the negative cycle, most attempts to "catch-up" on sleep occur on weekends with an extremely phase-delayed schedule. This is a critical problem because the human circadian system adapts more easily to phase delays; endogenous rhythms are able to re-set quickly to later bed and wake times, but have more difficulty accommodating to phase advances (earlier sleep schedules). The problematic result is that large numbers of youth are struggling with the burdens of eveningness, sleep deprivation and the consequences of repeated circadian shifts. This is of particular concern for rapidly developing teens because adequate sleep is critical for optimal brain development.

This research will advance current knowledge on the role of eveningness as a mechanism contributing to poorer outcomes during adolescence. We aim to reduce eveningness among 10-18 year olds via an innovative intervention; the Transdiagnostic Sleep and Circadian Intervention (TranS-C) which integrates elements from four evidence-based treatments (Cognitive Behavior Therapy for Insomnia, Interpersonal and Social Rhythm Therapy, Chronotherapy, and Motivational Interviewing) derived from basic research on the circadian system. We will randomly allocate adolescents (10-18 year olds) with an evening circadian tendency, and who are 'at risk' in at least one of five health domains (emotional, cognitive, behavioral, social, physical), to either: (a) TranS-C or (b) Psychoeducation. Measures will be taken pre-treatment, at the end of treatment, and at 6 and 12 months post-treatment.

We aim to evaluate if an intervention to reduce eveningness among adolescents improves sleep and functioning in five health-relevant domains (emotional, cognitive, behavioral, social and physical) in the short and long term. The major hypothesis to be tested is that TranS-C, relative to Psychoeducation, will

improve sleep and circadian function, advance the timing of the endogenous circadian phase via the dim light melatonin onset protocol (DLMO), and decrease risk across the five health domains (emotional, cognitive, behavioral, social, and physical).

2. METHOD

2.1. Study Design

Based in a university clinic, youth will be randomly assigned, stratified by sex and age (10-14, 15-18), in a 1:1 parallel group design, to receive either TranS-C or PE. Sibling pairs will be randomized to the same condition.

Assessors will be blind to treatment allocation. Sequentially numbered, opaque, sealed envelopes will be generated using a computer-generated random number list. A project coordinator will conduct randomization after all eligibility assessments are completed. Assessments will be conducted at baseline and at the end of treatment. The Committee for the Protection of Human Subjects approved the study.

2.2. Participants

Participants will be recruited through clinicians or advertisements. Individuals will be eligible if they (a) are between 10 and 18 years old, living with a parent or guardian, and attending a class/job by 9am at least 3 days per week; (b) are fluent in English; (c) are able and willing to give informed assent; and (d) report eveningness as demonstrated by scoring within the lowest quartile of the Children's Morningness-Eveningness Preferences Scale (CMEP; 27 or lower) and have a 7-day sleep diary showing a sleep onset time of 10:40pm or later for 10-13 year olds, 11pm or later for 14-16 year olds, and 11:20pm or later for 17-18 year olds at least 3 nights per week.[61,62] In addition, this sleep pattern will have to have been present for the past 3 months. Finally, participants will have to fall into an 'at risk' range on measures of at least one of the five health domains reviewed above.

Exclusion criteria will be (a) an active, progressive physical illness or neurological degenerative disease directly related to the onset and course of the sleep disturbance; (b) evidence of obstructive sleep apnea, restless legs syndrome, or periodic limb movement disorder[59]; (c) significantly impairing pervasive developmental disorder; (d) bipolar disorder, schizophrenia, or another current Axis I disorder if there is a risk of harm if treatment is delayed. Participants will cease taking medications that alter sleep (e.g., hypnotics) 4 weeks prior to the assessment (2 weeks for melatonin) or will be excluded. Finally, history of substance dependence in the past six months or current suicide risk sufficient to preclude treatment on an outpatient basis will be exclusionary.

In other words, receipt of another sleep treatment will be the only type of treatment excluded. We want to be sure that any improvements in sleep could be attributed to TranS-C or PE, not the other sleep treatment. Other medications will be allowed. A medication-free group would be unrepresentative. We will also include youth with Axis I psychiatric comorbidity (except for bipolar disorder and schizophrenia), even if they are receiving treatment for that comorbidity.

2.3. Treatments

Therapists will be doctoral or master's level. Weekly supervision will be conducted separately for TranS-C and PE. Sessions will be audio recorded. Treatment integrity will be evaluated by AGH for TranS-C with the Cognitive Therapy Rating Scale (CTRS)[63] and by NZ for PE on a 1-100 scale, on which higher scores will be awarded for alliance building, reflective listening, and providing PE without emphasizing behavior change.

A checklist of elements specific to TranS-C and PE will be used to rate presence/absence and focus on behavior change (a distinguishing feature of the treatments) for a random subset of tapes.

Treatment will involve 6 individual, weekly 50 minute sessions delivered during the school year to minimize the impact of summer schedule variability[41]. During the treatment phase, youth in TranS-C will be encouraged to complete their own sleep diary each morning for the purpose of treatment planning (particularly for sleep restriction). Youth in PE will not complete a sleep diary.

2.3.1. Transdiagnostic Sleep and Circadian Intervention for Youth (TranS-C)

TranS-C[1] is grounded in sleep and circadian basic science and combines elements from four evidence-based interventions: Cognitive Behavior Therapy for Insomnia[42,64,65], Interpersonal and Social Rhythm Therapy[66], Chronotherapy[67] and Motivational Interviewing[48] (See Table 1). TranS-C is a modular approach which allows the treatment sessions to be focused on the specific sleep problem experienced by each patient. The goal is to reverse maintaining psychosocial, behavioral and cognitive processes via 4 cross-cutting modules, 4 core modules and 7 optional modules.

- The four *Cross Cutting Modules* are: case formulation; education; behavior change and motivation; goal setting. "Cross-cutting" modules are introduced in the first session and are typically featured every session thereafter.
- The four *Core Modules* are: establishing regular sleep-wake times including learning a wind-down and wake-up routine; improving daytime functioning; correcting unhelpful sleep-related beliefs; and maintenance of behavior change. "Core modules" apply to the vast majority of patients.
- The *Optional Modules* are: improving sleep efficiency; reducing time in bed; dealing with delayed or advanced phase; reducing sleep-related worry/vigilance; promoting compliance with CPAP/exposure therapy for claustrophobic reactions to CPAP; negotiating sleep in a complicated environment and reducing nightmares. "Optional modules" are used less commonly and only if indicated by the case formulation.

The modular format will allow the treatment sessions to be focused on the specific sleep problem experienced by each patient. The treatment manual recommends a specific order in which modules are typically completed but suggests that clinicians be sensitive to differences between patients as to which processes are maintaining their distress and to address those processes at an earlier stage of treatment. Specific assessments are recommended to guide the treatment provider as to when the optional modules should be used.

2.3.2. Psychoeducation (PE)

Psychoeducation (PE) is an active comparison treatment associated with sleep improvement.[30] PE constitutes a conservative control for treatment location, experience and skill level of the therapists, the number and quality of handouts, therapist attention, amount and frequency of contact with the therapist, duration of treatment, and beliefs and expectations about the efficacy of treatment held by the teens. Sessions will focus on the inter-relationship between sleep, stress, diet, health, exercise, accidents, and mood. These sessions will involve obtaining a detailed description from the teen about their experience with the topic and general education. Participants will also be given the choice of sampling meditation, yoga, and/or outdoors appreciation. There will be no explicit focus on sleep except briefly mentioning sleep as a common contributor to each topic. If a participant raises issues related to sleep or requests

advice on implementing change, the therapist will respectfully return to the content of the session. The emphasis will be on providing information but not on specifically facilitating behavior change.

3. MEASURES

Except where specified, assessments will be administered before and after treatment. Assessments will be audio recorded. A random subset will be reviewed.

3.1. Diagnosis

The KSADS[69] will be administered separately to youth and one parent/caregiver to assess for participant current and lifetime Axis I disorders at the pre-treatment assessment.

3.2. Sleep Outcomes

3.2.1 Sleep Diary.[15]

An a priori decision was made to investigate weeknight average total sleep time (TST) and bedtime (BT) average as primary outcomes to best capture the sleep problems of interest.[60] Secondary outcomes will be the discrepancy between weeknight and weekends for TST, BT, and waketime (WUP). Trained research assistants will phone the participants each morning to collect their sleep diary. In scheduling the call, the participants will specifically be told to not use the call as an alarm clock and to select a time as close as possible to rise time but after they are already out of bed. The training of the research assistants will specifically include not engaging in conversation other than collecting the sleep diary data. (See Table 2 for calculations of sleep diary variables).

Other secondary outcomes will be ***Sleepiness Scale***[16], ***Pittsburgh Sleep Quality Index (PSQI)***[18,26] and ***CBCL Sleep Composite (parent report).***[8]

3.3. Circadian Outcomes

3.3.1 Children's Morningness-Eveningness Preferences Scale (CMEP*)* [9]

CMEP will be a primary outcome. Scores range from 10 (Extreme evening preference) to 43 (Extreme morning preference).

3.3.2 Dim Light Melatonin Onset (DLMO)

DLMO will be a secondary outcome. DLMO is the gold standard index of the endogenous circadian phase[30]. DLMO is defined as the interpolated time at which melatonin exceeds 3.0 pg/ml. The selection of this threshold is based upon prior experience with melatonin as a marker of circadian phase and the visual inspection of each participant's DLMO record [70]. This method of DLMO assessment will also provide a circadian phase estimate for the highest percentage of participants, including participants with low melatonin production.

Melatonin is a hormone produced by the pineal gland; its levels remain low during the daytime, begin to increase approximately 2 hours prior to habitual bedtime, and peak in the first part of the night. Synthesis and production of melatonin is predominantly regulated by the light-dark cycle.[33] Circulating melatonin levels are a preferred circadian marker because they are comparatively robust and less prone to masking from other external influences compared to measures like to core body temperature, cortisol, and heart rate.[34] However, bright light in the evening can suppress or "mask" nighttime melatonin production,[32]

which necessitates its measurement in dim light conditions.

DLMO will be assessed with the serial saliva sampling method one night before and after treatment in an overnight stay in the Psychology Department at UC Berkeley based on established protocol[70]. Several methods have been used to assess melatonin, including its concentration in plasma or salvia and its metabolite (aMTS6S) in plasma or urine.[39] We will collect saliva as it has become the preferred sampling method as it is non-invasive and more acceptable to patients.[39] Light levels will be determined using Fisher Scientific Extech Light Meter 407026 (Pittsburgh, PA). Following current convention, dim light (<50 lux, but preferably <20 lux[35,36]) will be initiated 1 hour before the earliest melatonin onset.[37,38]

Thirteen saliva samples will be collected for each participant before and after treatment, beginning 5.5 hours before average bedtime (computed from 7 nights of sleep diary) and ending 30 minutes after average bedtime. Saliva (~1 ml) samples will be collected in 30-minute intervals in dim light (< 50 lux) using untreated Sarsedt Salivettes (Starstedt, Germany). Saliva samples will be centrifuged at 3300 RPM for 5 minutes. If <1mL saliva is yielded after centrifuging, samples will be centrifuged for an additional 5 minutes at 3500 RPM. Samples will be frozen and stored at -80 °C and later assayed for melatonin by SolidPhase (Portland, Maine) using radioimmunoassay test kits (APLCO Diagnostics, Windham, NH). Assay sensitivities will be 0.3 pg/mL and the minimum detectable dose will be 0.05 pg/mL. Mean intra- and inter-assay coefficients of variation (CV) will be 7.9 and 9.4%, respectively. [40] Saliva samples will be collected from all randomized participants.

3.4. Functioning in five health domains.

For each of the five health domains (i.e., emotional, cognitive, behavioral, social, and physical health), three clusters of composite scores will be calculated using the cumulative risk index[71,72] by taking the mean of standardized summary scores for specific measures within that domain.

3.4.1. Youth Self-Report Composite Risk Score.

The first cluster will be the *Youth Self-Report Composite Risk Score (primary)* which will be derived from psychometrically validated questionnaires representing each of the five health domains.

- *Domain 1. Emotional health* will be indexed by a composite of the 17-item Children's Depression Rating Scale-Revised (CDRS; range 17-113; higher scores = worse depression)[41] and the 39-item Multidimensional Anxiety Scale for Children (MASC; range 0-117; higher scores = worse anxiety).[42]
- *Domain 2. Cognitive Health* will be indexed by a composite of the 20-item Attentional Control Scale (ACS)[43] (range 4-80; higher scores = better attentional control) and the six school-related items from the Youth Social Adjustment Scale – Self Report (YSAS).[44]
- *Domain 3. Behavioral Health* will be indexed by a composite of the 8-item Sensation Seeking Scale for Children[45] and the Alcohol and Substance Use Questionnaire[46] to assess consumption of caffeine, alcohol, and recreational drugs in the past 30 days (1-7 rating scale; higher scores= more frequent use). For the purpose of the present study we will add questions on caffeine and energy drinks to the latter.
- *Domain 4. Social Health* will be indexed by the average of three subscales (ie, friends, family, romantic relationships) from the Youth Social Adjustment Scale – Self Report[44] (higher scores = more impaired adjustment).

- *Domain 5. Physical Health* will be indexed by the composite of the Modifiable Activity Questionnaire for Adolescents (MAQ; Calculated as the number of hours per week being active/exercising; higher scores = greater numbers of active hours)[47] and the Physical Health Questionnaire-15 (PHQ-15; range 0-30; higher scores = worse somatic complaints).[48]

3.4.2. *Youth Ecological Momentary Assessment (EMA) Composite Risk Score.*

The second cluster will be the *Youth Ecological Momentary Assessment (EMA) Composite Risk Score* which will be derived from phone calls twice per day on weekdays and four times per day on weekends. The questions asked during the calls will be adapted from Silk et al[73]. The rationale for including EMA is to index 'real world' functioning in each of the five health domains.

- *Domain 1. Emotional Health* will be indexed with a short version of the Positive and Negative Affect Schedule for Children[50]; 4 items measuring positive affect and 5 items measuring negative affect will be rated on a 5-point Likert scale. A Positivity Ratio will be calculated. Diener [51] proposed that a high ratio of positive to negative emotion (the positivity ratio) predicts subjective well-being. Prior research has shown that sleep deprivation and eveningness are associated with a lower positivity ratio.[52]
- *Domain 2. Cognitive Health.* Using questions adapted from previous research,[43] participants will be asked 'At the moment the phone rang, what were you doing?'. Participants will then be asked to rate their concentration, distractedness and focus related to this task on a 5 point Likert scale. The response to these ratings will be averaged.
- *Domain 3. Behavioral Health*. Participants will be asked about eating, drinking or chewing gum or smoking at the moment the phone rang. We will tabulate the average weekly frequency and intake of junk food, caffeine, alcohol, nicotine and other substances.
- *Domain 4. Social Health*. We will assess who the participant is with at the time of the call. Positivity Ratio (see EMA for Emotional Health) will be calculated when the participant is alone, with a family member or with a friend.
- *Domain 5. Physical Health*. Physical activity will be assessed using questions from previous research[53]. We will calculate a total of the binary variable (active = 1 and inactive = 2).[54]

The Youth Ecological Momentary Assessment (EMA) Composite Risk Score will be derived by taking the average scores for the week for each domain.

Participants will receive calls from a trained interviewer for one week at pre-treatment and one week at post-treatment. The frequency of the assessments will be twice on weekdays between 4 and 9pm and four times on weekends between 11am and 9pm, with a total of 36 calls for the entire study. Participants will be instructed to turn off their cell phones during school time. If a participant does not answer on the first attempt, the call will be attempted again immediately and then again after 5 minutes. There will be at least 30 minutes between each call. Each call will consist of a brief structured interview to evaluate the five health-relevant risk domains. The interview delivered at each phone call will be based on Silk et al.[49] and adapted to index each of the five health domains. The coding of the EMA will also be adapted from the methods of Silk et al.[49] Specifically, the interview responses will be transcribed verbatim into a primary database. From that database, five coders will independently code a subset of the data (5%) with agreement with an "expert coder" (NG). In order to be a certified coder, coders will have to match at over 80% accuracy with the expert coder for a minimum of 54 consecutive calls. Then each coder will independently code a subset of the data.

3.4.3. Parent-Reported Composite Risk Score via the Child Behavior Checklist (CBCL). [55]

The third cluster will be the *Parent-Reported Composite Risk Score* comprised of a composite score of parent responses to CBCL subscales representing the five health domains. Parents will rate this 113-item assessment of psychological and behavioral functioning of their child (rating scale 0-2; higher scores = more problematic behaviors). CBCL subscales will be used as the parent-reported composite risk score.

- *Domain 1. Emotional Health* will be assessed with the Anxious/Depressed and Withdrawn/Depressed subscale.
- *Domain 2. Cognitive Health* will be assessed with the Thought Problems and Attention Problems subscale.
- *Domain 3. Behavioral Health* will be assessed with the Rule-Breaking Behavior and Aggressive Behavior subscale.
- *Domain 4. Social Health* will be assessed with the Social Problems subscale.
- *Domain 5. Physical Health* will be assessed with the Somatic Complaints subscale.

3.5. Medications Tracking Log.

A Medications Tracking Log will be completed.

3.6. Credibility/expectancy questionnaire (CEQ)[74]

The CEQ will be administered at the end of the second therapy session to index expectation of improvement and credibility of treatment.

4. TIMELINE FOR ASSESSMENTS AND TREATMENT

Study flow is illustrated in Figure 1. Adolescents and parents/guardians will be screened via telephone. Eligible adolescents will complete a sleep diary for 7 nights to ascertain the presence of Inclusion. If met, an in-person assessment will be conducted during which the KSADS and questionnaires will be completed. If the participant continued to meet criteria, the activities from this point forward will be conducted within the school semester because holiday schedules differ markedly during adolescence[41].

To determine DLMO collection times and wake-up times, an additional 7 nights of sleep diary will be collected immediately prior to the overnight stay in the lab. The overnight assessment of DLMO will be conducted in the Psychology Department at the University of California, Berkeley and will be held on a Friday or Saturday night. The rationale for this choice is to ensure the protocol doesn't interfere with school. Groups of 1 to 5 participants will be tested each evening. Each participant will have their own bedroom. We will ensure the participant is exposed to <50 lux at all times, but prefer <20 lux. The lighting in each bedroom will be replaced with dim light bulbs. When the participant leaves the bedroom (e.g., to go to the bathroom) they will wear welding glasses. A light metre will be used to check the illumination of computer and cell phone screens. The light meter will be held next to participants eyes to measure the amount of light the participant is exposed to. Across the evening the participants will be allowed to engage in a narrow range of tasks that represent a standardized regiment of calm/quiet activities (e.g., reading, playing a board game, watching a movie, completing homework). We will assist the participants to set their computers/phones to the lowest brightness. In order to complete the DLMO protocol, the participant will stay up 45 minutes later relative to their usual school day bedtime. To minimize the impact of this, we will allow the participants to sleep in by 30 minutes relative to their usual school day waketime. The participant will arrive approximately 6.5 hours before their bedtime. If participants ingest anything except water before the saliva sample, they will rinse their mouths and

brushed their teeth with water. Ingestion of caffeine, fruits, chocolate, non-steroidal anti-inflammatory drugs, and alcohol will be prohibited.

After the overnight, the participant will be randomized and complete a further 7 night sleep diary and answer phone calls to collect Ecological Momentary Assessment (EMA) data. This additional sleep diary will be collected so that sleep diary data will be concurrent with EMA. These measures will be the basis of the primary and secondary outcomes. Treatment will commence one week later.

After treatment, the procedures for the overnight assessment to collect DLMO will be repeated, along with an in-person interview and 7-days of EMA and sleep diary. The participants will be reimbursed $30 for participating in the pre- and post-treatment assessments and $40 for the 6-FU and 12-FU. Parents will be reimbursed $30 for participating in the pre- and post-treatment assessments, $20 for the 6-FU, and $20 for the 12-FU.

5. DATA ANALYSIS

Sample size will be determined via power analysis. Power analyses will be conducted based on the average of Cohen's *d* (0.48) across estimations of the effect of treatment on sleep duration (for sleep outcomes) and the five primary health outcomes. Specifically, for sleep outcomes Cohen's *d* will be calculated from the pre-post deviation scores across TranS-C and Psychoeducation conditions. For the five health domains we will use: our pilot data for emotional health and behavioral health[56] recent meta-analyses for cognitive health and physical health[57,58]; and unpublished data from a collaborator's lab for the impact of poor sleep on social interactions. G*Power 3.1 was used to estimate sample size using Cohen's $d = 0.48$, assuming significance of 0.05 and power of at least 80%. Sixty nine participants are needed for each condition. We will recruit 20% more for potential attrition. There will be no interim analyses.

Data analysis will be conducted in Stata 14 (StataCorp, 2015). All analyses will be adjusted for age and sex, which will be the stratification factors used during randomization. Using intent-to-treat[32], multilevel modeling with maximum likelihood estimation with the assumption of missing at random will be used to examine continuous outcomes. The fixed component of the model will include stratification factors (age and sex), an indicator for time period (Time=0 pre-treatment, Time=1 post-treatment), an indicator for treatment condition (Treatment=1 TranS-C, Treatment=0 PE), and a Time by Treatment interaction term. The random part of the model will include a subject-specific random intercept and a time and subject-specific error term. The treatment effect of interest will be the interaction, representing the difference in mean change from pre-treatment to post-treatment between TranS-C and PE. The model will also provide estimates of the mean pre-to-post change in the PE condition (coefficient of Time) and in the TranS-C condition (coefficient of Time plus interaction coefficient), and the significance of these changes will also be reported regardless of the significance of the interaction because PE may be an active control and can be beneficial. Using Hochberg's[40] procedure, the outcomes will be considered two subfamilies of analyses. The error rate in each subfamily will be controlled under 0.025 using the Hochberg's step-up procedure, so that the overall family-wise error rate will not exceed 0.05.

Table 1. DESCRIPTIONS OF EVIDENCE BASED TREATMENT SOURCES FOR TRANS-C

Source	Description
Source 1. Cognitive Behavior Therapy for Insomnia (CBT-I).	There is robust evidence for CBT-I from multiple meta-analyses[10-13] and a systematic review for CBT-I in adults[4]. The evidence for CBT-I among adolescents is small but promising.[14-18] The studies conducted among youth to date include combining CBT-I components with mindfulness[14] or bright light,[16] delivering CBT-I over the internet or in a group[18] or in a classroom setting,[19] involving parents in the treatment [15] and including an emphasis on motivational interviewing.[19] Although much more treatment research is needed, this emerging literature justified including a focus on CBT-I in TranS-C. In particular, TranS-C-Youth draws on the CBT-I components that increase homeostatic pressure to sleep (stimulus control and sleep restriction) and reduce arousal (cognitive therapy).
Source 2. Delayed Sleep Phase Type (DSPT).	The broader spectrum of eveningness, rather than the extreme end represented by the disorder DSPT, is very common in teens. So this will be our focus. TranS-C-Youth will be informed by the small treatment literature on DSPT in youth,[16,20-22] as well as practice parameters[23] that indicate evidence for timed light exposure (with a light box) and planned and regular sleep schedules (chronotherapy) in adults. TranS-C-Youth includes the latter two interventions, with adaptations. First, many people are not motivated to use a light box; hence, TranS-C-Youth aims to help patients develop habits of exposing themselves to natural morning light and evening dim light with youth-selected electronic curfews. Second, traditional chronotherapy involving progressively delaying bedtimes and waketimes until reaching the desired alignment can be highly disruptive to family and work schedules. Third, in a study of 1285 high school students in Norway, the majority of students with delayed sleep phase (8.4%) reported considerable difficulty advancing bedtimes.[24] As such, in TranS-C-Youth we tend to adopt a planned sleep modification protocol involving moving bedtimes earlier by 20-30 minutes per week. We select this slow change approach on the basis of our clinical experience, which is mainly with teens who have a severe mental illness or who are 'at risk' in one or more domains of their lives. With these youth we have found this schedule to be achievable and we capitalize on the youth's feeling a sense of accomplishment, which further increases motivation for change. However, it should be noted that it is possible that the schedule we are currently using in TranS-C might maintain a disrupted lifestyle among youth given that the process of changing times once per week could take 5 weeks to complete. Research to determine the ideal sleep modification for the various groups of youth, and that balances circadian and motivational processes, is needed.
Source 3. Interpersonal and social rhythms therapy (IPSRT).	IPSRT is a treatment approach that is designed to maintain stability in social rhythms. The evidence base for stabilizing circadian rhythms with IPSRT in bipolar disorder and depression is growing, including in adolescence.[25-27] Teens tend to have irregular sleep/wake cycles and social and personal schedules. In particular, waking early on weekdays for school, college or work and then sleeping in on weekends[28] can result in a chronically jet-lagged state to which the human circadian system cannot adjust. Accordingly, TranS-C-Youth includes aspects of IPSRT deigned to stabilize bed and wake rhythms, as well as other social rhythms (eg, meal times, socializing, exercise etc), drawing from the treatment manual developed by Frank *et al*.[29] This is because the sleep and circadian systems are surprisingly sensitive to non-photic cues, including physical activity and social interaction. Hence, stabilizing these daily rhythms help stabilize the sleep-wake schedule.

Table 2: CALCULATIONS OF SLEEP DIARY VARIABLES

Sleep Diary variables	Calculation
Total sleep time (TST)	time in bed – sleep onset latency - wake after sleep onset - terminal wakefulness.
Time in bed	time getting into bed – time getting out of bed
Sleep onset latency	time to fall asleep
Wake after sleep onset	sum of the duration of each awakening after sleep onset
Terminal wakefulness	time getting out of bed for the day - time of the final awakening
Bedtime	time getting into bed
Wakeup time	time of final awakening
Discrepancy between weeknights and weekends for total sleep time, bedtime, and wakeup time	Weeknight average - weekend average for total sleep time, bedtime, wakeup time

Note. Definition derived based on Buysse et al. (2006) and Carney et al (2012)

References: Carney, C. E., Buysse, D. J., Ancoli-Israel, S., Edinger, J. D., Krystal, A. D., Lichstein, K. L., & Morin, C. M. (2012). The consensus sleep diary: standardizing prospective sleep self-monitoring. *Sleep*, *35*(2), 287-302.
Buysse, D. J., Ancoli-Israel, S., Edinger, J. D., Lichstein, K. L., & Morin, C. M. (2006). Recommendations for a standard research assessment of insomnia. *Sleep*, *29*(9), 1155–1173.

REFERENCES

1. Harvey AG, Buysse DJ. Treating Sleep Problems: A Transdiagnostic Approach. New York: Guilford; in press.
2. Harvey AG. A transdiagnostic approach to treating sleep disturbance in psychiatric disorders. Cognitive Behavior Therapy. 2009;38:35-42.
3. Harvey AG. A Transdiagnostic Intervention for Youth Sleep and Circadian Problems. Cognitive and Behavioral Practice. 2015;23(3):341-355.
4. Morin CM, Bootzin RR, Buysse DJ, Edinger J, D., Espie CA, Lichstein KL. Psychological and behavioral treatment of insomnia: An update of recent evidence (1998-2004). Sleep. 2006;29:1396-1406.
5. Morin CM, Espie CA. Insomnia : A clinical guide to assessment and treatment. New York: Kluwer Academic/Plenum Publishers; 2003.
6. Perlis ML, Aloia M, Kuhn B. Behavioral Treatment for Sleep Disorders: A Comprehensive Primer of Behavioral Sleep Medicine. Amsterdam: Elsevier; 2011.
7. Frank E, Kupfer DJ, Thase ME, et al. Two Year Outcomes for interpersonal and social rhythm therapy in individuals with bipolar I disorder. Archives of General Psychiatry. 2005;62:996-1004.
8. Wirz-Justice A, Benedetti F, Terman M. Chronotherapeutics for Affective Disorders: A Clinician's Manual for Light & Wake Therapy. 1 ed. Basel: Karger; 2009.
9. Miller WR, Rollnick S. Motivational interviewing: Preparing people for change. New York: Guilford Press; 2002.
10. Murtagh DR, Greenwood KM. Identifying effective psychological treatments for insomnia: a meta-analysis. Journal of Consulting and Clinical Psychology. 1995;63:79-89.
11. Smith MT, Perlis ML, Park A, et al. Comparative meta-analysis of pharmacotherapy and behavior therapy for persistent insomnia. American Journal of Psychiatry. 2002;159:5-11.
12. Irwin MR, Cole JC, Nicassio PM. Comparative Meta-Analysis of Behavioral Interventions for Insomnia and Their Efficacy in Middle-Aged Adults and in Older Adults 55+ Years of Age. Health Psychology. 2006;25:3-14.
13. Morin CM, Culbert JP, Schwartz SM. Nonpharmacological Interventions for insomnia: a meta-analysis of treatment efficacy. American Journal of Psychiatry. 1994;151:1172-1180.
14. Bootzin RR, Stevens SJ. Adolescents, substance abuse, and the treatment of insomnia and daytime sleepiness. Clinical Psychology Review. 2005;25:629-644.
15. Schlarb A, Liddle C, Hautzinger M. JuSt-a multimodal program for treatment of insomnia in adolescents: a pilot study. Nature and Science of Sleep. 2010;3:13-20.
16. Gradisar M, Dohnt H, Gardner G, et al. A randomized controlled trial of cognitive-behavior therapy plus bright light therapy for adolescent delayed sleep phase disorder. Sleep. 2011;34(12):1671.

17. Paine S, Gradisar M. A randomised controlled trial of cognitive-behaviour therapy for behavioural insomnia of childhood in school-aged children. Behaviour research and therapy. 2011;49(6):379-388.
18. de Bruin EJ, Oort FJ, Bögels SM, Meijer AM. Efficacy of internet and group-administered cognitive behavioral therapy for insomnia in adolescents: A pilot study. Behavioral sleep medicine. 2014;12(3):235-254.
19. Cassoff J, Knäuper B, Michaelsen S, Gruber R. School-based sleep promotion programs: Effectiveness, feasibility and insights for future research. Sleep medicine reviews. 2013;17(3):207-214.
20. Okawa M, Uchiyama M, Ozaki S, Shibui K, Ichikawa H. Circadian rhythm sleep disorders in adolescents: Clinical trials of combined treatments based on chronobiology. Psychiatry & Clinical Neurosciences. 1998;52(5):483-490.
21. Regestein QR, Monk TH. Delayed sleep phase syndrome: A review of its clinical aspects. American Journal of Psychiatry. 1995;152:602-608.
22. Gradisar M, Smits MG, Bjorvatn B. Assessment and Treatment of Delayed Sleep Phase Disorder in Adolescents: Recent Innovations and Cautions. Sleep Medicine Clinics. 2014.
23. Sack RL, Auckley D, Carskadon MA, Wright KPJ, Vitiello MV, Zhdanova IV. Circadian rhythm sleep disorders: Part II, advanced sleep phase disorder, delayed sleep phase disorder, free-running disorder, and irregular sleep-wake rhythm: An American academy of sleep medicine review. Sleep: Journal of Sleep and Sleep Disorders Research. 2007;30:1484-1501.
24. Saxvig IW, Pallesen S, Wilhelmsen-Langeland A, Molde H, Bjorvatn B. Prevalence and correlates of delayed sleep phase in high school students. Sleep medicine. 2012;13(2):193-199.
25. Miklowitz DJ, Otto MW, Frank E, et al. Psychosocial treatments for bipolar depression: a 1-year randomized trial from the systematic treatment enhancement program. Archives of General Psychiatry. 2007;64:419-426.
26. Frank E, Kupfer DJ, Thase ME, et al. Two-year outcomes for interpersonal and social rhythm therapy in individuals with bipolar I disorder. Archives of General Psychiatry. 2005;62:996-1004.
27. Hlastala SA, Kotler JS, McClellan JM, McCauley EA. Interpersonal and social rhythm therapy for adolescents with bipolar disorder: Treatment development and results from an open trial. Depression and Anxiety. 2010;27:456-464.
28. Hysing M, Pallesen S, Stormark KM, Lundervold AJ, Sivertsen B. Sleep patterns and insomnia among adolescents: a population-based study. Journal of sleep research. 2013;22(5):549-556.
29. Frank E. Treating bipolar disorder: A clinician's guide to interpersonal and social rhythm therapy. NY: Guilford Press; 2005.
30. Harvey AG, Soehner AM, Kaplan KA, et al. Treating insomnia improves sleep, mood and functioning in bipolar disorder: A pilot randomized controlled trial. Journal of Consulting and Clinical Psychology. 2015;83(3):564-577.

31. Ryan RM, Deci EL. Self-determination theory and the facilitation of intrinsic motivation, social development, and well-being. American psychologist. 2000;55(1):68.
32. Lewy AJ. Circadian Rhythms and Mood Disorders: A Guide for the Perplexed. The Journal of clinical psychiatry. 2015;76(5):1,478-664.
33. Scheer FA, Czeisler CA. Melatonin, sleep, and circadian rhythms. Sleep medicine reviews. 2005;9(1):5-9.
34. Kauchi M, Shimazu Y. Optimization of Burnable Poison-Loading in a PWR with Carbon Coated Particle Fuel. American Nuclear Society, 555 North Kensington Avenue, La Grange Park, IL 60526 (United States);2002.
35. Crowley SJ, Acebo C, Fallone G, Carskadon MA. Estimating dim light melatonin onset (DLMO) phase in adolescents using summer or school-year sleep/wake schedules. SLEEP-NEW YORK THEN WESTCHESTER-. 2006;29(12):1632.
36. Crowley SJ, Suh C, Molina TA, Fogg LF, Sharkey KM, Carskadon MA. Estimating the dim light melatonin onset of adolescents within a 6-h sampling window: the impact of sampling rate and threshold method. Sleep Medicine. 2016;20:59-66.
37. Lewy AJ, Sack RA, Singer CL. Assessment and treatment of chronobiologic disorders using plasma melatonin levels and bright light exposure. Psychopharmacology bulletin. 1984;20(3):561-565.
38. Lewy AJ, Sack RL. The dim light melatonin onset as a marker for circadian phase position. Chronobiol Int. 1989;6:93-102.
39. Pandi-Perumal SR, Smits M, Spence W, et al. Dim light melatonin onset (DLMO): a tool for the analysis of circadian phase in human sleep and chronobiological disorders. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2007;31(1):1-11.
40. Wyatt J, Stepanski E, Kirkby J. Circadian phase in delayed sleep phase syndrome: predictors and temporal stability across multiple assessments. Sleep. 2006;29(8):1075-1080.
41. Poznanski EO, Grossman JA, Buchsbaum Y, Banegas M, Freeman L, Gibbons R. Preliminary studies of the reliability and validity of the children's depression rating scale. Journal of the American Academy of Child Psychiatry. 1984;23:191-197.
42. March JS, Sullivan K, Parker J. Test-retest reliability of the Multidimensional Anxiety Scale for Children. Journal of anxiety disorders. 1999;13(4):349-358.
43. Derryberry D, Reed MA. Anxiety-related attentional biases and their regulation by attentional control. Journal of Abnormal Psychology. 2002;111:225-236.
44. Weissman MM, Orvaschel H, Padian N. Children's symptom and social functioning self-report scales. Comparison of mothers' and children's reports. The Journal of Nervous and Mental Disease. 1980;168:736-740.
45. Hoyle RH, Stephenson MT, Palmgreen P, Lorch EP, Donohew RL. Reliability and validity of a brief measure of sensation seeking. Personality and individual differences. 2002;32(3):401-414.

46. Johnston LD, O'Malley PM, Bachman JG, Schulenberg JE. Monitoring the Future: National Results on Adolescent Drug Use. Overview of Key Findings, 2008. National Institute on Drug Abuse (NIDA). 2009.
47. Aaron DJ, Kriska AM. Modifiable activity questionnaire for adolescents. Medicine and Science in Sports and Exercise. 1997;29:s79-s82.
48. Kroenke K, Spitzer RL, Williams JB. The PHQ-15: validity of a new measure for evaluating the severity of somatic symptoms. Psychosomatic medicine. 2002;64(2):258-266.
49. Silk JS, Forbes EE, Whalen DJ, et al. Daily emotional dynamics in depressed youth: A cell phone ecological momentary assessment study. Journal of experimental child psychology. 2011;110(2):241-257.
50. Laurent J, Catanzaro SJ, Joiner TE, Jr., et al. A measure of positive and negative affect for children: Scale development and preliminary validation. Psychological Assessment. 1999;11(3):326-338.
51. Diener E. Subjective well-being: The science of happiness and a proposal for a national index. American Psychologist. 2000;55:34-43.
52. Dagys N, McGlinchey EL, Talbot L, Kaplan K, Dahl RE, Harvey A. Double Trouble? Chronotype, Sleep Deprivation and Adolescence. Journal of Child Psychology and Psychiatry. in press:PMCID: PMC Journal - In Process.
53. Rofey DL, Hull EE, Phillips J, Vogt K, Silk JS, Dahl RE. Utilizing Ecological Momentary Assessment in pediatric obesity to quantify behavior, emotion, and sleep. Obesity. 2010;18:1270-1272.
54. Kanning M, Schlicht W. Be active and become happy: an ecological momentary assessment of physical activity and mood. Journal of sport & exercise psychology. 2010;32(2):253.
55. Achenbach TM, Rescorla LA. Manual for the ASEBA School-Age Forms & Profiles: Child Behavior Checklist for Ages 6 - 18, Teacher's Report Form, & Youth Self-Report. Burlington, VT: University of Vermont, Research Center for Children, Youth & Families; 2001.
56. Talbot LS, McGlinchey EL, Kaplan KA, Dahl RE, Harvey AG. Sleep deprivation in adolescents and adults: changes in affect. Emotion. 2010;10(6):831-841.
57. Dewald JF, Meijer AM, Oort FJ, Gerard A, Kerkhof GA, Bogels SM. The influence of sleep quality, sleep duration and sleepiness on school performance in children and adolescents: A meta-analytic review. Sleep Medicine Reviews. 2010;14:179-189.
58. Cappuccio FP, Taggart FM, Kandala NB, et al. Meta-analysis of short sleep duration and obesity in children and adults. Sleep. 2008;31:619-626.
59. Horne JA, Ostberg OA. A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. Int J Chronobiol. 1976;4:97-110.
60. Gradisar M, Gardner G, Dohnt H. Recent worldwide sleep patterns and problems during adolescence: a review and meta-analysis of age, region, and sleep. Sleep Med. 2011;12: 110-118.
61. Maslowsky J, Ozer EJ. Developmental trends in sleep duration in adolescence and young adulthood: evidence from a national United States sample. J Adolesc Health. 2014;54: 691-697.

62. Gianotti F, Cortesi F. Sleep patterns and daytime function in adolescence: an epidemiological survey of an Italian high school student sample. In: Carskadon MA, ed. Adolescent Sleep Patterns: Biological, Social, and Psychological Influences. Cambridge, UK: Cambridge University Press; 2002:132-147.
63. Becker SP, Ramsey RR, Byars KC. Convergent validity of the Child Behavior Checklist sleep items with validated sleep measures and sleep disorder diagnoses in children and adolescents referred to a sleep disorders center. Sleep Med. 2015;16:79-86.
64. Poznanski E, Freeman L, Mokros H. Childrens Depression Rating ScaleRevised. Psychopharmacol Bull. 1985;21:979-989.
65. Kaufman J, Birmaher B, Brent D, et al. Schedule for Affective Disorders and Schizophrenia for School-Age ChildrenPresent and Lifetime Version (K-SADS-PL): initial reliability and validity data. J Am Acad Child Adolesc Psychiatry. 1997;36:980-988.
66. Russo MF. A sensation seeking scale for children: further refinement and psychometric development. J Psychopathol Behav Assess. 1993;15:69-86.
67. Stephenson MT, Hoyle RH, Palmgreen P, Slater MD. Brief measures of sensation seeking for screening and large-scale surveys. Drug Alcohol Depend. 2003;72: 279-286.
68. Young J, Beck A. Cognitive Therapy Scale: Rating Manual. Philadelphia: University of Pennsylvania; 1980.
69. Bei B, Allen NB, Nicholas CL, Dudgeon P, Murray G, Trinder J. Actigraphy-assessed sleep during school and vacation periods: a naturalistic study of restricted and extended sleep opportunities in adolescents. J Sleep Res. 2014;23:107-117.
70. Carney CE, Buysse DJ, Ancoli-Israel S, et al. The consensus sleep diary: standardizing prospective sleep self-monitoring. Sleep. 2012;35:287-302.
71. Wolfson AR, Carskadon MA. Sleep schedules and daytime functioning in adolescents. Child Dev. 1998;69:875-887.
72. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989;28:193-213.
73. de la Vega R, Tome-Pires C, Sole E, et al. The Pittsburgh Sleep Quality Index: validity and factor structure in young people. Psychol Assess. 2015;27:e22.
74. Carskadon MA, Vieira C, Acebo C. Association between puberty and delayed phase preference. Sleep. 1993;16:258-262.