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Gaëlle Rached
Cleveland Clinic
Emma Kate Baker
Flinders University
Makoto Kawai
Stanford University
Ruth O'Hara
Stanford University
Booil Jo
Stanford University
Lawrence Fung
Stanford University
Philippe Mourrain
Stanford University
Jennifer Phillips
Stanford University
Joachim Hallmayer
Stanford University
Antonio Y Hardan
hardanay@stanford.edu

Stanford University

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A Randomized Double-Blind Controlled Trial of Hypnotics in Children with Autism Spectrum Disorder: Study Design and Statistical Considerations

Gaëlle Rached, MD, MSc[1], Emma Kate Baker PhD[2], Makoto Kawai, MD[3], Ruth O'Hara, PhD[3], Booil Jo, PhD[3], Lawrence Fung, MD, PhD[3], Philippe Mourrain, PhD[3], Jennifer Phillips, PhD[3], Joachim Hallmayer, MD[3], Antonio Y Hardan, MD[3*]

1 Department of Psychiatry and Psychology, Center for Behavioral Health, Neurological Institute, Cleveland Clinic, Cleveland, OH, USA.
2 Flinders Health and Medical Research Institute (Sleep Health), Flinders University, Bedford Park, South Australia, Australia
3 Department of Psychiatry and Behavioral Sciences, Stanford University, Stanford, CA, United States

Corresponding author: Antonio Y Hardan MD, hardanay@stanford.edu

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Abstract (350 words)

Background
Sleep disturbances are highly prevalent in children with autism spectrum disorder (autism), contributing to significant behavioral difficulties and family stress. Behavioral interventions and melatonin are considered first-line treatments. However, many children do not respond to these treatments, thereby necessitating other pharmacological interventions with few studies have examined how these medications impact sleep physiology in this population. Altered sleep architecture in autistic individuals, including sleep onset delay, reduced rapid eye movement (REM) sleep, Non-REM sleep fragmentation, and abnormal Non-REM slow wave sleep, may be influenced by pharmacologic agents. The investigations discussed here address critical gaps by evaluating the effects of three hypnotic agents, diphenhydramine, zolpidem, and suvorexant, on objective sleep measures in autistic children.

Methods
This report summarizes the design of three randomized, double-blind, placebo-controlled crossover trials evaluating diphenhydramine, zolpidem, and suvorexant in children and adolescents with autism aged 8–17 years. Each 8-week trial enrolls 26 participants, with a crossover from placebo to active treatment (or vice versa) at week four. Recruitment began in August 2023 and is ongoing at Stanford University. Objective sleep assessments include polysomnography (PSG), actigraphy, Withings Sleep Sensor mat, and salivary biomarkers for melatonin and cortisol. Baseline evaluations include comprehensive diagnostic, neuropsychological, and behavioral assessments. Safety and efficacy are monitored using standardized tools, including the Dosage Record Treatment Emergent Symptom Scale (DOTES) and the Clinical Global Impression (CGI) scale. Primary outcomes include changes in sleep architecture (sleep latency, NREM consolidation and quantity, REM quantity, total sleep time, sleep efficiency), while secondary outcomes evaluate the impact on core autism features and associated behaviors. Linear mixed-effects models will estimate treatment effects.

Discussion
The studies discussed here are the first investigations to systematically evaluate the effects of these three pharmacologic agents on sleep architecture in autistic children using gold-standard sleep assessments. By targeting distinct neurochemical pathways, histaminergic, GABAergic, and hypocretinergic/orexinergic, this research may elucidate mechanisms underlying sleep dysfunction in autism. Findings may inform personalized, effective sleep interventions, improving daytime functioning and quality of life for autistic children and their families.

Trial registration

These trials are registered through clinicaltrials.gov: NCT05501678 registered 2022-08-15 (Diphenhydramine) https://clinicaltrials.gov/study/NCT05501678, NCT05540574 registered

2022-09-14 (Zolpidem) https://clinicaltrials.gov/study/NCT05540574, and NCT05546554 registered 2022-09-21 (Suvorexant) https://clinicaltrials.gov/study/NCT05546554.
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Keywords (3 at least)

Autism Spectrum Disorder, Sleep disorders, sleep fragmentation/nighttime awakenings, psychopharmacology, diphenhydramine, zolpidem, suvorexant.

Manuscript

1. Background

Sleep disturbances in children with autism spectrum disorder (hereafter autism) represent a significant clinical challenge with a profound impact on patients and their families (1). Autism is a neurodevelopmental disorder characterized by social communication challenges, sensory sensitivities, and repetitive/restricted behaviors (RRBs; American Psychiatric Association, 2013). Sleep disruptions in this population include bedtime resistance, prolonged sleep latency, reduced total sleep, decreased sleep efficiency, reduced total sleep time, increased wake after sleep onset (WASO), sleep fragmentation, and daytime sleepiness (3–8). Sleep problems in autistic children are associated with increased daytime attentional, learning, and behavioral issues, including increased aggression, and represent a primary source of stress for parents/caregivers. Parental reports indicate that insufficient sleep tends to exacerbate the severity of core autism behaviors (RRB and social communication difficulties) (9,10) and other maladaptive behaviors (e.g., self-injury, tantrums, and aggression) (11,12). Moreover, the child's sleep problems frequently disrupt the sleep and well-being of the entire family unit (13).

Thus, normalization of sleep could have a substantial impact on the overall health of both the child and the family. Although the precise role of the full human sleep architecture, typically described as five cycles of alternating NREM and REM sleep bouts, remains incompletely understood, several critical biological functions have been clearly demonstrated for NREM sleep, which accounts for approximately 80% of total sleep time (14). These functions include growth hormone production (15,16), synaptic remodeling (17), neuronal genomic DNA repair (18,19), toxin clearance, and glymphatic activity (20,21). Among NREM stages, slow-wave sleep (SWS) is the most restorative and is particularly critical for energy homeostasis and many of the processes noted above (17). In contrast to common assumptions, the definition and functional roles of REM sleep remain largely unclear (22), with emotional memory consolidation being the most consistently supported function (23). Consequently, sleep onset delay and sleep fragmentation disproportionately disrupt NREM sleep, particularly SWS, thereby impairing biological processes essential for brain development, neural wiring, homeostasis, repair, and overall health (17). It is therefore essential to investigate targeted interventions aimed at improving sleep in individuals with ASD, with a specific focus on enhancing NREM and SWS initiation, as well as NREM consolidation and quantity throughout the night.

Behavioral interventions and parent-based psychoeducation are recommended first-line treatments for sleep disturbances in autism (24,25). These approaches have demonstrated modest improvements in sleep outcomes among children and adolescents with ASD (26,4). Nonetheless, pharmacological options are often required when these approaches are insufficient (25). Melatonin is the most commonly used pharmacological agent, with numerous randomized controlled trials and meta-analyses supporting its use

in autistic children (27). Owing to its over-the-counter availability, melatonin has become widely used as a form of self-medication for sleep difficulties. Nevertheless, melatonin is not a hypnotic per se. Meta-analysis studies have shown that it has little to no effect on sleep quantity or sleep architecture (28,29). As a primary output signal of the circadian clock, melatonin is secreted exclusively during the dark phase and serves chiefly to convey circadian timing information to the brain and peripheral tissues (30). Accordingly, its therapeutic efficacy is greatest in circadian rhythm disorders, such as jet lag or delayed sleep–wake phase disorder, rather than in directly inducing or maintaining sleep (31,32). Alternative pharmacological agents with true hypnotic properties should therefore be considered.

Other medications such as antihistaminergic/H1 receptor antagonists, GABA agonists (benzodiazepine and nonbenzodiazepine such as zolpidem), and dual hypocretin/orexin receptor antagonists (DORAs; e.g., suvorexant) are agents that could target sleep problems in children, including autism (33). However, to our knowledge, there are no randomized controlled trials (RCTs) examining the effects of any hypnotic agents on sleep in autism, particularly on sleep physiology.

Hypnotic agents used to treat sleep issues can be broadly classified into two mechanistic categories: antagonists of wake-promoting circuits, such as antihistamines and dual orexin receptor antagonists (DORAs), and modulators of sleep-promoting circuits, such as GABA receptor agonists including benzodiazepines and non-benzodiazepine “Z-drugs.” Diphenhydramine (Benadryl), suvorexant (Belsomra), and zolpidem (Ambien) exemplify these distinct pharmacological classes and act on different neurotransmitter systems involved in sleep–wake regulation. Importantly, despite their divergent mechanisms, all three agents have demonstrated beneficial effects on sleep architecture, with particular efficacy in enhancing NREM sleep. Diphenhydramine and other H1 antihistamines promote sleep primarily through antagonism of histaminergic wake-promoting neurons and have consistently been shown to reduce sleep onset latency and increase NREM sleep duration, including slow-wave sleep (SWS) (34–37). In neurotypical adults, diphenhydramine decreases sleep latency and increases total sleep time without significant next-day psychomotor impairment or rebound insomnia (38,39). Similar effects have been reported in children, including reductions in sleep latency and nocturnal awakenings with modest increases in sleep duration (40–42). Although diphenhydramine possesses anticholinergic properties that may contribute to side effects, this mechanism may also partially underlie its efficacy in promoting NREM sleep, which is physiologically characterized by low cholinergic tone relative to wakefulness and REM sleep.

More recently, DORAs such as suvorexant have gained attention for their ability to consolidate sleep by selectively inhibiting orexin-mediated arousal. Unlike many traditional hypnotics that primarily facilitate sleep initiation, DORAs are particularly effective at reducing nighttime awakenings and stabilizing sleep across the night, with a predominant effect on NREM sleep. In neurotypical adults with primary insomnia, suvorexant has been shown to reduce sleep latency, increase total sleep time, and

improve subjective sleep quality without adverse neurophysiological effects (43). Preliminary evidence in non-autistic adolescents suggests similar improvements in sleep quality and duration with good tolerability (44). Although DORAs have not yet been systematically evaluated for pediatric sleep fragmentation, their NREM-consolidating properties make them an especially promising therapeutic option for disorders characterized by frequent nocturnal awakenings, including ASD.

Finally, zolpidem, a non-benzodiazepine GABA A receptor agonist, acts by enhancing inhibitory GABAergic signaling within sleep-promoting circuits. Disruptions in GABA signaling have been consistently reported in autistic individuals and are thought to contribute to altered sleep regulation (45). Meta-analyses of randomized, placebo-controlled trials in adults demonstrate that zolpidem reliably reduces sleep latency, decreases the number of nighttime awakenings, and increases total sleep time, with associated improvements in subjective sleep quality (8,46–48). These effects are largely mediated through increases in NREM sleep quantity and stability, supporting the relevance of GABAergic modulation as a mechanistically grounded approach for improving sleep architecture

Despite the high prevalence of sleep disturbances and altered sleep physiology in autistic individuals, few studies have used objective measures to examine the effects of various therapeutic agents on sleep physiology (45). More critically, very few studies have examined the efficacy of hypnotic agents in autism using a randomized controlled trial design (45). Polysomnography (PSG) provides insights into the underlying sleep architecture, yet its application in treatment studies targeting sleep in autism remains sparse (49,50). This is in part due to the high cost and high rate of sensory sensitivities experienced by autistic individuals, leading to difficulties with compliance with PSG assessment. These limitations have impeded the development and delivery of targeted, etiologically based treatments. However, research has demonstrated that systematic desensitization protocols can significantly enhance the success rates of PSG and other objective sleep assessments (e.g., actigraphy) in autistic individuals (51).

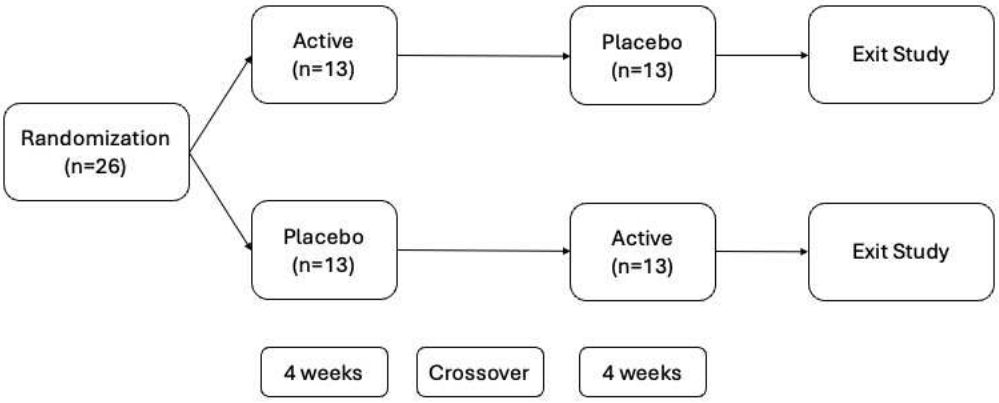
The goal of this manuscript is to summarize the design of 3 studies that aimed to systematically evaluate the effects of three pharmacological agents, diphenhydramine, zolpidem, and suvorexant, on sleep architecture in children with autism, employing a robust randomized double-blind crossover placebo-controlled design. By addressing this gap, we aim to provide a better understanding of how targeted sleep interventions can improve sleep and daytime functioning in autistic youth. Our pharmacological probing study of sleep architecture will allow us to, for the first time, examine whether we can effectively modulate altered sleep parameters in autism and assess their impact on sleep quality, clinical features, and daytime functioning.

2. Methods and Study Design

a. Study Design and Rationale

This study comprises three separate randomized double-blind, crossover, placebo-controlled 8-week trials (NCT05501678, NCT05540574, and NCT05546554). For further information, contact the corresponding author, Antonio Y. Hardan, MD. Each trial aims to evaluate the effects of one of the three hypnotic agents on sleep physiology in autistic children and adolescents between the ages of 8 and 17 years. Subjects randomized to the placebo group during the first four weeks will crossover to the active group during the second 4 weeks. Similarly, subjects receiving the active compound during the first four weeks will receive the placebo during the second 4 weeks. The crossover design ensures that participants serve as their own controls, reducing confounding variables and allowing for more precise estimation of treatment effects. Each trial will include 26 participants, with a total of 78 participants across the three trials (Figure 1).

Figure 1. Participant Enrollment, Randomization, and Flow Through the Double-Blind Crossover Trial



During this trial, PSG, actigraphy, and saliva samples will be collected at baseline, after the 1st four weeks, and again at the end of the trial (week 8) before exiting the study. Additionally, after a participant exits one trial (e.g., diphenhydramine), they will be invited to enroll in another trial (e.g., zolpidem or suvorexant) if they are interested and remain eligible.

The Stanford Autism Center Parent Advisory Board and the Autism Center of Excellence Advisory Board provided input into the design of this trial and continue to inform its implementation. This trial is coordinated by the Department of Psychiatry and Behavioral Sciences at Stanford University. All procedures are performed by trained personnel under

the supervision of the principal investigator and Dr. Makoto Kawai, co-Investigator, who is a sleep specialist. Data management is conducted using REDCap (Research Electronic Data Capture); further detail is provided in Data Management and Security section. Trial oversight is provided by the Stanford University Institutional Review Board and an independent Data and Safety Monitoring Board (DSMB), comprising Glen Elliot, MD, Rachel Manber, PhD, and Tamar Green, MD, with Booil Jo, PhD serving as a non-voting biostatistician member. No separate steering committee or endpoint adjudication committee is used for this trial.

Parents/guardians sign an informed consent form prior to participating in any study activities, and children aged 12 years and above who are capable of understanding the study requirements also sign an assent form. An investigational new drug (IND) exemption was obtained for the diphenhydramine trial, and IND applications were filed for the zolpidem and suvorexant trials. Important protocol modifications require approval from the NICHD program officer, submission to the FDA as an amendment to the IND application for the zolpidem and suvorexant trials, and approval from the Stanford University Institutional Review Board, prior to implementation.

b. Participants

Recruitment

Participants will be recruited through multiple channels, including the Simons Foundation Powering Autism Research (SPARK) research match program, the Stanford Autism and Developmental Disorders research registry, social media outreach, study flyers, and presentations at scientific and community conferences.

Pre-Treatment Screening Phase

After providing informed consent, eligible participants will undergo a comprehensive screening process, including the collection of demographic information, medical and psychiatric history, and full diagnostic and cognitive testing (Table 2), including diagnostic confirmation of autism. Diagnostic evaluations will include the Autism Diagnostic Interview-Revised (ADI-R) (52,53) and the Autism Diagnostic Observation Schedule-2nd Edition (ADOS-2) (54) to confirm ASD diagnoses based on DSM-5 criteria. Intellectual functioning will be measured using the Stanford Binet, 5th Edition (SB5) (55), while adaptive behavior will be assessed with the Vineland Adaptive Behavior Scales, Third Edition (VABS-3) (56). Children also complete the Affect Recognition subtest of the NEuroPSYchological Assessment, 2nd Edition (NEPSY-2) (57).

As part of this initial, neuropsychological evaluation, parents also complete a comprehensive questionnaire battery including assessment of behavioral and social functioning, and pubertal status with the following measures: the Child Behavior Checklist (CBCL) (Achenbach & Ruffle, 2000), Social Responsiveness Scale-2 (SRS-2) (58), Repetitive Behavior Scale-Revised (RBS-R) (59), Sensory Profile Questionnaire (SPQ) (60,61), Stanford Social Dimension Scale (SSDS) (62), Dimensional Assessment of Repetitive Behaviors

(DARB) (63), Aberrant Behavior Checklist, Second Edition (ABC-2) (64), the Tanner Staging Questionnaire.

Once the diagnosis of autism has been confirmed, participants undergo a sleep assessment. This assessment includes a detailed sleep history, 2 nights of PSG for a detailed physiological sleep assessment, actigraphy for objective monitoring of sleep-wake patterns, and saliva samples for analysis of cortisol and melatonin levels. The sleep history gathers information pertaining to the presence and duration of difficulties falling asleep, sleep continuation difficulties, early morning awakenings, sleep location, bedtime routine, and naps. The following sleep questionnaires will also be collected: Child Sleep Health Questionnaire (CSHQ) and Parent Sleep Health Questionnaire (PSHQ). The CSHQ is the most frequently employed measure assessing the quality and type of sleep experienced by children and has been used in multiple studies to examine sleep behavior in individuals with neurodevelopmental diagnoses (65–68). Thirty-three items are grouped into 8 subscales of CSHQ: bedtime resistance, sleep onset delay, sleep duration, sleep anxiety, night wakings, parasomnias, sleep disordered breathing (SDB), and daytime sleepiness. Owens et al. (69) demonstrated internal consistency and validity of the CSHQ. The PSHQ is a self-report measure of caregiver sleep that was adapted from the CSHQ (70). Thirty-one items are grouped into 5 subscales: daytime sleepiness, night wakings, sleep duration, parasomnias, and general sleep problems.

Importantly, due to the high rates of sensory sensitivities in autistic individuals, families have the option to undergo a systematic desensitization protocol to prepare the participant for the PSG, as well as get them accustomed to the sleep PSG cap. This protocol enables families to receive a PSG cap in advance and systematically increase the time their child wears the cap. Previous work by our team has shown this to be an effective strategy for increasing adherence to PSG in autistic children (51). Upon completion of the aforementioned pre-treatment screening process, participants undergo further trial-specific screening to determine eligibility for the medication trials. Additionally, to optimize participation among autistic individuals with severe symptomatology, modifications to the protocols were made to accept actigraphy as the sole measure, and the PSG was not required for all participants.

c. Inclusion/Exclusion Criteria

Eligible participants have screening visits performed within 6 weeks of the baseline visits to ensure they meet all inclusion and exclusion criteria listed in Tables 1 and 2, respectively. Planned recruitment characteristics across the six core PRO EDI domains (age, sex, gender, race/ethnicity/ancestry, socioeconomic status, and geographic location) are summarized in Table 3. Participants taking specific medications known to interact with the study drugs will be excluded from the relevant trial. These include melatonin, benzodiazepines, antiepileptic drugs (when indicated for epilepsy/seizure disorder), centrally-acting antihistamines, and other agents with potential interactions specific to each trial drug. Children taking anticholinergic agents (e.g., trihexyphenidyl, thioridazine)

and medications inhibiting CYP2D6 will be excluded from the diphenhydramine trial. Children taking medications that inhibit CYP3A4 and CYP1A2 will be excluded from the zolpidem trial. Children taking agents that inhibit CYP3A will be excluded from the suvorexant trial.

Table 1: Inclusion Criteria by Study Drug

Inclusion Criteria	**DPH**	**Zolpidem**	**Suvorexant**
Outpatients between 8 and 17 years of age at time of consent (initial proposal)	x	x	x
Current age range after FDA input	8-17 years	12-17 years	13-17 years
DSM-5 criteria for ASD confirmed with ADI-R and ADOS-2	x	x	x
Males and females	x	x	x
Availability of PSG and/or actigraphy data	x	x	x
Sleep disturbances (CSHQ score ≥41)	x	x	x
Reliable care provider	x	x	x
Stable medications (≥2 weeks, Prozac ≥4 weeks)	x	x	x
No planned changes in interventions	x	x	x
Willingness to participate in study procedures	x	x	x
Sleep efficiency ≤85% or less and/or total sleep time less than 7 hours and/or wake after sleep onset of more than 30 minutes as measured by PSG or actigraphy		x	x

DPH: Diphenhydramine; ADI-R: Autism Diagnostic Interview, Revised; ADOS-2: Autism Diagnostic Observation Schedule, Second Edition; ASD: Autism Spectrum Disorder; PSG: Polysomnography; CSHQ: Children's Sleep Habits Questionnaire

Table 2: Exclusion Criteria by Study Drug

Exclusion Criteria	**Diphenhydramine**	**Zolpidem**	**Suvorexant**
Dual protection contraception (sexually active females)	X	x	x
Active suicidal ideation or severe psychiatric diagnoses	x	x	x
Unstable medical problems (migraine, asthma, etc.)	x	x	x
Genetic/metabolic/infectious etiology for ASD	x	x	x
Pregnancy or unreliable contraception	x	x	x
Use of interfering medications	x	x	x
Hypersensitivity to study drug	x	x	x
Severe side effects from study drug	x	x	x
Adequate prior trial of study drug	x	x	x
Medication interactions (CYP pathways)	x	x	x

Other specific exclusions (e.g., narcolepsy, substance use)	x	x	x

Table 3: Planned Participant Recruitment Characteristics (PRO EDI)

Characteristic	Reported Criteria / Category
Age	DPH: 8–17 yrs; Zolpidem: 12–17 yrs; Suvorexant: 13–17 yrs, Collected as part of standard demographic intake at screening
Sex	Males and females, Collected as part of standard demographic intake at screening
Gender	Collected as part of standard demographic intake at screening
Race/Ethnicity/Ancestry	Collected as part of standard demographic intake at screening
Socioeconomic Status	Collected via demographic survey (household income, individual parent income, parent education, parent occupation and number of adults/children in the household).
Geographic Location	Stanford University (San Francisco Bay Area) and the State of California

d. Treatment Screening Phase

Once eligibility criteria are met, participants will complete the remaining screening procedures (Figure 2), which include the Clinical Global Impression - Severity (CGI-S) subscale (71,72), the Dosage Record Treatment Emergent Symptom Scale (DOTES) (73), vital signs assessment, a urine pregnancy test (for females of childbearing age), and the Columbia-Suicide Severity Rating Scale (C-SSRS) (74).

Timepoint	Screen	Baseline (0)	Wk 1	Wk 2	Wk 3	Wk 4†	Wk 5	Wk 6	Wk 7	Wk 8
Enrollment										
Eligibility screen	X									
Informed consent / assent	X									
Randomization		X								
Interventions										
Period 1 (active or placebo)		X	X	X	X					
Period 2 (crossover)						X	X	X	X	X
Assessments										
ADI-R / ADOS-2 / IQ / Vineland-III	X									

Medical history / physical exam	X									
Vital signs	X	X	X	X	X	X	X	X	x	X
DOTES	X	X	X	X	X	X	X	X	x	X
Urine pregnancy test*	X									X
C-SSRS**	X		X	X	X	X	X	X	X	X
Polysomnography	X					X				x
Actigraphy	X			X	X				X	X
Cortisol / melatonin saliva	X					X				X
CSHQ	X	X				X				X
PSHQ / ABC / SRS-2 / SSDS / RBS-R / DARB / SPQ-2 / CBCL / NEPSY-2	X					X				X
Concomitant medication log		X	X	X	X	X	X	X	X	X
CGI-Severity	X	X	X	X	X	X	X	X	X	X
CGI-Improvement			X	X	X	X	X	X	X	X

Figure 2. *Schedule of Enrolment, Interventions, and Assessments (Diphenhydramine, Zolpidem, and Suvorexant Trials)*ADI-R = Autism Diagnostic Interview-Revised; ADOS-2 = Autism Diagnostic Observation Schedule 2; IQ = Stanford-Binet V; Vineland III = Vineland Adaptive Behavior Scales, 3rd Edition; VS = Vital signs; DOTES = Dosage Record Treatment Emergent Symptom Scale; C-SSRS = Columbia Suicide Severity Rating Scale; CSHQ = Children's Sleep Habits Questionnaire; PCHQ = Parent Sleep Habit Questionnaire; ABC = Aberrant Behavior Checklist; SRS-2 = Social Responsiveness Scale, 2nd edition; SSDS = Stanford Social Dimensions Scale; RBS-R = Repetitive Behavior Scale-Revised; DARB = Dimensional Assessment of Repetitive Behaviors; SPQ-2 = Sensory Profile Questionnaire, 2nd Edition; CBCL = Child Behavior Checklist; VABS-3 = Vineland Adaptive Behavioral Scale – 3rd Edition; NEPSY-2 Affect Recognition = The affect recognition subtest of the NEuroPSYchological Assessment; Tx = Treatment; CGI = Clinical Global Impressions-Severity (CGI-S) and Improvement (CGI-I).

*Pregnancy test for FCBA.** BL, Week 4, and week 8 for DPH.

Randomization and Treatment

The assignment of participants to the specific trial will be based on previous medication history, age, and parents' preferences. If no clear preference by parents is expressed, participants will be randomly assigned to one of the 3 trials as long as they are eligible to enroll. If a participant is eligible to 2 trials, then the participant will be randomly assigned to one of these two trials.

Once assigned to a specific trial, participants will be randomized 1:1 to either active treatment or placebo for the first four weeks, followed by a crossover to the alternate condition for an additional four weeks. Randomization lists will be generated and managed by an independent member of the research team. In each trial, 13 participants will be randomized to the placebo arm and 13 to the active arm for 4 weeks. At the end of this period, those receiving the placebo will switch to the active compound, and vice versa. Permuted block randomization (block sizes of 2 and 4) will ensure balanced group sizes and double-blinding. Allocation is implemented by an unblinded, independent investigator (Grace Gengoux, PhD) who has no direct contact with participants, in coordination with Universal Compounding Pharmacy, which prepares and dispenses study medication and

matching placebo according to the randomization sequence. Active medication and placebo are encapsulated in identical indistinguishable capsules to maintain blinding of participants, caregivers, and study staff. Study staff who enroll participants and assess outcomes remain blinded to treatment allocation throughout the trial. Treatment allocation is unblinded only after a participant completes their involvement in the trial. If unblinding is medically necessary for participant safety, the principal investigator or the study physician may contact the unblinded, independent investigator (Grace Gengoux, PhD) to request unblinding of the affected participant.

e. Visits

Outcome Assessment

Sleep physiology and clinical outcomes will be reassessed at the midpoint (week 4) and endpoint (week 8) of the trial (Figure 2 and table 4).

Table 4: Primary, Secondary, and Exploratory Efficacy Outcome Measures and Corresponding Instruments Assessed at Baseline, Week 4, and Week 8

	Instrument
Primary Outcome Measures	
Sleep latency, NREM sleep architecture	Polysomnography (PSG) and/or Actigraphy
Secondary outcome Measure	
Sleep Efficiency	Actigraphy and/or PSG
Exploratory Outcome Measures	
Parent-reported sleep behaviors	Children's Sleep Habits Questionnaire (CSHQ), Parent Sleep Habits Questionnaire (PSHQ)
Global functioning	Clinical Global Impression Scale (CGI)
Social Communication	Social Responsiveness Scale, 2nd Edition (SRS-2), Stanford Social Dimension Scale (SSDS)
Repetitive behaviors	Repetitive Behavior Scale - Revised (RBS-R), Dimensional Assessment of Repetitive Behaviors (DARB)
Sensory processing	Sensory Profile Questionnaire (SPQ)
Affect recognition	NEPSY-II (Affect Recognition subtest)
General psychopathology	Child Behavior Checklist (CBCL) Aberrant Behavior Checklist, 2nd Edition (ABC-2)

Baseline Visit

After an initial screening visit, eligible participants will proceed to a baseline visit, during which comprehensive pretreatment assessments will be conducted, including assessments of autism symptomatology. These assessments will include the CGI-S scale, vital signs, the DOTES, and the CSHQ. These measures will establish baseline values for sleep and clinical features prior to intervention.

Dosing

Within each trial, each participant will receive one of three hypnotic agents—diphenhydramine, zolpidem, or suvorexant—or placebo, with dosing tailored to the medication. For diphenhydramine, participants will start at 25 mg at bedtime, increasing to 50 mg after one week or two if tolerated. Zolpidem will begin at 5 mg at bedtime and increase to 10 mg after one week or two if well tolerated. Suvorexant will start at 5 mg at bedtime and increase weekly by 5 mg to a maximum of 20 mg as tolerated. For zolpidem and suvorexant, participants will be maintained at the lowest effective and tolerated dose. In cases of adverse effects, doses will be adjusted to the highest tolerated level, and participants will remain on that dose for the study duration.

Adherence

Adherence to the dosing regimen will be closely monitored through parental administration dosing logs, pill counts at the end of each treatment arm, and regular follow-ups during study visits and phone calls. If adherence drops below 90%, participants will be given a warning, and noncompliance over two consecutive visits (below 90% adherence or no-show) will result in withdrawal from the study. To support participant retention, families are seen weekly throughout the trial and receive regular reminder calls; participants in the zolpidem and suvorexant trials receive two calls per week whenever a medication dose adjustment occurs. Flexible scheduling is offered to accommodate caregiver work schedules and children's school attendance (early morning or after school and after business hours), and participants are compensated for completing study procedures.

Concomitant Medications

Concurrent interventions, including behavioral and educational therapies, will be allowed provided they remain stable for at least four weeks prior to enrollment and throughout the study. Participants taking non-exclusionary medications (e.g., melatonin, stimulants) will be required to be on a stable regimen for at least 2 weeks prior to entry into the study, with the exception of fluoxetine, which is required to be stable for 4 weeks prior to entry into the study. Special diets or supplements established at least 4 weeks prior to enrollment will be permitted, but changes during the trial are discouraged to minimize confounding effects. Finally, to monitor all concomitant interventions, a weekly log will be obtained from all

participants during the safety and/or clinical assessment visits and will include the dosage and frequency of all concomitant medications.

Safety

Vita signs (blood pressure, heart rate, weight, height, and temperature) will be monitored closely throughout the trial. They will be obtained at screening, baseline visits, and at every visit during the trial. Safety will be a primary consideration, with DOTES administered at each visit to assess potential side effects of the medications. The DOTES will be modified from their original versions to include specific questions about potential side effects reported with diphenhydramine, zolpidem, and suvorexant. Assessments for suicidal ideation will take place using the Columbia-Suicide Severity Rating Scale (C-SSRS). For diphenhydramine, the C-SSRS is collected at screening, baseline, week 4, and week 8. For zolpidem and suvorexant, the C-SSRS is collected at every study visit. A urine pregnancy test will also be conducted for females of childbearing age at baseline, crossover, and at the end of the trial.

The independent Data and Safety Monitoring Board (DSMB) described in Study Design and Rationale meets quarterly to review data quality and timeliness, participant recruitment and retention, and participant risk-benefit, including all adverse events and serious adverse events, as well as any breaches of confidentiality; meeting frequency may be increased if warranted. No predefined statistical stopping rules for safety-based early termination have been established. However, the board can increase the frequency of the meetings, if needed. In addition to DSMB oversight, the research team, including the principal investigator and co-investigators, meets weekly to review study implementation, protocol deviations, and adherence. No formal external monitoring is conducted; the study lab manager performs regular review of consent documentation and protocol adherence.

3. Statistical Analyses and Data Management

a. Primary Objectives

The primary objective is to evaluate the effects of diphenhydramine, zolpidem, and suvorexant on sleep architecture, including total sleep time, sleep efficiency, and sleep latency, as measured by PSG.

b. Primary Safety Outcomes

Safety outcomes will include the frequency and severity of adverse events, assessed using the DOTES.

c. Primary Efficacy Outcomes

Efficacy outcomes will focus on changes in PSG- and/or actigraphy-derived sleep parameters, including NREM, REM sleep duration, total sleep time, sleep efficiency, and frequency spectral analysis.

d. Secondary Objectives and Outcomes

Secondary objectives include evaluating the impact of improved sleep (as assessed via PSG, actigraphy, and questionnaires) on core features of autism (e.g., RRB and social communication) and associated behaviors (e.g., irritability, hyperactivity). The following instruments are being collected at baseline, week 4, and week 8.

Child Sleep Habits Questionnaire (CSHQ): The CSHQ is the most frequently employed measure assessing the quality and type of sleep experienced by children as reported by parents/caregivers (69,75). It has been used in multiple studies to examine sleep behavior in individuals with neurodevelopmental diagnoses, including our own study of children with Phelan McDermid Syndrome (65–67). Thirty-three items are grouped into 8 subscales: bedtime resistance, sleep onset delay, sleep duration, sleep anxiety, night wakings, parasomnias, sleep disordered breathing, and daytime sleepiness. To calculate subscale scores, each item is rated on a scale from 1 to 3, with higher scores indicating greater sleep disturbance. Owens et al. (2000) (69) demonstrated internal consistency and validity of the CSHQ by comparing a community sample and a clinical sample. The CSHQ will be obtained during the screening phase, at baseline, at week 4, and at week 8.

Parent Sleep Habits Questionnaire (PSHQ): The PSHQ is a self-report measure of caregiver sleep, adapted from the CSHQ (70). Thirty-one items are grouped into 5 subscales: daytime sleepiness, night wakings, sleep duration, parasomnias, and general sleep problems. The PSHQ will be collected during the screening phase and at weeks 4 and 8.

Clinical Global Impression Scale (CGI): This clinician-rated scale consists of 3 subscales: severity of illness (CGI-S), global improvement (CGI-I), and therapeutic index (72). The severity of the illness is scored from 1= normal to 7= extremely ill. The patient's improvement is scored on a 7-point scale, which ranges from marked improvement (1) to no change (4) to very much worse (7). The CGI-S has been widely used in psychopharmacological studies and has shown to be highly sensitive to medication effects (76). The CGI-I is a subscale scored from 1 (very much improved) to 7 (very much worse). A score of 4 reflects no change. A positive response is defined as a score of 2 (much improved) or 1 (very much improved). The scale will be completed at each visit by a clinical investigator, and assessment of the severity of illness and improvement will specifically focus on the target symptom of sleep.

Several behavioral scales will be obtained during the screening phase and at weeks 4 and 8, to examine the relationships between changes in sleep parameters and clinical features. These measures will include:

Child Behavior Checklist (CBCL): The CBCL is a parent-report questionnaire in which the child is rated on various behavioral and emotional problems (77) and is one of the most widely-used standardized measures for evaluating maladaptive behavioral and emotional problems in children aged 3 through early adulthood (78). It assesses internalizing and

externalizing behaviors, including social withdrawal, anxiety and depression, destructive behavior, social problems, thought problems, attention problems, and aggressive behaviors.

Social Responsiveness Scale, Second Edition (SRS-2): The SRS-2 is a norm-referenced, 65-item parent-report questionnaire developed to measure social behaviors, in both clinical and non-clinical populations (58,79). The psychometric properties have been tested in younger and older subjects (79).

Repetitive Behavior Scale - Revised (RBS-R): The RBS-R is an empirically derived clinical rating scale for assessing the presence and severity of various forms of restricted, repetitive behavior (80–83). The RBS-R consists of 6 subscales: Stereotyped Behavior, Self-injurious Behavior, Compulsive Behavior, Routine Behavior, Sameness Behavior, and Restricted Behavior. The scale provides an overall raw score for the severity of repetitive behaviors and separate severity measures for each subtype.

Sensory Profile Questionnaire (SPQ): The SPQ is a 125-item parent-report questionnaire evaluating sensory abnormalities. It includes a summary section with 9 factors (e.g., sensory seeking, oral sensory sensitivity) and a sensory processing section with 6 subscales (e.g., auditory, visual, touch). The SPQ was standardized on 1,200 children. The psychometric properties of the SPQ have been examined in different samples, including individuals with autism (60,61).

Stanford Social Dimension Scale (SSDS): The SSDS is a 71-item parent-report questionnaire in which the child is rated on various dimensions of social functioning, including social motivation, social affiliation, expressive social communication, social recognition, and unusual approach (62). Validation was conducted with n= 175 parents of heterogeneous sample individuals with ASD (Mage= 7.19 years, SDage= 3.96) that included children with and without ID. Further, the factor structure derived in the ASD sample was largely stable in a sample of 624 parents of children who were either typically developing or had neurodevelopmental or neuropsychiatric disorders (CFI= 946, TLI= .930, RMSEA= .044, SRMR= .026) (62). The SSDS shows utility for identifying distinct and clinically meaningful ASD subgroups (84).

Dimensional Assessment of Repetitive Behaviors (DARB): The DARB was developed and validated following methods outlined by the NIH Patient-Reported Outcome Measurement Information System (PROMIS) framework. Comprehensive, multi-trait, multi-method factor analyses across existing restricted and repetitive behaviors (RRB) instruments (85) and meta-analysis of factor analyses conducted by our team has identified the following eight RRB subdomains: repetitive motor behaviors, insistence on sameness, restricted interests, unusual interests, self-injurious behaviors, sensory sensitivity, obsessions and compulsions, and repetitive language.

Aberrant Behavior Checklist, Second Edition (ABC-2): The ABC-2 (64) is a 58-item informant rating scale that provides information about problematic behavior along five scales: irritability, social withdrawal, stereotypic behavior, hyperactivity/ noncompliance, and inappropriate speech.

NEuroPSYchological Assessment, 2nd Edition (NEPSY-2): The Affect Recognition subtest of the NEPSY-2 will be administered. The NEPSY-2 (57) is a comprehensive direct assessment of neuropsychological functioning in children ages 3-16. Cognitive processes assessed include executive functioning and attention, memory and learning, sensorimotor processing, language, social perception, and visuospatial processing. The Affect Recognition subtest is a measure of social perception and will be administered to participants as a part of this project.

e. Data Analysis Plan and Considerations

All participants who are randomized and have at least one post-baseline follow-up assessment will be included in the analyses. The primary analyses will evaluate the effect of each hypnotic on sleep parameters (e.g., total sleep time, sleep efficiency, and latency) using linear mixed-effects regression models. These models will include Randomization Group (Drug-Placebo vs. Placebo-Drug), Time (baseline, crossover, and endpoint), and their interactions as fixed effects, with sleep outcomes as dependent variables. Missing data will be assumed to be missing at random (MAR), and robust standard errors will be used because they are less sensitive to parametric assumptions. Significance will be assessed using a Type 1 error rate of $\alpha = 0.05$.

Secondary analyses will focus on the relationship between sleep improvements and changes in behavioral outcomes, including restricted and repetitive behaviors and irritability. The false discovery rate for secondary outcomes will be controlled using the Benjamini-Hochberg procedure to limit Type 1 error inflation due to multiple comparisons. For all outcomes that show significant efficacy, we will use exploratory bivariate correlations to investigate the association between baseline characteristics and improvements in relevant outcomes. For all exploratory analyses, type 1 error will be maintained at .05, as the purpose of these analyses will be to identify possible associations that will require confirmation in future studies.

f. Sample Size Calculation and Power Estimation

With an expected dropout rate of 10%, each trial will recruit 26 participants to achieve 83% power to detect a 0.50 SD effect size (Cohen's d) at a 5% significance level. The crossover design minimizes required sample size by allowing each participant to serve as their own control.

g. Data Management and Security

Study data are collected and managed using REDCap (Research Electronic Data Capture) hosted at Stanford University. Coded, de-identified data are stored on an encrypted server. Polysomnography data are transferred via secure memory card or directly to an encrypted server immediately following recording, after which the data are deleted from the memory card. Paper records and any data containing protected health information (PHI) are kept in locked file cabinets in offices that are secured when unoccupied, with electronic PHI stored on password-protected servers behind a firewall. Backups are similarly secured, and all laptops and removable storage devices are encrypted. All statistical analyses are conducted on encrypted, password-protected computers.

4. Discussion

The proposed study represents a much-needed approach to understanding and improving sleep in autistic children by testing three pharmacological agents with distinct mechanisms of action. Diphenhydramine, zolpidem, and suvorexant target different neurotransmitter systems implicated in sleep-wake regulation, providing an opportunity to delineate their effects on both sleep physiology and behavioral outcomes in autistic children. These agents represent unique opportunities to examine how modulation of histaminergic, GABAergic, and orexin pathways impacts sleep parameters in this population. This differentiation in pharmacological action is critical for understanding the broader implications of sleep modulation on autism symptoms.

Diphenhydramine, a first-generation antihistamine, acts by antagonizing H_1 receptors, thereby promoting NREM/SWS. Although it is widely used as an over-the-counter sleep aid, its effects on the sleep architecture of autistic youth have not been systematically investigated. Its hypnotic properties result from blockade of histamine H1 receptors in the central nervous system, which are involved in promoting wakefulness. Preclinical studies across several species have shown that antihistamines increase NREM sleep including restorative SWS specifically through H_1 receptor (34–37).

Zolpidem, a nonbenzodiazepine hypnotic, selectively targets the alpha-1 subunit of the GABA-A receptor complex, inducing sleep while minimizing the risk of dependence. Unlike benzodiazepines that non-selectively bind all $GABA_A$ receptor subtypes, zolpidem demonstrates preferential binding to α1 subunits relative to α2, α3, and α5 subunits**,** with a high α1/α5 affinity ratio (86). This selective binding profile may explain the relative absence of myorelaxant and anticonvulsant effects while preserving deep sleep (stages 3 and 4 also known as SWS). Zolpidem has no appreciable binding affinity for dopaminergic, serotonergic, adrenergic, histaminergic, or muscarinic receptors (87).

Suvorexant, a dual orexin receptor antagonist, represents a novel mechanism for promoting sleep by reducing wake drive. Orexin (hypocretin)-containing neurons normally stimulate wake-promoting nuclei in the brainstem and hypothalamus while inhibiting sleep-promoting nuclei in the ventrolateral and median preoptic areas. By blocking orexin

receptors expressed throughout the brain, suvorexant inhibits wake-promoting circuits, thus promotes and maintains (NREM) sleep through this physiologic mechanism (88).

By using a crossover design and multimodal sleep measures, including traditional approaches such as PSG in participants' homes, actigraphy, and a sleep-sensor mat, this study addresses significant gaps. The use of actigraphy and salivary biomarkers further strengthens the methodology, enabling analysis of their relationship with sleep and behavior. This comprehensive approach is anticipated to yield insights into the potential of targeted interventions to alleviate both sleep disturbances and associated autism symptoms.

The studies discussed above focus on target engagement strategies by assessing the impact of 3 different medications on sleep physiology. This approach enables the examination of the mechanism of action and will lead to hypothesis-driven intervention development. It also supports precision medicine by linking target modulation to clinical outcomes. It also increases the efficiency of the scientific process by reducing the risk of late-stage trial failure by validating target modulation in humans. Finally, target engagement strategies facilitate the identification of subgroups that are most likely to benefit from one or more of these hypnotics. However, this approach has several limitations. Clinical benefits may be observed without clear target engagement, especially if the brain networks being examined are not related to the drug's mechanism of action (89). Additionally, reliable measurement of target engagement is difficult due to the heterogeneity of sleep physiology and the variability of the data collected from night to night. In fact, identified biomarkers sometimes fail to translate into practice or to outperform current diagnostic methods, limiting their utility for guiding treatment. Therefore, in the 3 trials discussed here, we have complemented our target engagement strategies with the inclusion of comprehensive clinical and behavioral phenotyping to allow the examination of the effect of the 3 drugs, not only on sleep physiology, but on the subjective quality of sleep and core autism features, as well as associated behaviors.

The findings of this study are expected to advance our understanding of the bidirectional relationship between sleep and autism symptoms. Improved sleep may lead to a cascade of positive outcomes, including better social communication, reduced irritability, and enhanced overall functioning. Several studies have documented improvements in sleep-related outcomes, such as increased total sleep time, improved sleep efficiency, reduced sleep onset latency, as well as improvements in daytime behaviors and overall functioning following behavioral and other non-pharmacological interventions in autistic children (90–92). However, it is important to recognize the variability in treatment response across individuals. For instance, combining medication with behavioral interventions has been found to be more effective for reducing aggressive behavior than medication alone (93). Additionally, the effectiveness of interventions can vary based on individual needs and the specific behavioral challenges being addressed.

A potential limitation of our trial is the exclusion of younger children (aged <8 years), which limits its applicability to this subgroup of autistic children. Additionally, the short-term nature of the trials precludes conclusions about the long-term efficacy and safety of the interventions. This is particularly important in light of the evidence suggesting the limited efficacy of hypnotics when administered chronically. Future studies should explore the long-term effects of these agents and their impact on neurodevelopmental trajectories in autism. Finally, due to regulatory reasons and limited experience in youth, the age range of participants was restricted for the zolpidem (age range 12 to 17 years) and suvorexant (age range 13 to 17 years), which limits the generalizability of the findings for these 2 drugs to younger children. However, there is an intention to request modification to expand the age range once more research experience is acquired in the current investigations.

Despite these limitations, the findings of these studies have the potential to inform clinical practice and guide the development of targeted sleep interventions. Improved sleep in children with autism may also benefit caregivers and contribute to better daytime functioning, including reduced behavioral challenges and enhanced quality of life. The results are expected not only to validate the safety and efficacy of these pharmacological agents but also to provide a template for future investigations into sleep interventions for neurodevelopmental disorders.

5. List of abbreviations

- ABC-2: Aberrant Behavior Checklist, Second Edition
- ADI-R: Autism Diagnostic Interview-Revised
- ADOS-2: Autism Diagnostic Observation Schedule, Second Edition
- ASD: Autism Spectrum Disorder
- CBCL: Child Behavior Checklist
- CGI: Clinical Global Impression (CGI-S: Severity; CGI-I: Improvement)
- C-SSRS: Columbia-Suicide Severity Rating Scale
- DARB: Dimensional Assessment of Repetitive Behaviors
- DOTES: Dosage Record and Treatment Emergent Symptom Scale
- DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
- DSMB: Data and Safety Monitoring Board
- IND: Investigational New Drug
- NREM: Non-rapid Eye Movement
- PRO EDI: Participant Recruitment/Reporting on Equity, Diversity, and Inclusion
- PSG: Polysomnography
- RBS-R: Repetitive Behavior Scale-Revised
- REDCap: Research Electronic Data Capture
- REM: Rapid Eye Movement
- SPQ: Sensory Profile Questionnaire
- SRS-2: Social Responsiveness Scale, Second Edition
- SSDS: Stanford Social Dimension Scale

6. Declarations

Ethics approval and consent to participate

This study was approved by the Stanford University Institutional Review Board under the following protocols: IRB-66941 (Randomized Placebo-Controlled Crossover Trial of Diphenhydramine for Sleep in Children with Autism; initial approval 2022-10-18, most recent approval 2026-08-24, protocol version dated 2026-08-18), IRB-67221 (Randomized Placebo-Controlled Crossover Trial of Zolpidem for Sleep in Children with Autism; initial approval 2022-11-09, most recent approval 2026-06-26, protocol version dated 2026-06-10), and IRB-67222 (Randomized Placebo-Controlled Crossover Trial of Suvorexant for Sleep in Children with Autism; initial approval 2022-11-09, most recent approval 2026-06-30, protocol version dated 2026-06-10). All participants will provide written informed consent prior to participation.

Consent for publication

Not applicable

Post-trial care

Upon completion of the trial, participants are referred back to their primary care team (e.g., child psychiatrist, developmental pediatrician, child neurologist, or pediatrician), and the investigation team provides recommendations for the ongoing management of sleep disturbances based on the participant's trial experience. In the event of a study-related injury or illness, the study team will assist participants in obtaining appropriate medical treatment; reimbursement for related costs of care will first be sought from the participant's insurer, managed care plan, or other benefits program, with the participant responsible for any applicable co-payments or deductibles.

Availability of data and materials

Not applicable

Protocol availability and dissemination

The full study protocol and statistical analysis plan are available upon request from the corresponding author (Antonio Y. Hardan, hardanay@stanford.edu). Findings will be disseminated through presentations at national and international scientific conferences and through publication in peer-reviewed journals, with the final accepted manuscripts deposited in PubMed Central in accordance with the NIH Public Access Policy. Results will also be shared with non-academic audiences, including parents and professionals in clinical and educational settings, in coordination with the Stanford Autism Center Dissemination and Outreach Core. No participant identifiers will be included in any disseminated results.

Competing interests

Not applicable

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Authors' contributions

G.R. and E.K.B. drafted the original manuscript. B.J. contributed to the development of the statistical methodology and analysis planning. M.K., R.O., L.F., P.M., and J.P., contributed to study design and critical review and editing of the manuscript. A.Y.H. and JH contributed to conceptualization, study design, supervision, and funding acquisition, and reviewed and edited the manuscript. All authors reviewed and approved the final version of the manuscript.

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