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Protocol and Design of the REPOSE Study: A double-blinded, randomized, placebo-controlled trial to evaluate the efficacy of suvorexant to improve postoperative sleep and reduce delirium severity in older non-cardiac surgical patients

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ABSTRACT

Introduction

Postoperative delirium occurs in up to 40% of older surgical patients and has been associated with prolonged hospital stays, long-term cognitive impairment, and increased one-year postoperative mortality. Postoperative sleep disturbances may increase delirium risk, but studies investigating pharmacotherapies to improve postoperative sleep to prevent delirium remain limited. Suvorexant is a selective antagonist of orexin 1 and 2 receptors and is approved for insomnia pharmacotherapy by the Food and Drug Administration. It has potential to improve postoperative sleep and reduce postoperative delirium rates, but randomized controlled trials (RCT) are needed to determine efficacy and safety of postoperative suvorexant administration. The REPOSE study (**r**educing delirium by **e**nhancing **po**stoperative **s**leep with suvor**e**xant) is a single-center, randomized, double-blind RCT that aims to evaluate the efficacy and safety of suvorexant in increasing total sleep time and decreasing delirium in older patients undergoing non-cardiac surgery.

Methods and analysis

REPOSE will enroll 130 patients (age ≥ 65 years) undergoing non-cardiac surgery with planned postoperative inpatient stay. Participants will be randomized to receive 20mg oral suvorexant or placebo nightly on postoperative nights 0, 1, and 2. The primary endpoint is total sleep time on the first postoperative night, as measured using an electroencephalography (EEG) headband. The secondary endpoint is peak postoperative delirium severity as measured by 3-minute diagnostic interview for confusion assessment method severity scores.

Ethics and dissemination

Ethical approval was obtained from the Duke Institutional Review Board (PRO 00111869). Results of the REPOSE study will be published in a peer-reviewed journal and presented at academic conferences. Trial data will be deposited in clinicaltrials.gov

Trial registration number

NCT05733286

ARTICLE SUMMARY

Strengths and limitations of this study

- This is a randomized, double-blind, placebo-controlled trial evaluating the efficacy and safety of suvorexant in older patients following non-cardiac surgery.
- Total sleep time and sleep architecture is quantified using electroencephalography and subjective sleep quality with Richards-Campbell sleep questionnaires.
- Because the study drug is not continued on discharge, the study is restricted to evaluating shorter courses of suvorexant in hospitalized surgical patients, and thus this study will not provide information on whether longer outpatient courses of therapy could improve sleep at home.
- Single-center setting limits the generalizability to other populations due to potential site-specific biases.

INTRODUCTION

Postoperative delirium is a disorder characterized by acute confusion, impaired attention, disorganized thinking, and disturbances in consciousness, and typically occurs in the first three days following surgery [1]. Postoperative delirium affects up to 40% of older surgical patients and is associated with increased hospital length of stay, long-term cognitive decline, Alzheimer's disease and related dementias, and increased 1-year postoperative mortality [2–5]. Although delirium is associated with poor postoperative outcomes, there are few interventions that prevent delirium, in part due to the difficulty of addressing unmodifiable delirium risk factors, such as older age and baseline cognitive impairment [6].

Some potentially modifiable risk factors for delirium are sleep disturbances [7]. Sleep is a fundamental physiological process that influences cognition, emotional well-being, immune function, and homeostasis [8–11]. Following surgical procedures, patients frequently experience disruptions in sleep patterns attributed to various factors, such as noise and light present in the hospital environment, postoperative pain, and the effects of medications administered during the perioperative period [12–14]. Thus, strategies that minimize postoperative sleep disturbances and promote sleep hygiene may decrease the risk of postoperative delirium. Additionally, the appropriate administration of pharmacologic sleep aids may help prevent postoperative delirium. However, few studies have widely investigated pharmacologic sleep aids for postoperative delirium prevention, in part because some sedating pharmacologic sleep aids may increase delirium risk. For instance, benzodiazepines, often given for sedation in the intensive care unit (ICU), have been reported to potentially exacerbate postoperative delirium in older patients [15–19]. Consequently, recent guidelines from the American Geriatric Society discourage the use of benzodiazepines in older patients [20].

Suvorexant is an emerging alternative pharmacotherapy for treating sleep disturbances. This medication received Food and Drug Administration approval in 2014 for the treatment of insomnia and acts by blocking orexin receptors. Orexin is a wake-promoting neuropeptide pivotal for sleep regulation [21,22]. By promoting sleep, suvorexant improves both sleep onset latency and wake after sleep onset. Interestingly, suvorexant administration acutely reduces cerebrospinal fluid phosphorylated tau levels, an Alzheimer's disease biomarker, which suggests that manipulating the orexin pathway may affect Alzheimer's Disease-related pathology [23–25]. Additionally, suvorexant increases total sleep time in older adults with probable Alzheimer's Disease dementia, suggesting that suvorexant is an ideal candidate for postoperative sleep pharmacotherapy in older surgical patients at risk for delirium [26].

To evaluate suvorexant's efficacy in increasing postoperative sleep and reducing postoperative delirium severity, we are conducting a single-center, double-blind, placebo-controlled, randomized trial. Our hypothesis is that suvorexant, an effectively decreases postoperative delirium severity and enhances total sleep time (TST), sleep onset latency, and subjective sleep quality in the older surgical patients. Our study aims to provide valuable insights into the potential therapeutic role of suvorexant to improve postoperative sleep in older surgical patients.

METHODS AND ANALYSIS

Study design

This randomized, double-blind, placebo-controlled trial will be conducted at a single center at Duke University Medical center in Durham, NC, USA. The trial began on 28 June 2024 and is estimated to finish enrollment in late 2025. The study design schedule is outlined in table 1 and is approved by the Duke Institutional Review Board (IRB). At least 130 participants will be randomized to intervention so that at least 116 participants will have complete data for analysis, accounting for 10% attrition.

Table 1. Schedule of study events.

	Preop	Postop day 0	Postop day 1	Postop day 2	Postop day 3	Postop day 4	Postop day 5
Questionnaires							
Montreal Cognitive Assessment (MOCA)	X						
Athens Insomnia Scale	X						
Insomnia Severity Risk Index	X						
Epworth Sleepiness Scale	X						
Delirium Assessment	X	X[2]	X[2,3]	X[2,3]	X[2,3]	X[2,3]	X[2,3]
Modified Richards-Campbell Sleep Quality			X[2]	X[2]	X[2]	X[2]	X[2]
Medications							
Suvorexant vs. placebo		X[2]	X[2]	X[2]			
Procedures							
Nightly EEG		X[2]	X[2]	X[2]			
Wrist actigraphy	X[1]						
Psychomotor vigilance task (PVT)	X		X[2]	X[2]	X[2]		
Pupillometry	X	X[2]	X[2]	X[2]	X[2]		

[1]Activity is optional, must be worn for at least three days prior to surgery
[2]These activities will not be performed after hospital discharge
[3]Performed twice daily

Study population

This study will enroll patients undergoing non-cardiac surgery with planned postoperative inpatient overnight stay undergo randomization and receive a least one dose of study drug. Inclusion and exclusion criteria are listed in table 2.

Table 2 Inclusion and exclusion criteria of the REPOSE study with rationale.

Inclusion Criteria	Rationale
1. Age 65 and older	Older surgical patients have higher insomnia symptom burden, shorter total sleep times and higher risk of delirium compared to younger patients
2. Undergoing non-cardiac, non-intracranial surgery, any surgical procedure not involving the skull, brain, cerebrovascular structures	Cardiac surgery patients are often exposed to sedatives postoperatively in ICU, and neurologic surgery patients may have increased sensitivity to suvorexant, possibly increasing risk of adverse events
3. Scheduled postoperative inpatient overnight stay	Study drug administration and assessments must occur while in the hospital as they are not feasible in outpatient setting in this study
4. Able to give informed consent or has legally authorized representative able to give informed consent on their behalf	Required to maintain ethical standards
5. English-speaking	Delirium assessment and sleep questionnaires are only available in English, and non-English speaking is a barrier to informed consent.
Exclusion Criteria	
1. Inmate of correctional facility	Inmates have unique healthcare needs and environmental factors that may confound study outcomes
2. Body mass index > 40	Obese patients may have altered pharmacokinetics of suvorexant leading to decreased drug effect
3. Legal blindness	Vision required to complete study assessments
4. Unable to perform study-related questionnaires and assessments	Study-related questionnaires and assessments required for data analysis
5. Use of outpatient sedating sleep aids (see table 3) > 2 times per any week in 1 month preceding day of surgery	To avoid concomitant administration of other sedating sleep aids with suvorexant, which has not been well-studied.
6. History of psychotic disorder, including schizophrenia, schizoaffective disorder, schizophreniform or brief psychotic disorder	May increase risk of adverse events, since suvorexant may cause increased suicidal ideation
7. History of liver failure with documented international normalized ratio (INR) of >1.2 or with history of hepatic encephalopathy	Liver disease may decrease suvorexant metabolism and clearance and increase risk of adverse events
8. History of severe sleep apnea or obesity hypoventilation syndrome requiring home bilevel positive airway pressure therapy or home ventilator or other forms of noninvasive ventilation	Clinically significant respiratory depression effects of suvorexant in patients with severe central sleep apnea have not been ruled out in other studies.
9. Chronic lung disease requiring home oxygen therapy	Mild respiratory depression effects of suvorexant may increase risk of adverse events in this patient population
10. History of narcolepsy	Suvorexant is contraindicated in narcolepsy
11. Use of systemic (oral, intravenous, intramuscular, subcutaneous) moderate or strong CYP3A inhibitors within 1 week prior to surgery	Potential drug interactions; CYP3A enzymes metabolize suvorexant
12. Use of systemic (oral, intravenous, intramuscular, subcutaneous) moderate or strong CYP3A inducers within 1 week prior to surgery	Potential drug interactions; CYP3A enzymes metabolize suvorexant
13. Current or planned administration of digoxin, or is currently experiencing digoxin toxicity	Potential drug interactions; suvorexant administration results in decreased digoxin metabolism.
14. Undergoing surgery that will result in inability to take medications by mouth including laryngectomy, tracheostomy, and oral resection/reconstructive surgery	Study drug requires oral administration or durable enteral access such as large bore feeding tube, which are not typically placed after these surgeries.
15. Undergoing surgery that will require postoperative strict bowel rest, including gastrectomy, esophagectomy, and pancreaticoduodenectomy	Patients on strict bowel cannot take enteral meds and thus have no route to receive suvorexant.
16. Undergoing surgery in an area that will make it unsafe to wear a headband, such as scalp or forehead procedures	EEG headband is required for the measurement of total sleep time and sleep architecture
17. Inappropriate for study inclusion based on the judgement of the principal investigator	Individuals may have unique risk factors that make them unsuitable for study participation

Potential candidates will be identified screened for eligibility using the electronic health record. Eligible participants will be contacted through either an automated MyChart message or a phone call by a designated study team member using the IRB-approved phone script. All subjects will be informed of the purpose, procedures, and intent of the study and be provided a consent form prior to enrollment. Informed written consent will be obtained before the subject initiates any study activities or begins any screening procedures that are not considered standard patient care activities. All sexes, races, and ethnicities will be recruited [27].

Intervention

At least 130 participants will be randomized to receive suvorexant (20 mg) or a matched placebo for the first three postoperative nights while in the hospital. Patients will be administered suvorexant or placebo orally. However, in the case that participants are not able to take medications by mouth due to difficulty swallowing, the medication can be administered via an indwelling nasogastric or gastrostomy tube, if one is already present and is usable. Patients will be assigned to blinded treatment groups through stratified permuted block randomization in a 1:1 ratio for suvorexant or placebo. Stratification will be based on age (≥70 and <70 years of age) and sex (male vs. female) to assure balanced age and sex between study groups. Administration will occur starting on postoperative day 0 through postoperative day 2, between 8-10 pm.

Because suvorexant is primarily metabolized by CYP3A, the primary clinical team for enrolled subjects will be advised to avoid moderate or strong CYP3A inhibitors [28]. If recent exposure (<12 hours) to a moderate CYP3A inhibitor is noted in the electronic health record, the study drug dose will be halved, and if exposed to a strong inhibitor (within 12 hours of study drug administration), the study drug will not be administered. However, eligibility for future doses on subsequent postoperative nights is retained if criteria are met. Non-sedating sleep aids like melatonin are allowed anytime, while sedating sleep aids (table 3) are generally restricted on nights of the study drug. To allow for standard of care treatment of in-hospital insomnia, patients are permitted sedating sleep aids for persistent sleeplessness 1-hour after study drug administration up until midnight. The use of rescue sedating sleep aids for sleeplessness will be reported between placebo and suvorexant. Patients that receive rescue sedating sleep aids will not be excluded from the primary analysis.

Table 3 Sedating sleep aids restricted in the REPOSE study.

Sedating Sleep Aid	Common Name
Mirtazapine	Remeron
Trazodone	Desyrel, Oleptro
Flurazepam	Dalmane
Temazepam	Restoril
Triazolam	Halcion
Estazolam	Prosom
Quazepam	Doral
Clonazepam	Klonopin
Lorazepam	Ativan
Midazolam	Versed
Alprazolam	Xanax
Diazepam	Valium
Zolpidem	Ambien
Zaleplon	Sonata
Eszopiclone	Lunesta
Diphenhydramine	Benadryl
Doxylamine	Unisom
Hydroxyzine	Atarax, Vistaril
Suvorexant	Belsomra
Doxepin	Silenor

This will be a double-blind study. The study team and participants will be blinded to treatment allocation. In the case that three unexpected, related serious adverse events are reported in this study, the enrollment of new participants will be halted and an unblinded staff statistician will perform analyses to determine whether these related SAEs are associated with suvorexant vs. placebo. This information will then be used by the medical monitor to decide whether to continue the study.

Study outcomes & assessment

Primary endpoint

The primary endpoint is total sleep time, which is defined as the amount of time spent sleeping during the lights out period (9PM to 6AM), on the first night after surgery that the patient receives study drug. Total sleep time will be assessed through nightly electroencephalography (EEG). A headband with frontal electrodes along with a 3D accelerometer will be used to record EEG data and the data will be saved for later analysis to determine sleep stage and total sleep time (figure 1) [29]. This sleep EEG will allow for determination of total sleep time despite the frequent interruptions of sleep that occur postoperatively in the hospital wards. The headband is designed to be less invasive than standard polysomnography so that study subject sleep is minimally impacted by EEG monitoring and EEG recording adherence is optimized.

Secondary endpoint

The secondary endpoint is peak postoperative delirium severity scores up through postoperative day 5 or discharge. The 3-minute diagnostic interview for confusion assessment method (3D-CAM) will be used to assess delirium in patients who are able to communicate verbally [30,31]. In non-verbal or intubated patients, the confusion assessment method for the intensive care unit (CAM-ICU) will be used instead[32]. Assessment will

first occur in the afternoon, prior to 9 PM, on postoperative day 0. Subsequently, from postoperative days 1 to 5, assessments will be systematically documented twice daily until the conclusion of postoperative day 5 or hospital discharge, whichever occurs first. The first assessment will be administered prior to 12PM, and the second assessment will be administered between 12-9PM.

Exploratory endpoints

The exploratory endpoints include sleep architecture, self-reported sleep quality, pupillary unrest, sustained attention, and the average total sleep time over all nights that subjects receive study drug. Infrared pupillometry will be used to measure pupil diameter fluctuations under ambient light conditions at preoperative and postoperative time points [33]. Finally, the psychomotor vigilance task will determine alertness and sustained attention by recording participants' reactions to randomly displayed stimuli on a tablet and their reaction times, lapses, and errors [34,35]. Pupillometry and psychomotor vigilance task assessments will be administered before surgery and then daily through postoperative day 3 (see table 1).

Effect modification by baseline cognitive status, insomnia symptoms, excessive sleepiness, and sleep habits will be assessed using the Montreal Cognitive Assessment, Insomnia Severity Index, Epworth Sleepiness Scale, and the Athens Insomnia Scale, respectively (Table 4). Study participants will also be offered a wrist actigraph to wear before surgery to quantitatively measure preoperative sleep duration and sleep habits. This will be done as an optional sub-study and when feasible. Participants will be asked to wear the wrist actigraph for at least 3 nights so that circadian rhythms and average total sleep time can be determined [36].

Table 4 Summary of study questionnaires and assessments.

Questionnaires	Assesses	Task
Montreal Cognitive Assessment (MOCA)	Cognition	Tasks such as trail-making, drawing, naming objects, memory recall, attention span, verbal fluency, abstraction, delayed recall, and orientation.
3-minute Diagnostic Interview for Confusion Assessment Method (3D-CAM)	Delirium	Structured interview with observer ratings to assess delirium symptoms such as orientation, memory, attention, hallucinations, and level of consciousness. Subsequent observer ratings determine sleepiness, stupor, hypervigilance, clarity of ideas, speech, attention fluctuation, distraction, consciousness fluctuation, and potential acute changes.
Insomnia Severity Risk Index (ISI)	Insomnia	Scaled responses (0-4) regarding severity of insomnia problems, satisfaction with sleep patterns, and sleep interference with daily functioning.
Athens Insomnia Scale (AIS)	Insomnia	Scaled responses (0-3) regarding sleep latency, awakenings, total sleep duration, sleepiness, and overall sleep quality.
Epworth Sleepiness Scale (ESS)	Daytime sleepiness	Scaled responses (0-3) regarding the likelihood of sleeping in various daytime situations.
Assessments		
Electroencephalogram (EEG)	Sleep patterns	Dry electrodes within headband that non-invasively records brainwaves while sleeping.
Wrist actigraphy	Sleep patterns	Wrist-worn device with 3-axis accelerometers and lux meter.
Psychomotor Vigilance Task (PVT)	Attention	Randomly displayed stimuli on a tablet to which the participants respond by tapping on the screen; records their reaction times, lapses, and errors.
Pupillometry	Cognition	Evaluation of pupil diameter fluctuations under ambient light conditions through an infrared camera.

Data management

All participants will be assigned a subject study number so that their data will be de-identified. EEG data will be accessed through a secure cloud-based platform while pupillometry and PVT data will be stored on a secure local drive. All other data will be stored on the secure web-based Research Electronic Data Capture (REDCap) software. Technical appendix, statistical code, and the relevant dataset will be available from the Vivli Clinical Research Data Repository (https://vivli.org/).

Adverse events and safety

Adverse events will be assessed for daily by study staff. The principal investigator will determine whether the adverse event was unrelated, unlikely related, possibly related, probably related, or definitely related to study treatment. Any symptom, sign, illness, or experience that develops or worsens in severity will be identified as an adverse event and reported to the sponsor and IRB, if necessary. All adverse events occurring during the study period will be recorded in the source document and case report form. The most common side effects of suvorexant include headache, diarrhea, xerostomia, cough, abnormal dreams, dizziness, drowsiness, and daytime tiredness. Minor side effects include sleep paralysis, sleepwalking, itchiness, nausea, vomiting, palpitations, daytime sedation, and worsening of depression and suicidal ideation [37,38].

In the case that three unexpected, related serious adverse events are reported in this study, an unblinded staff statistician will perform analyses to determine whether these related serious adverse events are associated with suvorexant vs. placebo. This information will then be used by a designated medical monitor, an appointed physician not involved in the study, to decide whether to continue the study.

Statistical analysis

Since some patients may miss a study drug dose on the first postoperative night, the primary analysis will be conducted on a modified intent-to-treat to basis comparing total sleep time on the first night that a patient received a study drug dose with a two-sample t-test. Secondary analysis will compare peak postoperative delirium severity scores between suvorexant and placebo groups with a two-sample t-test that the participant received study drug. This modified intent-to-treat analysis will only include those patients who received study drug dose. Based on American Academy of Sleep Medicine insomnia clinical practice guidelines, we will consider a 20-minute difference in TST a clinically meaningful difference [39]. We expect that a sample size of 130 subjects will yield a total of 116 subjects with complete primary and secondary endpoint data. Given a standard deviation (SD) of approximately 35 min for TST in healthy adults, a sample size of 58 subjects per group will provide 86% power to detect a 20-minute difference in TST between treatment groups using a two-sample t-test with a two-sided alpha= 0.05 [26].

For the secondary endpoint, we will consider a 50% reduction in peak postoperative delirium severity scores a clinically meaningful difference. Given a delirium severity SD of 1.8 and a mean peak 3D-CAM delirium severity score of 1.9 in the placebo group a sample size of 58 patients per group will provide 80% power to detect a 0.95 point difference between treatment groups using a two-sided t-test with alpha=0.05. In order to control for preoperative delirium status, as well as other potential confounders we will subsequently use multivariable linear regression to assess the presence of treatment effect. Our other exploratory outcomes will be delirium incidence and duration, assessed via logistic regression, time-to-event and zero-inflated log-linear modeling.

Exploratory endpoint analysis will compare the effects on subjective sleep quality, postoperative pupil diameter fluctuations, average response latency in psychomotor vigilance testing, and total average electrographic sleep time over postoperative days 0, 1, and 2, if applicable, between suvorexant and placebo groups.

Precision variables include preoperative measures including the score on the Montreal Cognitive Assessment (MOCA), excessive daytime sleepiness measured with Epworth sleepiness scale, and poor preoperative sleep habits measured with the Athens Insomnia Scale [40–42].

Ethics and dissemination

The study was approved by the Duke Institutional Review board (PRO 00111869) and registered on clinicaltrials.gov (NCT05733286). This study will be conducted according to US and international standards of Good Clinical Practice, applicable government regulations, and Institutional research policies and procedures. Results will be published in a peer-reviewed journal, as well as presented at academic conferences.

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Competing interests
All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/disclosure-of-interest/. Support for this study is provided by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co. (to MJD). MJD acknowledges additional support from a Foundation for Anesthesia Education and Research grant and a National Alzheimer's Coordinating Center grant. No competing interests are identified.

Author contributions
MD conceptualized the study. MD, JF, MH, MW, JV, NP, MA, MS, WM, KR, MT, and CS contributed to the study design. JF, DT, SW, and MD contributed to drafting the test and preparing figures and tables. All authors critically reviewed and edited the final draft.

Patient and public Involvement
Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication
Consent obtained directly from patient(s).

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Tables

Table 1. Schedule of study events.

	Preop	Postop day 0	Postop day 1	Postop day 2	Postop day 3	Postop day 4	Postop day 5
Questionnaires							
Montreal Cognitive Assessment (MOCA)	X						
Athens Insomnia Scale	X						
Insomnia Severity Risk Index	X						
Epworth Sleepiness Scale	X						
Delirium Assessment	X	X[2]	X[2,3]	X[2,3]	X[2,3]	X[2,3]	X[2,3]
Modified Richards-Campbell Sleep Quality			X[2]	X[2]	X[2]	X[2]	X[2]
Medications							
Suvorexant vs. placebo		X[2]	X[2]	X[2]			
Procedures							
Nightly EEG		X[2]	X[2]	X[2]			
Wrist actigraphy	X[1]						
Psychomotor vigilance task (PVT)	X		X[2]	X[2]	X[2]		
Pupillometry	X	X[2]	X[2]	X[2]	X[2]		

[1]Activity is optional, must be worn for at least three days prior to surgery
[2]These activities will not be performed after hospital discharge
[3]Performed twice daily

Table 2 Inclusion and exclusion criteria of the REPOSE study with rationale.

Inclusion Criteria	Rationale
1. Age 65 and older	Older surgical patients have higher insomnia symptom burden, shorter total sleep times and higher risk of delirium compared to younger patients
2. Undergoing non-cardiac, non-intracranial surgery, any surgical procedure not involving the skull, brain, cerebrovascular structures	Cardiac surgery patients are often exposed to sedatives postoperatively in ICU, and neurologic surgery patients may have increased sensitivity to suvorexant, possibly increasing risk of adverse events
3. Scheduled postoperative inpatient overnight stay	Study drug administration and assessments must occur while in the hospital as they are not feasible in outpatient setting in this study
4. Able to give informed consent or has legally authorized representative able to give informed consent on their behalf	Required to maintain ethical standards
5. English-speaking	Delirium assessment and sleep questionnaires are only available in English, and non-English speaking is a barrier to informed consent.
Exclusion Criteria	
1. Inmate of correctional facility	Inmates have unique healthcare needs and environmental factors that may confound study outcomes
2. Body mass index > 40	Obese patients may have altered pharmacokinetics of suvorexant leading to decreased drug effect
3. Legal blindness	Vision required to complete study assessments

4. Unable to perform study-related questionnaires and assessments	Study-related questionnaires and assessments required for data analysis
5. Use of outpatient sedating sleep aids (see table 3) > 2 times per any week in 1 month preceding day of surgery	To avoid concomitant administration of other sedating sleep aids with suvorexant, which has not been well-studied.
6. History of psychotic disorder, including schizophrenia, schizoaffective disorder, schizophreniform or brief psychotic disorder	May increase risk of adverse events, since suvorexant may cause increased suicidal ideation
7. History of liver failure with documented international normalized ratio (INR) of >1.2 or with history of hepatic encephalopathy	Liver disease may decrease suvorexant metabolism and clearance and increase risk of adverse events
8. History of severe sleep apnea or obesity hypoventilation syndrome requiring home bilevel positive airway pressure therapy or home ventilator or other forms of noninvasive ventilation	Clinically significant respiratory depression effects of suvorexant in patients with severe central sleep apnea have not been ruled out in other studies.
9. Chronic lung disease requiring home oxygen therapy	Mild respiratory depression effects of suvorexant may increase risk of adverse events in this patient population
10. History of narcolepsy	Suvorexant is contraindicated in narcolepsy
11. Use of systemic (oral, intravenous, intramuscular, subcutaneous) moderate or strong CYP3A inhibitors within 1 week prior to surgery	Potential drug interactions; CYP3A enzymes metabolize suvorexant
12. Use of systemic (oral, intravenous, intramuscular, subcutaneous) moderate or strong CYP3A inducers within 1 week prior to surgery	Potential drug interactions; CYP3A enzymes metabolize suvorexant
13. Current or planned administration of digoxin, or is currently experiencing digoxin toxicity	Potential drug interactions; suvorexant administration results in decreased digoxin metabolism.
14. Undergoing surgery that will result in inability to take medications by mouth including laryngectomy, tracheostomy, and oral resection/reconstructive surgery	Study drug requires oral administration or durable enteral access such as large bore feeding tube, which are not typically placed after these surgeries.
15. Undergoing surgery that will require postoperative strict bowel rest, including gastrectomy, esophagectomy, and pancreaticoduodenectomy	Patients on strict bowel cannot take enteral meds and thus have no route to receive suvorexant.
16. Undergoing surgery in an area that will make it unsafe to wear a headband, such as scalp or forehead procedures	EEG headband is required for the measurement of total sleep time and sleep architecture
17. Inappropriate for study inclusion based on the judgement of the principal investigator	Individuals may have unique risk factors that make them unsuitable for study participation

Table 3 Sedating sleep aids restricted in the REPOSE study.

Sedating Sleep Aid	Common Name
Mirtazapine	Remeron
Trazodone	Desyrel, Oleptro
Flurazepam	Dalmane
Temazepam	Restoril
Triazolam	Halcion
Estazolam	Prosom
Quazepam	Doral
Clonazepam	Klonopin
Lorazepam	Ativan
Midazolam	Versed
Alprazolam	Xanax
Diazepam	Valium
Zolpidem	Ambien
Zaleplon	Sonata
Eszopiclone	Lunesta
Diphenhydramine	Benadryl

Doxylamine	Unisom
Hydroxyzine	Atarax, Vistaril
Suvorexant	Belsomra
Doxepin	Silenor

Table 4 Summary of study questionnaires and assessments.

Questionnaires	Assesses	Task
Montreal Cognitive Assessment (MOCA)	Cognition	Tasks such as trail-making, drawing, naming objects, memory recall, attention span, verbal fluency, abstraction, delayed recall, and orientation.
3-minute Diagnostic Interview for Confusion Assessment Method (3D-CAM)	Delirium	Structured interview with observer ratings to assess delirium symptoms such as orientation, memory, attention, hallucinations, and level of consciousness. Subsequent observer ratings determine sleepiness, stupor, hypervigilance, clarity of ideas, speech, attention fluctuation, distraction, consciousness fluctuation, and potential acute changes.
Insomnia Severity Risk Index (ISI)	Insomnia	Scaled responses (0-4) regarding severity of insomnia problems, satisfaction with sleep patterns, and sleep interference with daily functioning.
Athens Insomnia Scale (AIS)	Insomnia	Scaled responses (0-3) regarding sleep latency, awakenings, total sleep duration, sleepiness, and overall sleep quality.
Epworth Sleepiness Scale (ESS)	Daytime sleepiness	Scaled responses (0-3) regarding the likelihood of sleeping in various daytime situations.
Assessments		
Electroencephalogram (EEG)	Sleep patterns	Dry electrodes within headband that non-invasively records brainwaves while sleeping.
Wrist actigraphy	Sleep patterns	Wrist-worn device with 3-axis accelerometers and lux meter.
Psychomotor Vigilance Task (PVT)	Attention	Randomly displayed stimuli on a tablet to which the participants respond by tapping on the screen; records their reaction times, lapses, and errors.
Pupillometry	Cognition	Evaluation of pupil diameter fluctuations under ambient light conditions through an infrared camera.

Figures

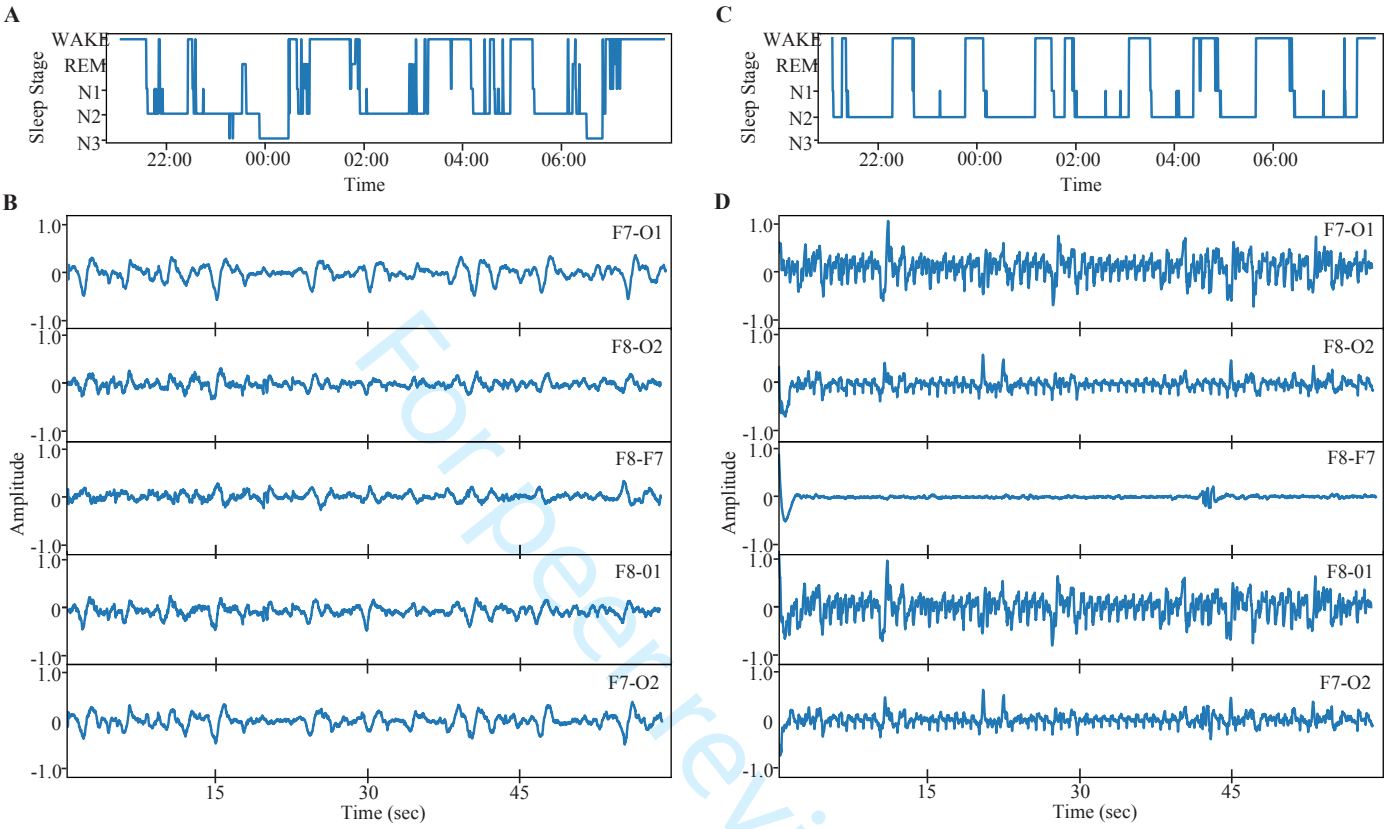
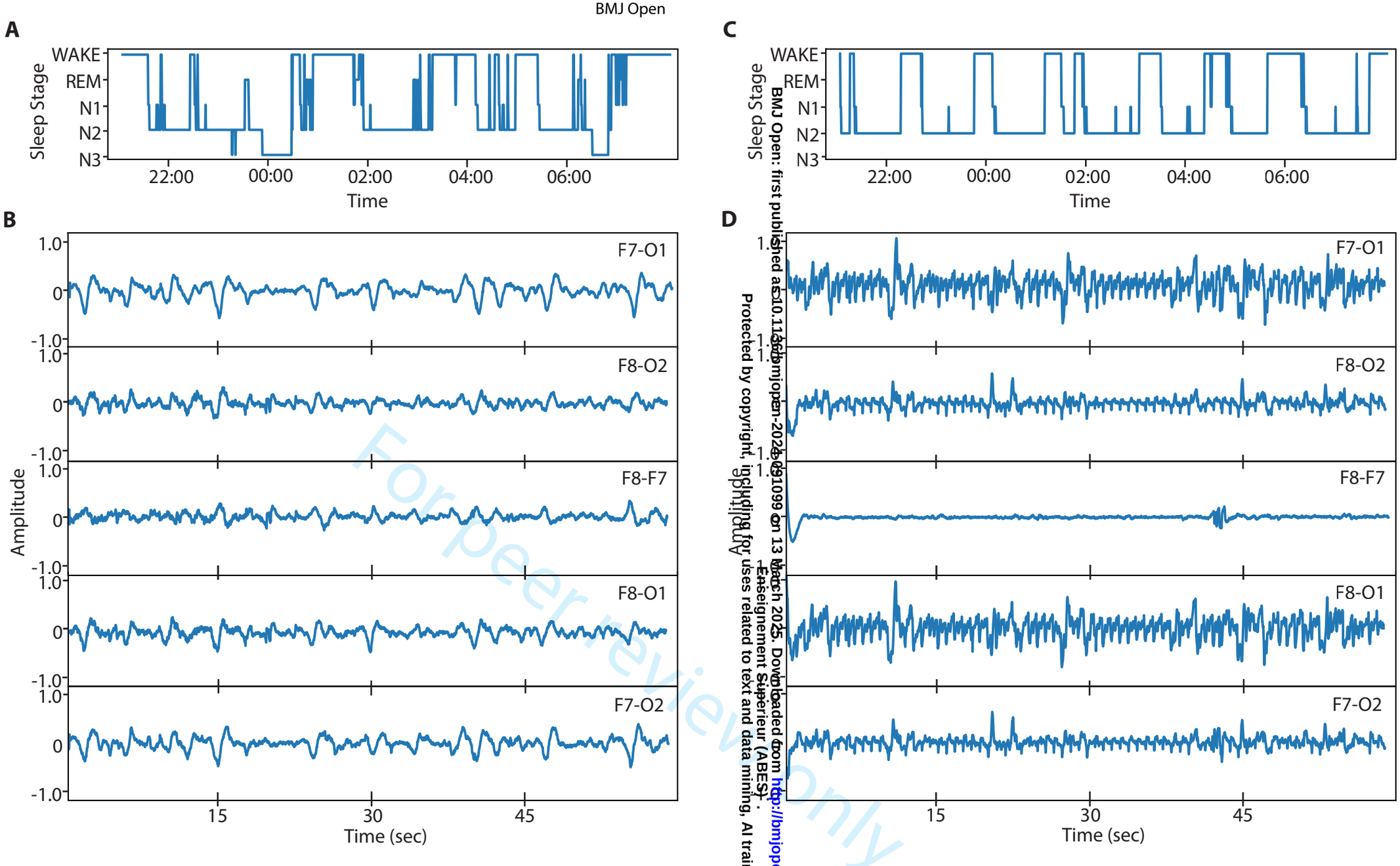


Figure 1 EEG recordings of relatively acceptable sleep architecture (**A** and **B**) and relatively disturbed sleep architecture (**C** and **D**). **(A)** Sleep architecture is preserved in one night of interrupted sleep, with sleep stages N2 and N3 observed alongside short periods of REM in a hypnogram constructed from EEG data. **(B)** N3 sleep is captured in a 60-second interval across 5 channels, derived from pairings of the 4 electrodes (F7, F8, O1, O2). **(C)** Sleep architecture is disturbed in one night of interrupted sleep, as suggested by observation of N2 sleep without N3 or REM stages. **(D)** N2 sleep is recorded across the 5 channels in a 60 second period of irregular sleep.



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Protocol and Design of the REPOSE Study: A double-blinded, randomized, placebo-controlled trial to evaluate the efficacy of suvorexant to improve postoperative sleep and reduce delirium severity in older non-cardiac surgical patients

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Protocol and Design of the REPOSE Study: A double-blinded, randomized, placebo-controlled trial to evaluate the efficacy of suvorexant to improve postoperative sleep and reduce delirium severity in older non-cardiac surgical patients

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ABSTRACT

Introduction

Postoperative delirium occurs in up to 40% of older surgical patients and has been associated with prolonged hospital stays, long-term cognitive impairment, and increased one-year postoperative mortality. Postoperative sleep disturbances may increase delirium risk, but studies investigating pharmacotherapies to improve postoperative sleep to prevent delirium remain limited. Suvorexant is a selective antagonist of orexin 1 and 2 receptors and is approved for insomnia pharmacotherapy by the Food and Drug Administration. It has potential to improve postoperative sleep and reduce postoperative delirium rates, but randomized controlled trials (RCT) are needed to determine efficacy of postoperative suvorexant administration. The REPOSE study (**r**educing delirium by **e**nhancing **po**stoperative **s**leep with suvor**e**xant) is a single-center, randomized, double-blind RCT that aims to evaluate the efficacy of suvorexant in increasing total sleep time and decreasing delirium in older patients undergoing non-cardiac surgery.

Methods and analysis

REPOSE will enroll 130 patients (age ≥ 65 years) undergoing non-cardiac surgery with planned postoperative inpatient stay. Participants will be randomized to receive 20 mg oral suvorexant or placebo nightly on postoperative nights 0, 1, and 2. The primary endpoint is total sleep time on the first postoperative night, as measured using an electroencephalography (EEG) headband. The secondary endpoint is peak postoperative delirium severity as measured by 3-minute diagnostic interview for confusion assessment method (3D-CAM) severity scores. Primary endpoint data will be analyzed with a two-sample t-test using an intent-to-treat approach to compare total sleep time on the first night that a patient received a study drug dose. Secondary and exploratory endpoint data will be analyzed using two-sample t-tests between groups.

Ethics and dissemination

Ethical approval was obtained from the Duke Institutional Review board (protocol # 00111869). Results of the REPOSE study will be published in a peer-reviewed journal and presented at academic conferences. Trial data will be deposited in clinicaltrials.gov.

Trial Registration Number

NCT05733286

ARTICLE SUMMARY

Strengths and limitations of this study

- This study will determine whether postoperative suvorexant administration increases postoperative total sleep time, as measured with electroencephalography (EEG) headbands that directly quantify electrographic sleep time.
- The secondary outcome measure of delirium severity is assessed by a trained staff member twice-daily using the 3D-CAM delirium assessment.
- Because the drug and sleep measurements are not continued after discharge, this study will not provide information on whether suvorexant improves sleep following hospital discharge.
- The single-center setting limits the generalizability to other populations due to potential site-specific biases.

INTRODUCTION

Postoperative delirium is a disorder characterized by acute confusion, impaired attention, disorganized thinking, and disturbances in consciousness, and typically occurs in the first three days following surgery [1]. Postoperative delirium affects up to 40% of older surgical patients and is associated with increased hospital length of stay, long-term cognitive decline, Alzheimer's disease and related dementias, and increased 1-year postoperative mortality [2–5]. Although delirium is associated with poor postoperative outcomes, there are few interventions that prevent delirium, in part due to the difficulty of addressing unmodifiable delirium risk factors, such as older age and baseline cognitive impairment [6].

One potentially modifiable risk factor for delirium is postoperative sleep disturbance [7–10]. Sleep is a fundamental physiological process that influences cognition, emotional well-being, immune function, and homeostasis [11–14]. Following surgical procedures, patients frequently experience sleep disruptions due to excessive hospital noise and light, postoperative pain, and the effects of medications administered during the perioperative period [15–17]. Thus, strategies that mitigate postoperative sleep disturbances and promote sleep hygiene may decrease the risk of postoperative delirium [18–20]. Additionally, the appropriate administration of pharmacologic sleep aids may help prevent postoperative delirium. However, few studies have widely investigated pharmacologic sleep aids for postoperative delirium prevention, in part because some sedating pharmacologic sleep aids may increase delirium risk. For instance, benzodiazepines, often given for sedation in the intensive care unit (ICU), exacerbate postoperative delirium in older ICU patients [21–25]. Consequently, recent guidelines from the American Geriatric Society discourage the use of benzodiazepines in older adults [26].

Suvorexant is an emerging alternative pharmacotherapy for treating sleep disturbances. This medication received Food and Drug Administration approval in 2014 for the treatment of insomnia and acts by blocking orexin receptors. Orexin is a wake-promoting neuropeptide pivotal for sleep regulation [27,28]. By blocking orexin receptors, suvorexant improves both sleep onset latency and wake after sleep onset. Interestingly, suvorexant administration acutely reduces cerebrospinal fluid phosphorylated tau levels, an Alzheimer's disease biomarker, which suggests that blocking the orexin pathway may affect Alzheimer's Disease-related pathology [29–31]. Additionally, suvorexant increases total sleep time in older adults with probable Alzheimer's Disease dementia. Thus, suvorexant may be an ideal candidate for postoperative sleep pharmacotherapy in older surgical patients at high risk for delirium [32].

To evaluate suvorexant's efficacy in increasing postoperative sleep and reducing postoperative delirium severity, we are conducting a single-center, double-blind, placebo-controlled, randomized trial. Our primary hypothesis is that postoperative suvorexant administration increases total sleep time (TST) in older surgical patients. Secondarily, we hypothesize that suvorexant administration decreases postoperative delirium severity. Our study aims to provide valuable insights into the potential therapeutic role of suvorexant to improve postoperative sleep and reduce delirium severity in older surgical patients.

METHODS AND ANALYSIS

Study design

This randomized, double-blind, placebo-controlled trial will be conducted at a single center at Duke University Medical center in Durham, NC, USA. The trial began on 28 June 2024 and is estimated to finish enrollment in late 2025. The study design schedule is outlined in table 1 and is approved by the Duke Institutional Review Board (IRB). Participants will be enrolled and randomized to intervention until 130 participants have complete primary outcome data for analysis.

Table 1. Schedule of study events.

	Preop	Postop day 0	Postop day 1	Postop day 2	Postop day 3	Postop day 4	Postop day 5
Questionnaires							
Montreal Cognitive Assessment (MOCA)	X						
Athens Insomnia Scale	X						
Insomnia Severity Risk Index	X						
Epworth Sleepiness Scale	X						
Delirium Assessment	X	X[2]	X[2,3]	X[2,3]	X[2,3]	X[2,3]	X[2,3]
Modified Richards-Campbell Sleep Quality			X[2]	X[2]	X[2]	X[2]	X[2]
Medications							
Suvorexant vs. placebo		X[2]	X[2]	X[2]			
Procedures							
Nightly EEG		X[2]	X[2]	X[2]			
Wrist actigraphy	X[1]						
Psychomotor vigilance task (PVT)	X		X[2]	X[2]	X[2]		
Pupillometry	X	X[2]	X[2]	X[2]	X[2]		

[1]Activity is optional, must be worn for at least three days prior to surgery
[2]These activities will not be performed after hospital discharge
[3]Performed twice daily

Study population

This study will enroll patients undergoing non-cardiac surgery with planned postoperative inpatient overnight stay undergo randomization and receive a least one dose of study drug. Inclusion and exclusion criteria are listed in table 2. Exclusion criteria include factors that affect suvorexant administration safety, pharmacokinetics or metabolism/excretion, and the ability to safely wear the EEG headband (e.g., intracranial surgery, etc.). Given the complexity of patient and surgical factors that could affect safety of suvorexant administration or study assessment, we will also sparingly exclude some cases based on principal investigator judgement. The reasons for these principal investigator determinations will be provided in the results of the study.

Table 2 Inclusion and exclusion criteria of the REPOSE study with rationale.

Inclusion Criteria	Rationale
1. Age 65 and older	Older surgical patients have higher insomnia symptom burden, shorter total sleep times and higher risk of delirium compared to younger patients.
2. Undergoing non-cardiac, non-intracranial surgery, any surgical procedure not involving the skull, brain, cerebrovascular structures	Cardiac surgery patients are often exposed to sedatives postoperatively in ICU, and neurologic surgery patients may have increased sensitivity to suvorexant, possibly increasing risk of adverse events.
3. Scheduled postoperative inpatient overnight stay	Study drug administration and assessments must occur while in the hospital as they are not feasible in outpatient setting in this study.
4. Able to give informed consent or has legally authorized representative able to give informed consent on their behalf	Required to maintain ethical standards.
5. English-speaking	Delirium assessment and sleep questionnaires are only available in English, and non-English speaking is a barrier to informed consent.
Exclusion Criteria	
1. Inmate of correctional facility	Inmates have unique healthcare needs and environmental factors that may confound study outcomes.
2. Body mass index > 40	Obese patients may have altered pharmacokinetics of suvorexant leading to decreased drug effect.
3. Legal blindness	Vision required to complete study assessments.
4. Unable to perform study-related questionnaires and assessments	Study-related questionnaires and assessments required for data analysis.
5. Use of outpatient sedating sleep aids (see table 2) > 2 times per any week in 1-month preceding day of surgery	To avoid concomitant administration of other sedating sleep aids with suvorexant, which has not been well-studied.
6. History of psychotic disorder, including schizophrenia, schizoaffective disorder, schizophreniform or brief psychotic disorder	May increase risk of adverse events, since suvorexant may cause increased suicidal ideation.
7. History of liver failure with documented international normalized ratio (INR) of >1.2 or with history of hepatic encephalopathy	Liver disease may decrease suvorexant metabolism and clearance and increase risk of adverse events.
8. History of severe sleep apnea or obesity hypoventilation syndrome requiring home bilevel positive airway pressure therapy or home ventilator or other forms of noninvasive ventilation	Clinically significant respiratory depression effects of suvorexant in patients with severe central sleep apnea have not been ruled out in other studies.
9. Chronic lung disease requiring home oxygen therapy	Mild respiratory depression effects of suvorexant may increase risk of adverse events in this patient population.
10. History of narcolepsy	Suvorexant is contraindicated in narcolepsy.
11. Use of systemic (oral, intravenous, intramuscular, subcutaneous) moderate or strong CYP3A inhibitors within 1 week prior to surgery	Potential drug interactions; CYP3A enzymes metabolize suvorexant.
12. Use of systemic (oral, intravenous, intramuscular, subcutaneous) moderate or strong CYP3A inducers within 1 week prior to surgery	Potential drug interactions; CYP3A enzymes metabolize suvorexant.
13. Current or planned administration of digoxin, or is currently experiencing digoxin toxicity	Potential drug interactions; suvorexant administration results in decreased digoxin metabolism.
14. Undergoing surgery that will result in inability to take medications by mouth including laryngectomy, tracheostomy, and oral resection/reconstructive surgery	Study drug requires oral administration or durable enteral access such as large bore feeding tube, which are not typically placed after these surgeries.
15. Undergoing surgery that will require postoperative strict bowel rest, including gastrectomy, esophagectomy, and pancreaticoduodenectomy	Patients on strict bowel cannot take enteral meds and thus have no route to receive suvorexant.
16. Undergoing surgery in an area that will make it unsafe to wear a headband, such as scalp or forehead procedures	EEG headband is required for the measurement of total sleep time and sleep architecture.
17. Inappropriate for study inclusion based on the judgement of the principal investigator	Individuals may have unique risk factors that make them unsuitable for study participation.

Potential candidates will be identified and screened for eligibility using the electronic health record. Eligible participants will be contacted through either an automated MyChart message or a phone call by a designated study team member using the IRB-approved phone script. All subjects will be informed of the purpose, procedures, and intent of the study and be provided a consent form (see Supplementary Material) prior to enrollment. Informed written consent will be obtained before the subject initiates any study activities or begins any screening procedures that are not considered standard patient care activities. All sexes, races, and ethnicities will be recruited [33].

Intervention

At least 130 participants will be randomized to receive suvorexant (20 mg) or a matched placebo for the first three postoperative nights while in the hospital. Patients will be administered suvorexant or placebo orally unless they are not able to take medications by mouth due to difficulty swallowing, in which case the medication can be administered via an indwelling nasogastric or gastrostomy tube, if one is already present and is usable. Patients will be assigned to blinded treatment groups through stratified permuted block randomization in a 1:1 ratio for suvorexant or placebo. Stratification will be based on age (≥70 and <70 years of age) and sex (male vs. female) to assure balanced age and sex between study groups. Administration will occur starting on postoperative day 0 through postoperative day 2, between 8-10 PM. After an order for the study drug is placed, the investigational drug pharmacy will be responsible for randomizing, bar-coding, and labeling the study drug. The study team will then deliver the study drug to the bedside RN, who will scan the study drug into the electronic medical record after administration, in order to accurately track study drug administration for each participant. The study team and participants will remain blinded to treatment allocation throughout this process.

Because suvorexant is primarily metabolized by CYP3A, the primary clinical team for enrolled subjects will be advised to avoid moderate or strong CYP3A inhibitors [34]. If recent exposure (<12 hours) to a moderate CYP3A inhibitor is noted in the electronic health record, the study drug dose will be halved, and if exposed to a strong inhibitor (within 12 hours of study drug administration), the study drug will not be administered. However, eligibility for future doses on subsequent postoperative nights is retained if criteria are met. Non-sedating sleep aids like melatonin are allowed anytime, while sedating sleep aids (table 3) are generally restricted on nights of the study drug. To allow for standard of care treatment of in-hospital insomnia, patients are permitted sedating sleep aids for persistent sleeplessness 1-hour after study drug administration up until midnight. The use of rescue sedating sleep aids for sleeplessness will be reported between placebo and suvorexant. Patients that receive rescue sedating sleep aids will not be excluded from the primary analysis.

Table 3 Sedating sleep aids restricted in the REPOSE study.

Sedating Sleep Aid	Common Name
Mirtazapine	Remeron
Trazodone	Desyrel, Oleptro
Flurazepam	Dalmane
Temazepam	Restoril
Triazolam	Halcion
Estazolam	Prosom
Quazepam	Doral
Clonazepam	Klonopin
Lorazepam	Ativan
Midazolam	Versed
Alprazolam	Xanax
Diazepam	Valium
Zolpidem	Ambien
Zaleplon	Sonata
Eszopiclone	Lunesta
Diphenhydramine	Benadryl
Doxylamine	Unisom
Hydroxyzine	Atarax, Vistaril
Suvorexant	Belsomra
Doxepin	Silenor

Several strategies will be used to promote retention and completeness of follow-up data. First, in the case that study drug is discontinued for any reason after randomization, participants will still be encouraged to remain in the study to continue the other study-related assessments. Second, if the participant is withdrawn from the study for any reason, every effort will be made to continue collecting data from the electronic medical record.

In the case that three unexpected, related serious adverse events are reported in this study, the enrollment of new participants will be halted and an unblinded staff statistician will perform analyses to determine whether these related serious adverse events are associated with suvorexant versus placebo. This information will then be used by the designated medical monitor to decide whether to continue the study.

Study outcomes & assessment

Primary Endpoint

The primary endpoint is total sleep time, which is defined as the amount of time spent sleeping during the lights out period (9 PM to 6 AM), on the first night after surgery that the patient receives study drug. Total sleep time will be assessed using electroencephalography (EEG) during postoperative nights 0 through 2, or until hospital discharge, whichever occurs first. A headband with frontal electrodes along with a 3D accelerometer will be used to record EEG data, and the data will be saved for later analysis to determine sleep stage and total sleep time (figure 1) [35]. This sleep EEG will allow for determination of total sleep time despite the frequent interruptions of sleep that occur postoperatively in the hospital wards. The headband is designed to be less invasive than standard polysomnography so that study subject sleep is minimally impacted by EEG monitoring and EEG recording adherence is optimized.

Sleep scoring of the EEG will be performed by trained sleep technologists overseen by sleep medicine physicians. Each thirty second epoch will be scored according to American Academy of Sleep Medicine Manual for sleep stage and associated events [36]. In epochs with poor EEG quality where sleep stage is indeterminate, sleep presence will be imputed based on adjacent epoch staging. In epochs where the adjacent epoch staging is also indeterminate, the accelerometer data will be used to estimate whether the patient was asleep or awake.

Secondary Endpoint

The secondary endpoint is peak postoperative delirium severity scores up through postoperative day 5 or discharge. The 3-minute diagnostic interview for confusion assessment method (3D-CAM) will be used to assess delirium in patients who are able to communicate verbally [37–39]. The 3D-CAM measures delirium severity through a cognitive assessment including ten orientation items, short-term recall, and digit span tasks. It then scores the presence of key delirium features, such as acute or fluctuating course, inattention, disorganized thinking, and altered level of consciousness [39]. In non-verbal or intubated patients, the confusion assessment method for the intensive care unit (CAM-ICU) will be used instead[40]. Assessment will first occur in the afternoon, prior to 9 PM, on postoperative day 0. Subsequently, from postoperative days 1 to 5, assessments will be systematically documented twice daily until the conclusion of postoperative day 5 or hospital discharge, whichever occurs first. The first assessment will be administered prior to 12 PM, and the second assessment will be administered between 12-9 PM.

Exploratory Endpoints

Sleep architecture and other sleep features

Using the EEG headband data, differences in postoperative sleep architecture (including stage 2 and 3 NREM sleep and REM sleep) will be compared in patients who received suvorexant compared to those who received placebo using two-sample t-tests. No multiple comparison correction for multiple sleep stages is planned because these are exploratory analyses. Average total sleep time over all nights that subjects receive study drug will also be compared using two-sample t-tests.

Subjective sleep quality

To assess subjective sleep quality, the Richards-Campbells subjective sleep quality questionnaire will be administered daily from postoperative day 1 until postoperative day 5 or hospital discharge, whichever occurs first. The total subjective sleep quality score will be compared between placebo and suvorexant groups using a two-sample t-test.

Sleep-related impairment in sustained attention

Sleep deprivation results in decreased ability to sustain attention, which can be measured with the 5-minute psychomotor vigilance task [41]. The psychomotor vigilance task measures simple reaction times to a visual stimulus over a minute to assess for slowed responses and lapses (i.e., failed response to visual stimuli) [41,42]. Response times, speed, and lapses will be compared between suvorexant and placebo treated groups to see if postoperative nightly suvorexant has an effect on these sustained attention measures. Using the NASA PVT+ application on an Apple iPad, the psychomotor vigilance task will be collected before surgery, and daily on postoperative day 1 and ending on postoperative day 3 or hospital discharge, whichever occurs first. Analyses will also examine pre-to-postoperative change in sustained attention measures to adjust for preoperative performance variability between subjects.

Delirium incidence and duration

The incidence and duration of postoperative delirium in treatment groups will also be reported. Although this study does not have adequate power to detect differences in delirium incidence, this data could be useful to guide future larger studies or in a meta-analysis of all studies of suvorexant and delirium.

Pupillary unrest in ambient light

Pupillary unrest under ambient light is an index of spontaneous pupil fluctuations that occur secondary to activity of the locus coeruleus, an important brainstem nucleus involved in maintenance of wakefulness and attentional control [43,44]. Decreased wakefulness has been associated with decreased pupillary unrest at ambient light, suggesting that pupillary unrest at ambient light is a marker of sleep deprivation-related alterations in wakefulness and attention. Here, infrared pupillometry will be used to measure pupil diameter fluctuations under ambient light conditions both before surgery and daily up through postoperative day 3 [45]. We will compare postoperative changes in pupillary unrest at ambient light in both suvorexant and placebo-treated using a two-sided t-test.

Effect modification factors

Suvorexant effect modification by baseline cognitive status, insomnia symptoms, excessive sleepiness, and sleep habits will be assessed by preoperatively administering the Montreal Cognitive Assessment, Insomnia Severity Index, Epworth Sleepiness Scale, and the Athens Insomnia Scale, respectively (table 4). Study participants will also be offered a wrist actigraph to wear before surgery to quantitatively measure preoperative sleep duration and sleep habits. This will be done as an optional sub-study and when feasible. Participants will be asked to wear the wrist actigraph for at least 3 nights so that circadian rhythms and average total sleep time can be determined [46]. Effect modification by these baseline factors will be assessed by comparing point estimate outcome effect sizes in subgroups (baseline cognitive impairment vs. normal cognition, excessive sleepiness presence, insomnia symptom presence, and preoperative short vs. long sleep). These results will be considered hypothesis generating for future study designs on postoperative sleep pharmacotherapy.

Table 4 Summary of study questionnaires and assessments.

Questionnaires	Assesses	Task
Montreal Cognitive Assessment (MOCA)	Cognition	Tasks such as trail-making, drawing, naming objects, memory recall, attention span, verbal fluency, abstraction, delayed recall, and orientation
3-minute Diagnostic Interview for Confusion Assessment Method (3D-CAM)	Delirium	Structured interview with observer ratings to assess delirium symptoms such as orientation, memory, attention, hallucinations, and level of consciousness. Subsequent observer ratings determine sleepiness, stupor, hypervigilance, clarity of ideas, speech, attention fluctuation, distraction, consciousness fluctuation, and potential acute changes
Insomnia Severity Risk Index (ISI)	Insomnia	Scaled responses (0-4) regarding severity of insomnia problems, satisfaction with sleep patterns, and sleep interference with daily functioning
Athens Insomnia Scale (AIS)	Insomnia	Scaled responses (0-3) regarding sleep latency, awakenings, total sleep duration, sleepiness, and overall sleep quality
Epworth Sleepiness Scale (ESS)	Daytime sleepiness	Scaled responses (0-3) regarding the likelihood of sleeping in various daytime situations
Assessments		
Electroencephalogram (EEG)	Sleep patterns	Dry electrodes within headband that non-invasively records brainwaves while sleeping
Wrist actigraphy	Sleep patterns	Wrist-worn device with 3-axis accelerometers and lux meter
Psychomotor Vigilance Task (PVT)	Attention	Randomly displayed stimuli on a tablet to which the participants respond by tapping on the screen; records their reaction times, lapses, and errors
Pupillometry	Cognition	Evaluation of pupil diameter fluctuations under ambient light conditions through an infrared camera

Data management and monitoring

All participants will be assigned a subject study number so that their data will be de-identified. EEG data will be accessed through a secure cloud-based platform while pupillometry and PVT data will be stored on a secure local drive. All other data will be stored on the secure web-based Research Electronic Data Capture (REDCap) software. Technical appendix, statistical code, and the relevant dataset will be available from the Vivli Clinical Research Data Repository (https://vivli.org/). This study will be monitored according to the Duke Clinical Quality Management Plan, which includes biannual independent reviews of all study-related documents and facilities. The principal investigator will also permit study-related monitoring, audits and inspections of all study-related documents and facilities by the IRB, sponsor, government regulatory bodies and university compliance and quality assurance groups.

Adverse events and safety

Adverse events will be assessed for daily by study staff. The principal investigator will determine whether the adverse event was unrelated, unlikely related, possibly related, probably related, or definitely related to study drug treatment. Any symptom, sign, illness, or experience that develops or worsens in severity will be identified as an adverse event and reported to the sponsor and IRB, if necessary. All adverse events occurring during the study period will be recorded in the source document and case report form. The most common side effects of suvorexant include headache, diarrhea, xerostomia, cough, abnormal dreams, dizziness, drowsiness, and daytime tiredness. Minor side effects include sleep paralysis, sleepwalking, itchiness, nausea, vomiting, palpitations, daytime sedation, and worsening of depression and suicidal ideation [47,48]. Study-drug related

adverse events will be reported by placebo versus suvorexant group in the manuscript results. Study subjects may be withdrawn from the study at any time by the principal investigator.

In the case that three unexpected, related serious adverse events are reported in this study, an unblinded staff statistician will perform analyses to determine whether these related serious adverse events are associated with suvorexant or placebo. This information will then be used by a designated medical monitor, an appointed physician not involved in the study, to decide whether to continue the study.

Statistical analysis

Since some patients may miss a study drug dose on the first postoperative night, the primary analysis will be conducted on a modified intent-to-treat basis comparing total sleep time on the first night that a patient received a study drug dose with a two-sample t-test. Secondary analysis will compare peak postoperative delirium severity scores between suvorexant and placebo groups with a two-sample t-test that the participant received study drug. This modified intent-to-treat analysis will only include those patients who received study drug dose. Based on American Academy of Sleep Medicine insomnia clinical practice guidelines, we will consider a 20-minute difference in TST a clinically meaningful difference [49]. We expect that a sample size of 130 subjects will yield a total of 116 subjects with complete primary and secondary endpoint data. Given a standard deviation (SD) of approximately 35 min for TST in healthy adults, a sample size of 58 subjects per group will provide 86% power to detect a 20-minute difference in TST between treatment groups using a two-sample t-test with a two-sided alpha= 0.05 [32].

For the secondary endpoint, we will consider a 50% reduction in peak postoperative delirium severity scores a clinically meaningful difference. A 50% reduction in delirium severity is reasonable, as a study that included non-pharmacological sleep promotion was found to reduce delirium incidence by approximately 50% [50]. Given a delirium severity SD of 1.8 and a mean peak 3D-CAM delirium severity score of 1.9 in the placebo group, a sample size of 58 patients per group will provide 80% power to detect a 0.95-point difference between treatment groups using a two-sided t-test with alpha of 0.05. In order to control for preoperative delirium status, as well as other potential confounders we will subsequently use multivariable linear regression to assess the presence of treatment effect. Delirium incidence and duration, two exploratory outcomes, will be assessed via logistic regression, time-to-event, and zero-inflated log-linear modeling.

Exploratory endpoint analysis will compare the effects on subjective sleep quality, postoperative pupil diameter fluctuations, average response latency in psychomotor vigilance testing, and total average electrographic sleep time over postoperative days 0, 1, and 2, if applicable, between suvorexant and placebo groups.

Precision variables include preoperative measures including the score on the Montreal Cognitive Assessment (MOCA), excessive daytime sleepiness measured with Epworth sleepiness scale, and poor preoperative sleep habits measured with the Athens Insomnia Scale [51–53].

Ethics and dissemination

The study was approved by the Duke Institutional Review board (PRO 00111869) and registered on clinicaltrials.gov (NCT05733286). This study will be conducted according to US and international standards of Good Clinical Practice, applicable government regulations, and institutional research policies and procedures. Results will be published in a peer-reviewed journal, as well as presented at academic conferences.

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Competing Interests
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Author Contributions
MD conceptualized the study. MD, JF, MH, CP, MW, JV, NP, MA, MS, WM, KR, MT, and CS contributed to the study design. JF, DT, SW, and MD contributed to drafting the test and preparing figures and tables. All authors critically reviewed and edited the final draft. MD is the guarantor.

Patient and Public Involvement
Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient Consent for Publication
Consent obtained directly from patient(s).

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Figure Legends

Figure 1 EEG recordings of relatively acceptable sleep architecture (**A** and **B**) and relatively disturbed sleep architecture (**C** and **D**). **(A)** Sleep architecture is preserved in one night of interrupted sleep, with sleep stages N2 and N3 observed alongside short periods of REM in a hypnogram constructed from EEG data. **(B)** N3 sleep is captured in a 60-second interval across 5 channels, derived from pairings of the 4 electrodes (F7, F8, O1, O2). **(C)** Sleep architecture is disturbed in one night of interrupted sleep, as suggested by observation of N2 sleep without N3 or REM stages. **(D)** N2 sleep is recorded across the 5 channels in a 60 second period of irregular sleep.

Tables

Table 1 Schedule of study events.

	Preop	Postop day 0	Postop day 1	Postop day 2	Postop day 3	Postop day 4	Postop day 5
Questionnaires							
Montreal Cognitive Assessment (MOCA)	X						
Athens Insomnia Scale	X						
Insomnia Severity Risk Index	X						
Epworth Sleepiness Scale	X						
Delirium Assessment	X	X[2]	X[2,3]	X[2,3]	X[2,3]	X[2,3]	X[2,3]
Modified Richards-Campbell Sleep Quality			X[2]	X[2]	X[2]	X[2]	X[2]
Medications							
Suvorexant vs. placebo		X[2]	X[2]	X[2]			
Procedures							
Nightly EEG		X[2]	X[2]	X[2]			
Wrist actigraphy	X[1]						
Psychomotor vigilance task (PVT)	X		X[2]	X[2]	X[2]		
Pupillometry	X	X[2]	X[2]	X[2]	X[2]		

[1]Activity is optional, must be worn for at least three days prior to surgery
[2]These activities will not be performed after hospital discharge
[3]Performed twice daily

Table 2 Inclusion and exclusion criteria of the REPOSE study with rationale.

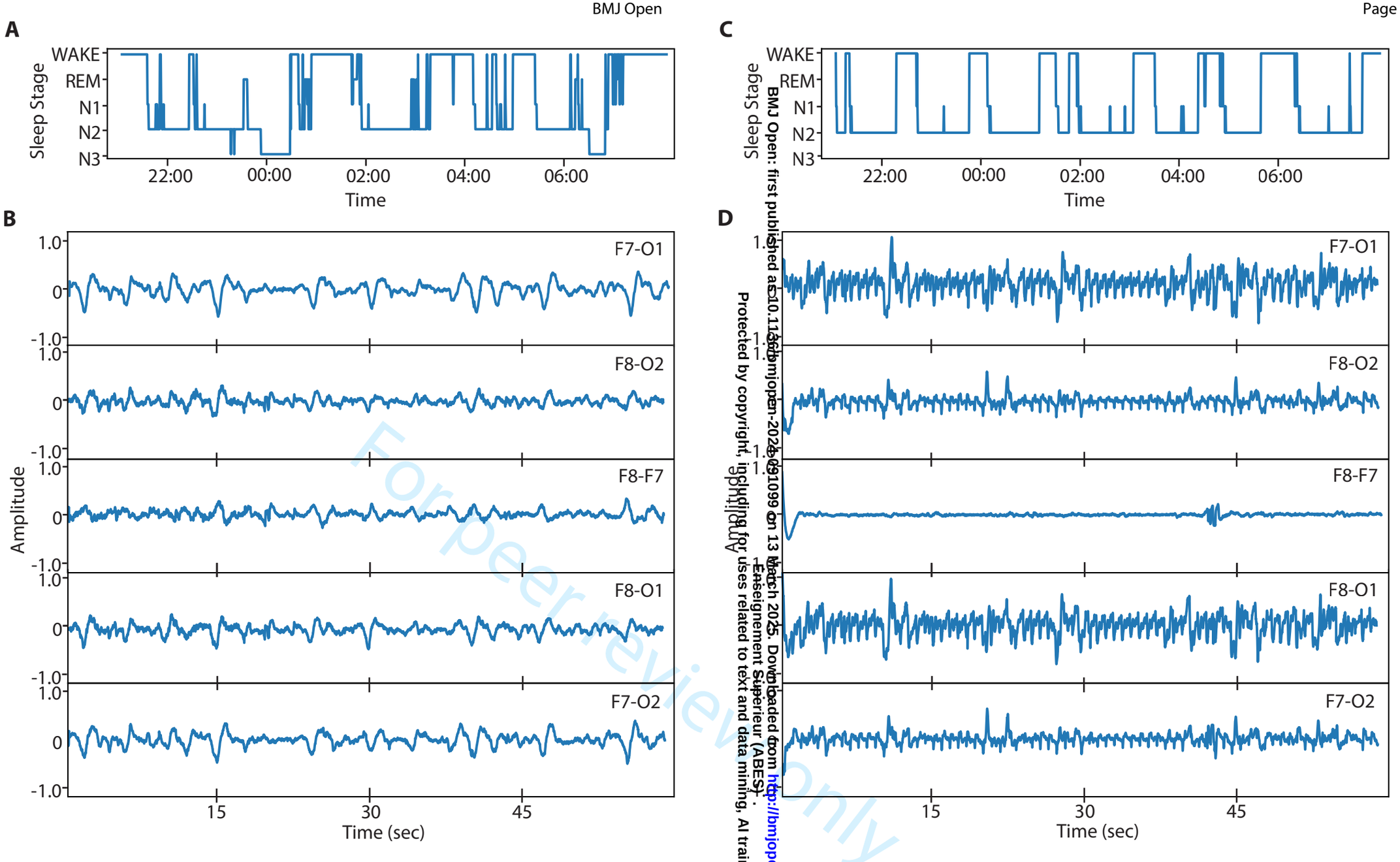
Inclusion Criteria	Rationale
1. Age 65 and older	Older surgical patients have higher insomnia symptom burden, shorter total sleep times and higher risk of delirium compared to younger patients.
2. Undergoing non-cardiac, non-intracranial surgery, any surgical procedure not involving the skull, brain, cerebrovascular structures	Cardiac surgery patients are often exposed to sedatives postoperatively in ICU, and neurologic surgery patients may have increased sensitivity to suvorexant, possibly increasing risk of adverse events.
3. Scheduled postoperative inpatient overnight stay	Study drug administration and assessments must occur while in the hospital as they are not feasible in outpatient setting in this study.
4. Able to give informed consent or has legally authorized representative able to give informed consent on their behalf	Required to maintain ethical standards.
5. English-speaking	Delirium assessment and sleep questionnaires are only available in English, and non-English speaking is a barrier to informed consent.
Exclusion Criteria	
1. Inmate of correctional facility	Inmates have unique healthcare needs and environmental factors that may confound study outcomes.
2. Body mass index > 40	Obese patients may have altered pharmacokinetics of suvorexant leading to decreased drug effect.
3. Legal blindness	Vision required to complete study assessments.
4. Unable to perform study-related questionnaires and assessments	Study-related questionnaires and assessments required for data analysis.
5. Use of outpatient sedating sleep aids (see table 2) > 2 times per any week in 1-month preceding day of surgery	To avoid concomitant administration of other sedating sleep aids with suvorexant, which has not been well-studied.
6. History of psychotic disorder, including schizophrenia, schizoaffective disorder, schizophreniform or brief psychotic disorder	May increase risk of adverse events, since suvorexant may cause increased suicidal ideation.
7. History of liver failure with documented international normalized ratio (INR) of >1.2 or with history of hepatic encephalopathy	Liver disease may decrease suvorexant metabolism and clearance and increase risk of adverse events.
8. History of severe sleep apnea or obesity hypoventilation syndrome requiring home bilevel positive airway pressure therapy or home ventilator or other forms of noninvasive ventilation	Clinically significant respiratory depression effects of suvorexant in patients with severe central sleep apnea have not been ruled out in other studies.
9. Chronic lung disease requiring home oxygen therapy	Mild respiratory depression effects of suvorexant may increase risk of adverse events in this patient population.
10. History of narcolepsy	Suvorexant is contraindicated in narcolepsy.
11. Use of systemic (oral, intravenous, intramuscular, subcutaneous) moderate or strong CYP3A inhibitors within 1 week prior to surgery	Potential drug interactions; CYP3A enzymes metabolize suvorexant.
12. Use of systemic (oral, intravenous, intramuscular, subcutaneous) moderate or strong CYP3A inducers within 1 week prior to surgery	Potential drug interactions; CYP3A enzymes metabolize suvorexant.
13. Current or planned administration of digoxin, or is currently experiencing digoxin toxicity	Potential drug interactions; suvorexant administration results in decreased digoxin metabolism.
14. Undergoing surgery that will result in inability to take medications by mouth including laryngectomy, tracheostomy, and oral resection/reconstructive surgery	Study drug requires oral administration or durable enteral access such as large bore feeding tube, which are not typically placed after these surgeries.
15. Undergoing surgery that will require postoperative strict bowel rest, including gastrectomy, esophagectomy, and pancreaticoduodenectomy	Patients on strict bowel cannot take enteral meds and thus have no route to receive suvorexant.
16. Undergoing surgery in an area that will make it unsafe to wear a headband, such as scalp or forehead procedures	EEG headband is required for the measurement of total sleep time and sleep architecture.
17. Inappropriate for study inclusion based on the judgement of the principal investigator	Individuals may have unique risk factors that make them unsuitable for study participation.

Table 3 Sedating sleep aids restricted in the REPOSE study.

Sedating Sleep Aid	Common Name
Mirtazapine	Remeron
Trazodone	Desyrel, Oleptro
Flurazepam	Dalmane
Temazepam	Restoril
Triazolam	Halcion
Estazolam	Prosom
Quazepam	Doral
Clonazepam	Klonopin
Lorazepam	Ativan
Midazolam	Versed
Alprazolam	Xanax
Diazepam	Valium
Zolpidem	Ambien
Zaleplon	Sonata
Eszopiclone	Lunesta
Diphenhydramine	Benadryl
Doxylamine	Unisom
Hydroxyzine	Atarax, Vistaril
Suvorexant	Belsomra
Doxepin	Silenor
Quetiapine	Seroquel

Table 4 Summary of study questionnaires and assessments.

Questionnaires	Assesses	Task
Montreal Cognitive Assessment (MOCA)	Cognition	Tasks such as trail-making, drawing, naming objects, memory recall, attention span, verbal fluency, abstraction, delayed recall, and orientation
3-minute Diagnostic Interview for Confusion Assessment Method (3D-CAM)	Delirium	Structured interview with observer ratings to assess delirium symptoms such as orientation, memory, attention, hallucinations, and level of consciousness. Subsequent observer ratings determine sleepiness, stupor, hypervigilance, clarity of ideas, speech, attention fluctuation, distraction, consciousness fluctuation, and potential acute changes
Insomnia Severity Risk Index (ISI)	Insomnia	Scaled responses (0-4) regarding severity of insomnia problems, satisfaction with sleep patterns, and sleep interference with daily functioning
Athens Insomnia Scale (AIS)	Insomnia	Scaled responses (0-3) regarding sleep latency, awakenings, total sleep duration, sleepiness, and overall sleep quality
Epworth Sleepiness Scale (ESS)	Daytime sleepiness	Scaled responses (0-3) regarding the likelihood of sleeping in various daytime situations
Assessments		
Electroencephalogram (EEG)	Sleep patterns	Dry electrodes within headband that non-invasively records brainwaves while sleeping
Wrist actigraphy	Sleep patterns	Wrist-worn device with 3-axis accelerometers and lux meter
Psychomotor Vigilance Task (PVT)	Attention	Randomly displayed stimuli on a tablet to which the participants respond by tapping on the screen; records their reaction times, lapses, and errors
Pupillometry	Cognition	Evaluation of pupil diameter fluctuations under ambient light conditions through an infrared camera



Consent to Participate in a Research Study
REPOSE Study: Efficacy of suvorexant to improve postoperative sleep and reduce delirium severity in older surgical patients: A double-blinded, randomized, placebo-controlled trial

CONCISE SUMMARY

The purpose of this study is to evaluate Suvorexant to improve postoperative sleep and decrease the rate of and severity of delirium, a syndrome of confusion that occurs after surgery.

After your surgery when it is time to go to sleep at night, you will receive either Suvorexant 20mg or a placebo (a placebo is an inactive substance given in the same form as the active drug, Suvorexant). You will receive this again for up to three nights while in the hospital following surgery.

During the time you are enrolled in the study, you will wear a headband for the first 3 nights after surgery to measure your sleep, complete questionnaires assessing your sleep, perform delirium and alertness assessments, have your pupil size measured, and have blood samples collected at various times.

Prior to your surgery, you might also have the opportunity to wear a wristband device that measures your sleep at home.

Your participation in the study will last 4 weeks, the last visit being a telephone call.

The risks of the study are described in this document. Some of the risks include drowsiness, headaches, unusual dreams, cough, and diarrhea.

If you are interested in this study, please continue reading below.

You are being asked to take part in this research study because you are having surgery and are expected to stay in the hospital overnight. Research studies are voluntary and include only people who choose to take part. Please read this consent form carefully and take your time making your decision. As your study doctor or study staff discusses this consent form with you, please ask him/her to explain any words or information that you do not clearly understand. We encourage you to talk with your family and friends before you decide to take part in this research study. The nature of the study, risks, inconveniences, discomforts, and other important information about the study are listed below.

Please tell the study doctor or study staff if you are taking part in another research study.

[Principal Investigator Name] will conduct the study and it is funded by [Funder or Sponsor Name]. [Funder or Sponsor Name] is funding this study and will pay [Location Study is Being Performed] to perform this research, and these funds may reimburse part of [Principal Investigator Name]'s salary.

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WHO WILL BE MY DOCTOR ON THIS STUDY?

If you decide to participate, [Principal Investigator Name] will be your doctor for the study and will be in contact with your regular health care provider throughout the time that you are in the study and afterwards, if needed.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to determine whether Suvorexant administered after surgery improves sleep and reduces the severity of delirium in older surgery patients. After surgery, older patients sometimes experience delirium, a disturbance of mental abilities resulting in confused thinking and reduced awareness. Suvorexant is approved by the FDA for the treatment of insomnia, a disorder that involves difficulty falling or staying asleep. Suvorexant may help improve sleep in hospitalized older patients after surgery and reduce delirium severity, but this is unknown. Therefore, this study is investigating whether Suvorexant improves sleep and decreases delirium severity in older surgery patients.

Sleep deprivation is associated with problems with the immune system, which helps fight infection, heart disease, earlier onset dementia, and increased death rates. Thus, there is increasing focus on improving sleep in vulnerable patient populations such as older surgical patients, because they are at increased risk for postoperative complications and susceptible to sleeping problems before and after surgery.

Since delirium is associated with higher hospitalization costs and postoperative complication rate, there is a critical need to find an FDA-approved medicine to decrease delirium. There is also a need for safe and effective sleep medicines for older hospitalized patients. Commonly used hypnotic sleep aids such as benzodiazepines (Xanax, Ativan, Klonopin) and non-benzodiazepines (Lunesta, Sonata, Ambien) are avoided in hospitalized patients because they increase delirium, but this leaves older hospitalized patients with few, if any, options for safe sleep aids.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

Approximately [Number of Anticipated Enrollment] people will take part in this study at [Location Study is Being Performed].

WHAT IS INVOLVED IN THE STUDY?

If you agree to be in this study, you will be asked to sign and date this consent form. If you do not sign consent form, you will continue to receive care, but not as part of this study.

Outlined below is what will be asked of you while participating in the research study.

You will be randomly assigned (like the flip of a coin) to receive either Suvorexant or placebo**.** You have a 50/50 chance of receiving study drug.

Before Surgery

- Confirm eligibility to participate in the study.

Subject/LAR Initials _____

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- Record medical history and current medications.
- Assessments and questionnaires that evaluate sleep quality, insomnia severity, memory, and delirium.
- Psychomotor vigilance test that uses a computer to measure your reaction time for attention and alertness
- Pupillometry, to measure small spontaneous fluctuations in pupil size
- Optional: Prior to surgery and while at home, we may provide you with a wrist activity monitor which is a device worn on your wrist that determines your sleep patterns by measuring your rest/activity cycles. If you decide to participate in the wrist activity monitor, we would ask you wear it a minimum of 3 days to maximum of 6 weeks.

Day of Surgery

➢ Prior to Surgery
- Confirm your eligibility to participate in the study
- If not completed at time of consent - sleep quality, insomnia severity, memory and delirium assessments and questionnaires; psychomotor vigilance test and pupillometry that measures spontaneous fluctuations in your pupil size.
- Blood sampling to examine inflammation by measuring proteins called interleukin 6 - about ½ tablespoon (10 milliliters)
- Randomization- like a flip of a coin to determine if you will be assigned to take Suvorexant or a placebo. (a placebo is an inactive substance given in the same form as the active drug, Suvorexant)
- Medication review

➢ After Surgery
- Delirium assessment at night after surgery
- Confirm eligibility to receive study drug.
- Administration of Suvorexant or placebo
- Measure your sleep with the EEG headband device (which looks at brain waves). The headband placement will be placed no earlier than 4:30pm and removal of the headband will be prior to 10am the next morning.
- Pupillometry, to measure small spontaneous fluctuations in pupil size

Note: If your surgery happens to go later than 8pm, due to the operative period crossing into the study drug and sleep period, the activities listed above would not be performed on the night of your surgery. The administration of Suvorexant or placebo and sleep measurement with the EEG headband device would instead first be administered the next night on post-op day 1 and would occur each night until post-op day 3 (or until discharge if that occurs sooner.)

Post-op Day 1 & 2 (or until discharge if occurs sooner)
- Delirium assessment in the morning and again in the afternoon

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- Sleep quality assessment
- Confirm eligibility to receive study drug.
- Administration of Suvorexant or placebo
- Measure your sleep with EEG headband device (which looks at brain waves). The headband will be placed no earlier than 4:30pm and removal of the headband will be prior to 10am the next morning.
- Psychomotor vigilance test
- Pupillometry
- Blood sampling- about ½ tablespoon each day (10 milliliters each day)

Post-op Days 3, 4 & 5 (or until discharge if occurs sooner)

- Delirium assessment in the morning and again at night
- Sleep quality assessment

Note: If on your day of surgery, the surgery happens to go past 8pm, the following activities could be performed on post-op day 3:

- Confirm eligibility to receive study drug.
- Administration of Suvorexant or placebo
- Measure your sleep with the EEG headband device (which looks at brain waves). The headband will be placed no earlier than 4:30pm and removal of the headband will be prior to 10am the next morning.

4-week post-op

- Phone call to see if you are having any health problems.

HOW LONG WILL I BE IN THIS STUDY?
You will be in this study for 4 weeks, with the last visit being a phone call. You can choose to stop participating at any time without penalty or loss of any benefits to which you are entitled. However, if you decide to stop participating in the study, we encourage you to talk to your doctor first.

WHAT ARE THE RISKS OF THE STUDY?
As a result of your participation in this study, you may be at risk for the following side effects. You should discuss these with the study doctor and your regular health care provider if you choose. Suvorexant may cause some, all or none of the side effects listed below.

Most common side effects of Suvorexant:

- Headache
- Diarrhea
- Dry Mouth

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- Cough
- Abnormal Dreams
- Dizziness
- Drowsiness

Less common side effects of Suvorexant include:

- Sleep paralysis
- Sleep walking
- Itchiness
- Nausea
- Vomiting
- Palpitations
- Daytime sleepiness and impairment
- Worsening of depression and suicidal ideation

Risks of Drawing Blood:
Risks associated with drawing blood from your arm include momentary discomfort and/or bruising. Infection, excess bleeding, clotting, or fainting are also possible, although unlikely.

Risks of Wearing the EEG headband device:
Risks associated with wearing the EEG headband device include slight discomfort caused by the forehead sensors placed against the skin. Approximately 0.1% of patients may have a red spot on their forehead as a result of wearing the sensor for an extended period of time.

Drug and Food Interactions
For your safety, you must tell the study doctor or nurse about all the prescribed medical foods and drugs, herbal products, over-the-counter (OTC) drugs, vitamins, natural remedies, and alcohol that you are taking before you start the study and before starting to take any of these products while you are on the study.

There may be risks, discomforts, drug interactions or side effects that are not yet known.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?
There are currently no known benefits of Suvorexant administration in older adults after surgery. Since Suvorexant has been shown to decrease time to sleep onset and improve sleep maintenance in outpatients with insomnia, Suvorexant has the potential to improve postoperative sleep, which could improve patient satisfaction and postoperative cognition as well as prevent the development of delirium after surgery.

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WILL MY INFORMATION BE KEPT CONFIDENTIAL?
Participation in research involves some loss of privacy. We will do our best to make sure that information about you is kept confidential, but we cannot guarantee total confidentiality. Your personal information may be viewed by individuals involved in this research and may be seen by people including those collaborating, funding, and regulating the study. We will share only the minimum necessary information to conduct the research. Your personal information may also be given out if required by law.

As part of the study, results of your study-related laboratory tests and procedures may be reported to the study sponsor. In addition, your records may be reviewed to meet federal or state regulations. Reviewers may include representatives from the Food and Drug Administration, the Institutional Review Board, research staff and non-research staff (for billing and health care operations). If any of these groups review your research record, they may also need to review your entire medical record.

The study results will be retained in your research record for [Insert length of time] At that time, either the research information not already in your medical record may be destroyed or information identifying you will be removed from such study results. Any research information in your medical record will be kept indefinitely.

Some information collected in research studies is maintained in your medical record. However, for this study that information will be inaccessible until the end of the study, unless your physician(s) decides that it is necessary for your care.

This information may be further disclosed by the funder of this study. If disclosed by the funder, the information is no longer covered by federal privacy regulations. If this information is disclosed to outside reviewers for audit purposes, it may be further disclosed by them and may not be covered by federal privacy regulations.

While the information and data resulting from this study may be presented at scientific meetings or published in a scientific journal, your name or other personal information will not be revealed.

Some people or groups who receive your health information might not have to follow the same privacy rules. Once your information is shared outside of [Location study is being performed], we cannot guarantee that it will remain private. If you decide to share private information with anyone not involved in the study, the federal law designed to protect your health information privacy may no longer apply to the information you have shared. Other laws may or may not protect sharing of private health information.

WHAT ARE THE COSTS TO YOU?
You or your insurance provider will be responsible and billed for all costs related to your routine medical care, including copayments and deductibles. Routine medical care services are those that you would have received for your condition if you were not participating in this research study. Not all

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services are covered by insurance. Some procedures or scans may require pre-authorization by your insurance plan. We will notify you if we learn that a service is not covered by your insurance plan as part of the pre-authorization process. If it is not covered, you will be responsible for paying for it. The amount of your out-of-pocket expense will depend on your insurance plan. For beneficiaries with Medicare Advantage Plans, traditional Medicare is billed for the routine cost of a research study. You may have more or higher co-pays than with a Medicare Advantage plan. Please discuss the costs of the study with [Principal Investigator's Name]**.** At your request, a Financial Counselor in the clinic may provide you with an estimate of costs for routine services.

The study sponsor has agreed to pay for services and procedures that are done solely for research purposes. Please talk with the principal investigator/ study team about the specific services and procedures that the sponsor will pay for, and the ones for which you or your insurance will be responsible.

We will monitor your patient care charges to make sure that costs are directed appropriately. If you have any questions or concerns about appropriate billing, contact your study team coordinator so that he/she can help find a resolution.

[Study Sponsor or funder] will provide the study drug free of charge to you. Your study doctor may request that you stop the study drug before the normal end period, if he/she thinks that continuing the study medication could result in harm to you.

WHAT ABOUT COMPENSATION?
You will be compensated up to a maximum of $75 for your expenses related to your participation.

- If you wear the EEG headband for at least 1 night after surgery, you will be compensated $50 at time of discharge from the hospital for your participation in the study.
- You will be compensated an additional $25 if you choose to wear a wrist band monitor (which measures your sleep patterns) at home for 3 nights before surgery.

WHAT ABOUT RESEARCH RELATED INJURIES?
Immediate necessary medical care is available at [Location] in the event that you are injured as a result of your participation in this research study. However, there is no commitment by [Name of location], your physicians, or the study supporter or funder to provide monetary compensation or free medical care to you in the event of a study-related injury.

For questions about the study or research-related injury, [Insert PI Contact Information Here].

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WHAT ABOUT MY RIGHTS TO DECLINE PARTICIPATION OR WITHDRAW FROM THE STUDY?

You may choose not to be in the study, or, if you agree to be in the study, you may withdraw from the study at any time. If you withdraw from the study, no new data about you will be collected for study purposes unless the data concern an adverse event (a bad effect) related to the study. If such an adverse event occurs, we may need to review your entire medical record.

Your decision not to participate or to withdraw from the study will not involve any penalty or loss of benefits to which you are entitled, and will not affect your access to health care. If you do decide to withdraw, we ask that you contact [Insert PI Contact Information Here].

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

Your doctor may decide to take you off this study if your condition gets worse, if you have serious side effects, or if your study doctor determines that it is no longer in your best interest to continue. The sponsor or regulatory agencies may stop this study at any time without your consent.

The use of your data and samples may result in commercial profit. You will not be compensated for the use of your data and samples other than what is described in this consent form.

A description of this clinical trial will be available on https://clinicaltrials.gov/ as required by U.S. Law The clinical trial number for this study is NCT05733286. This Web site will not include information that can identify you. At most, the website will include a summary of the results you can search this website at any time.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or a research-related injury, or if you have problems, concerns, questions or suggestions about the research, contact [Insert PI contact information here].

For questions about your rights as a research participant, or to discuss problems, concerns or suggestions related to the research, or to obtain information or offer input about the research, contact [Insert information here].

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OPTIONAL ACTIVITY TO CONSENT TO

Optional wrist activity monitor (Please initial one)

_____ Yes- I wish to participate in the home wrist activity monitor measurement.

_____No- I do not wish to participate in the home wrist activity monitor measurement.

STATEMENT OF CONSENT

"The purpose of this study, procedures to be followed, risks and benefits have been explained to me. I have been allowed to ask questions, and my questions have been answered to my satisfaction. I have been told whom to contact if I have questions, to discuss problems, concerns, or suggestions related to the research, or to obtain information or offer input about the research. I have read this consent form and agree to be in this study, with the understanding that I may withdraw at any time. I have been told that I will be given a signed and dated copy of this consent form."

_____	_____	_____
Signature of Subject	Date	Time
_____	_____	_____
Signature of Person Obtaining Consent	Date	Time
_____	_____	_____
Signature of Legal Representative	Date	Time

_____
Relationship to Subject