Slow Wave Induction by Propofol to Eliminate Depression (SWIPED) Trial: Phase I

Washington University Human Research Protection Office Protocol: 202008037

National Clinical Trial (NCT) Identified Number: NCT04680910

Principal Investigators: Ben J.A. Palanca, M.D., Ph.D., M.Sc. & Eric J. Lenze, M.D.

Sponsor: Washington University School of Medicine in St. Louis

Funded by: National Institute of Mental Health Grant U01MH128483

Version Number: v.3.1.5

30 January 2023

Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
2.3.31.3, 2.3.3, 8.2	Suicide Risk Management Protocol triggered by MADRS or C-SSRS Change timing and number of MADRS, C-SSRS, and SHAPS	Broadening of trigger for Suicide Risk Management Protocol Capture acute changes in depression, anhedonia, and suicidality, with consideration that best time is likely 7 days after second infusion
1.3., 10.1.5	Approximate range for data collection, update of team roster	Increase flexibility for participants and staff. New team members added
1.3, 3, 8.2, 9, 10.2	Incorporate NIH Toolbox and PVT to assess cognition	Assess feasibility for Phase II.
1.1, 1.3	Evaluate depression at 10 weeks	Comparison with other antidepressant trials
5,1, 7.3	EMR check for eligibility Email reminders	Address unresponsive patient

Table of Contents

STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR), and the National Institute of Mental Health Terms and Conditions of Award. The Principal Investigator(s) will assure that no deviation from, or changes to the protocol will take place without and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Slow Wave Induction by Propofol to Eliminate Depression Trial (SWIPED): Phase I
Study Description:	This is Phase I of a two-phase clinical trial to evaluate whether serial infusions of propofol can enhance slow wave sleep (SWS) and lead to improvements in cognition and depression. Phase I evaluates the safety and feasibility of targeting electroencephalographic (EEG) slow waves in 15 geriatric patients with treatment-resistant depression. If pre-specified milestones are met, a Phase II randomized controlled trial will evaluate short- and long-term effects on sleep structure, cognitive impairment, and depression severity in 70 geriatric patients.
Objectives:	Primary: Establish that propofol can safely 1) induce EEG slow waves during infusion and 2) promote the presence and persistence of SWS measures on subsequent nights in geriatric TRD patients Secondary: Inform design of Phase II to identify optimal dosing frequency, persistent of effects and recruitment criteria.
Primary Endpoints:	Safety: Number of adverse events and serious adverse events directly attributable to infusions. Feasibility: 1) EEG slow waves during the propofol infusions (sedation slow wave activity) and 2) Measures of slow wave sleep (sleep slow wave activity).
Secondary Endpoints:	Safety: Changes in suicidality (C-SSRS), in cognitive performance (MoCA). Feasibility: Changes in duration of N3 and REM sleep and proportion of total sleep time for these stages. Delta sleep ratio.
Tertiary Endpoints:	Changes in circadian rhythm, affect, anhedonia, depression symptoms
Study Population:	Inclusion: Age 60 or greater, English-speaking, TRD (non-responsiveness to at least two adequate trials of oral antidepressants for current episode). Exclusion: Symptomatic coronary artery disease, marked congestive heart failure/cardiomyopathy (NYHA > Class III, LVEF <40%, or greater than mild RV systolic dysfunction), prior reaction to propofol, resting heart rate < 50 bpm, ECT/TMS/vagal nerve stimulation in the past 6 weeks, body mass index >35, C-SSRS of 4 or greater, MoCA score <23, non-prescribed used of amphetamines, opioids, marijuana, cocaine, or phencyclidine, intake of > 14 beers/week (or equivalent), anesthetic exposure in past 4 weeks, concurrent use of benzodiazepines > 2 mg/day lorazepam or equivalent, trazodone > 50 mg/day, or gabapentin > 600 mg/day.
Phase:	Phase I – 15 participants at single site
Description of Sites:	Clinical Coordinating Center/Data Coordinating and Statistical Center/Clinical Site: Washington University School of Medicine in St. Louis (WUSM)
Description of Study Intervention:	Intravenous propofol will be administered on two study sessions monitored by a board-certified anesthesiologist. With the aid of pharmacokinetic modeling, the dose will be titrated at an individual level to elicit safe induction of electroencephalographic (EEG) slow waves monitored during 64-channel EEG acquisition. The dosing from the first infusion will be used to facilitate rapid targeting for the second infusion. Infusions will last approximately 1-2 hours.
Study Duration:	1 Year
Participant Duration:	13 weeks: Study duration 3 weeks, 2-week of follow up, 10-week follow up

1.2 SCHEMA

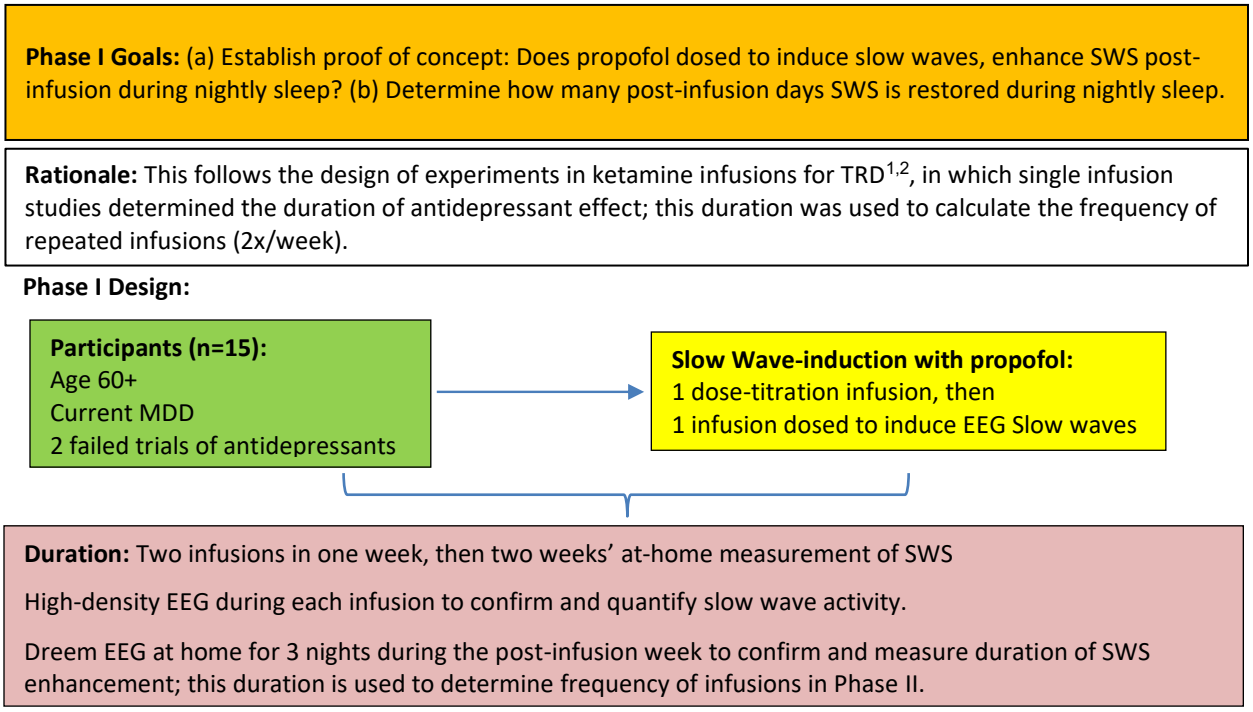

Figure 1. PICOT (Participant, Intervention, Control, Outcomes, Timing) Summary of Study Design

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedures	Phone Screening Day -14 to -1	Enrollment/Baseline Visit 1, Day 1	Enrollment/Baseline Call At home, Day 1 +2 days	Pre-infusion 1 At home, Day 1-7	Pre-infusion 2* At home, Day 2-7	Study Visit 2 Day 5 +/- 7 days	Study Visit 3 Day 9 +/-7 days	Post-infusion 2 At home, Day 11 +/-6 days	Post-infusion 3 At home, Day 14 +/-6 days	Post-infusion 4 At home, Day 17 +/-9 days	Post-infusion 5 At home, Day 20 +/-5 days	Post-infusion 6 At home, Day 23 +/-5 days	Follow up Study Visit 4 Day 30 +/-1 week	Final Follow up At home, Day 80 +/-1 week
Informed consent		X												
Demographics	X	X												
Medical history	X	X				X	X							
Night Sleep Recording [a]				X	X	X	X	X	X	X	X	X		
Administer propofol infusion						X	X							
Concomitant medication review		X				X	X							
Physical exam (including height and weight)		X				X	X							
Vital signs		X				X	X							
Height	X	X												
Weight	X	X												
Urine Drug Screen		X												
C-SSRS			X							X			X	X
MADRS			X							X			X	X
SHAPS			X							X			X	X
PHQ-9	X													
HD-EEG						X	X						X	
Feeling Scale						X	X							
MoCA		X											X	
NIH Cognition Toolbox Battery and PVT		X											X	
Adverse event review and evaluation		X		X	X	X	X	X	X	X	X	X	X	
Blood Draw *						X	X						X	
Wrist actigraphy		X		X	X	X	X	X	X	X	X	X		
Sleep diary		X		X	X	X	X	X	X	X	X	X		
MEQ		X												
STOP-BANG		X												
Complete Case Report Forms		X		X	X	X	X	X	X	X	X	X	X	X

a: At home sleep recording using Dreem headband
* Asterisk indicates optional study procedures for added flexibility
C-SSRS: Columbia-Suicide Severity Rating Scale
MADRS: Montgomery-Asberg Depression Rating Scale
SHAPS: Snaith-Hamilton Pleasure Scale
PHQ-9: Patient Health Questionnaire-9
HD-EEG: High-density Electroencephalography
MoCA: Montreal Cognitive Assessment
MEQ: Morningness-Eveningness Questionnaire
STOP-BANG: Snoring, Tired, Observed Apnea, high blood Pressure, Body mass index, Age, Neck circumference, male Gender Questionnaire
PVT: Psychomotor Vigilance Test

Table 1: Schedule of Activities.

2 INTRODUCTION

2.1 STUDY RATIONALE

Treatment-resistant depression (TRD) in older adults is a leading cause of disability, excess mortality from suicide, and dementia. Cognitive problems and sleep disturbances are common, contributing to recurrence and poor long-term outcomes. Disrupted slow wave sleep is at the nexus of depression and cognitive dysfunction in older adults. Novel approaches to target this core pathophysiology are lacking. Our mechanistic project is designed to elucidate the relationships between TRD and sleep disturbances in older adults. Through personalized infusions targeting electroencephalographic (EEG) patterns, we aim for a systematic characterization of the relationships between the propofol-induced EEG slow waves and enhancement of slow wave sleep. Through the repurposing of propofol as a therapeutic probe, this innovative proposal will establish whether EEG slow waves are a viable therapeutic target for novel antidepressant approaches.

2.2 BACKGROUND

A. Significance

A.1. Major Depressive Disorder: A Major Health Problem That Contributes to Poor Cognitive Outcomes

Treatment-resistant depression (TRD) in older adults is a leading cause of disability[3], excess mortality from suicide[4,5], and dementia[6-8]. With the aging population, the prevalence of **late life TRD (LL-TRD)** is likely to increase over time[9,10]. Using failure of two oral antidepressant classes as a defining characteristic of TRD, we demonstrated that additional trials of traditional antidepressants such as venlafaxine are futile[11]. Moreover, long-term outcomes are dismal, with high recurrence rates[12,13]. While ECT[14,15] and TMS[16] are alternatives for some, novel treatments are desperately needed. New treatments should target core pathophysiology; an important candidate is sleep disruption[17] that contributes not only to difficult-to-treat depression[18] but also deficits in alertness and executive function[19]. Therefore, derangements in sleep architecture have been posited as a treatment target for novel interventions in LL-TRD.

Cognitive problems are common in LL-TRD. Executive functions (EF) are cognitive processes involved in goal-directed behavior[20,21]. They impact everyday function, including activities involved in medical and self-care[22]. EF include inhibition of prepotent responses, set-shifting (cognitive flexibility), and working memory[23], governed by distinct but connected prefrontal cortex (PFC) regions[21,24-26]. EF impairment often coexists with LL-TRD[21,27], posited as due to microvascular lesions affecting white matter tracts connecting prefrontal and subcortical structures[28]. EF impairments are associated with poor responses to oral antidepressant treatment, including nonresponse to aripiprazole augmentation[12,20,22,29-32]. Cognitive disturbances are associated with poor functionality, progression to Alzheimer's disease and related dementias, and survival.

Related to EF, impairments in alertness and processing speed are commonly seen in those with depression and sleep disturbances. Psychomotor vigilance testing allows quantitation of both psychomotor speed and lapses in alertness[33,34]. Depressive mood is associated with more lapses and longer reaction times[34]. Furthermore, analyses of the Wisconsin Sleep Cohort study have demonstrated an association with depression and psychomotor response speed, following adjustments for age and sex[33]. Additional analysis of this cross-sectional cohort showed that those with depression have more lapses. Intrasubject longitudinal measurements demonstrated that slower psychomotor speed was associated with a higher

odds ratio for the development of depression. Thus, psychomotor speed and lapses (reduced alertness) may reflect core sleep-related cognitive difficulties in depression.

A.2. Disrupted Slow Wave Sleep (SWS) is at the Nexus of Depression and Cognitive Dysfunction in Older Adults

Sleep is a daily critical period for restoration of physiologic and brain function, and for good mental health. It is divided into rapid eye movement (REM) and non-rapid eye movement (NREM) sleep. **SWS, also known as NREM Stage 3 (N3)[35],** is linked to the subjective feelings of restorative sleep[36], reduced neurohumoral stress response[37], and memory consolidation[38]. SWS is defined by the dominance of electroencephalographic (EEG) sleep slow waves, whose measurement provides markers of synaptic plasticity[39-41]. SWS plays an important role in memory processing; during SWS memories appear to be replayed through hippocampal-dependent pathways[42]. Synaptic remodeling for learning and memory occurs during SWS, potentially through release of brain-derived neurotrophic factor (BDNF)[43]. The squared amplitude, or **power in these slow waves of SWS can be quantified as the slow wave activity (SWA)**. From a neurophysiologic standpoint, SWA is potentiated by a longer duration of wakefulness but dissipates over the course of sleep[44]. Changes in SWA between subsequent cycles of SWS are thought to reflect dissipation of sleep pressure and synaptic homeostasis[45]. SWA is a putative marker of homeostatic processes required for modeling neural connections based on recent experience. Early evidence suggests that enhancement of SWS may improve memory[46,47].

More recently, the electrophysiologic waves of SWS have been shown to regulate the biochemical milieu within the brain through the glymphatic system[48] by stimulating cerebrospinal fluid waves[49] that flush out lactate[50]. Proper functioning of this system may prevent deposition of pathology underlying Alzheimer's disease and related dementias by allowing drainage of amyloid-beta[48,51] and tau[52]. Power in these slow waves is inversely correlated with tau and amyloid-beta deposition in older adults, suggesting utility as a prognostic/diagnostic marker for cognitive impairment[53]. Anesthetic induction of states resembling SWS, with high EEG delta power have been correlated with greater glymphatic influx[54,55], opening the door for pharmacologic targeting of slow waves to manipulate metabolic and physiologic processes that may protect against long-term cognitive impairment.

Quality of SWS is reduced by stress and likely impacts depression. The proportion of SWS declines with each decade of aging such that the aged are at particular risk of deficiency. Chronic deficits in SWS potentially contribute to a cycle of future deficits through damage to circuitry regulating sleep and circadian rhythms. Reduced SWS is also a risk factor for recurrence of depression[56]. Overall, SWS is important for physiologic homeostasis and cognitive processes, with an unmet need in the those with LL-TRD.

A.3. Electroencephalographic Sleep Slow Waves are Novel Targets for Antidepressants

Abnormalities in sleep slow wave expression have long been associated with depression. Reduced nighttime SWA, particularly in the first cycle[57-62], has been considered as part of the core pathophysiology, even when accounting for age[63]. Delta sleep EEG metrics during N2 (**Figure 2A**) and SWS/N3 (**Figure 2B**) accounted for the largest proportion of variance in depression symptoms[64], particularly for depressed mood. Furthermore, patients with depression tend to show higher peak SWA not at the first N3 cycle but later, consistent with the hypothesis that patients with depression have impaired homeostasis of synaptic plasticity[65]. Thus, the **delta sleep ratio (DSR)** is computed by dividing the SWA for the 1st N3 cycle by the SWA of the 2nd N3 cycle[66], with a ratio > 1.5 observed in those without depression. DSR has also been used as a predictor for treatment response and vulnerability to recurrence. Shifting of SWA to the early part of sleep with imipramine predicted antidepressant response[62]. Low DSR predicted antidepressant responsiveness to ketamine[67]. Lower DSR (< 1.1) was associated with early recurrence of unipolar MDD

following discontinuation of antidepressant therapy[66] or vulnerability to depression after interferon alpha treatment[68]. In concordance, older antidepressants augment slow wave sleep; these include lithium[69-71], trazodone, nefazodone, mirtazapine[72], sertraline[73], and clomipramine[62]. Furthermore, newer antidepressants, such as ketamine[74] and agomelatine[75] augment time in SWS or SWA metrics. Despite these observations, no studies have specifically targeted SWS to treat TRD and cognitive function in older adults.

Restoration of SWS to the early cycles of overnight sleep coincides with normalization of REM (**Figure 2C**) sleep architecture. SWS normally predominates in early sleep cycles, with replacement of REM later in the evening. Intrusion of REM into early sleep cycles and greater durations are commonly observed in patients with depression, with subsequent delay and reduced duration observed with antidepressant response.

Overall, objective metrics based on EEG sleep slow waves are associated with depression, treatment response, and cognitive functioning. The potential for increasing SWS with pharmacological treatments opens the possibility of SWA and SWS enhancement as a pathway for novel antidepressant management strategies aimed at normalizing REM sleep architecture.

A.4. Propofol induces EEG slow waves during infusion and alleviates N3 sleep deficiency on nights following infusion

Propofol is a commonly used sedative in anesthetic practice. Low doses induce a shift toward lower frequencies in the EEG with some resemblance to N2 (**Figure 2D**). Higher doses induce EEG slow waves resembling those of N3/SWS[76] (**Figure 2E**), while even greater doses induce burst suppression (**Figure 2F**). The ability of propofol to recapitulate states resembling SWS in humans is aligned with the ability of propofol to fulfill rodent deficits of SWS[77]. Prolonged infusion in rodents reduced delta band power in the early sleep cycles[78]. The ability of propofol to provide subjective feelings of restorative sleep has motivated use as a treatment for refractory insomnia[79,80]. In adult patients with chronic refractory insomnia, **five days of a 2-hour propofol infusion led to SWS enhancement** (from 10 to 20% of total sleep time) with persistent augmentation 6 months after therapy[80]. From a safety standpoint, the pharmacokinetic modeling of propofol is well-established[81-85]. Sedation at projected serum concentrations of 3-4 mcg/ml without airway or cardiovascular support has been safely employed in young volunteers to elucidate the neural circuitry of propofol EEG slow waves[76,86,87]. The ability of propofol to recapitulate electrophysiologic and homeostatic properties of SWS has not yet been linked to antidepressant effects.

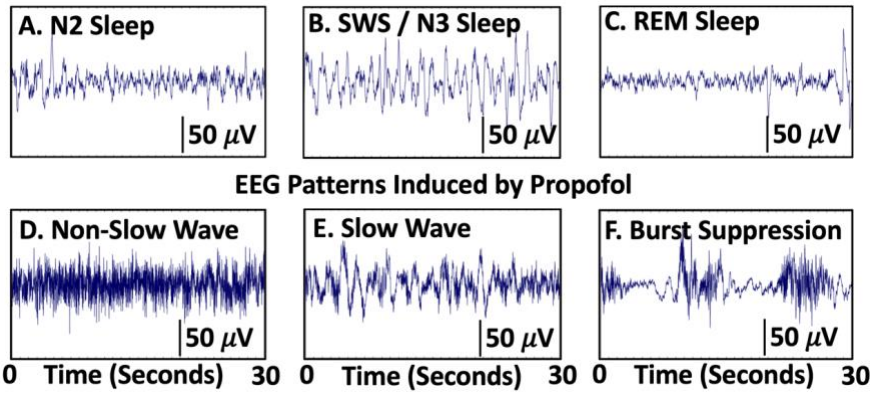

Figure 2. EEG Patterns During Natural Sleep and Propofol Sedation From a 71-year-old female with TRD. These data demonstrate the similarities and differences in EEG patterns across varied states of arousal. **A.** EEG during N2 sleep. **B.** Large amplitude slow waves during N3/SWS. **C.** REM Sleep with large amplitude deflections due to rapid eye movement artifacts. F7-F8 EEG data were recorded using a wireless wearable headband (Dreem). **D.** Non-slow wave EEG patterns with minimal slow waves during propofol infusion. **E.** Slow wave EEG patterns, resembling N3 sleep, during the same infusion. **F.** At higher infusion rates of propofol, burst suppression is induced. **D-F** were recorded using 64-channel high-density EEG. All data were 0.1-0.6 Hz bandstop- and 0.5-40 Hz bandpass-filtered.

These data demonstrating a favorable side effect profile during routine clinical use, titratability, and effects of propofol on sleep architecture place it in a unique position as an experimental therapeutic probe for temporally linking target engagement of electroencephalographic markers and clinical effects.

A.5. Additional putative antidepressant actions of propofol

Antidepressant effects of propofol, independent of SWS induction/enhancement, have been suggested. While binding to GABA receptors is its primary mechanism[88,89], propofol has additional molecular mechanisms that include antagonism of NMDA[90] and action at AMPA receptors[91,92]. In rodent models, propofol pretreatment augmented the antidepressant effects of ketamine[93] and moderate-dose ECT.[94]

In surgical patients and those undergoing endoscopies, propofol exposure sometimes produces transient improved mood and euphoria[95,96], amorous behavior[97,98], and elation[99] which can last for several hours[100]. These effects appear to be dose-dependent; low-dose sub-anesthetic propofol infusions targeting plasma concentrations of 0.9 mcg/ml yielded no improvements in mood 4 hours after infusion[101]. Higher doses of propofol capable of inducing burst suppression (**Figure 2F**) in humans has been associated with improvements in depression scores[102] with some antidepressant responses sustained for up to 3 months.

Since propofol has several potential antidepressant actions–SWS induction and enhancement as well as NMDA antagonism and AMPA receptor agonism–it will be important to delineate effects that are attributable to changes in sleep architecture from other effects. This requires a Phase I study to determine the ability of propofol to induce EEG slow waves and restore SWS in LL-TRD patients, and then a Phase II clinical trial to assess the association of SWS enhancement with cognitive and clinical outcomes.

B. Innovation

B.1. Theoretical and Experimental: Pharmacologic targeting of neurophysiologic states during unconsciousness and sleep

Traditional monoaminergic antidepressants target specific molecular receptors and ion channels. In doing so, they disrupt multiple adaptive processes regulated by these receptors, but may not directly correct the underlying pathophysiology. These medications must be given chronically, and downsides of this approach include side effects and potential risks in medically ill individuals[103]. In contrast, we are utilizing propofol as a probe to both target EEG states resembling sleep and to increase the propensity for subsequent N3 sleep. In this way, our goal is to facilitate endogenous neural circuitry to restore normal architecture of sleep. We anticipate that this approach will yield new pharmacologic and non-pharmacologic avenues for alleviating TRD.

In this proposal, we are shifting the focus from targeting the monoaminergic neurotransmitter system, toward the restoration of SWS to correct a core pathophysiology. This is similar to the efforts with other novel antidepressants such as ketamine[74] and the neurosteroid brexanolone[104], which are thought to correct pathophysiology associated with TRD and post-partum depression, respectively. These states may facilitate the relearning of interactions between patients and the external world to reconfigure pathologic circuits underlying depression. In this study, propofol is being repurposed for its ability to induce states that address deficiencies of SWS and tested for its longer-term ability to alleviate depression and associated cognitive dysfunction.

B.2. Experimental: High-density EEG provide biomarkers for target engagement during propofol infusion. Wireless wearable EEG devices provide biomarkers of treatment effect on sleep post-infusion

Personalized medicine[105] requires dosing based on individualized need. Here, neurophysiologic markers will allow target dosing of propofol in the initial treatment and in subsequent infusions to maximize safe

target engagement (i.e., induction of EEG slow waves during the infusion). High-density EEG maximizes signal-to-noise and allows secondary analyses on circuits during propofol infusions. Furthermore, we will leverage the potential of at-home sleep EEG recordings as a report of the effects on brain circuitry. The use of wireless wearable devices (**Figure 3**)[106,107] addresses feasibility issues of cost, logistics, interpretability, and instrumentation—all issues that hamper longitudinal investigation of sleep architecture.

B.3. Theoretical and Experimental: Targeting of depression through direct manipulation of SWS

Disorder of REM sleep expression has been posited as a marker and mechanism contributing to TRD. Patients with abnormal REM commonly express a short time interval (latency) between sleep onset and REM, and a greater proportion of total sleep time. Dysregulation of REM sleep, via early expression or overexpression, both yield deficiency in N3. The restoration of N3/REM sleep architecture has been posited as a contributor to antidepressant effect. This proposal is innovative in targeting SWS expression, given that deficits in this stage may contribute to damage in thalamocortical and limbic circuitry critical for cognition and emotional regulation.

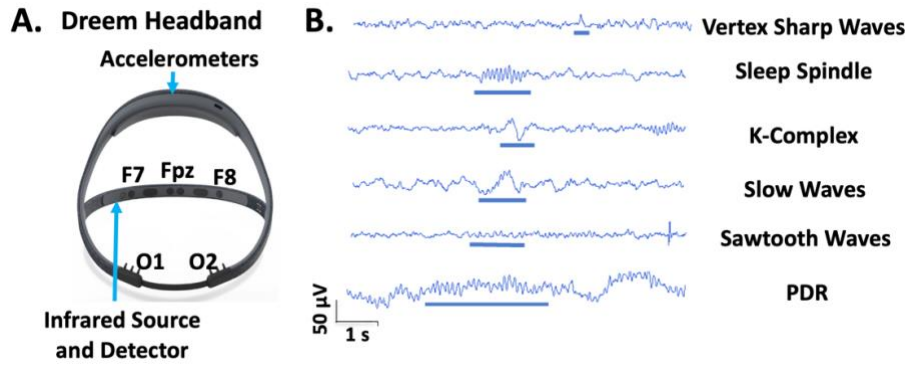

Figure 3. Wireless wearable headbands for serial at-home unattended overnight sleep recordings. A. Our group has been utilizing the Dreem headband to record sleep from geriatric patients prior to cardiac surgery[107]. The device has dry EEG electrodes (F7, Fpz, F8, O1, O2), accelerometers, and infrared plethysmography. **B**. Example EEG markers recorded by the Dreem to allow sleep staging. Vertex Sharp Waves for N1, Sleep spindles and K-complexes for N2, Slow waves for N3. Sawtooth Waves for REM, Posterior dominant rhythm (PDR) for wakefulness (W). Through use of the Dreem to record preoperative sleep of 90 cardiac surgical patients (age 60 or greater), the proportion of sleep time was 17.8% REM, 8% N1, 70.8% N2, 0.4% N3, consistent with previous literature[108]. Among 26 geriatric patients with two recordings, paired Wilcoxon sign-rank tests showed no significant difference in proportion of total sleep time for any stage (all $p > 0.05$).

B.4. Theoretical and Experimental: Investigation of circuit markers related to underlying mechanisms

We view propofol as a drug that can either be repurposed as a possible treatment for depression, but more likely be used as a therapeutic probe to understand the relationship between SWS enhancement and antidepressant effects. We address key steps in the FAST-FAIL approach for new drug discovery[109]. Published data (**§**A) and preliminary data (**§**C) show preclinical/clinical evidence supporting target engagement for therapeutics. EEG slow waves during infusion represent our biomarker for compound activity at neurobiological target and dosing-based target engagement. We propose dosing congruent with clinical anesthesia and volunteer studies for safe and efficacious target engagement. Phase II studies are proposed to address behavioral outcomes (alertness, executive function, and fluid cognition composite) as well as biomarkers of effect (N3 sleep). These studies will lay the groundwork for sleep slow wave enhancement via pharmacologic and non-pharmacologic interventions.

B.5. Experimental: Repurposing of anesthetic agents to improve cognitive outcomes

Sedative anesthetics have been associated with acute confusion and cognitive decline in the perioperative setting. Here we are addressing the provocative hypothesis that these agents may *improve cognitive outcomes* either directly (addressing acute/chronic sleep deprivation) or indirectly through alleviating the cognitive impairments of depression. This complements our work in repurposing anesthetics as antidepressants[110,111].

C.1. Preliminary Studies

C.1.1. Infrastructure for Recruitment of TRD Patients

Data: Our group has a large pool of geriatric patients for recruitment, including a recently completed large-scale trial of LL-TRD (OPTIMUM) and a geriatric depression clinic. These referral sources have been successful for the pilot stages of the proposed work. Since the initiation of recruitment (1/12/21), we approached 4 older adults with TRD and completed infusions in two participants. One remains active for future participation.

Relevance: Excellent feasibility of recruiting geriatric TRD patients into a protocol requiring infusions and at-home sleep recordings.

C.1.2. Cognitive Task Performance and the Psychomotor Vigilance Test

Data: We (Dr. Lenze) have previous experience with evaluating both measures of executive function and global cognition using the **NIH Toolbox Cognition Battery**[32]. We have previously utilized the **NIH Toolbox Cognition Battery Fluid Composite** in a randomized placebo-controlled investigation that evaluated whether vortioxetine improved cognitive training[112]. One-hundred participants, age 65 years or older, were randomly assigned to take either placebo or 10 mg vortioxetine for a 26-week interval with a target cognitive training engagement of 150 minutes/week. The NIH Toolbox Cognition battery was administered at **4-, 12-, and 26-weeks following randomization**. The computer-based instrument allowed assessment of fluid and crystallized cognition through the following five component tests (and tested cognitive domains): The Flanker Inhibitory Control Test (executive function-sustained attention and inhibitory control), the Dimensional Change Card Sort test (executive function-cognitive flexibility), the List Sorting Working Memory Test (working memory), the Picture Sequence Memory Test (episodic memory), and the Pattern Comparison Processing Test (processing speed). We utilized age-corrected standardized scores, excluding participants who failed to complete a 2-week lead-in period and those who had scores above 10a determined cutoff of one standard deviation above age-matched controls. At 12 weeks, we observed greater improvement in the estimated Fluid Cognition Composite Change from Baseline (+4.19 favoring vortioxetine over placebo, with a standard error of 1.52, p = 0.0063, Cohen's d effect size of 0.57). Smaller effects were noted at 4- and 26-weeks.

The **Psychomotor Vigilance Test (PVT)**[114] is a common task used to assess vigilance/alertness in the context of poor sleep and psychiatric illness. Adaptions allowing short testing bouts of a few minutes have been validated [115], all the way to 3 minutes[116,117]. The PVT requires the participant to respond as quickly as possible and to maintain sustained vigilance due to the incorporation of a random intertrial interval of several seconds. The task generates a right skewed distribution in reaction time (RT), that can be assessed in terms of lapses (outliers) as well as overall metrics of speed (the reciprocal of reaction time, RRT). With sleep deprivation, there are an increased number of lapses (reaction time > 500 ms)[118]. We (Dr. Palanca) have prior experience with the execution of a 3-minute computerized version of the PVT in healthy non-depressed study participants undergoing general anesthesia (**Figure 4**)[113]. We (Drs. Palanca, Lenze, and Farber) have extended our experience in patients with TRD undergoing electroconvulsive therapy (ECT)[119].

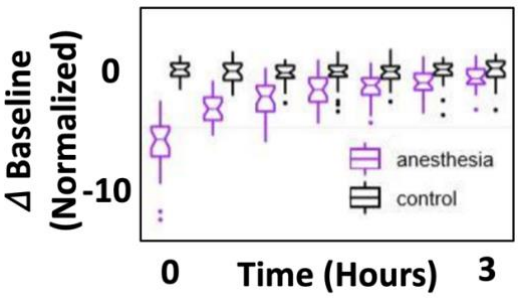

Figure 4. Return to baseline PVT response time following general anesthesia. Change in baseline scores are plotted for 30 healthy volunteers following 3-hours of isoflurane anesthesia (purple) or following 3-hours of watching videos (black)[113].

Relevance: These data demonstrate 1) successful longitudinal administration of the NIH Cognition Toolbox in the geriatric population, 2) ability to detect change in the global fluid cognition following an intervention, 3) successful implementation of the 3-minute computerized versions of the PVT.

These data will be important for a future planned Phase II study.

C.1.3. Precision Targeting of Propofol EEG Slow Waves During High-density EEG

Data: We have carried out serial infusions on two participants with LL-TRD and have demonstrated proof of concept of the proposed work. Both participants underwent two propofol infusions lasting 2 hours. Estimated propofol target effect-site concentrations were projected using published pharmacokinetic models[85] implemented in an iOS application, AnestAssist. The infusion bolus and rates were tailored to the patients' sex, age, height, and weight. The first infusion session was utilized to evaluate safety endpoints and EEG changes in response to propofol bolus and infusions. This dose-titration session facilitated the second infusion sessions, focused on establishing safe and stable target engagement of EEG slow waves. An anesthesiologist controlled the infusion rate (80-200 mcg/kg/min) while monitoring participant safety with a study nurse. Minimal airway support (chin lift) and supplemental oxygen were supplied to further augment safety. Fasting and monitoring guidelines were followed according to society guidelines. High-density EEG data were acquired using a MagStim/Philips/EGI system and 64-channel GSN nets. Elefix conductive gel was injected within the Ag/AgCl electrode sensors to minimize impedances above 100 kOhms/electrode. Data (500 Hz sampling) were acquired with a Net Amps 400 amplifier and Net Station version 5.0 via a Late 2012 Mac Pro Workstation.

We have induced targeted EEG slow waves in two participants, extending proof of concept. Example EEG data for the first participant are included in **Figure 2C-E**. Data from the second participant's dose-titration session are shown in **Figure 5**. While Non-Slow Wave EEG patterns are noted at lower targeted

effect site concentrations of propofol 1.5-2 mcg/ml (**Figure 5A-B**), Slow Wave EEG patterns noted at higher concentrations (**Figure 5C-D**) were targeted during the remainder of the infusion (effect-site concentration of 2.3-2.4 mcg/ml, as demonstrated in the time-frequency power spectrogram (**Figure 5E**). This contour plot graphs the power at each frequency as a function of time. The persistence of the combination of power at low frequency oscillations (<4 Hz) and "spindle-like" activity at 13-14 Hz is observed.

Relevance: These data demonstrate our ability to 1) safely administer serial infusions of propofol and 2) target propofol dosing to induce EEG slow waves in the outpatient setting.

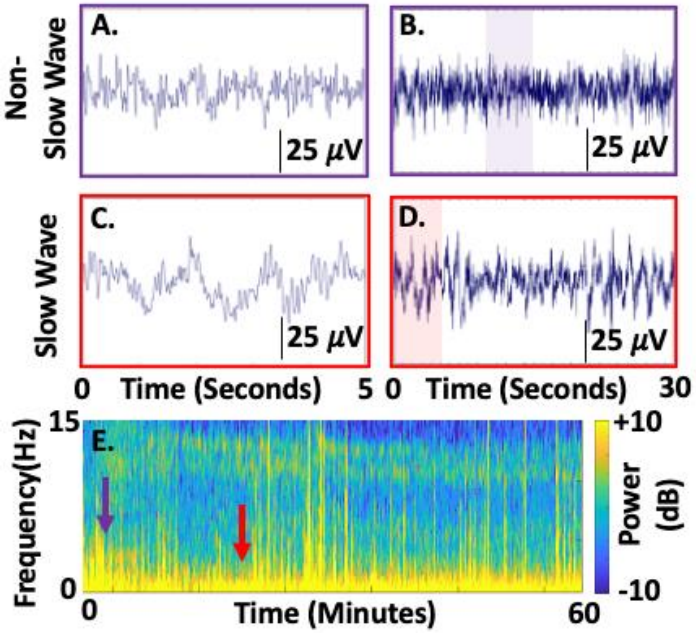

Figure 5. Targeting of Slow Wave EEG During Propofol Infusion for a 77-year-old male with TRD. Propofol was administered intravenously during the first infusion/dose-titration session. **A.** During short boluses of propofol, Non-Slow Wave EEG patterns were observed with mixed alpha (8-13 Hz) and beta (13-30 Hz) activity and minimal slow wave oscillations. **B.** Lack of slow waves is also noted in a 30-second epoch, where the effect site concentration is estimated to be 2 mcg/ml. Period in **A** is highlighted in purple, with similar activity as in **Figure 2D**. **C.** Low frequency EEG oscillations resembling sleep slow waves are induced during the maintenance of targeted propofol effect site concentration. **D.** Additional examples of slow waves are in this 30-second epoch, with period in **C** in red shading. These EEG slow waves resemble **Figure 2E**. The effect site concentration is ~2.4 mcg/ml. **E.** Time-frequency spectrogram of EEG data from the Fp1-Cz channel shows the distribution of power at different frequencies as a function of time. Epochs for A-B and C-D are indicated by purple and red arrows, respectively, with the latter portion of the infusion targeting Slow Wave EEG patterns.

C.1.4. At-home Sleep Recordings and Potentiation of Sleep SWA Following Propofol Infusions

Data: We have years of experience utilizing wireless wearable devices to longitudinally record sleep EEG markers in elderly cardiac surgical patients. The Dreem (**Figure 3A**) has been the main vehicle for collecting EEG data for the prospective observational investigation of perioperative sleep in geriatric cardiac surgical patients, "Prognosticating Delirium Recovery Outcomes Using Wakefulness and Sleep Electroencephalography (P-DROWS-E, ClinicalTrials.gov NCT03291626, NIA R01AG057901, PI Palanca). Each Dreem has dry EEG sensors including Fpz (ground), F7, F8, O1 and O2 for recording multichannel EEG. Additionally, it has an infrared light source and sensor to measure heart rate and a 3-axis set of accelerometers for tracking head position and respiratory effort. Accelerometers are utilized to provide actigraphy data to assist in automatic sleep staging, detection of arousals, and head position. Using the Dreem, we have recorded over 471 overnight sessions from 100 patients in probing putative relationships between postoperative delirium and sleep EEG markers (slow waves and spindles). **Geriatric patients are trained to instrument themselves with the device and record their own overnight sleep records.** Deidentified data are preprocessed by the device manufacturer and imported by research staff into MATLAB analysis platform. Through custom-written scripts for MATLAB (Mathworks, Natick, MA, USA),

raw data are down-sampled to 250 Hz and frequency bandpass filtered at 0.5-50 Hz using EEGLAB[120], an open-source analysis toolbox. European data format (EDF) records are imported into Respironics Sleepware G3 software (version 3.7.1., Philips Respironics, Inc., Murrysville, PA, USA) and evaluated by American Academy of Sleep Medicine (AASM) certified sleep technologists who scored greater than 90% agreement on assessments through the AASM inter-scorer reliability program. Manual scoring proceeded for 30-second epochs, using modified AASM scoring rules previously developed for single frontal EEG analyses[121] and described recently[106]. The sleep stages are aligned with quantitative EEG analytical measures. Scorable preoperative records were provided by 82% of patients while 94% completed recordings after surgery. Data from 26 patients who recorded multiple nights of in-home recordings showed no differences in sleep stage durations, suggesting that only one night is required for establishing baseline sleep structure. We have extended our use of the Dreem to a current investigation on EEG markers of sleep for weeks over the index course of ECT (CET-REM study). These sleep data, from a consumer grade device designed for comfort during sleep, reinforce the feasibility of repeated use following one or more weeks of serial propofol infusions.

Leveraging this approach, a 71-year-old female recorded her own overnight sleep for two nights prior to propofol infusions (**Figure 6A**). The two hypnograms demonstrate transitions among AASM stages of wakefulness (W), stages of NREM (N1, N2, and N3/SWS), and REM (R). These two recordings are consistent with: 1) prolonged overnight recordings with adequate quality for sleep staging, 2) cycling into deep stages of (R), 3) dominance of N1 and N2 sleep with a paucity of N3 sleep at baseline despite a long TST. Overnight sleep was also monitored using the Dreem on the evenings of the first and second propofol infusions (**Figure 6B**). Progressive augmentation of the total duration of N3 sleep and proportion of total sleep time were noted after each propofol session.

Relevance: These data demonstrate the following: 1) Success in leveraging innovative technology required for conducting longitudinal sleep studies, 2) Ability to augment N3 sleep through propofol infusions, and 3) The possibility of persistence of effects in that successive propofol infusions may have a synergistic effect in augmenting sleep slow waves on subsequent nights. We are in a key position to probe the effects of serial propofol infusions on N3 sleep expression in geriatric patients with TRD.

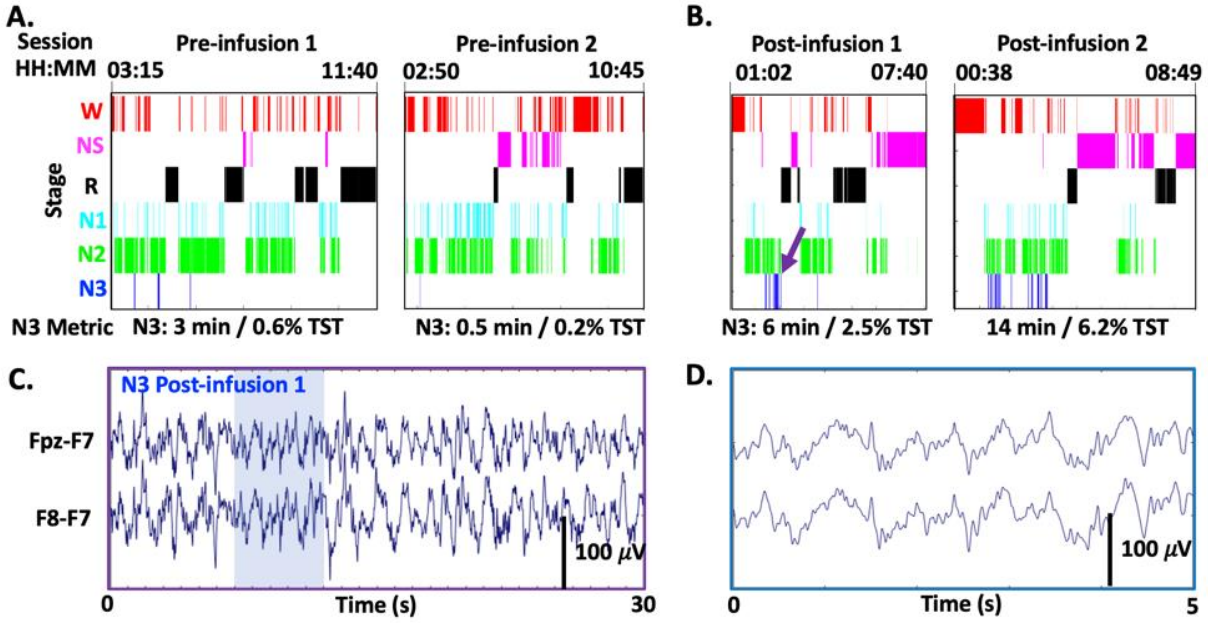

Figure 6. Potentiation of SWS Following Propofol Infusions Monitored Through Wireless Wearable Headbands. **A.** Hypnograms demonstrate sleep structure of two overnight recordings from a 71-year-old female with TRD, recorded on the week before propofol infusion sessions. Consistent with prior literature, N3 was sparse, accounting for only 3 minutes/0.6% total sleep time (TST) or 0.5 minutes/0.2% TST. **B.** Overnight sleep recordings from the same participant demonstrates augmentation of N3 sleep on the night of the first propofol infusion session (Post-infusion 1, 6 minutes/2.5% TST) and night of the second infusion session (Post-infusion 2, 14 minutes/6.2% TST). **C.** Frontal EEG tracings at time indicated by purple arrow in **B**, from a representative N3 epoch of the Post-infusion 1 overnight recording. The traces demonstrate sleep slow waves in Fpz-F7 and F8-F7 channels. **D.** Expansion of blue highlighted period in **C**. Epoch Labels: W, Wakefulness; NS, Non-scorable; R, REM; N1, NREM Stage 1; N2, NREM Stage 2; N3, NREM Stage 3/SWS. All data were obtained using the Dreem and scored according to our recently published modified AASM criteria[106].

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Propofol Infusion:

Propofol is a commonly used sedative in anesthetic practice and critical care medicine.

Per the propofol package insert[122], the most common risk associated with propofol infusions includes burning/stinging or pain at injection site, bradycardia, arrhythmia, hypotension, hypertension, hypoxemia, hypercapnia, airway obstruction and apnea. Less likely risk (< 1%) include anaphylaxis/anaphylactoid reaction, premature atrial contractions, syncope, hypertonia/dystonia, paresthesia, myalgia, pruritus, amblyopia, and cloudy urine. While case of rare anaphylactic[123-126] or anaphylactoid[127-129] reactions have been reported, allergic reactions occur at an estimated 1:60,000 exposures[130]. There have been previous anecdotal connections to food allergies, but recent data shows no association between propofol allergy and allergies to egg, soy, or peanuts[131].

Adverse events (AEs) related to propofol are commonly encountered by anesthesiologists in clinical practice performing procedures such as colonoscopies or transesophageal echocardiographic studies. Patients with chronic obstructive pulmonary disease (COPD) and obstructive sleep apnea (OSA) are safely anesthetized with propofol. Finally, serious adverse events (SAEs) include hospitalization, anaphylaxis, cardiac arrest, stroke, or death. Patients will be attended by a board-certified anesthesiologist during each sedation session, with all standard sedation and airway management equipment available should any adverse events occur.

IV Placement and Blood Draws:

Patients will undergo serial propofol infusions via an intravenous catheter (IV). The placement of the IV could cause tenderness or bruising at the insertion site, as well as dizziness or fainting. Blood can be drawn from the IV catheters or through separate venipuncture, with similar risk as for IV placement.

Dreem EEG:

Patients will be asked to sleep with the Dreem device at home for up to 1 week prior to their first propofol infusion session, as well as the night after each infusion session. Patients may also be asked to sleep with the Dreem device for up to 2 weeks following their final infusion session. We have observed no definitive

abrasions or skin irritation related to hundreds of Dreem recording acquired from over 150 geriatric cardiac surgical patients[106,107].

Skin irritation may occur from wearing the dry electrodes on the Dreem headband. Some discomfort may also occur, particularly those over patient's hair. Some individuals have reported difficulty sleeping while wearing the device.

Genetic Research:

There may be information obtained from the genetic testing that indicates that the participant, or potentially a family member (since we inherit genes from our parents, and pass genes on to our children) are at risk for a particular disease or condition. For example, genetic sequencing may indicate that an individual is more prone to develop certain types of cancer or other types of diseases, (e.g. Alzheimer's or other inherited diseases). This information might harm the participant if shared with employer or insurance carrier. Depending on the test and result, participants may also be uncomfortable with the findings of the genetic research.

High-Density EEG:

Risk of injury related to high-density EEG acquisition during propofol infusion is minimal. Skin abrasions from scalp electrode placement or discomfort upon removal of scalp electrodes may occur.

STOP-BANG/MADRS/SHAPS/PHQ-9/C-SSRS/MoCA/MEQ/NIH Cognitive Toolbox Battery:

There are no known risks associated with assessment of obstructive sleep apnea risk/depression/anhedonia/suicidal ideation via surveys. Patients may become uncomfortable should their self-rated severity not improve at the desired rate. Moreover, patients may be uncomfortable conveying thoughts of death. We are not aware of any risks with serial cognitive assessments.

Breach of Confidentiality:

The risk of unintended release of personal health information (PHI) exists.

2.3.2 KNOWN POTENTIAL BENEFITS

There is no benefit to individual subjects in this study. Society may benefit from a better understanding of the interaction between propofol sedation, slow wave sleep and depression.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

This mechanistic clinical trial addresses a critical nexus between sleep, mood, and cognition in the geriatric population. We expect the successful outcomes of this research to open a pathway for novel pharmacologic and non-pharmacologic interventions to promote SWS enhancement. Propofol could be further exploited as a therapeutic probe to elucidate relationships between sleep structure and antidepressant response. This research addresses questions that have profound implications for society. With the rise in the aging population, we hope to provide translatable biomarkers and approaches for future precision medicine, with a long-term goal of improving public health and quality of life for those afflicted with TRD.

We hope that enrolled patients may benefit from the study through promotion of sleep quality and lowering of depressive symptom severity. Patients with treatment-resistant depression can build agency by knowing that they are contributing to helping others through scientific research. We are also in a key

position to educate study participants on the importance of sleep. We will also share data with patients regarding their brain activity and sleep structure. The study will require multiple infusions of propofol, a sedative commonly used for clinical procedures. Propofol is well-tolerated when monitored by qualified practitioners based on patient vital signs and comorbidities.

Overall, we feel that the potential benefits outweigh potential risks, and there is sufficient clinical equipoise to justify conducting research.

Propofol adverse events:

A board-certified anesthesiologist with ACLS certification will supervise propofol infusions with collaboration of a certified registered nurse anesthetist or anesthesia trainee. The anesthesiologist will be physically present until the patient is awake and recovering from the anesthetic. Patients will have adhered to ASA fasting and monitoring guidelines. Medications, including narcotics and benzodiazepines, will be continued ad libitum—except angiotensin converting enzyme inhibitors or angiotensin receptor blockers, which are normally held prior to procedures requiring sedation or general anesthesia. Patients with obstructive sleep apnea or COPD will not be excluded, as propofol sedation remains safe. ASA standard monitoring (blood pressure pulse oximetry, ECG, CO_2 capnography, suction, airway, and resuscitation equipment) will be employed. Bolus dosing of propofol will be done carefully to minimize risk of apneic events.

The potential benefits of mitigating depression, cognitive impairment, and poor sleep in the geriatric population justify this greater than minimal risk study intervention.

Bruising/bleeding/nerve injury/infection related to venipuncture:

Only qualified nursing and physician staff will carry out these procedures. Aseptic technique will be utilized to minimize risk of skin and blood stream infection. Venipuncture for IV placement is necessary for the propofol infusion and possible rescue medications. Blood biobanking will be useful for future substudies.

Genetic Research:

Results of genetic testing will not be shared with insurers or employers. Participant anonymity in the study will maintained using study code to separate PHI and genetic test results. Genetic analyses will not be shared with study patients who request their own findings.

Abrasions from HD-EEG and Dreem sleep recordings:

The coordinators undergo rigorous training in high-density EEG acquisition, as well as in utilization of the Dreem EEG headband. Scalp will be monitored before cap placement to evaluate any vulnerability. Scalp will be inspected after cap removal to assess for any abrasions. Participant satisfaction and absence of scalp pain will be evaluated by research staff.

Patients will be instructed on proper use of the Dreem to minimize discomfort and possibility of abrasions during serial overnight recordings. Locations of dry electrodes will be varied over time to minimize the possibility of repeated pressure to the exact same scalp locations. Devices will be cleaned with 3% hydrogen peroxide spray and wipes between uses to minimize the risk of skin pathogen transmission. Follow-up will evaluate for any discomfort or disruption of sleep. Participants with significant discomfort/poor sleep quality will be closely evaluated and rescreened/rescheduled for study infusion days to ensure that representative sleep baseline data and post-infusion data will be acquired.

Breach of Confidentiality:

To minimize breach of confidentiality risk, the minimum necessary data will be collected to achieve the study objectives, datasets will be de-identified after study completion, and data and code keys will be

stored in password-protected databases. All electronic documents are stored on secure servers that are password protected and have various state-of-the art firewall protections with frequent upgrades of these protections. The study coordinator and team members will ensure that all paper documents are locked in a filing cabinet in a locked office of a member of the study team. Access to all study documents is limited to members of the research team and will be controlled by the principal investigators.

Suicide:

Patients who are identified as being acutely suicidal will be excluded from the study. Nevertheless, since the rate of completed suicide in the USA remains high (i.e., about twice the rate of homicide) and most Americans who commit suicide suffer from depression, all participants eligible to participate in this study are at a statistically higher risk for suicide than the general population. However, the participants' absolute risk for completing suicide during this brief study remains very low (i.e., about 1 in 3,000 to 10,000) and participation in the study does not create or increase the risk of completed suicide. Most experts believe that one of the most efficient ways to decrease suicidal risk in older depressed individuals is to treat their depression. Furthermore, all participants will be formally assessed frequently throughout the study.

We will use the rater-administered Columbia Suicide Severity Rating Scale (C-SSRS, *https://cssrs.columbia.edu/wp-content/uploads/C-SSRS1-14-09-Baseline.pdf*) to assess severity and intensity of suicidal ideation both current (past month) and lifetime.

At different assessment points, the research staff will assess for passive death wish, and suicidal ideation, intent, or plan when they administer the MADRS. The first items of the C-SSRS will also be assessed and reviewed (using past week as range). A MADRS 2+ score on item 10 or a C-SSRS score of 4 or greater (active suicidal ideation with some intent to act with or without a specific plan) would be an exclusion for the study; instead, these individuals would be referred for psychiatric management. The study psychiatrist (Dr. Lenze) would review these patients and any individual with lifetime suicide attempt, to determine the participant is safe to participate/continue in the study and what additional risk management procedures are needed, if any. The patient's outpatient psychiatric care provider would be contacted.

If a participant endorses suicidal ideation, intent, or plan, the trained raters will follow an operationalized protocol that has been developed to manage high-risk participants in other study of depressed participants potentially at risk for suicide. This protocol has already been used successfully by the investigators to manage several acutely suicidal patients. Briefly, the protocol entails a specific determination of the suicidal risk and prescribes a set of actions. For instance, when a participant is determined to be at high and immediate risk, the rater is instructed to stay with the participant until he or she has contacted a study psychiatrist to discuss the situation and to devise a plan according to standard procedure. For this reason, raters will have cell phones, and at least one study psychiatrist will be reachable at all times. In case of extreme emergency, raters are instructed to call their hospital security team or 911 for immediate help and to initiate commitment proceedings. This may lead to a clinical intervention that is lifesaving and may not have occurred had the participant not been participating in the study.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
1. Safety: Evaluate whether the intervention is safe and well-tolerated	1. Adverse events and serious adverse events, including incidence, severity, and likelihood of relation to intervention.	1. Evaluate whether serial propofol infusions are safe (<5% serious adverse events directly attributable to infusions)
2. Feasibility: Evaluate whether propofol infusions allow (A) Efficient induction of SWA and (B) promote the expression and persistence of sleep slow waves	2. A) Sedation slow wave activity (SWA, 0.5-4 Hz EEG power) during propofol sedation. B) Change in sleep slow wave activity during N2/N3 Sleep (post-infusion – pre-infusion)	2. Evaluate in geriatric TRD patients that propofol infusions can (A) efficiently induce EEG slow waves during infusion (SWA for most of the sedation time) and (B) augment total sleep SWA in greater or equal to 40% of study completers.
Secondary		
1. Safety: Evaluate whether propofol infusions are associated with augmented (A) suicidality or (B) cognitive impairment.	1. (A) Change in Suicidality (C-SSRS), (B) Change in Cognitive Performance (MoCA), and (C) NIH Toolbox Cognition Battery	1. (A) Suicidality screening for need of emergency psychiatric care. (B) Examine changes in cognition that may be associated with propofol infusion.
2. Feasibility: Evaluate changes in sleep structure	2. Changes in duration of N3 and REM sleep and proportion of total sleep time for these stages. Delta sleep ratio (DSR, calculated as the SWA of the 1st N3 cycle divided by the SWA of the 2nd N3 cycle).	2. Established markers for sleep macrostructure.
Tertiary/Exploratory		
Examine feasibility of acquiring propofol-associated changes in (A) circadian rhythms, (B) affect, (C) anhedonia, (D) depression symptoms	(A) Circadian rhythms using wrist actigraphy/molecular markers/MEQ, and sleep diary, (B) Measure of affect (feeling scale), (C) Measure of anhedonia (SHAPS), (D) Measure of Depressive Symptoms (MADRS)	These measures are important for evaluating feasibility of collection in Phase II.

4 STUDY DESIGN

4.1 OVERALL DESIGN

Our hypothesis is that targeted propofol infusion in TRD patients will induce slow wave activity during sedation and augment subsequent sleep slow wave activity. We will recruit 15 participants for this open label single arm Phase I trial. All participants will undergo two propofol infusions 2-6 days apart, with each infusion maximizing expression of EEG slow waves. To minimize bias, there will be no specific gender or ethnic background consideration for enrollment. This will be a single site investigation at Washington University Medical Center.

Study Intervention

Propofol will be infused through a peripheral IV, with the assistance of target-controlled infusion software and pumps, with an anticipated infusion duration of 1-2 hours. Concurrent high-density EEG will be acquired as in **§C.1.3.** but with an updated recording rig and sensor nets that use either Elefix conductive gel or salt solution. An Axis P3364LV network camera, synchronized to EEG recordings, will provide video for post-hoc analysis. Participants will be discharged home after nurse monitoring and fulfillment of post-anesthetic care unit criteria[132].

Patients will be instructed by staff on operation of the Dreem headband for at-home overnight sleep EEG recordings. Patients will demonstrate ability to successfully wear the Dreem and initiate recordings without assistance. The device, charger, instruction sheet, and a link to a 2-minute instructional video will be provided to patients. This paradigm has been successful in the acquisition of preoperative sleep recordings in over 150 geriatric cardiac surgical patients[106,107] and eight patients who underwent ECT for TRD (ClinicalTrials.gov NCT04451135)**.**

Dreem recordings will be obtained prior to the first propofol infusion and on evenings of propofol infusions. Additionally, recordings will be obtained for up to 6 nights within a 2-week period after the final infusion, to evaluate persistence of restoration of sleep architecture. Participants will exchange the device with staff during each in-person visit, to allow device examination and data download.

Planned subgroup analyses include stratification by sex and age. For the purposes of Phase II of the study, additional subgroup analyses will be performed based on baseline sleep structure (e.g. total sleep time and proportion of time in N3 sleep), and time interval separating the two infusions.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

This non-controlled study is a Phase I trial for gauging the safety and feasibility prior to the launch of a Phase II randomized placebo-controlled trial of 70 participants to evaluate the effect of serial propofol infusions on slow wave sleep, cognition, and depression.

The overall investigation is modeled after the FAST Trials by establishing 1) safe target-engagement of a physiologic biomarker (EEG sleep slow waves) through propofol and 2) EEG slow waves as a novel antidepressant engagement target for future pharmacologic and non-pharmacologic therapies.

Progression milestones to the Phase II trial include: 1) Safe (<5% infusions with serious adverse events directly attributable to propofol), 2) Successful induction of SWA during propofol infusions in ≥60% of all participants, and 3) Enhancement of SWS in ≥40% of all participants over the subsequent week. Phase I data will also strengthen execution of Phase II by identifying optimal dosing frequency, persistence of SWS enhancement, and optimal recruitment strategies.

4.3 JUSTIFICATION FOR DOSE

For propofol, standard clinical administration is via the intravenous route. From a safety standpoint, the pharmacokinetic modeling of propofol is well-established[85]. Sedation at projected serum concentrations of 3-4.5 mcg/ml without airway or cardiovascular support has been safely employed to elucidate the neural circuitry of EEG slow waves[76,86,87]. Dosing of propofol will be established by safe induction of EEG slow waves tailored to the individuals response and vital signs; no specific dose is predetermined at a patient level. For further details on dosing strategy. For detailed dosing strategy, please refer to section 6.1.2.

4.4 END OF STUDY DEFINITION

A study completer will be defined as a participant who has safely completed the baseline sleep recording, both propofol infusions, and both post-sedation sleep recordings.

The end of study will be reached when the last participant has completed the last study visit or procedure listed in the Schedule of Activities (SoA), Section 1.3.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

To be eligible for study participation, an individual must meet all following criteria:

1. Provision of signed and dated informed consent form
2. Stated willingness to comply with all study procedures and availability for the duration of the study
3. Age 60 or greater
4. English speaking (as an interpreter will not be readily available should a participant need to convey any safety concerns during the propofol infusion sessions or require guidance on conducting at-home sleep recordings)
5. Treatment-resistant Depression (non-responsive to at least two adequate trials of oral antidepressants for current episode).

When available, electronic medical records over the previous five years will be used to confirm safety and eligibility. Women and members of minority groups will be included in accordance with the NIH Policy on Inclusion of Women and Minorities as Participants In Research Involving Human Subjects.

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Presence of symptomatic coronary artery disease
2. Presence of marked congestive heart failure/cardiomyopathy (NYHA > Class III, LVEF <40%, greater than mild RV systolic dysfunction)
3. Prior reaction to propofol
4. Resting heart rate < 50 bpm
5. Treatment with Electroconvulsive therapy/Transcranial Magnetic Stimulation/vagal nerve stimulation within 6 weeks
6. Body mass index > 35
7. C-SSRS of 4 or greater (active suicidal ideation with some intent and with/without a specific plan)
8. MoCA score < 23 (at least mild dementia)
9. Non-prescribed used of amphetamines, opioids, marijuana, cocaine, or phencyclidine
10. Intake of > 14 beers/week (or equivalent)
11. Anesthetic exposure in the past 4 weeks
12. Concurrent use of benzodiazepines > 2 mg/day lorazepam or equivalent, trazodone > 50 mg/day, or gabapentin > 600 mg/day.

5.3 LIFESTYLE CONSIDERATIONS

In accordance with ASA Guidelines for perioperative fasting, study participants are asked to:

- Abstain from food at least 8 hours before start of propofol infusions.
- Abstain from clear fluids at least 2 hours before start of propofol infusions.
- Avoid non-prescribed used of amphetamines, opioids, marijuana, cocaine, or phencyclidine or high alcohol intake to maintain study eligibility.

Participants will also be asked to continue all medications throughout the study period, except angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers. These medications are commonly held on the morning of anesthetic sedation to reduce the possibility of hypotension.

5.4 SCREEN FAILURES

Individuals who do not meet the criteria for participation in this trial (screen failure) because of failure to meet inclusion/exclusion criteria may be rescreened. Rescreened participants will be assigned the same participant number as for the initial screening if they are able to follow study procedures at a future time.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Target sample size for this Phase I trial is 15 TRD male and female patients aged 60 or greater with an expected 20% attrition rate. Our group has a large pool of geriatric patients for recruitment, including a recently completed large-scale trial of LL-TRD (OPTIMUM) and a geriatric depression clinic. These referral sources have been successful for the pilot stages of the proposed work. Additionally, we will employ recruitment services through Volunteers for Health, Facebook ads, and Centerwatch.

Potential participants will be contacted by phone and/or email to gauge interest and preliminary screening.

The following strategies will be employed to maximize retention: 1) Participants will be contacted by their preferred method on the day before any study visits for reminder and confirmation, 2) Study staff will contact patients on day of at-home sleep recordings to remind them to initiate sleep recording, and the next day to address and questions/concerns, and 3) a portable internet modem will be sent home with participants to allow for remote monitoring of at-home sleep recordings, to minimize attrition due to data loss/poor quality data.

Participants will be compensated for their time and effort. Compensation is broken down as follows:

- $30 for each baseline home sleep study (2 maximum)
- $15 for each sedation session (2 maximum)
- $25 for each post sedation home sleep study (7 maximum)
- $40 for follow up study questionnaires/test
- $305 possible for completion of all study procedures

Payment will be prorated based on the number of completed study procedures list above. Upon retrieval of study devices and completion of the final study visit, payment will be processed and sent to the participants' residence in form of a check. Transportation is commonly a limitation for involvement. Remuneration for drivers ($20) will be employed, if needed.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

Propofol is an intravenous sedative-hypnotic agent for use in the induction and maintenance of anesthesia or sedation[122]. Intravenous injection of a therapeutic dose of propofol induces hypnosis, with minimal excitation, usually within 40 seconds from the start of injection. The half time of the blood-brain equilibration is approximately 1 to 3 minutes, accounting for the rate of induction of anesthesia. The mechanism of action is poorly understood; however, propofol is thought to produce its sedative/anesthetic effects by the positive modulation of the inhibitory function of the neurotransmitter GABA through the ligand gated $GABA_A$ receptor.

6.1.2 DOSING AND ADMINISTRATION

Propofol will be administered intravenously in a post-anesthesia recovery unit or clinical trials research unit, concordant with clinical practice and requisite monitoring and safety guidelines.

Pharmacokinetic models will be used to generate a preliminary bolus and infusion schedule. Infusion bolus and rates will be tailored to the participants' sex, age, height, and weight. To precisely target EEG slow waves with concurrent spontaneous ventilation we anticipate the need for infusion rates ranging from 20 mcg/kg/min to 200 mcg/kg/min, with starting infusion rates ranging between 150 and 200 mcg/kg/min. Infusion rates above 100 mcg/kg/min will be restricted for short periods designated to quickly raise effect site concentrations while maintaining safety in the monitored anesthetic setting, based on effect site

concentrations projected by the pharmacokinetic model[85]. During periods of stable pharmacokinetics, infusion rates are anticipated to be under 100 mcg/kg/min, as observed during acquisition of our pilot data (2 participants, 2 infusion sessions each), targeting propofol effect site concentrations of 3-4.5 mcg/ml projected by the pharmacokinetic model[85]. This range is consistent with infusion rates used to maintain sedation in the ICU during mechanical ventilation (former) and for total intravenous anesthesia during surgical procedures.

The first propofol infusion will be utilized to evaluate safety endpoints and EEG changes in response to propofol bolus and infusions. This dose-titration session will facilitate the second infusion session, which will focus on establishing safe and stable target engagement of EEG slow waves. There is no maximum dose of propofol to propose based on existing literature.

Safety for study participants will be ensured through continual supervision of a board-certified anesthesiologist for the duration of all study drug infusions. The anesthesiologist will be physically present until the patient is awake and recovering from the anesthetic. When available, a certified registered nurse anesthetist (CRNA) will also assist with supervised drug infusion, clinical monitoring, and airway interventions. The infusions sessions will be conducted in rooms of the Washington University Clinical Trials Research Unit (CTRU), supplemental nursing staff and resuscitation equipment are readily available.

Following cessation of propofol, the participant will continue to be monitored by nursing staff until they meet standard post-anesthesia care unit (PACU) discharge criteria[132]. Based on clinical practice and our pilot participants, the recovery period is projected to take 60-90 minutes. As per institutional guidelines, the patient will need to be taken home by a responsible adult. Rideshare services (i.e. Uber or cab will be available but a study team member or trusted individual will need to accompany the participant to their residence).

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

Propofol will be acquired and stored by the Principal Investigator. The study medication is stored in a locked medication cabinet. Access is only available to physician and nurse research team members. A log is maintained to register inventory and dispensing, with entries signed and dated. Annual lab inspections by the WUSM Environmental Health and Safety (EHS) are also in place to ensure safe and secure storage of study medications.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Propofol (Diprivan, Fresenius-Kabi) is formulated in a white, oil-in-water emulsion. The pKa is 11. The octanol/water partition coefficient for propofol is 6761:1 at a pH of 6 to 8.5. In addition to the active component, propofol, the formulation also contains soybean oil (100 mg/mL), glycerol (22.5mg/mL), egg lecithin (12 mg/mL), disodium edetate (0.005%), and sodium hydroxide to adjust pH[122].

6.2.3 PRODUCT STORAGE AND STABILITY

Propofol will be stored according to guidelines between 4° to 25°C (40° to 70°F) in a locked cabinet accessible only by study physicians and nurses. Stability of the drug will be inspected visually for particulate matter and discoloration prior to administration. Each propofol vial is intended for a single use.

6.2.4 PREPARATION

Infusion tubing will be primed with propofol and infused into crystalloid (Lactated Ringers solution) utilized as a carrier fluid.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

To minimize bias, study team members scoring overnight sleep recordings will be blinded to the interval between day of infusion and data acquisition. In addition, masking of total drug infused and infusion rates will be extended to those performing depression, behavioral, and cognitive assessments. Finally, all raters and those performing statistical analyses will be blinded to timing of the data acquisition (pre/post-propofol, timing of acquisition relative to the day of infusion). This will minimize the possibility that the hypothesis of sleep slow wave augmentation biases detection of sleep slow waves/scoring of N3/SWS epochs.

6.4 STUDY INTERVENTION COMPLIANCE

An in-person adherence reminder session will take place at the initial study visit. This session will include:

- The importance of following study guidelines for adherence to serial at-home sleep recordings and fasting guidelines.
- Instructions about the purpose, use, and care of the Dreem headband and Dreem internet modem.
- Instructions regarding wear of the Dreem including timing, importance of charging the Dreem for data verification, and what to do in the event of a missed night.
- Instructions to complete a daily sleep diary entry.
- Notification that participants will be contacted regularly throughout study period for adherence reminders.
- Importance of contacting the research team if experiencing problems with the Dreem headband and/or internet modem.

Study team will contact patients 1) on the evening before initiation of overnight sleep recordings, 2) on the day following the overnight recordings, 3) as need to check satisfaction and troubleshoot recordings after the 2nd infusion of propofol. Participants will be asked about any problems they are having using the Dreem devices and be reminded to charge the headband. By sending participants home with both headband and internet modem, research team members will be able to remotely monitor and acquire the sleep EEG data once participants connect the headband to a power source after each recording.

Multiple methods will be employed to assess at-home sleep recording adherence: 1) phone call/email contact on evening of at-home night recording and day following, 2) daily sleep diary entries, 3) remote monitoring and acquisition of at-home sleep EEG recordings (Dreem-viewer), and 4) reasons for non-compliance. Successful completion of at-home sleep recordings or reasons for missing data will be

recorded on the appropriate case report forms. Sleep EEG data from Dreem-viewer will be downloaded into a designated, secure data storage drive.

6.5 CONCOMITANT THERAPY

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the Case Report Form (CRF) on enrollment and study infusion days include concomitant prescription medications, over-the-counter medications, and supplements.

Prescribed antidepressants and other psychotropic medications will be continued by participants. These medications will be recorded in case report forms. While acute administration of opioids and benzodiazepines can augment the possibility of respiratory depression with propofol, the team does not expect chronic use to affect safety of participants. Patients taking commonly prescribed medications that affect N3 sleep (benzodiazepines, trazodone, and gabapentin) above dose-related thresholds will be excluded from participation.

Angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) will be held on the day of study infusions in mitigate hypotension risk.

6.5.1 RESCUE MEDICINE

In the unlikely event that they are needed, rescue medication and airway equipment to treat any anticipated or unanticipated side effect will be immediately available. Resuscitation capabilities will be immediately available. The following rescue medications will be available glycopyrrolate, phenylephrine, ephedrine, epinephrine, and crystalloids for interventions if needed. Patients requiring repeated boluses of ephedrine (total dose > 50 mg) for persistent hypotension would be replaced after study session termination. The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication will be recorded on the appropriate CRF.

An automatic external defibrillator is also available on site for emergencies.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Discontinuation from propofol infusion does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

Propofol infusion will be stopped for the following AE refractory to clinician interventions:

- Profound treatment-resistant bradycardia, defined as a heart rate less than 40 beats per minute for more than three minutes

- Profound treatment-resistant hypotension, defined as a 30% decrease from baseline MAP for more than 10 minutes
- Inability to maintain a patent airway and/or sustained decrease in SpO2 below 92% despite the use of simple airway maneuvers and supplementation of up to 6 liters per minute of oxygen
- Sustained cardiac conduction abnormalities

The data to be collected at the time of study intervention discontinuation will include the following:

- Vital signs will be monitored on recorded on appropriate CRF until resolution of clinically significant event.
- Participants will be contacted 1 day, 1 week, and 2 weeks after the clinically significant event to monitor for adverse events, serious adverse events, and/or unanticipated problems.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.

An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Significant study procedure non-compliance (e.g. lack of fasting on the morning prior to propofol infusion)
- Poor tolerance of study procedures (e.g. discomfort during Dreem overnight sleep recordings).
- Patients requiring repeated boluses of ephedrine (total dose > 50 mg) for persistent hypotension would be replaced after study session termination.

Participants withdrawn or discontinued before both propofol infusions have been completed will be replaced and will not count towards recruitment target or milestones.

The PI reserves the right to discontinue the study protocol at any time for patient safety. The reason for participant discontinuation or withdrawal from the study will be recorded on the appropriate Case Report Form (CRF).

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for 2 scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit with 1 week and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). Up to three emails will be sent over the course of a month. These contact attempts should be documented in the participant's medical record or study file.

Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

Not applicable. Data for this Phase I study only concern safety and feasibility.

8.2 SAFETY AND OTHER ASSESSMENTS

Preliminary screening (At home):

- Phone screening script
- Patient Health Questionnaire-9 (PHQ-9)

Visit 1: Enrollment/Baseline:

- Verify inclusion/exclusion criteria
- Written informed consent
- Contact information and demographic information
- Montgomery-Asberg Depression Rating Scale (MADRS)
- Columbia-Suicide Severity Rating Scale (C-SSRS)
- Snaith-Hamilton Pleasure Scale (SHAPS)
- Montreal Cognitive Assessment (MoCA)
- NIH Cognition Toolbox Battery and Psychomotor Vigilance Test (PVT)
- Morningness-Eveningness Questionnaire (MEQ)
- Snoring, Tired, Observed Apnea, high blood Pressure, Body mass index, Age, Neck circumference, male Gender (STOP-BANG) Questionnaire to screen for obstructive sleep apnea risk[133,134] to screen for possible obstructive sleep apnea.
- Urine drug screen and direct screening for illicit drug use (non-prescribed used of amphetamines, opioids, marijuana, cocaine, or phencyclidine).
- History and focused physical examination comparable to that preoperative assessment. The history will focus on adverse reactions to propofol, other anesthetics, and airway/intubation history. The physical examination will focus on airway, cardiac, pulmonary, and neurological systems to evaluate for signs of acute cardiopulmonary illnesses warranting deferral of study procedures.

Pre-Infusion (At home):

- Overnight sleep EEG recording using the Dreem device
- Sleep diary
- Wrist actigraphy

Visit 2: Propofol Infusion – Titration and EEG Slow Wave Induction:

- High-density EEG recorded before and throughout infusion

- Identification of optimal dosing to induce EEG slow waves
- Feeling Scale, before induction and after return of consciousness
- Blood draw 10-15 mls by study physician or nurse (optional)

Post-infusion (At-home):

- Overnight sleep EEG recording using the Dreem device on night of infusion
- Sleep diary
- Wrist actigraphy

Visit 3: Propofol Infusion – EEG Slow Wave Induction:

- High-density EEG recorded before and throughout infusion
- Optimal dosing to induce EEG slow waves
- Feeling Scale, before induction and after return of consciousness
- Blood draw 10-15 mls by study physician or nurse (optional)

Post-Infusion (At home):

- Overnight sleep EEG recording using the Dreem device on night of infusion
- Overnight sleep EEG recording using the Dreem device for up to 5 additional nights during the 2-week period after the final infusion
- Sleep diary
- Wrist actigraphy
- Montgomery-Asberg Depression Rating Scale (MADRS)
- Columbia-Suicide Severity Rating Scale (C-SSRS)
- Snaith-Hamilton Pleasure Scale (SHAPS)

Visit 4: Follow up 1:

- Montgomery-Asberg Depression Rating Scale (MADRS)
- Columbia-Suicide Severity Rating Scale (C-SSRS)
- Snaith-Hamilton Pleasure Scale (SHAPS)
- Montreal Cognitive Assessment (MoCA)
- NIH Cognition Toolbox Battery and Psychomotor Vigilance Test (PVT)
- High-density EEG
- Blood draw 10-15 mls by study physician or nurse (optional)

Visit 5: Final follow up (In person or at home):

- Montgomery-Asberg Depression Rating Scale (MADRS)
- Columbia-Suicide Severity Rating Scale (C-SSRS)
- Snaith-Hamilton Pleasure Scale (SHAPS)

Participants will also be asked to wear a wrist actigraphy watch starting on the first pre-infusion sleep recording throughout the study until the final visit.

Propofol Infusion Sessions with Concurrent High-density EEG

A board-certified anesthesiologist with ACLS certification will supervise propofol infusions with collaboration of a certified registered nurse anesthetist or anesthesia trainee. Patients will have adhered

to ASA fasting and monitoring guidelines. Medications, including narcotics and benzodiazepines, will be continued ad libitum—except angiotensin converting enzyme inhibitors or angiotensin receptor blockers, which are normally held prior to procedures requiring sedation or general anesthesia. Patients with obstructive sleep apnea or COPD will not be excluded, as propofol sedation remains safe. ASA standard monitoring (blood pressure pulse oximetry, ECG, CO_2 capnography, suction, airway, and resuscitation equipment) will be employed. Propofol will be infused through a peripheral IV, with the assistance of target-controlled infusion software and pumps, with an anticipated infusion duration of 1-2 hours. High-density EEG will be acquired as in **§C.1.3.** but with an updated recording rig. An Axis P3364LV network camera, synchronized to EEG recordings, will provide video for post-hoc analysis. Participants will be discharged home after nurse monitoring and fulfillment of post-anesthetic care unit criteria[132].

At-home Overnight Sleep EEG Recordings

Patients will be instructed by staff on initiating recordings with the Dreem. Patients will demonstrate ability to successfully wear the Dreem and initiate recordings without assistance. The device, charger, instruction sheet, and a link to a 2-minute instructional video will be provided to patients. This paradigm has been successful in the acquisition of preoperative sleep recordings in over 150 geriatric cardiac surgical patients[106,107] and eight patients who underwent ECT for TRD (ClinicalTrials.gov NCT04451135)**.**

EEG Data Preprocessing and Spectral Analysis

Dreem EEG data will undergo preprocessing (**§C.1.4**). Briefly, raw data will be down-sampled and filtered using EEGLAB[120]. EDF records will be imported into Respironics Sleepware G3 software and evaluated by AASM-certified sleep technologists. Manual scoring will proceed for 30-second epochs, using modified AASM scoring rules previously developed for single frontal EEG[121]. These approaches have been detailed in a recent protocol on an ongoing delirium investigation (ClinicalTrials.gov NCT03291626, NIH R01AG057901)[106]. N2 and N3 (sleep slow waves present in > 20% epoch) will be utilized in quantitation of EEG metrics. Eye movements in frontal EEG will allow scoring of REM sleep epochs. To maximize **rigor and reproducibility**, staff will be blinded to the timing of acquisition for clinical/cognitive outcomes during sleep staging and EEG quantitative analyses.

High-density EEG data will also be preprocessed in EEGLAB[120]. As previously described for preprocessing of SWA, data will be lowpass filtered at 40 Hz prior to decimation to 125 Hz. A 0.1-0.6 bandstop filter will be applied to remove respiratory artifact prior to high pass filtering at 0.5 Hz[53].

Measurement of SWA and Delta Sleep Ratio (DSR)

Multitaper methods will be used for power spectral analysis using the MATLAB Chronux toolbox[135]. Spectral estimates will be based on 6-second non-overlapping time windows, time-bandwidth product of 3, and 5 tapers. Distributions of power in the 20-30 Hz and 1-4.5 Hz bands will be utilized in a semiautomated fashion to reject artifactual epochs[53]. SWA for each night will be quantified during the first and second cycles of N3, using custom-written MATLAB scripts that average total power spectral estimates within the 0.5-4 Hz frequency band at one minute intervals[136]. Secondary analyses will rely on the **delta sleep ratio (DSR)** for each night of sleep, which will be computed by **dividing the SWA of the first N3 cycle by the quantity of the second N3 cycle**.

Depressive/Anhedonia/Suicidality/Affect Symptoms

The **Montgomery-Åsberg Depression Rating Scale (MADRS)**[137] will be administered to study participants on enrollment and on follow up in-person or telephone appointments. We have conducted thousands of MADRS assessments and have training and reliability testing methods to ensure excellent interrater reliability. Additionally, severity of anhedonia will also be assessed using the Snaith-Hamilton Pleasure

Scale (SHAPS)[138], while the C-SSRS will be employed for suicidality screening and need for emergency psychiatric care. Affect before and after each infusion will be assessed using the Feeling Scale[139].

Cognitive Symptoms

The Montreal Cognitive Assessment (MoCA)[140] will be administered to study participants on enrollment and again at the final follow up visit. The MoCA test subjects for the presence of impairments.

The brief and pragmatic **NIH Toolbox Cognitive Battery**[32] will be employed. Its use is recommended for all NIH-funded neurocognitive studies to maximize rigor and reproducibility. Administration will occur on the iPad, based on our previous experience[112]. The **Flanker Inhibitory Control Test** requires subjects to focus on an arrow stimulus while inhibiting attention to stimuli that arise on either flank. During the **Dimensional Change Card Sort Test**, participants match bivalent test pictures to target pictures while switching between dimensions of color and shape. For the **List Sorting Working Memory Test**, subjects are first asked to order objects (either food or animals) from smallest to largest and then presented with both food and animals. The task is then to report food in size order and then animals in size order. For the **Picture Sequence Memory Test**, participants are asked to recall a series of pictures that progressively increase in length. For the **Pattern Comparison Processing Test**, subjects are asked to determine whether two objects presented side-by-side are identical. **The Fluid Cognition Composite Score** will be computed from performance on these tasks. As effects of depression and sleep disruption have been noted on the Flanker Inhibitory Control Test, scores on that task will be used as a measure of executive function. We acknowledge that Fluid Cognition is not the exact same construct as executive function (it also contains some memory and attention tasks) but it is a pragmatic and widely-used construct which corresponds highly with executive function[141].

The psychomotor vigilance test (**PVT)** will be administered on an iPad. Participants are asked to immediately touch the screen when a counter starts incrementing. Task metrics will be downloaded. The reciprocal of the median reaction time (RT) will be computed to yield the RRT (psychomotor speed). The number of lapses (RT >500 ms) will also be counted for secondary analyses. These assessments will be performed following consent, on treatment sessions prior to propofol infusion, and at follow up assessments. There is no transmission of data to 3rd parties.

Wrist Actigraphy for Assessment of Circadian Rhythms

Patients will be offered the ActTrust 2 wrist actigraph (Condor Instruments, São Paulo, Brazil) which allows collection of longitudinal non-dominant wrist actigraphy measures of rest and activity from the point of enrollment to the follow up 4th Study Visit. These signals will be analyzed to evaluate circadian rhythms and changes induced by propofol. A sleep diary will be completed by participants to corroborate with physiologic signals. The Morningness-Eveningness Questionnaire (MEQ)[142], completed at enrollment, will be compared to these data.

Blood Biobanking (Optional)

Optional blood sampling will occur at Study Visits 2, 3, and 4. These will be done near the beginning and middle of the propofol infusions, as well as at the follow up visit. Following centrifugation, plasma will be banked. Samples may also be processed for storage in PAXGene RNA tubes for future gene expression analyses. Overall, no more than 50 mls of blood/5-10 teaspoons will be drawn over the course of the study. Biomarkers to be assayed include RNAseq gene expression to allow detection of differences between internal circadian time and true time[143], proteomic analysis via Olink Neurology 384 Explore to measures levels of inflammatory cytokines (e.g. IL-6, IL-8) and markers axonal injury (neurofilament light chain), or genotyping of sleep/circadian loci (e.g. adenosine deaminase or adenosine receptor typing).

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

An adverse event (AE) is any untoward medical occurrence in a subject participating in an investigational study or protocol regardless of causality assessment. An adverse event can be an unfavorable and unintended sign (including an abnormal laboratory finding), symptom, syndrome or disease associated with or occurring during the use of an investigational product whether or not considered related to the investigational product.

Examples of adverse events include dizziness, fainting, skin irritation, pain (IV site, airway maneuvers, or EEG recording), disrupted sleep from overnight EEG recordings, hypotension, or respiratory depression/apnea.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, or a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Examples of SAEs would include need for hospitalization, anaphylaxis, cardiac arrest, stroke, or death.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.3.3.3 EXPECTEDNESS

The principal investigator will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

Expected adverse events are those adverse events that are listed in the protocol, the Investigator's Brochure (current edition), drug labeling or in the study informed consent document. These will include bradycardia, hypotension, hypercapnia, airway obstruction, and apnea.

Unexpected adverse events are those that 1) are not described in the Investigator's Brochure or drug labeling, 2) are not anticipated in the study informed consent. This includes adverse events for which the specificity or severity is not consistent with the description in the informed consent.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The study coordinator will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

Adverse events will be reported to the IRB at the continuing review and to the NIMH DSMB and NIMH annually.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

SAEs would be reported to the WU Human Research Protection Office (IRB) within 24 hours. Resumption of the study would only occur after approval of the IRB.

Reporting of events to the NIMH DSMB will follow the NIMH's reportable events policy. The following table outlines the NIMH's reportable events policy for AEs, SAEs, death, unanticipated problems, protocol deviations, non-compliance, suspensions and terminations.

Reportable Event	When is Event Reported to the NIMH	Reported By
IRB/ISM/DSMB/OHRP/FDA Suspensions or Terminations	Any suspension or termination of approval must include a statement of the reason(s) for the action and must be reported promptly to the NIMH PO within **3 business days of receipt.**	Regulatory or Monitoring Entity and Investigator
Deaths related to study participation	Deaths must be reported within **5 business days** of the Principal Investigator first learning of the death.	Investigator
Unexpected Serious Adverse Events related to study participation	Reported to the NIMH PO within **10 business days** of the study team becoming aware of the SAE.	Investigator
Unanticipated Problems Involving Risks to Subjects or Others	Reported to the NIMH PO within **10 business days** of the investigator learning of the event.	Investigator
Serious or Continuing Noncompliance *http://videocast.nih.gov/pdf/ohrp072414.pdf*	Reported to the NIMH PO within **10 business days** of IRB determination.	Institution
Adverse Event	For all AEs and SAEs that are deemed expected and/or unrelated to the study, a summary should be submitted to the NIMH PO with the **annual progress report.** (SAEs will be documented for the NIMH DSMB in reports for thrice-yearly meetings.)	Investigator
Protocol Deviations	With the **annual progress report**	Investigator

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the WU HRPO (IRB), NIMH DSMB, and NIMH. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB and NIMH PO/DSMB within 10 business days of the investigator becoming aware of the event.
- Ups involving risk to subjects or others will be reported to the IRB and NIMH PO/DSMB within 10 business days of learning of any events suggesting that the research procedures place participants or others at an unanticipated greater risk of harm.
- Any other UP will be reported to the IRB under continuing review.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Full disclosure of unanticipated problems will be disclosed by the principal investigator.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Primary Safety/feasibility Endpoint(s):

- Adverse events and serious adverse events, including incidence, severity, and likelihood of relation to propofol infusion. Hypothesis: Serial propofol infusions will be safe and well-tolerated in study participants, with less than 5% serious adverse events directly attributable to infusions.
- Measure of slow wave activity during propofol infusion. Hypothesis: Propofol infusion will efficiently induce EEG SWA during sedation in at least 60% of participants.
- Change in total slow wave activity during N2/N3 sleep post-infusion compared to pre-infusion. Hypothesis: Propofol infusion will augment total sleep SWA over the subsequent week in at least 40% of study completers.

Secondary Safety/feasibility Endpoint(s):

- Measure of suicidality using the Columbia-Suicide Severity Rating Scale (C-SSRS). Hypothesis: There will be no significant changes in suicidality associated with propofol infusions.
- Measure of cognitive performance using the Montreal Cognitive Assessment (MOCA), NIH Toolbox Cognition Battery and Psychomotor Vigilance Test (PVT). Hypothesis: There will be no significant changes in cognitive performance associated with propofol infusions.
- Measures of duration of N3 and REM sleep and proportion of total sleep time for these stages, delta sleep ratio.

Tertiary Endpoint(s):

- Changes in circadian rhythm study period using wrist actigraphy and blood biomarkers. Hypotheses: Propofol infusions with increase amplitude of circadian rhythms or enhance circadian rhythmicity. Morningness-eveningness will modulate whether sleep SWA is potentiated by propofol infusions.
- Measure of affect using the Feeling Scale. Hypothesis: Affect will be improved after propofol infusion.
- Measure of anhedonia using the Snaith-Hamilton Pleasure Scale (SHAPS). Hypothesis: Anhedonia will not be exacerbated post-infusion compared to baseline.
- Feasibility measure of propofol induced SWA to alleviate depressive symptom using the Montgomery-Asberg Depression Rating Scale (MADRS). Hypothesis: Depressive symptoms will not worsen post-infusion compared to baseline.

9.2 SAMPLE SIZE DETERMINATION

We carried out a sample size calculation based on the two pre-treatment and two post-treatment sleep recordings obtained from our first participant (Figure 4A-B). We utilized a mean N3 duration (minutes) of 1.75 (pre-treatment) and 10 (post-treatment) and combined standard deviation of 4.19. For paired measurements within participants, these estimates would only lead to a sample size of 6. This first participant had an > 400% augmentation of her baseline N3 duration, which may be greater compared to others in Aim 1. Furthermore, we expect a 20% attrition such that targeting 15 participants seems compatible with a convenience sample size for gauging safety, feasibility, and persistence of post-intervention sleep SWA promotion.

9.3 STATISTICAL ANALYSES

9.3.1 GENERAL APPROACH

Given the small sample size for this exploratory study, only descriptive statistics will be performed.

The small sample size and lack of normative values for SWA/SWS measures present challenges in evaluating enhancement of SWA. Many adults older than 60 years of age do not show any SWS, thus an augmentation of at least 1 minute of SWS relative to baseline would constitute enhancement for this initial study.

9.3.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

Number of AE and SAE will be tabulated across participants. SAE frequency will be compared to the milestone threshold of 5%.

Slow Wave Activity (SWA) will be calculated as the total EEG 0.5-4 Hz power/minute during propofol treatment (sedation SWA) and during overnight SWS (sleep SWA). Sleep SWA will be measured from at-home recording taken before and following infusions, contingent on recordings meeting quality metrics.

Descriptive statistics will evaluate rates of tolerability and adverse events, duration of sedation SWA and sleep SWA (median and interquartile ranges).

We have set a feasibility threshold of augmentation of sleep SWA for 40% of study completers. A targeted treatment that works well in 40% of depressed older adults would be of high public health significance, particularly among those with TRD. For comparison, the recent OPTIMUM study results found that the top-performing agent, aripiprazole, brought about remission in 33% of completers. It is our hope that the research will allow us to better pre-select individuals that are particularly likely to benefit.

9.3.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

We will perform descriptive statistics on C-SSRS and MoCA scores, respectively.

For sleep structure measures (N3 and REM total duration/proportion of total sleep time, DSR), we perform descriptive statistics (median and interquartile ranges) at each respective time point.

9.3.4 SAFETY ANALYSES

See sections 9.4.2. and 9.4.3.

9.3.5 BASELINE DESCRIPTIVE STATISTICS

Descriptive statistics will be compiled for age, sex, years of depression
No inferential statistical analyses will be carried out on baseline measures.

9.3.6 PLANNED INTERIM ANALYSES

Interim analyses are not planned for this open-label study.

9.3.7 SUB-GROUP ANALYSES

Primary and secondary safety/feasibility endpoints will be analyzed based on age, sex, time separating propofol infusions. Additional analyses will be based on medical comorbidity (Cumulative Illness Rating Scale Score), baseline MOCA score (23-26 for cognitively impaired) vs (26-30 for cognitively intact), and age of onset of first episode of MDD (to address the importance of late onset depression).

Additionally, structure of baseline sleep (e.g. duration and proportion of total sleep time for N3 and REM) will be utilized in sub-group analysis. If high variance in SWS enhancement is observed, we could perform univariate regression analyses to evaluate for the presence of covariates driving the high variance. Such analyses would be useful to determine whether the intervention is better targeted for particular subgroups (e.g. patients with a low, but non-zero proportion of N3, or infusions separated by longer intervals of greater than 5 days may be less effective than treatments separated by 2-3 days).

These analyses will be helpful in targeting enrollment for Phase II.

9.3.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

For visualization, individual participant data (sleep SWA, DSR, MADRS, C-SSRS, SHAPS, and feeling scale) will be listed by time point.

9.3.9 EXPLORATORY ANALYSES

Not applicable. Tertiary exploratory data will be acquired to confirm feasibility of acquisition for Phase II.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention. The following consent materials are submitted with this protocol: Informed consent document and telephone screening questionnaire.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the signed informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, the NIMH, and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and the NIMH.

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, NIMH, and WUSM. This confidentiality is extended to cover testing of biological samples and clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored on site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites research staff will be secured and password protected. At the end of the study, all study databases will be de-identified.

To further protect the privacy of study participants, a Certificate of Confidentiality will be issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping

assure confidentiality and privacy to participants. This certificate may not be effective for information held in foreign countries.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data obtained for this study will be de-identified, analyzed, and stored for use in studies conducted in the future. De-identified data may be shared with other researchers including those outside of the study. Permission to store and share data will be included in the informed consent. Bank biospecimens will be stored for up to 5 years after publication on the primary outcomes. Genetic testing will be conducted for patients who agree to the optional blood draw component.

To date, there are no publicly accessible sleep data sets acquired from geriatric patients with depression. These are needed to facilitate future research and enhance **reproducibility and rigor** in this field. We will share our data with the National Sleep Research Resource within three years after completion of the study. Furthermore, we will share our data on the NIMH Data Archive twice per year. To **maximize rigor**, we will publish a protocol of our approach and pre-specified analyses by the end of Year 2 of funding.

We will upload our data in a timely manner to the **NIMH Data Archive (NDA)** as per notice NOT-MH-19-033, to enable us to share our data with other investigators in the research community. The NDA will include the following Data Structures in the project's Data Dictionary: 1) Sedation Slow Wave Activity, 2) Sleep Slow Wave Activity, 3) NIH Toolbox Cognition Battery Executive Function Score, 4) Psychomotor Vigilance Task median reaction time, 5) NIH Toolbox Cognition Battery Fluid Cognition Measure Score, 6) Montgomery-Åsberg Rating Scale Score, 7) Snaith-Hamilton Pleasure Scale (SHAPS) Score, 8) Columbia-Suicide Severity Rating Scale (C-SSRS) Score, 9) Delta Sleep Ratio.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Co-Principal Investigator	**Co-Principal Investigator**
Ben Julian A. Palanca, M.D., Ph.D., M.Sc. Associate Professor of Anesthesiology and Psychiatry	Eric J. Lenze, M.D. Wallace and Lucille K. Renard Professor of Psychiatry, Professor of Anesthesiology
Washington University School of Medicine in St. Louis	Washington University School of Medicine in St. Louis
660 S. Euclid Avenue, Campus Box 8054	660 S. Euclid Avenue, Campus Box 8134
314-323-1902	314-362-3794
palancab@wustl.edu	lenzee@wustl.edu

Study Team and Roles/Responsibilities

Washington University School of Medicine / Barnes-Jewish Hospital (BJH)

Co-Principal Investigator: Ben Julian A. Palanca, M.D., Ph.D., M.Sc., Associate Professor of Anesthesiology and Psychiatry

As a cardiothoracic anesthesiologist and translational neuroscientist with expertise in electroencephalographic (EEG) changes induced by sleep, anesthesia, and delirium – together with Dr. Lenze, Dr. Palanca will be responsible for the overall design and execution of the proposed studies, oversight and management of the project, ensuring timely progression to meet milestones.

Co-Principal Investigator: Eric J. Lenze, M.D., Professor of Psychiatry and Anesthesiology

As a geriatric psychiatrist with a distinguished program as clinical trialist on mental and cognitive disorders – together with Dr. Palanca will be responsible for the overall study design, coordination with the surgical teams, and will provide general oversight and management of the project, ensuring timely progression to meet milestones.

Co-Investigator: ShiNung Ching, Ph.D., Associate Professor of Electrical Systems Engineering and Biomedical Engineering

A dynamic systems and control engineer and expert on pharmacologic modeling of anesthetic effects on the electroencephalogram, Dr. Ching will provide expertise on precision targeting of propofol-induced EEG slow waves through open loop technology and real-time processing of scalp EEG, and signal processing.

Co-Investigator: Nuri B. Farber, M.D., Professor of Psychiatry

A senior psychiatrist on the electroconvulsive therapy (ECT) service with extensive experience with treatment-resistant depression and a complementary background in NMDA antagonists, Dr. Farber will provide guidance on study execution, patient recruitment, training of staff for administration of the MADRS, data analysis, data interpretation, and manuscript preparation.

Co-Investigator: Brendan P. Lucey, M.D., MSCI, Associate Professor of Neurology

As the section head for Sleep Medicine and an expert on the relationships between sleep disorders and Alzheimer's disease, he will provide assistance with study design, technical expertise of sleep recordings from wireless wearable devices, data collection, analysis, and interpretation.

Co-Investigator: S. Kendall Smith, M.D., Ph.D., Assistant Professor of Anesthesiology

Given her experience on TimeSignature and circadian rhythms, she will contribute to acquisition and analysis of physiologic and molecular markers for substudies on changes in circadian rhythms induced by the intervention.

Co-Investigator: Nan Lin, Ph.D., Professor of Mathematics and Statistics

Dr. Lin will serve as the biostatistician for the study. He will perform statistical analysis of the data. He and the research team have collaborated multiple prior projects.

Clinical Lab Manage/Data Manager: TBN

This team member will serve a key role in coordinating staff, effort, and products related to the proposed investigation, given Dr. Palanca's clinical commitments. A master's or Ph.D.-trained professional with background in neuroscience will be recruited. They will be in charge of maintaining study compliance, data acquisition, analysis, and manuscript drafting.

Research Coordinators: Emily Lenard, M.S.W., Aris Perez, Jennifer Wulfers

These team members will support participant recruitment, screening, and intake. With her experience in administering the MADRS, SHAPS, and the C-SSRS, they will assist in data collection of these outcomes, and manuscript preparation.

Research Coordinators: Orlandrea Hyche, B.S.; Allyson Quigley

Ms. Hyche and Quiqley will score sleep stages of EEG data recorded by Dreem devices. They will review the efficacy of automatic detection of slow waves and sleep spindles and will assist in modifying the algorithms as needed. Augmentation of effort will be needed in Year 4 to aid in data dissemination.

Clinical Research Nurse Coordinator: TBN

A Nurse Coordinator will assist in recruitment, managing clinical outcomes, and patient monitoring for adverse events. She will coordinate filings with the IRB and ClinicalTrials.gov. This team member will be guided by Drs. Lenze and Farber's staff on analysis and interpretation of the MADRS.

Postdoctoral Research Fellow: TBN

They will also contribute to the recording and quantitative analysis of sleep and high-density EEG data. The postdoctoral fellow will supplement research assistant efforts and work with Dr. Ching on precision targeting of propofol-induced EEG slow waves, data analysis, and manuscript drafting.

Certified Registered Nurse Anesthetists: TBN

Certified registered nurse anesthetists (CRNAs) will collaborate with attending anesthesiologists during propofol study sessions to maximize safety. They will aid in airway maneuvers, clinical monitoring, and manipulation of propofol infusion rates.

University of Pittsburgh Medical Center

Consultant: Charles F. Reynolds, III, M.D., Distinguished Professor Psychiatry

A world expert on the contributions of sleep abnormalities to mental illness and as a distinguished clinical trialist, he will provide guidance on study design, data analysis, interpretation, and manuscript preparation.

10.1.6 SAFETY OVERSIGHT

The principal investigator will be responsible for the overall monitoring of the data and safety of study participants.

Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) convened by NIMH. The DSMB includes experts in scientific disciplines needed to monitor the data and ensure patient safety during the conduct of this study, including addiction and mental health experts, clinical trial experts, biostatisticians, and bioethicists. DSMB members have no association with the project investigators, and no conflicts of interest with study outcomes. The DSMB will meet at least three times a year to assess safety and data of the study. The DMSB will operate under the rules of an approved charter. The DSMB will provide its input to NIMH staff.

DSMB procedures conform with usual standards, including reviewing emerging trial data and maintaining confidentiality. The main responsibilities of the NIMH DSMB include, but are not limited to the following: (1) reviewing the research protocol, consent form(s) and plans for data and safety monitoring prior to the initiation of the study; (2) monitoring of the progress of the study, including data quality, timeliness, recruitment and retention of study participants, adverse events, serious adverse events (SAEs), reasons for participant withdrawal, adherence to the timeline of the study, protocol deviations, performance across study sites, and factors that may affect the risks and benefits of the study such as emerging literature; and (3) making directives about the continuation, modification, or termination of the study, based on the balance of adverse events and beneficial outcomes. Throughout the study, notification of SAEs as well as any proposed investigator-initiated changes in the protocol will be submitted to the NIMH DSMB. Based on its review of the protocol, the NIMH DSMB will identify the data parameters and format of the information to be regularly reported. The NIMH DSMB may at any time request additional information from the Principal Investigators.

All SAEs and adverse events (AEs will only be reported to the NIMH DSMB annually) will be tabulated and submitted to the NIMH DSMB in the triannual DSMB data reports. Based on review of safety data, the

NIMH DSMB will issue directives concerning the conduct of the study. Recommendation/directives made by the DSMB may include amending safety monitoring procedures, modifying the protocol or consent, terminating the study, or continuing the study as designed.

10.1.7 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

- Monitoring for this study will be performed by Department of Anesthesiology Division of Clinical and Translational Research.
- An initial review will be performed after the first 3 participants have completed study procedures.
- Regulatory staff will be provided copies of monitoring reports within 7 days of visit.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

We will perform internal quality management of study conduct, data and biological specimen collection, documentation, and completion.

Following written Standard Operating Procedures (SOPs), the study staff will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into Research Electronic Data Capture (REDCap), a 21 CFR Part 11-compliant data capture system. The data system includes password protection and internal

quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.1.9.2 STUDY RECORDS RETENTION

Study documents will be retained for a minimum of 3 years after the study is completed and closed by the IRB.

10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations. All deviations must be addressed in study source documents, reported to the NIMH Program Official/DSMB and Washington University Human Research Protection Office. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

10.1.11 PUBLICATION AND DATA SHARING POLICY

Sharing of participant data (EEG, sleep studies, and blood samples) is mandatory for enrollment. Permission for further use of these data and samples can be withdrawn by study participants at any time.

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers after the completion of the primary endpoint by contacting the principal investigators.

In addition, this study will comply with the NIH Genomic Data Sharing Policy, which applies to all NIH-funded research that generates large-scale human or non-human genomic data, as well as the use of these data for subsequent research. Large-scale data include genome-wide association studies (GWAS), single nucleotide polymorphisms (SNP) arrays, and genome sequence, transcriptomic, epigenomic, and gene expression data.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the NIMH has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ABBREVIATIONS

AE	Adverse Event
ACLS	Advanced Cardiovascular Life Support
AMPA	Alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid
ANCOVA	Analysis of Covariance
ASA	American Society of Anesthesiologists
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
C-SSRS	Columbia-Suicide Severity Rating Scale
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DSR	Delta Sleep Ratio
DRE	Disease-Related Event
EC	Ethics Committee
EF	Executive Function
eCRF	Electronic Case Report Forms
EEG	Electroencephalography
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GABA	Gamma-aminobutyric acid
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HD-EEG	High-density electroencephalography
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
IV	Intravenous
LL-TRD	Late Life Treatment Resistant Depression
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MADRS	Montgomery-Asberg Depression Rating Scale
MDD	Major Depressive Disorder
MEQ	Morningness-Eveningness Questionnaire
MoCA	Montreal Cognitive Assessment

MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
N3	Non-rapid Eye Movement Sleep Stage 3
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
PHI	Personal Health Information
PHQ-9	Patient Health Questionnaire-9
PFC	Prefrontal Cortex
PVT	Psychomotor Vigilance Test
QA	Quality Assurance
QC	Quality Control
REM	Rapid Eye Movement Sleep
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
STOP-BANG	Snoring, Tired, Observed Apnea, high blood Pressure, Body mass index, Age, Neck circumference, male Gender Questionnaire
SWA	Slow Wave Activity
SWS	Slow Wave Sleep
TRD	Treatment-Resistant Depression
UP	Unanticipated Problem
US	United States
WUSM	Washington University School of Medicine

10.3 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
2	4/2/22	Clarification of terms and procedures.	Preparation for DSMB initial review.
2.1	4/11/22	Addition to section 2.3.1, 2.3.3., 10.1.11	Addressed risk of genetic testing and mitigation measures, sharing
3.1	6/21/22	Additions to 1.1, 1.3, 2.3, 2.3.3, 4.1, 4.2, 5.2, 6.1, 9.3	Revision of exclusion criteria, assess for possible OSA as confounder, screen for illicit drug use, addressing propofol risks, monitoring during study, analytical plan of descriptive statistics only, transparency on "go" criteria for further study
3.1.1	9/7/22	6.1.2, 5.3, 6.5.1, 8.2	Improved clarity of propofol dosing and wording
3.1.2	9/28/22	1.3, 2.3.1, 8.2, 10.2	Inclusion of the PHQ-9 in phone screen, EEG recording on follow up
3.1.3	10/4/22	1.3, 2.3.3, 8.2, 10.1.5	Change timing and number of MADRS, C-SSRS, and SHAPS; update team roster
3.14	11/2/22	5.5	Correction of remuneration to be consistent with SOA and maximize retention to study follow up

11 REFERENCES

1. aan het Rot M, Collins KA, Murrough JW, et al. Safety and efficacy of repeated-dose intravenous ketamine for treatment-resistant depression. *Biol Psychiatry.* 2010;67(2):139-145.
2. Singh JB, Fedgchin M, Daly EJ, et al. A Double-Blind, Randomized, Placebo-Controlled, Dose-Frequency Study of Intravenous Ketamine in Patients With Treatment-Resistant Depression. *Am J Psychiatry.* 2016;173(8):816-826.
3. Lenze EJ, Rogers JC, Martire LM, et al. The association of late-life depression and anxiety with physical disability: a review of the literature and prospectus for future research. *Am J Geriatr Psychiatry.* 2001;9(2):113-135.
4. Wolkowitz OM, Reus VI, Mellon SH. Of sound mind and body: depression, disease, and accelerated aging. *Dialogues Clin Neurosci.* 2011;13(1):25-39.
5. Szanto K, Lenze EJ, Waern M, et al. Research to reduce the suicide rate among older adults: methodology roadblocks and promising paradigms. *Psychiatr Serv.* 2013;64(6):586-589.
6. Ownby RL, Crocco E, Acevedo A, John V, Loewenstein D. Depression and risk for Alzheimer disease: systematic review, meta-analysis, and metaregression analysis. *Arch Gen Psychiatry.* 2006;63(5):530-538.
7. Byers AL, Yaffe K. Depression and risk of developing dementia. *Nat Rev Neurol.* 2011;7(6):323-331.
8. Diniz BS, Butters MA, Albert SM, Dew MA, Reynolds CF, 3rd. Late-life depression and risk of vascular dementia and Alzheimer's disease: systematic review and meta-analysis of community-based cohort studies. *Br J Psychiatry.* 2013;202(5):329-335.
9. Thomas L, Mulsant BH, Solano FX, et al. Response speed and rate of remission in primary and specialty care of elderly patients with depression. *Am J Geriatr Psychiatry.* 2002;10(5):583-591.
10. Mulsant BH, Blumberger DM, Ismail Z, Rabheru K, Rapoport MJ. A systematic approach to pharmacotherapy for geriatric major depression. *Clin Geriatr Med.* 2014;30(3):517-534.
11. Buchalter ELF, Oughli HA, Lenze EJ, et al. Predicting Remission in Late-Life Major Depression: A Clinical Algorithm Based Upon Past Treatment History. *J Clin Psychiatry.* 2019;80(6).
12. Deng Y, McQuoid DR, Potter GG, et al. Predictors of recurrence in remitted late-life depression. *Depress Anxiety.* 2018;35(7):658-667.
13. Rush AJ, Warden D, Wisniewski SR, et al. STAR*D: revising conventional wisdom. *CNS Drugs.* 2009;23(8):627-647.
14. Kellner CH, Husain MM, Knapp RG, et al. Right Unilateral Ultrabrief Pulse ECT in Geriatric Depression: Phase 1 of the PRIDE Study. *Am J Psychiatry.* 2016;173(11):1101-1109.
15. Kellner CH, Husain MM, Knapp RG, et al. A Novel Strategy for Continuation ECT in Geriatric Depression: Phase 2 of the PRIDE Study. *Am J Psychiatry.* 2016;173(11):1110-1118.
16. Conelea CA, Philip NS, Yip AG, et al. Transcranial magnetic stimulation for treatment-resistant depression: Naturalistic treatment outcomes for younger versus older patients. *J Affect Disord.* 2017;217:42-47.
17. Murphy MJ, Peterson MJ. Sleep Disturbances in Depression. *Sleep Med Clin.* 2015;10(1):17-23.
18. Schroder CM, O'Hara R. Depression and Obstructive Sleep Apnea (OSA). *Ann Gen Psychiatry.* 2005;4:13.
19. Holanda FWNJ, de Almondes KM. Sleep and executive functions in older adults: A systematic review. *Dement Neuropsychol.* 2016;10(3):185-197.
20. Cristancho P, Lenze EJ, Dixon D, et al. Executive Function Predicts Antidepressant Treatment Noncompletion in Late-Life Depression. *J Clin Psychiatry.* 2018;79(3).

21. Snyder HR. Major depressive disorder is associated with broad impairments on neuropsychological measures of executive function: a meta-analysis and review. *Psychol Bull.* 2013;139(1):81-132.
22. Burdick DJ, Rosenblatt A, Samus QM, et al. Predictors of functional impairment in residents of assisted-living facilities: the Maryland Assisted Living study. *J Gerontol A Biol Sci Med Sci.* 2005;60(2):258-264.
23. Diamond A. Executive functions. *Annu Rev Psychol.* 2013;64:135-168.
24. Duncan J, Owen AM. Common regions of the human frontal lobe recruited by diverse cognitive demands. *Trends Neurosci.* 2000;23(10):475-483.
25. Miller EK, Cohen JD. An integrative theory of prefrontal cortex function. *Annu Rev Neurosci.* 2001;24:167-202.
26. Rajji TK, Sun Y, Zomorrodi-Moghaddam R, et al. PAS-induced potentiation of cortical-evoked activity in the dorsolateral prefrontal cortex. *Neuropsychopharmacology.* 2013;38(12):2545-2552.
27. Mulsant BH, Ganguli M. Epidemiology and diagnosis of depression in late life. *J Clin Psychiatry.* 1999;60 Suppl 20:9-15.
28. Alexopoulos GS, Murphy CF, Gunning-Dixon FM, et al. Microstructural white matter abnormalities and remission of geriatric depression. *Am J Psychiatry.* 2008;165(2):238-244.
29. Galvin JE, Roe CM, Coats MA, Morris JC. Patient's rating of cognitive ability: using the AD8, a brief informant interview, as a self-rating tool to detect dementia. *Archives of neurology.* 2007;64(5):725-730.
30. Kaneriya SH, Robbins-Welty GA, Smagula SF, et al. Predictors and Moderators of Remission With Aripiprazole Augmentation in Treatment-Resistant Late-Life Depression: An Analysis of the IRL-GRey Randomized Clinical Trial. *JAMA Psychiatry.* 2016;73(4):329-336.
31. Lowe B, Unutzer J, Callahan CM, Perkins AJ, Kroenke K. Monitoring depression treatment outcomes with the patient health questionnaire-9. *Med Care.* 2004;42(12):1194-1201.
32. Weintraub S, Dikmen SS, Heaton RK, et al. Cognition assessment using the NIH Toolbox. *Neurology.* 2013;80(11 Suppl 3):S54-64.
33. Plante DT, Hagen EW, Ravelo LA, Peppard PE. Impaired neurobehavioral alertness quantified by the psychomotor vigilance task is associated with depression in the Wisconsin Sleep Cohort study. *Sleep Med.* 2020;67:66-70.
34. Yun CH, Kim H, Lee SK, et al. Daytime sleepiness associated with poor sustained attention in middle and late adulthood. *Sleep Med.* 2015;16(1):143-151.
35. Berry RBB, R.; Gamaldo, C.E.; Harding, S.M.; Lloyd, R.M.; Marcus, C.L.; Vaughn, B.V. *The AASM Manual for Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications, Version 2.3.* Darien, Illinois: American Academy of Sleep Medicine; 2015.
36. Akerstedt T, Hume K, Minors D, Waterhouse J. Good sleep--its timing and physiological sleep characteristics. *J Sleep Res.* 1997;6(4):221-229.
37. Tasali E, Leproult R, Ehrmann DA, Van Cauter E. Slow-wave sleep and the risk of type 2 diabetes in humans. *Proc Natl Acad Sci U S A.* 2008;105(3):1044-1049.
38. Molle M, Yeshenko O, Marshall L, Sara SJ, Born J. Hippocampal sharp wave-ripples linked to slow oscillations in rat slow-wave sleep. *J Neurophysiol.* 2006;96(1):62-70.
39. Esser SK, Hill SL, Tononi G. Sleep homeostasis and cortical synchronization: I. Modeling the effects of synaptic strength on sleep slow waves. *Sleep.* 2007;30(12):1617-1630.
40. Riedner BA, Vyazovskiy VV, Huber R, et al. Sleep homeostasis and cortical synchronization: III. A high-density EEG study of sleep slow waves in humans. *Sleep.* 2007;30(12):1643-1657.
41. Vyazovskiy VV, Riedner BA, Cirelli C, Tononi G. Sleep homeostasis and cortical synchronization: II. A local field potential study of sleep slow waves in the rat. *Sleep.* 2007;30(12):1631-1642.

42. Rasch B, Buchel C, Gais S, Born J. Odor cues during slow-wave sleep prompt declarative memory consolidation. *Science.* 2007;315(5817):1426-1429.
43. Deuschle M, Schredl M, Wisch C, et al. Serum brain-derived neurotrophic factor (BDNF) in sleep-disordered patients: relation to sleep stage N3 and rapid eye movement (REM) sleep across diagnostic entities. *J Sleep Res.* 2018;27(1):73-77.
44. Dash MB. Infraslow coordination of slow wave activity through altered neuronal synchrony. *Sleep.* 2019;42(12).
45. Achermann P, Dijk DJ, Brunner DP, Borbely AA. A model of human sleep homeostasis based on EEG slow-wave activity: quantitative comparison of data and simulations. *Brain Res Bull.* 1993;31(1-2):97-113.
46. Marshall L, Molle M, Hallschmid M, Born J. Transcranial direct current stimulation during sleep improves declarative memory. *J Neurosci.* 2004;24(44):9985-9992.
47. Marshall L, Helgadottir H, Molle M, Born J. Boosting slow oscillations during sleep potentiates memory. *Nature.* 2006;444(7119):610-613.
48. Iliff JJ, Wang M, Liao Y, et al. A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid beta. *Sci Transl Med.* 2012;4(147):147ra111.
49. Fultz NE, Bonmassar G, Setsompop K, et al. Coupled electrophysiological, hemodynamic, and cerebrospinal fluid oscillations in human sleep. *Science.* 2019;366(6465):628-631.
50. Lundgaard I, Lu ML, Yang E, et al. Glymphatic clearance controls state-dependent changes in brain lactate concentration. *J Cereb Blood Flow Metab.* 2017;37(6):2112-2124.
51. Peng W, Achariyar TM, Li B, et al. Suppression of glymphatic fluid transport in a mouse model of Alzheimer's disease. *Neurobiol Dis.* 2016;93:215-225.
52. Iliff JJ, Chen MJ, Plog BA, et al. Impairment of glymphatic pathway function promotes tau pathology after traumatic brain injury. *J Neurosci.* 2014;34(49):16180-16193.
53. Lucey BP, McCullough A, Landsness EC, et al. Reduced non-rapid eye movement sleep is associated with tau pathology in early Alzheimer's disease. *Sci Transl Med.* 2019;11(474).
54. Hablitz LM, Vinitsky HS, Sun Q, et al. Increased glymphatic influx is correlated with high EEG delta power and low heart rate in mice under anesthesia. *Sci Adv.* 2019;5(2):eaav5447.
55. Xie L, Kang H, Xu Q, et al. Sleep drives metabolite clearance from the adult brain. *Science.* 2013;342(6156):373-377.
56. Buysse DJ, Frank E, Lowe KK, Cherry CR, Kupfer DJ. Electroencephalographic sleep correlates of episode and vulnerability to recurrence in depression. *Biol Psychiatry.* 1997;41(4):406-418.
57. Ganguli R, Reynolds CF, 3rd, Kupfer DJ. Electroencephalographic sleep in young, never-medicated schizophrenics. A comparison with delusional and nondelusional depressives and with healthy controls. *Arch Gen Psychiatry.* 1987;44(1):36-44.
58. Kupfer DJ, Ulrich RF, Coble PA, et al. Application of automated REM and slow wave sleep analysis: II. Testing the assumptions of the two-process model of sleep regulation in normal and depressed subjects. *Psychiatry Res.* 1984;13(4):335-343.
59. Reynolds CF, 3rd, Kupfer DJ. Sleep research in affective illness: state of the art circa 1987. *Sleep.* 1987;10(3):199-215.
60. Gillin JC, Duncan W, Pettigrew KD, Frankel BL, Snyder F. Successful separation of depressed, normal, and insomniac subjects by EEG sleep data. *Arch Gen Psychiatry.* 1979;36(1):85-90.
61. Benca RM, Obermeyer WH, Thisted RA, Gillin JC. Sleep and psychiatric disorders. A meta-analysis. *Arch Gen Psychiatry.* 1992;49(8):651-668; discussion 669-670.
62. Ehlers CL, Havstad JW, Kupfer DJ. Estimation of the time course of slow-wave sleep over the night in depressed patients: effects of clomipramine and clinical response. *Biol Psychiatry.* 1996;39(3):171-181.

63. Gillin JC, Duncan WC, Murphy DL, et al. Age-related changes in sleep in depressed and normal subjects. *Psychiatry Res.* 1981;4(1):73-78.
64. Perlis ML, Giles DE, Buysse DJ, Thase ME, Tu X, Kupfer DJ. Which depressive symptoms are related to which sleep electroencephalographic variables? *Biol Psychiatry.* 1997;42(10):904-913.
65. Pittenger C, Duman RS. Stress, depression, and neuroplasticity: a convergence of mechanisms. *Neuropsychopharmacology.* 2008;33(1):88-109.
66. Kupfer DJ, Frank E, McEachran AB, Grochocinski VJ. Delta sleep ratio. A biological correlate of early recurrence in unipolar affective disorder. *Arch Gen Psychiatry.* 1990;47(12):1100-1105.
67. Duncan WC, Jr., Selter J, Brutsche N, Sarasso S, Zarate CA, Jr. Baseline delta sleep ratio predicts acute ketamine mood response in major depressive disorder. *J Affect Disord.* 2013;145(1):115-119.
68. Lotrich FE, Germain A. Decreased delta sleep ratio and elevated alpha power predict vulnerability to depression during interferon-alpha treatment. *Acta Neuropsychiatr.* 2015;27(1):14-24.
69. Kupfer DJ, Reynolds CF, 3rd, Weiss BL, Foster FG. Lithium carbonate and sleep in affective disorders. Further considerations. *Arch Gen Psychiatry.* 1974;30(1):79-84.
70. Billiard M. Lithium carbonate: effects on sleep patterns of normal and depressed subjects and its use in sleep-wake pathology. *Pharmacopsychiatry.* 1987;20(5):195-196.
71. Friston KJ, Sharpley AL, Solomon RA, Cowen PJ. Lithium increases slow wave sleep: possible mediation by brain 5-HT2 receptors? *Psychopharmacology (Berl).* 1989;98(1):139-140.
72. Doghramji K, Jangro WC. Adverse Effects of Psychotropic Medications on Sleep. *Psychiatr Clin North Am.* 2016;39(3):487-502.
73. Jindal RD, Friedman ES, Berman SR, Fasiczka AL, Howland RH, Thase ME. Effects of sertraline on sleep architecture in patients with depression. *J Clin Psychopharmacol.* 2003;23(6):540-548.
74. Duncan WC, Sarasso S, Ferrarelli F, et al. Concomitant BDNF and sleep slow wave changes indicate ketamine-induced plasticity in major depressive disorder. *Int J Neuropsychopharmacol.* 2013;16(2):301-311.
75. Quera Salva MA, Vanier B, Laredo J, et al. Major depressive disorder, sleep EEG and agomelatine: an open-label study. *Int J Neuropsychopharmacol.* 2007;10(5):691-696.
76. Murphy M, Bruno MA, Riedner BA, et al. Propofol anesthesia and sleep: a high-density EEG study. *Sleep.* 2011;34(3):283-291A.
77. Tung A, Bergmann BM, Herrera S, Cao D, Mendelson WB. Recovery from sleep deprivation occurs during propofol anesthesia. *Anesthesiology.* 2004;100(6):1419-1426.
78. Tung A, Lynch JP, Mendelson WB. Prolonged sedation with propofol in the rat does not result in sleep deprivation. *Anesth Analg.* 2001;92(5):1232-1236.
79. Rabelo FA, Braga A, Kupper DS, et al. Propofol-induced sleep: polysomnographic evaluation of patients with obstructive sleep apnea and controls. *Otolaryngol Head Neck Surg.* 2010;142(2):218-224.
80. Xu Z, Jiang X, Li W, Gao D, Li X, Liu J. Propofol-induced sleep: efficacy and safety in patients with refractory chronic primary insomnia. *Cell Biochem Biophys.* 2011;60(3):161-166.
81. Shafer A, Doze VA, Shafer SL, White PF. Pharmacokinetics and pharmacodynamics of propofol infusions during general anesthesia. *Anesthesiology.* 1988;69(3):348-356.
82. Tackley RM, Lewis GT, Prys-Roberts C, Boaden RW, Dixon J, Harvey JT. Computer controlled infusion of propofol. *Br J Anaesth.* 1989;62(1):46-53.
83. Marsh BJ, Morton NS, White M, Kenny GN. A computer controlled infusion of propofol for induction and maintenance of anaesthesia in children. *Can J Anaesth.* 1990;37(4 Pt 2):S97.
84. Marsh B, White M, Morton N, Kenny GN. Pharmacokinetic model driven infusion of propofol in children. *Br J Anaesth.* 1991;67(1):41-48.

85. Schnider TW, Minto CF, Gambus PL, et al. The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers. *Anesthesiology.* 1998;88(5):1170-1182.
86. Mhuircheartaigh RN, Rosenorn-Lanng D, Wise R, Jbabdi S, Rogers R, Tracey I. Cortical and subcortical connectivity changes during decreasing levels of consciousness in humans: a functional magnetic resonance imaging study using propofol. *J Neurosci.* 2010;30(27):9095-9102.
87. Ni Mhuircheartaigh R, Warnaby C, Rogers R, Jbabdi S, Tracey I. Slow-wave activity saturation and thalamocortical isolation during propofol anesthesia in humans. *Sci Transl Med.* 2013;5(208):208ra148.
88. Peduto VA, Concas A, Santoro G, Biggio G, Gessa GL. Biochemical and electrophysiologic evidence that propofol enhances GABAergic transmission in the rat brain. *Anesthesiology.* 1991;75(6):1000-1009.
89. Irifune M, Takarada T, Shimizu Y, et al. Propofol-induced anesthesia in mice is mediated by gamma-aminobutyric acid-A and excitatory amino acid receptors. *Anesth Analg.* 2003;97(2):424-429, table of contents.
90. Orser BA, Bertlik M, Wang LY, MacDonald JF. Inhibition by propofol (2,6 di-isopropylphenol) of the N-methyl-D-aspartate subtype of glutamate receptor in cultured hippocampal neurones. *Br J Pharmacol.* 1995;116(2):1761-1768.
91. Mao LM, Hastings JM, Fibuch EE, Wang JQ. Propofol selectively alters GluA1 AMPA receptor phosphorylation in the hippocampus but not prefrontal cortex in young and aged mice. *Eur J Pharmacol.* 2014;738:237-244.
92. Krampfl K, Cordes AL, Schlesinger F, Wolfes H, Bufler J. Effects of propofol on recombinant AMPA receptor channels. *Eur J Pharmacol.* 2005;511(1):1-7.
93. Wang X, Yang Y, Zhou X, et al. Propofol pretreatment increases antidepressant-like effects induced by acute administration of ketamine in rats receiving forced swimming test. *Psychiatry Res.* 2011;185(1-2):248-253.
94. Luo J, Min S, Wei K, Zhang J, Liu Y. Propofol interacts with stimulus intensities of electroconvulsive shock to regulate behavior and hippocampal BDNF in a rat model of depression. *Psychiatry Res.* 2012;198(2):300-306.
95. O'Toole DP, Milligan KR, Howe JP, McCollum JS, Dundee JW. A comparison of propofol and methohexitone as induction agents for day case isoflurane anaesthesia. *Anaesthesia.* 1987;42(4):373-376.
96. McDonald NJ, Mannion D, Lee P, O'Toole DP, O'Boyle C, Keane PK. Mood evaluation and outpatient anaesthesia. A comparison between propofol and thiopentone. *Anaesthesia.* 1988;43 Suppl:68-69.
97. Canaday BR. Amorous, disinhibited behavior associated with propofol. *Clin Pharm.* 1993;12(6):449-451.
98. Kent EA, Bacon DR, Harrison P, Lema MJ. Sexual illusions and propofol sedation. *Anesthesiology.* 1992;77(5):1037-1038.
99. Kim JH, Byun H, Kim JH. Abuse potential of propofol used for sedation in gastric endoscopy and its correlation with subject characteristics. *Korean J Anesthesiol.* 2013;65(5):403-409.
100. D'Haese J, Camu F, Dekeyzer PJ, D'Haenen HA. Propofol and methohexitone anaesthesia: effects on the profile of mood state. *Eur J Anaesthesiol.* 1994;11(5):359-363.
101. Whitehead C, Sanders LD, Oldroyd G, et al. The subjective effects of low-dose propofol. A double-blind study to evaluate dimensions of sedation and consciousness with low-dose propofol. *Anaesthesia.* 1994;49(6):490-496.
102. Mickey BJ, White AT, Arp AM, et al. Propofol for Treatment-Resistant Depression: A Pilot Study. *Int J Neuropsychopharmacol.* 2018;21(12):1079-1089.

103. Maslej MM, Bolker BM, Russell MJ, et al. The Mortality and Myocardial Effects of Antidepressants Are Moderated by Preexisting Cardiovascular Disease: A Meta-Analysis. *Psychother Psychosom.* 2017;86(5):268-282.
104. Luscher B, Mohler H. Brexanolone, a neurosteroid antidepressant, vindicates the GABAergic deficit hypothesis of depression and may foster resilience. *F1000Res.* 2019;8.
105. Lenze EJ, Nicol GE, Barbour DL, et al. Precision clinical trials: a framework for getting to precision medicine for neurobehavioural disorders. *J Psychiatry Neurosci.* 2021;46(1):E97-E110.
106. Smith SK, Nguyen T, Labonte AK, et al. Protocol for the Prognosticating Delirium Recovery Outcomes Using Wakefulness and Sleep Electroencephalography (P-DROWS-E) study: a prospective observational study of delirium in elderly cardiac surgical patients. *BMJ Open.* 2020;10(12):e044295.
107. Kafashan MM, Hyche O, Nguyen T, et al. Perioperative sleep in geriatric cardiac surgical patients: a feasibility study using a wireless wearable device. *Br J Anaesth.* 2021;126(6):e205-e208.
108. Van Cauter E, Leproult R, Plat L. Age-related changes in slow wave sleep and REM sleep and relationship with growth hormone and cortisol levels in healthy men. *JAMA.* 2000;284(7):861-868.
109. Krystal AD, Pizzagalli DA, Mathew SJ, et al. The first implementation of the NIMH FAST-FAIL approach to psychiatric drug development. *Nat Rev Drug Discov.* 2018;18(1):82-84.
110. Nagele P, Palanca BJ, Gott B, et al. A phase 2 trial of inhaled nitrous oxide for treatment-resistant major depression. *Sci Transl Med.* 2021;13(597).
111. Siegel JS, Palanca BJA, Ances BM, et al. Prolonged ketamine infusion modulates limbic connectivity and induces sustained remission of treatment-resistant depression. *Psychopharmacology (Berl).* 2021.
112. Lenze EJ, Stevens A, Waring JD, et al. Augmenting Computerized Cognitive Training With Vortioxetine for Age-Related Cognitive Decline: A Randomized Controlled Trial. *Am J Psychiatry.* 2020;177(6):548-555.
113. Mashour GA, Palanca BJ, Basner M, et al. Recovery of consciousness and cognition after general anesthesia in humans. *Elife.* 2021;10.
114. Dinges DF, Powell JW. Microcomputer analyses of performance on a portable simple visual RT task during sustained operations. *Behavior Research Methods & Instrumentation.* 1985;17:652-655.
115. Basner M, Dinges DF. An adaptive-duration version of the PVT accurately tracks changes in psychomotor vigilance induced by sleep restriction. *Sleep.* 2012;35(2):193-202.
116. Basner M, Mollicone D, Dinges DF. Validity and Sensitivity of a Brief Psychomotor Vigilance Test (PVT-B) to Total and Partial Sleep Deprivation. *Acta Astronaut.* 2011;69(11-12):949-959.
117. Basner M, Rubinstein J. Fitness for duty: a 3-minute version of the Psychomotor Vigilance Test predicts fatigue-related declines in luggage-screening performance. *J Occup Environ Med.* 2011;53(10):1146-1154.
118. Doran SM, Van Dongen HP, Dinges DF. Sustained attention performance during sleep deprivation: evidence of state instability. *Arch Ital Biol.* 2001;139(3):253-267.
119. Palanca BJA, Maybrier HR, Mickle AM, et al. Cognitive and Neurophysiological Recovery Following Electroconvulsive Therapy: A Study Protocol. *Front Psychiatry.* 2018;9:171.
120. Delorme A, Makeig S. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *J Neurosci Methods.* 2004;134(1):9-21.
121. Lucey BP, McLeland JS, Toedebusch CD, et al. Comparison of a single-channel EEG sleep study to polysomnography. *J Sleep Res.* 2016;25(6):625-635.
122. Kabi F. Propofol Package Insert. In:2014.

123. de Leon-Casasola OA, Weiss A, Lema MJ. Anaphylaxis due to propofol. *Anesthesiology.* 1992;77(2):384-386.
124. Laxenaire MC, Gueant JL, Bermejo E, Mouton C, Navez MT. Anaphylactic shock due to propofol. *Lancet.* 1988;2(8613):739-740.
125. Tsai MH, Kuo PH, Hong RL, Yang PC. Anaphylaxis after propofol infusion for Port-A-Cath insertion in a 35-year old man. *J Formos Med Assoc.* 2001;100(6):424-426.
126. Koul A, Jain R, Sood J. A critical incident report: Propofol triggered anaphylaxis. *Indian J Anaesth.* 2011;55(5):530-533.
127. Laxenaire MC, Mata-Bermejo E, Moneret-Vautrin DA, Gueant JL. Life-threatening anaphylactoid reactions to propofol (Diprivan). *Anesthesiology.* 1992;77(2):275-280.
128. McHale SP, Konieczko K. Anaphylactoid reaction to propofol. *Anaesthesia.* 1992;47(10):864-865.
129. Ducart AR, Watremez C, Louagie YA, Collard EL, Broka SM, Joucken KL. Propofol-induced anaphylactoid reaction during anesthesia for cardiac surgery. *J Cardiothorac Vasc Anesth.* 2000;14(2):200-201.
130. Hepner DL, Castells MC. Anaphylaxis during the perioperative period. *Anesth Analg.* 2003;97(5):1381-1395.
131. Asserhoj LL, Mosbech H, Kroigaard M, Garvey LH. No evidence for contraindications to the use of propofol in adults allergic to egg, soy or peanutdagger. *Br J Anaesth.* 2016;116(1):77-82.
132. Aldrete JA. The post-anesthesia recovery score revisited. *J Clin Anesth.* 1995;7(1):89-91.
133. Chung F, Subramanyam R, Liao P, Sasaki E, Shapiro C, Sun Y. High STOP-Bang score indicates a high probability of obstructive sleep apnoea. *Br J Anaesth.* 2012;108(5):768-775.
134. Chung F, Yegneswaran B, Liao P, et al. STOP questionnaire: a tool to screen patients for obstructive sleep apnea. *Anesthesiology.* 2008;108(5):812-821.
135. Mitra PP, Bokil H. *Observed Brain Dynamics.* 1st ed. New York: Oxford University Press; 2008.
136. Latta F, Leproult R, Tasali E, Hofmann E, Van Cauter E. Sex differences in delta and alpha EEG activities in healthy older adults. *Sleep.* 2005;28(12):1525-1534.
137. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry.* 1979;134:382-389.
138. Snaith RP, Hamilton M, Morley S, Humayan A, Hargreaves D, Trigwell P. A scale for the assessment of hedonic tone the Snaith-Hamilton Pleasure Scale. *Br J Psychiatry.* 1995;167(1):99-103.
139. Hardy CJ, Rejeski WJ. Not what, but how one feels: the measurement of affect during exercise. *J Sport Exerc Psychol.* 1989;11:304-317.
140. Nasreddine ZS, Phillips NA, Bedirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc.* 2005;53(4):695-699.
141. Roca M, Parr A, Thompson R, et al. Executive function and fluid intelligence after frontal lobe lesions. *Brain.* 2010;133(Pt 1):234-247.
142. Horne JA, Ostberg O. A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. *Int J Chronobiol.* 1976;4(2):97-110.
143. Braun R, Kath WL, Iwanaszko M, et al. Universal method for robust detection of circadian state from gene expression. *Proc Natl Acad Sci U S A.* 2018;115(39):E9247-E9256.