**RESEARCH PROTOCOL**

**Title:** The impact of suvorexant on cognitive function and daytime symptoms among community-dwelling older adults with insomnia: A placebo-controlled, randomized clinical trial using remote monitoring and ecological momentary assessment

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**Lay Summary**

The purpose of this study is to employ ecological momentary assessment (EMA) methods to evaluate the impact of suvorexant on alert cognition and daytime symptoms among community-dwelling older adults with insomnia.

Traditional assessment methods such as retrospective questionnaires or standard neurocognitive tests enable measurement of symptoms at one point in time, in a research environment. By contrast, remote monitoring approaches such as ecological momentary assessment (EMA; e.g., administered via mobile device) enable ongoing, data-rich assessment of symptoms such as cognitive alertness, fatigue, and low mood in participants' natural environments.

**Specific Aims**

The long-term goal of this research is to improve outcomes for patients with sleep disorders. The overall objective of the current application is to test preliminarily remote monitoring and ecological momentary assessment (EMA) methods for measuring the impact of insomnia treatment on daytime symptoms (i.e., to employ EMA as an outcome measure). Based on prior research, our central hypothesis is that relative to placebo, suvorexant improves daytime insomnia symptoms as assessed via EMA.

Specific Aim 1: To employ ecological momentary assessment (EMA) methods to evaluate the impact of suvorexant on daytime insomnia symptoms among community-dwelling older adults with insomnia.

Hypothesis 1: Relative to placebo, suvorexant improves alert cognition and daytime symptoms as assessed via EMA.

**Design**

This is a single-site, double-blind, randomized, placebo-controlled clinical trial. The study employs a two-group (suvorexant, 20mg, qhs, versus placebo) parallel design and involves remote (baseline) assessments, 16-day active treatment phase with intensive ambulatory monitoring via wrist actigraphy and ecological momentary assessment (EMA). Outcome

assessments are conducted at two weeks while participants are on study treatment or placebo and include self- report questionnaires and comprehensive cognitive testing administered by computer.

## STUDY PROCEDURES

### Recruitment

Participants will be recruited to the study in several ways (i.e., volunteer lists, mailings based on EPIC searches, newspaper advertisements, online and social media advertisements, public presentations, and word of mouth and study fliers at the University of Maryland Sleep Disorders Center, Midtown Campus). Approaches to recruitment are described in "Recruitment" section below.

*Self-Screening Form Process*

In all recruitment pathways except for online and social media advertisements, the participants will be provided with study staff contact information, and the participant will call (or video chat, if requested) with study staff to be screened for the study.
For online and social media, advertisements, and recruitment pathways, the participants will be provided with study staff contact information. If interested in the study, the participant will complete an online preliminary screening questionnaire prior to being phone-screened. If individuals meet the initial study criteria via preliminary screening, then the information will be sent to the recruitment team for review before contacting the participant via phone.

### Phone Screening

Interested participants will speak remotely e.g., over the phone or via secure teleconferencing platforms like Zoom with study staff to confirm high likelihood of insomnia and low risk for major untreated medical, psychiatric, and other sleep disorders. This screening will assess all eligibility criteria (e.g., age, sleep difficulties, substance use, existing medical conditions) in addition to confirming that the volunteer will be available locally during the course of the study (i.e., confirming that the volunteer will not be traveling during the duration of the study). Individuals who pass the initial screening will be invited to complete remote assessments with trained project staff to confirm eligibility for the study. Given that participants will be older adults, project staff will provide technical assistance whenever possible.

### Eligibility/Consenting/Phone Call

Participants will receive the study consent form via email (or via snail mail if requested). The study team will work with potential participants to complete the informed consent process. Participants will provide their signed consent to participate in the study. Once signed consent is confirmed, participants will complete the remote assessments. Then the study staff will confirm eligibility and the sleep expert (i.e., PI) will confirm individual's study participation.

Once study participation is confirmed, the participant will be randomized to drug or placebo in a 1:1 ratio by the IDS pharmacy. Throughout the study participants will wear an actigraph. An actigraph is a wristwatch-like device that detects ambulatory movement, a validated proxy for sleep. Participants will also complete brief surveys four times per day for 16 days. At post-treatment, participants will complete validated questionnaires, neurocognitive tasks, and a brief satisfaction survey. Additional details presented below.

**Remote Assessments (Day 0)**

Study staff will schedule a time for participants to complete the remote assessments. These include a semi-structured interview, validated questionnaires (about 45-60 minutes), and computerized neurocognitive tasks (about 15-20 minutes). Participants will complete the remote assessments over one day (90 minutes) or two days (about 45 minutes each day). For participants who prefer to complete the remote assessments over two days, the first day will include the consent and interview. The second day will include the validated questionnaires and neurocognitive tasks.

Participants use a special research smartphone app for this study, which will capture daily surveys (described below). All study tasks will be remote, e.g., over the phone or via secure teleconferencing platforms like Zoom. During the remote assessments, participants will have many breaks to help them stay refreshed. Participants can also request a break after any task.

Neurocognitive tasks are computerized measures that include the psychomotor vigilance test (PVT), Stroop Task, and a Task-switching exercise developed for use among older adults. To help participants complete these tasks, study staff will email or text participants a link, which will enable completion of the computerized tasks on participants' smartphone, laptop, or desktop computer. In the tasks participants will be asked to respond to words, shapes, and colors on their screens.

**Home Sleep Apnea Test (Day 0)**

Participants will complete a Home Sleep Apnea Test (HSAT) early in the study to evaluate their breathing during sleep. The HSAT will determine if participants have obstructive sleep apnea (OSA). The HSAT device will be mailed to participants by a third-party company supporting this study. Participants will follow instructions on how to use the device. Participants will return the device using a pre-paid return mailing envelope. Participants will have 24-hour support if needed.

**Actigraphy Setup (Days 1-16)**

Once participants complete the remote assessments participants will set up their actigraph with study staff. Study staff will contact participants to review instructions and inquire of general questions of quiet time activities remotely e.g., over the phone or via secure teleconferencing platforms like Zoom. Participants will be instructed to wear an actigraph on their non-dominant hands for approximately 16 days. We will mail participants an actigraph along with a pre-paid mailing envelope. Actigraphs are expensive

research devices and must be returned. Study staff will call to remind participants when it is time to return the actigraph.

**Daily Survey Completion (Days 1-16)**
While participants wear the actigraph, they will also complete brief surveys on their mobile phones. The surveys are sent to participants 4 times a day for 16 days. Each survey takes less than 2 minutes to complete. Participants' phones will send them notifications for each survey. At the start of the study, participants will choose what time they want surveys to start. Every morning, participants will complete a survey that includes a brief sleep diary and questions about generalized quiet time activities and how they feel. Next, participants will complete three more surveys throughout the day. These surveys also ask about how they feel. These surveys will be given at random times throughout the day, about two hours apart over the next 12 hours. Study staff will be available to answer any questions or give support. Contact information for study staff and technical support will be given to them.

**Post Assessments (Prior to Day 16)**
Study staff will schedule a time for participants to complete the post-assessment before discontinuing study drug or placebo. These assessments include validated questionnaires (about 45-60 minutes), computerized neurocognitive tasks (about 15-20 minutes), and a brief satisfaction survey

**Unique Identifiers**
Study staff will assign each participant a unique 4-digit identification number, generated by an online random integer generator. Any information linking the subject ID to PHI will be kept in the master/coded list, which will be stored virtually in a limited access, password-protected drive on UMB-encrypted devices. The folder with all participant PHI will be accessible only to trained study staff authorized by the PI to access these files.

**Neurocognitive Testing**
General neurocognitive function will be assessed by using computerized testing which can be completed via a software package developed specifically for remote administration. Measures to be administered include sustained attention (psychomotor vigilance task [PVT]), inhibition (Stroop task), and task-switching/executive function (task-switching task). Participants will receive a link to complete the neurocognitive tasks. These tasks can be completed in approximately 15-20 minutes via smartphone, laptop, or desktop computer. It should be noted that no PHI will be entered or transmitted, participants will be identified using only a participant ID.

**Training in EMA and Actigrpahy**
Participants will be trained on how to use a secure mobile app, like RealLife Exp (by LifeData), which includes ecological momentary assessment (EMA) functionality. App versions for iOS and Android are available. As indicated above, participants will also be instructed on the proper use of a research actigraph and provided such device via tracked mail (e.g., FedEx) specific registration and data coding procedures are presented below:

1. Participants will be provided an actigraph, in addition to receiving training in using the mobile app.
2. Participants will be provided a reminder card as well as contact information for the study staff, should any questions arise during the study.
3. Trained study staff will instruct participants in detail regarding each step of the study, so that participants always know what to expect.

**Insomnia Treatment-Suvorexant (FDA-Approved)**
All packaging label-insert instructions and guidelines will be followed at all times during this study.

Eligible participants will be initiated on 10mg suvorexant (or placebo), po, qhs, including instructions on dosage, expectations, and potential side effects. Following this two-day period, individuals in the treatment condition will be increased to 20mg for a 14-day active treatment period (i.e., 16 nights taking a pill).

Individuals in the control condition will continue with placebo (16 nights taking a pill). Consistent with the Model Study Agreement and UMMC IDS Pharmacy policies and procedures, robust safety measures will be followed and, study staff will contact the participant after staring Suvorexant (or placebo).

**Home Sleep Apnea Test (HSAT)**
All eligible participants will undergo HSAT to evaluate sleep-disordered breathing. HSAT will be administered by a third-party provider, CleveMed. For individuals recruited from various sleep disorders center (including those who already have an OSA diagnosis and use a CPAP device) will have previously been referred for overnight polysomnography (PSG) or HSAT as part of their routine clinical care. These individuals may not be required to complete an HSAT; with participant consent, the presence of OSA for this study will be based on clinical PSG (or HSAT) findings.

**SAMPLE SIZE AND DATA ANALYSIS**
**Sample Size**
The DISS will serve as our primary endpoint, and the power/sample size analysis is based on this primary endpoint. Our mixed model approach depends on the size of the intra class correlations (ICC) between repeated measures. Based on results from our prior research), with a sample size of 20 completers each arm and 20% attrition rate, we would have the power of 0.92 to detect a medium effect size of Cohen's d=0.5 based on simulation analysis at the $\alpha$ level of 0.05. Given the measurement sensitivity of our approach, we anticipate sufficient power to detect differences between groups for both cognitive and sleep outcomes.

Multiple corrections will be performed at the critical p-values of 0.05, 0.025, and 0.017 to show minimum and maximum sensitivities using the false discovery (FDR) method, which

is contingent upon the number of outcome measures that exceed these given critical values.

**Statistical Analysis Plan**
All statistical analyses will be performed using the intention to treat principle; all subjects enrolled and randomized will be accounted for in the final analysis in their randomized group.

*Main Analysis*
The Primary Endpoint (PE) is the between-group di[erence (SUV vs PBO) in each DISS subscale at four EMA time-of-day assessments (Morning, Midday, Afternoon, Evening) across the study period. Based on our current MISP, we anticipate high adherence with >80% completion of all assessments. We will fit linear mixed-e[ects models for each subscale, including fixed e[ects for Group, Time of Day, Day (1–16 continuous), age, and sex; and a random intercept for each participant. The Group×Time interaction will be evaluated using a 4-degree-of-freedom Wald test to determine whether suvorexant and placebo di[er at any time of day. If needed, the generalized additive model (GAM) will be used to account for the non-linear time e[ects. Covariates will be limited to age and sex at birth. Multiple imputation will be implemented for missing data; to confirm the assumptions of multiple imputation that data is missing at random, we will perform sensitivity analyses.

*Secondary Analyses*
To examine the effects of treatment with each secondary EMA endpoint including fatigue/sleepiness, positive affect, and negative affect, we will employ the model described above (i.e., same approach as used in the primary analysis). To examine the effects of treatment on 1) sleep continuity variables (sleep onset latency, wake after sleep onset, sleep efficiency, and total sleep time) as measured by sleep diary and actigraphy, 2) self-report questionnaires, and 3) cognitive testing, scores will be compared both within and between-groups adjusting for baseline values using analysis of covariance (ANCOVA). This procedure is known to maximize power.

**Post Assessment**
Post Assessment Satisfaction Survey: A brief user experience/satisfaction survey will be administered to participants following the completion of the 16-day continuous monitoring phase.

**Safety Monitoring**
If a potential participant indicates thoughts of self harm, they will administratively withdrawn from the study. These individuals will be referred to the Carruthers Clinic/Outpatient Mental Health at the UMMC-Midtown Campus, as well as advised to contact their primary care providers (or mental health professional if they have one), to call or text the national suicide hotline directly at 988 (or 800-273-8255), 911, and/or to report

to their nearest emergency room. For all withdrawals due to thoughts of self-harm, the PI will follow-up to ensure this was done, or that adequate alternative steps were taken. Participants who are withdrawn from the study will be compensated for study procedures completed.

## NEUROCOGNITIVE TESTING

### Assessments

General neurocognitive function will be assessed by using computerized testing which can be completed via a software package developed specifically for remote administration. Measures to be administered include sustained attention (psychomotor vigilance task [PVT]), inhibition (Stroop task), and task-switching/executive function (task-switching task). Participants will receive a link to complete the neurocognitive tasks. These tasks can be completed in approximately 15-20 minutes via smartphone, laptop, or desktop computer. It should be noted that no PHI will be entered or transmitted, participants will be identified using only a participant ID.

To complete the three computerized tasks (Stroop, PVT, Task-Switch), participants will be emailed the link to download each task. Study staff will instruct participants on how to download the link and open the tasks on their home computer. Once the task is open, it will prompt participants to enter their unique ID. Study staff will stay on the phone with participants for the duration of the computerized tasks to provide technical support if needed. After participants complete each computerized task, their data will be automatically sent to the researchers. Participants will have breaks in between each individual task and based on participant need.

## RECRUITMENT

### Inclusion/Exclusion Criteria

*Inclusion*

1. Age 60-85 years old.
2. Meets Diagnostic and Statistical Manual – Fifth Edition (DSM-5) diagnostic criteria for chronic insomnia disorder.

*Exclusion*

1. High risk for untreated organic sleep disorders other than insomnia (narcolepsy, periodic limb movement disorder, etc) as determined by structured clinical interview and investigator clinical judgment.
2. Current diagnosis of an untreated major medical (e.g., diabetes, heart disease) or psychiatric (e.g., bipolar disorder) disorders.
3. History of suicide attempt within past 5 years.
4. History of alcohol or substance abuse (including prescription medication abuse) within past 5 years.
5. Heavy alcohol consumption (e.g., >5 drinks per day or > 14 drinks per week).
6. Heavy caffeine use (>4 cups of coffee/day [equivalent]).
7. Current tobacco or nicotine use.

8. History of previous allergic reaction, sensitivity, or severe side effects to sedative hypnotics.
9. Moderate/strong CYP3A inhibitors.
10. Refusal to discontinue or intent to initiate non-study prescription, OTC, or other sleep aids during study period.