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Lead Researcher Name: Sara C. Mednick	
Study Title: Enhancing memory consolidation in older adults	

CLINICAL TRIAL MASTER PROTOCOL AND INVESTIGATIONAL BROCHURE INFORMATION *

	Master Protocol	Investigator Brochure: <Specify Drug/Device>	Investigator Brochure: <Specify Drug/Device>	Sponsor Consent Form Template(s)
Version #:				
Version Date:				
<input checked="" type="checkbox"/> This study is investigator-authored (investigator developed the study and is conducting the study at UCI and/or with other non-UCI sites).				

* Add columns as applicable

NON-TECHNICAL SUMMARY

Provide a brief non-technical summary or synopsis of the study that can be understood by IRB members with varied research backgrounds, including non-scientists and non-affiliated members.
<p>The purpose of this research study is to understand the neural mechanisms underlying long-term memory formation in older adults. Both sleep and memory decrease with age. We are interested in discovering whether these two biological changes are related. This study is specifically focused on understanding what are the critical components of sleep that facilitate memory formation and are they impaired in older adults. We will be using the hypnotic zolpidem, a sleep drug that has been shown to increase a specific aspect of sleep that have been shown to correlate with memory improvement in young adults. The Food and Drug Administration (FDA) have approved zolpidem for use in certain sleep disorders, specifically in the treatment of sleeplessness (i.e., insomnia). In the current study, we will examine whether zolpidem (5mg), compared with placebo, increases memory-related sleep events in older adults and test the impact of these drug-related sleep changes on post-sleep memory recall.</p> <p>This is a research study because we are using pharmacological interventions to investigate our hypotheses about memory consolidation. We are not investigating the efficacy of zolpidem to treat conditions for which the FDA has already approved it.</p>

SECTION 1: PURPOSE AND BACKGROUND OF THE RESEARCH

1. Provide the scientific or scholarly rationale for the research. Describe the relevant background information and the specific gaps in current knowledge that this study intends to address.

Sleep quality, efficiency and continuity are all known to decrease with age (Spira et al. 2012; Stranges et al. 2012). One example of this is that spindle density, amplitude and duration are reduced in older adults compared with young subjects (Guazzelli et al. 1986; Wei et al. 1999; Crowley et al. 2002). This decline has been shown to be progressive through the aging process (Principe et al. 1982; Nicolas et al. 2001). Other studies have demonstrated decreases in spectral power in the spindle frequency range (i.e., sigma activity; 12.25–14 Hz) as early as middle age (Dijk et al. 1989; Landolt et al. 1996; Carrier et al. 2001). Disruptions have also been reported for slow wave sleep (SWS), specifically decreased slow wave activity (SWA) (.5-5Hz) (Dijk et al. 1989; Van Cauter et al. 2000). Co-occurring with these sleep impairments is the cognitive hallmark of aging: a progressive deterioration of declarative memory (Alexander et al. 2012). A primary deficit in aging is a deficit in associative memory (Chalfonte et al. 1996; Mitchell et al. 2000; Naveh-Benjamin 2000). This pattern has been observed with word (Castel et al. 2003), word-spatial location (Mitchell et al. 2000), word-font (Naveh-Benjamin et al. 2003), name-face (Naveh-Benjamin et al. 2004; Miller et al. 2008) and face-face pairs (Bastin et al. 2003). Age-related impairments in declarative associative learning are correlated with reductions in hippocampal activity as well as dorsolateral prefrontal activity (Dennis 2008). Recent studies examine the possibility that these age-related memory deficits, at least in part, may be from disrupted sleep, perhaps disrupted sleep spindles (12-15 Hz electrophysiological signals during sleep associated with memory consolidation). The current research study will measure specific sleep events (i.e., sleep spindles) in older adults and examine their role in sleep-dependent memory. We will use zolpidem as a tool to increase sleep spindles in order to examine whether spindles are critically important for memory consolidation during sleep in older adults.

2. Provide relevant preliminary data (animal and/or human).

We refer to two pharmacology/sleep studies that are relevant to the proposed work. First, we conducted a dose response study of ZOL (5mg & 10mg) to determine the optimal dose of ZOL for increasing the density of Stage Two sleep spindles in young adults (Brunner et al. 1991; Feinberg et al. 2000). The nap was scheduled to occur at 8:30AM to capitalize on circadian fluctuations in REM sleep (highest in the morning). This allowed us to maximize differences in sleep stages between the drug and placebo conditions. Results from this study showed that 1) 10mg dose of zolpidem was sufficient to pharmacologically-modulated sleep spindles in youngsters, and 2) demonstrated our ability to effectively conduct a dose-response investigation using pharmacological intervention (Mednick et al. 2015).

Next, we conducted a study in young adults investigating the effect of the three pharmacological interventions (10mg ZOL, 2.5g SO, and placebo) on four memory domains: verbal, motor, perceptual and emotional memory (Mednick et al. 2015). The encoding session began at 6AM, the drug-enhanced nap occurred at 8:30AM, and retrieval occurred at 3PM on the same day. As predicted, compared with placebo, ZOL improved verbal memory, but decreased perceptual learning. No changes were found for motor learning across drug conditions. Furthermore, these performance changes were associated with changes in specific sleep features. In line with prior studies, ZOL increased sleep spindle density and decreased REM sleep, but these changes did not affect motor learning. Verbal memory performance was significantly correlated with spindle density in ZOL ($r=0.38$,

$p=0.02$), and placebo ($r=0.34$, $p=0.02$), and marginally in SO ($r=0.29$, $p=0.08$). As we had hypothesized, perceptual learning was negatively correlated with spindle density in placebo ($r=-0.41$, $p=0.02$) and SO ($r=-.50$, $p=0.006$), but not ZOL ($p>0.44$). For motor memory, a negative correlation with spindle density was found in SO ($r=-0.38$, $p=0.03$), whereas a positive correlation was found in placebo ($r=0.35$, $p=0.05$), and no correlation was found in ZOL ($p>0.45$).

In order to further probe the relationship between Stage Two spindle density and enhancements in verbal memory independent of the drug conditions, we employed Analysis of Co-Variance (ANCOVA) using verbal memory performance as the dependent variable, drug condition as the independent variable, and spindle density as the covariate. The ANCOVA showed that when spindle density is accounted for, the main effect of drug condition disappeared ($p=0.40$), while the spindle density effect on performance was highly significant ($p<0.001$). Taken together, these results indicate that the verbal memory improvements with ZOL may represent an enhancement of a normal consolidation process during sleep, since similar correlations between spindles and verbal memory were found in all three drug conditions. In addition, the experimental manipulation of spindles and associated increases in verbal memory raise the possibility that sleep spindles may represent physiological processes critical for declarative verbal memory consolidation, evinced by the significant effect of spindles on performance in the ANCOVA analysis. Importantly, we did not find improved verbal memory to be related to any other sleep features (e.g., sleep duration, sleep efficiency, etc.) whether in the placebo condition or in changes associated with either of the active drugs.

For emotional memory, as hypothesized, memory discrimination (d_a) for negative stimuli ($p=0.03$) and high arousal ($p=0.04$) was significantly better in the ZOL condition compared with placebo. No differences were found in positive, neutral or low arousal emotional memories across drug conditions. Spindle density was correlated with negative valence and high-arousal memory in SO but not placebo or ZOL. This discrepancy may be indicative of a ceiling effect in spindles in the placebo and ZOL conditions, whereas decreases in spindles in the SO condition produced a greater range of spindles, leading to a significant correlation with memory performance. This hypothesis will be tested in older adults who show decreased spindles (Guazzelli et al. 1986; Wei et al. 1999; Crowley et al. 2002). In this population, we hypothesize that correlations between spindle density and emotional memory performance will also be found. Of note, differences in discrimination were not accompanied by alterations in measures of bias (d_b). Interestingly, we did not find any changes associated with REM sleep, except a significant correlation between REM and low arousal pictures, which is somewhat consistent with our hypothesis that spindles increase consolidation of emotional memories, and REM sleep increases processing of emotional arousal (Baran et al. 2012).

These studies demonstrate the specificity of sleep-dependent memory with respect to: 1) sleep feature (i.e., increased Stage Two sleep spindle density), 2) memory domain (i.e., increased declarative associative verbal and emotional memory, compared with non-declarative motor and perceptual learning), 3) pharmacological intervention (i.e., ZOL increased memory, compared with SO and placebo). Furthermore, we demonstrate our capacity for successfully carrying forth the proposed pharmacology, sleep, and memory studies.

Limitations of the pilot study, and their solutions:

- Localization of sleep spindles: A major limitation of the pilot study was the electrode configuration (i.e., no frontal sites), which prevented accurate assessment of sleep spindles in SWS or localization of spindles (frontal versus central) (Molle et al. 2011). Therefore, our analysis was confined to Stage Two sleep spindles at central sites. The proposed studies will record from 64 electrode sites to better measure the topography of spindles in all stages of NREM sleep. This improvement will allow us to dissociate the functional significance of

spindles in Stage Two and SWS, as well as differences between local and global sleep effects on memory consolidation. Furthermore, topographical changes in spindles have been found in older adults (i.e., decreased density of frontal spindles). We will examine whether behavioral changes due to the pharmacological intervention will be associated with changes to spindles in frontal or central sites in older adults.

- Automated Spindle Detection: Two major limitations to the prior data are that all spindles were hand-counted, and spindle morphology (amplitude, frequency, and duration) was not analyzed. In the current studies we will increase sophistication of analysis techniques of sleep spindles. This will allow us to examine 1) if the memory improvements were associated with fast or slow spindles, coupling with other electrophysiological events, 2) if the drugs changed additional aspects of spindles including amplitude, frequency and duration, and 3) if those changes were associated with performance changes. These advancements will hugely impact profundity of the conclusions we can draw from our results regarding the specificity of sleep for memory consolidation.
- Task Interference: The pilot study tested four tasks in a single session, which increased task interference. The proposed study will decrease task interference by testing only two memory tasks, declarative and non-declarative memory. This will provide a precise measurement of the magnitude of the drug effects on two memory domains that rely on non-overlapping neural mechanisms.
- Older adults dosage: Although we used a 10mg dose for younger adults, we will be using a 5mg dose for older subjects as this dose is a standard dose for this age group, and the 5mg dose did modulate sigma activity in younger subjects as well.

3. Describe the purpose, specific aims or objectives. Specify the hypotheses or research questions to be studied.

SPECIFIC AIM 1. To compare the effect of zolpidem versus placebo on sleep-dependent memory in declarative and non-declarative memory task in older adults.

Hypothesis 1A: Declarative memory will be improved after a nap with zolpidem compared to placebo.

Hypothesis 1B: Non-Declarative memory will show no differences between zolpidem and placebo.

SPECIFIC AIM 2: To assess sleep stages and spindles morphology (frequency, amplitude, and duration) in a nap with zolpidem versus placebo and their correlation with performance in older adults.

Hypothesis 2A: Improved declarative memory in the zolpidem condition will be mediated by the number of spindles in the naps of older adults.

Hypothesis 2B: Non-declarative memory in older adults will be mediated by the amount of REM sleep in both drug conditions.

Hypothesis 2C: Zolpidem will increase sleep spindles, compared with placebo.

4. Describe the primary outcome variable(s), secondary outcome variables, and predictors and/or comparison groups as appropriate for the stated study objectives/specific aims.

Our primary outcomes variable will be the level of memory recall. Specifically, we will assess memory performance change between baseline recall and post-intervention recall tests. We expect that zolpidem will improve memory recall compared to placebo.

Our secondary outcome variables will be electrophysiological activity during the naps. We expect that zolpidem will increase the activity of sleep spindles compared to placebo.

Our main comparison will be the experimental conditions (1) zolpidem, and 2) placebo.

We will examine several electrophysiological markers (spindles activity: fast and slow spindle density, amplitude and frequency) as predictors of memory performance.

5. List up to ten relevant references/articles to support the rationale for the research. Do not append an extensive NIH-grant-style bibliography.

Spira, A. P., K. Covinsky, et al. (2012). "Poor sleep quality and functional decline in older women." J Am Geriatr Soc **60**(6): 1092-1098.

Spira, A. P., K. Covinsky, et al. (2012). "Objectively measured sleep quality and nursing home placement in older women." J Am Geriatr Soc **60**(7): 1237-1243.

Guazzelli, M., I. Feinberg, et al. (1986). "Sleep spindles in normal elderly: comparison with young adult patterns and relation to nocturnal awakening, cognitive function and brain atrophy." Electroencephalogr Clin Neurophysiol **63**(6): 526-539.

Wei, H. G., E. Riel, et al. (1999). "Attenuated amplitude of circadian and sleep-dependent modulation of electroencephalographic sleep spindle characteristics in elderly human subjects." Neurosci Lett **260**(1): 29-32.

Crowley, K., J. Trinder, et al. (2002). "The effects of normal aging on sleep spindle and K-complex production." Clin Neurophysiol **113**(10): 1615-1622.

Nicolas, A., D. Petit, et al. (2001). "Sleep spindle characteristics in healthy subjects of different age groups." Clin Neurophysiol **112**(3): 521-527.

Dijk, D. J., D. G. Beersma, et al. (1989). "All night spectral analysis of EEG sleep in young adult and middle-aged male subjects." Neurobiol Aging **10**(6): 677-682.

Landolt, H. P., D. J. Dijk, et al. (1996). "Effect of age on the sleep EEG: slow-wave activity and spindle frequency activity in young and middle-aged men." Brain Res **738**(2): 205-212.

Carrier, J., S. Land, et al. (2001). "The effects of age and gender on sleep EEG power spectral density in the middle years of life (ages 20-60 years old)." Psychophysiology **38**(2): 232-242.

Van Cauter, E., R. Leproult, et al. (2000). "Age-related changes in slow wave sleep and REM sleep and relationship with growth hormone and cortisol levels in healthy men." JAMA **284**(7): 861-868.

Langtry, H.D. and Benfield, P. Zolpidem. A review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential. Drugs. 1990; 40: 291–313

SECTION 2: ROLES AND EXPERTISE OF THE STUDY TEAM

1. List all research team members who will interact or intervene with human subjects or will have access to identifiable private information about human subjects. *Include additional rows for Co-researchers and Research Personnel, as needed.*
2. For each research team member, indicate all applicable research activities the individual will perform. *Finalizing informed consent is reviewing, answering/asking questions, confirming competency, as necessary, and signing/confirming the informed consent.*
3. If applicable, list the Faculty Sponsor as a Co-Researcher who will have research oversight responsibilities.

Lead Researcher:

Name and Degree: Sara C. Mednick, PhD

Position/Title and Department: Associate Professor, Department of Cognitive Sciences

Team Member will: Screen/Recruit Finalize Informed Consent

Perform Research Activities (*describe below*) Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience):

Research activities/procedures: study design, recruitment, informed consent (signing/confirming), interact with participants, answering questions, confirming eligibility, analyzing participant data, disseminating results.

Qualification: Completion of CITI and HIPAA training. Her background in sleep and memory research, with a focus on aging provides adequate support for both the sleep-dependent learning aspect of this project and the older adults research. In 2003, she received her PhD in psychology from Harvard University working with Ken Nakayama and Robert Stickgold. She moved to the Salk Institute for Biological Studies in La Jolla, CA with a three-year, National Institute of Health funded, National Research Service Award fellowship, where she trained with Geoffrey Boynton and Sean Drummond. In fall 2007, she became faculty at University of California, San Diego and was awarded a five-year, National Institute of Mental Health funded, K01 Mentored Research Scientist Award. In 2011, Dr. Mednick moved her lab to UC Riverside. Most recently, Dr. Mednick has moved her lab to UC Irvine where she continues to conduct research. Dr. Mednick has conducted studies in conjunction with numerous academic institutions, the U.S. Navy, V.A. Medical Center and private businesses. Her articles have been published in such leading scientific journals as Nature Neuroscience and The Proceedings from the National Academy of Science.

Co-Researcher:

Name and Degree: Steven C. Cramer, MD

Position/Title and Department: Professor, UCI School of Medicine

Team Member will: serve as Faculty Sponsor with research oversight responsibilities

Screen/Recruit Finalize Informed Consent

Perform Research Activities (*describe below*) Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience):

Research activities/procedures: interact with participants, answering questions, perform physical examinations, collect and interpret medical history, and prescribe Zolpidem tartrate for the use described in this study.

Qualification: Dr. Steven C. Cramer is a Professor of Neurology, Anatomy & Neurobiology, and Physical Medicine & Rehabilitation at the University of California, Irvine. He is also the Clinical Director of the Sue & Bill Gross Stem Cell Research Center and Associate Director of the UC Irvine Institute for Clinical & Translational Science at UC Irvine, and co-PI of the NIH StrokeNet. Dr. Cramer graduated with Highest Honors from University of California, Berkeley; received his medical degree from University of Southern California; did a residency in internal medicine at UCLA; and did a residency in neurology plus and a fellowship in cerebrovascular disease at Massachusetts General Hospital. He also earned a Masters Degree in Clinical Investigation from Harvard Medical School.

His research focuses on neural repair after central nervous system injury in humans, with an emphasis on stroke and recovery of movement. Treatments examined include robotic, stem cell, brain

stimulation, biologic, drug, and telehealth methods. A major emphasis is on translating new drugs and devices to reduce disability after stroke, and on individualizing therapy for each person's needs. Dr. Cramer co-edited the book "Brain Repair after Stroke" and is the author of over 250 manuscripts

Co-Researcher:

Name and Degree: Sara Stern-Nezer, MD

Position/Title and Department: Assistant Professor, UCI School of Medicine

Team Member will: serve as Faculty Sponsor with research oversight responsibilities

Screen/Recruit Finalize Informed Consent

Perform Research Activities (*describe below*) Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience):

Research activities/procedures: interact with participants, answering questions, perform physical examinations, collect and interpret medical history, and prescribe Zolpidem tartrate for the use described in this study.

Qualification: Dr. Sara Stern-Nezer is an Assistant Clinical Professor in the Department of Neurology at the UC Irvine School of Medicine. She is also a writer and editor for the Neurocritical Care Society. Dr. Stern-Nezer received her medical degree from Stanford University in 2011 and completed her residency in neurology at Stanford Health Care in 2015. She also holds an MPH, specializing in epidemiology and biostatistics, from UC Berkeley.

Co-Researcher:

Name and Degree: Paola Malerba, PhD

Position/Title and Department: Faculty, Department of Cognitive Science

Team Member will: serve as Faculty Sponsor with research oversight responsibilities

Screen/Recruit Finalize Informed Consent

Perform Research Activities (*describe below*) Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience):

Research activities/procedures: study design, recruitment, interact with participants, answering questions, confirming eligibility, analyzing participant data, disseminating results.

Qualification: Paola obtained a PhD in Mathematics at Boston University in 2010 and she applies mathematical analysis and modeling to the understanding of brain rhythms. Within SaC Lab, she has studied the spatio-temporal patterns of slow oscillations on the electrode manifold. Using k-clustering and relative detection probability we have found that slow oscillations were clustered in three types: Global, Local or Frontal depending on their footprint on the electrode manifold during a time window. Global slow oscillations showed the strongest relationship with sleep spindles, both in amplitude and probability of detection. This research is laying the foundation for modeling work on the spatio-temporal occurrence of slow oscillations and spindles on the electrode manifold, to study how closed-loop stimulation during sleep changes sleep waves and possibly memory performance.

Co-Researcher:

Name and Degree: Trisha Maris (Hufnagel), B. Pharm

Position/Title and Department: Investigation Drug Pharmacist/Specialist

Team Member will: serve as Faculty Sponsor with research oversight responsibilities

Screen/Recruit Finalize Informed Consent

Perform Research Activities (*describe below*) Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience):

Research activities/procedures: provide the placebo and perform drug randomization

Qualification: Maris received her B.S. in General Chemistry from the University of California, Los Angeles and her B. Pharm in Pharmacy from Ohio State University. Before accepting the role of investigational drug pharmacist at UC Irvine Health in 2015, she excelled in her role as outpatient pharmacist lead for 12 years at UC Irvine Health (2005-2017).

Co-Researcher:

Name and Degree: Negin Sattari Barabadi, M.A.

Position/Title and Department: Graduate Student, Department of Cognitive Sciences

Team Member will: serve as Faculty Sponsor with research oversight responsibilities

Screen/Recruit Finalize Informed Consent

Perform Research Activities (*describe below*) Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience):

Research activities/procedures: study design, recruitment, interact with participants, answering questions, confirming eligibility, analyzing participant data, disseminating results.

Qualification: Completion of CITI and HIPAA training. She received her B.S in Computer Science from Iran and her MA in psychology from University of California, Riverside. Negin's research interests entail in the effect of sex hormones on sleep-related memory consolidation and learning. Negin also studied the effect of napping among older adults during her master's thesis.

Co-Researcher:

Name and Degree: Pin-Chun Chen, BS

Position/Title and Department: Graduate Student, Department of Cognitive Sciences

Team Member will: Screen/Recruit Finalize Informed Consent

Perform Research Activities (*describe below*) Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience):

Research activities/procedures: recruitment, interact with participants, answering questions, confirming eligibility, analyzing participant data.

Qualification: Completion of CITI and HIPAA training and has more than 3 years experience interacting with subjects and running a human subject study.

Co-Researcher:

Name and Degree: Frida Corona, BS

Position/Title and Department: Graduate Student, Department of Cognitive Sciences

Team Member will: Screen/Recruit Finalize Informed Consent

Perform Research Activities (*describe below*) Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience):

Research activities/procedures: recruitment, interact with participants, answering questions, confirming eligibility, analyzing participant data.

Qualification: Completion of CITI and HIPAA training and has more than 3 years experience interacting with subjects and running a human subject study.

Co-Researcher:

Name and Degree: Tenzin Tselha, M.S.

Position/Title and Department: Graduate Student, Department of Cognitive Sciences

Team Member will: Screen/Recruit Finalize Informed Consent

Perform Research Activities (*describe below*) Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience):

Research activities/procedures: recruitment, interact with participants, answering questions, confirming eligibility, analyzing participant data.

Qualification: Completion of CITI and HIPAA training and has more than 4 years' experience interacting with subjects and running a human subject study.

Research Personnel:

Name and Degree: Lexus Hernandez, BA

Position/Title and Department: Lab Technician, Department of Cognitive Sciences

Team Member will: Screen/Recruit Finalize Informed Consent

Perform Research Activities (*describe below*) Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience):

Research activities/procedures: recruitment, interact with participants, answering questions, confirming eligibility, analyzing participant data.

Qualification: Completion of CITI and HIPAA training and has more than 3 years experience interacting with subjects and running a human subject study.

SECTION 3: SUBJECT POPULATION(S) (INDIVIDUALS/RECORDS/SPECIMENS)

A. Subjects To Be Enrolled on this UCI protocol (Persons/Records/Biospecimens)

1. Complete the table of subject enrollments below. *Include additional rows for subject category/group, as needed.*
2. If the study involves the use of existing records or biological specimens, specify the maximum number to be reviewed/collected and the number needed to address the research question.

Category/Group (e.g., adults, controls, parents, children)	Age Range (e.g., 7-12, 13-17, adults)	Maximum Number to be Consented or Reviewed/Collected (include withdrawals and screen failures)	Number Expected to Complete the Study or Needed to Address the Research Question
Adults	60-75	60	45
Total: 60			

B. Overall Study Sample Size

If this is a multi-site study, provide the total number of subjects to be enrolled from all sites.

Not applicable: This study will only take place at UCI, and does not involve other sites.

Total number of subjects across all sites: <Type here>

C. Eligibility Criteria

1. Identify the criteria for inclusion and exclusion.

Subjects will be screened for neurological disorders (e.g., Parkinson’s disease, dementia, stroke) using several perceptual and cognitive tests (e.g., Digit Span Forward, Digit Span Backward). Inclusion criteria include ages 60-75, healthy with normal to corrected normal vision, at least 12 years of education and having a non-polarized chronotype (defined as a Horne-Ostberg Morningness-Eveningness Questionnaire score between 9 to 24), and prior experience with zolpidem.

Exclusionary criteria include: a) having a sleep disorder (reported or detected on the questionnaires); b) any personal or immediate family (i.e., first degree relative) history of diagnosed significant psychopathology; c) personal history of head injury with loss of consciousness greater than 2 minutes or seizures; d) history of substance dependence; e) current use of any medications that could effect sleep and/or cognition; f) any cardiac, respiratory or other medical condition which may affect cerebral metabolism (Subjects with a heart rate lower than 50 beats per minute or with blood pressure readings less than 90 mmHg (systolic) or 60 mmHg (diastolic) will be excluded) ; g) dementia using Mini Mental Status exam questionnaire I) Given the nature of the stimuli and presentation, anyone with non-correctable vision and audition impairments will also be excluded.

The contraindications for **zolpidem** include: alcohol intoxication, attention deficit disorder with hyperactivity, history of parasomnias (complex/abnormal behaviors during sleep), severe chronic obstructed lung disease, liver problems, hangover, loss of memory, hallucinations, having thoughts of

suicide. Prior to subsequent study visits, participants will be asked to review their responses on the screening form and to verify that none of the responses have changed.

Subjects will be screened for inclusion and exclusion criteria with an approved screening questionnaire.

2. If eligibility is based on age, gender, pregnancy/childbearing potential, social/ethnic group, or language spoken (e.g., English Speakers only), provide a scientific rationale.

Not applicable: Subject eligibility is not based on these factors.

We propose to study a healthy older adult population (60-75). Physical and psychological health is important for this study in order to avoid adverse effects on sleep. An education requirement of at least 12 years completed will be imposed, as education may affect performance on the cognitive tasks. We will be studying English speakers only, as second languages are processed differently than primary languages in the brain. We propose a large sample size in order to collect enough data to analyze individual differences in sleep-dependent learning for different memory domains. The PI's previous studies report about a 25% percent attrition rate.

SECTION 4: RECRUITMENT METHODS

Check any of the following methods that will be used to recruit subjects for this study:

This study involves no direct contact with subjects (i.e., use of existing records, charts, specimens).

Specify database or IRB-approved protocol number (HS#), if applicable: <Type here>

Advertisements, flyers, brochures, email, Facebook, and/or other media.

Specify where recruitment materials will be posted: Flyers will be posted at retirement communities, senior centers, senior living communities, UCI campus, and other areas where there is a large presence of older adults. Advertisements will also be posted on Craigslist and Facebook (via groups and on personal pages of research personnel).

If subjects will be recruited by mail, e-mail, or phone, specify how their contact information will be obtained:

We will also use a direct mailing company, Direct Connection, that will send the attached recruitment letter to approximately 8000 older adults in the Irvine community.

We will submit a mail list request to the ZotMail team in order to email our approved online script to all UCI faculty members and employees. The ZotMail team will send out the recruitment emails. If the faculty members/ employees are interested in this study, they will contact the study team. The study team will not access the list of emails, so we will not compromise their privacy/ confidentiality.



Submit recruitment materials for IRB approval.

The study will be listed on [Clinicaltrials.gov](https://clinicaltrials.gov). *All clinical research must be registered.*

The study will be listed on the [UC Irvine Health Clinical Trials](#) web page.



Submit the UCIMC Standard Research Recruitment Advertisement for IRB approval.

] The UCI Social Sciences Human Subjects Lab/Sona Systems will be used.



Submit the Social Science Human Subject Pool Recruitment Advertisement for IRB approval.

] Referral from colleagues

- Study team will provide colleagues with UCI IRB-approved recruitment materials for distribution to potential subjects (e.g., recruitment flyer, introductory letter);
- An IRB-approved recruitment letter will be sent by the treating physician. The letter will be signed by the treating physician and sent to his/her patients to inform them about how to contact study team members; and/or
- Colleagues obtain permission from interested patient to release contact information to researchers.
- Study team does not have access to patient names and addresses for mailing.
- If colleagues will screen their patients' medical records to determine subject eligibility and approach patients directly about study participation: *Complete Appendix T to request a partial waiver of HIPAA Authorization.*



Submit recruitment materials for IRB approval.

] Study team will contact potential subjects who *have given prior permission to be contacted* for research studies.

Specify when and how these individuals granted permission for future contact: Recruitment will also occur through the Consent-to-Contact registry (C2C). The study team will request the contact information from subjects who have submitted data to the C2C registry and who have given permission to be contacted regarding participation in research studies.

Specify database or IRB-approved protocol number (HS#): 2015-2494

] Study team members will approach their own patients, students, employees for participation in the study.

] Study team will screen UCIMC medical records to which they have access to determine subject eligibility. The patients' physicians will approach patients directly about study participation.



Complete Appendix T to request a partial waiver of HIPAA Authorization.

] Other Recruitment Methods: <Indicate the recruitment method(s) here>

SECTION 5: INFORMED CONSENT PROCESS

A. Methods of Informed Consent

1. Indicate all applicable informed consent methods for this study. *Submit the consent/assent document(s) with your e-IRB Application (e.g., Study Information Sheet, Recruitment script, Consent Form, etc.). Only IRB approved consent forms (containing the IRB approval footer) may be used to consent human subjects at UCI.*

Written (signed) informed consent will be obtained from subjects. Signed informed consent, parental permission, and/or child assent will be obtained from subjects, as applicable.

Requesting a waiver of written (signed) informed consent. Signed consent will not be obtained; consent will be obtained verbally or via the web. Informed consent, parental permission and/or child assent will be obtained from subjects, as applicable.



Complete Appendix P.

Requesting to seek surrogate consent from a legally authorized individual. Surrogate consent may be considered only in research studies relating to the cognitive impairment, lack of capacity or serious or life-threatening disease and conditions of the research subjects.



Complete Appendix E.

Requesting a waiver of informed consent. (i.e., consent will not be obtained). *Skip to Section 5.B.*



Complete Appendix O.

2. Indicate where the consent process will take place.

In a private room

In a waiting room

In an open unit

In a group setting

The internet

In public setting

Over the phone

Other (specify): <Type here>

3. Specify how the research team will assure that subjects have sufficient time to consider whether to participate in the research.

Subjects will be allowed to take home the unsigned consent form for review prior to signing it.

Subjects will be allowed <Type here> hours to consider whether to consent.

Other (specify): Eligible participants will be contacted via email and/or telephone to see if they are still interested in participating. If they still are, the research team will set up an appointment to meet with them to go over the consent form and other approved documents that are study-related. This meeting will take place at the UC Irvine Institute for Clinical and Translational Science (ICTS), subjects will be provided with free parking. During this appointment, eligible participants will be given 45 minutes (if needed, they will be given additional time) to read over the consent form and jot down any questions or concerns they may have. Afterwards, a member from the research team will go through all sections of the consent form with the individual and answer any questions they may have along the way. Once all sections are discussed and all questions have been answered, subjects will have the opportunity to decide if they want to participate in the study or not. If they agree to participate, the member from the research team will ask them to sign two copies of the consent form (one copy will be given to the participant for their own records) and the research team member will also sign both copies. If they are unsure if they want to participate, the research team member will give them an unsigned copy of the consent form to take home and will follow up with them in 1-2 days. If the subject decides not to participate in the study, they will be thanked for volunteering their time to come in for an

appointment and an unsigned consent form will be given for their records. Additionally, there will be no future communication initiated from the research team.

4. If children are enrolled in this study, describe the parental permission process and the child assent process.

Not applicable: Children are not enrolled in this study.
<Type here>

5. Some subjects may be vulnerable to coercion or undue influence, such as those who are economically or educationally disadvantaged, mentally disabled, or students (undergraduate, graduate, and medical students) and employees of UCI (administrative, clerical, nursing, lab technicians, post-doctoral fellows and house staff, etc.), describe the procedures to ensure the voluntary participation of these individuals.

Not applicable: Subjects are not vulnerable to coercion or undue influence.
 Other (specify): <Type here>

B. Health Insurance Portability and Accountability Act (HIPAA) Authorization

Indicate all applicable HIPAA authorization methods for this study.

Not applicable: Study does not involve the creation, use, or disclosure of Protected or Personal Health Information (PHI).

Requesting a Total waiver of HIPAA Authorization. HIPAA authorization will not be obtained at all for the study.



Complete Appendix T.

Requesting a Partial waiver of HIPAA Authorization. HIPAA authorization will not be obtained for screening/recruitment purposes. However, written (signed) HIPAA research authorization is obtained for further access to personal health information.



Complete Appendix T.

Written (signed) HIPAA Research Authorization will be obtained from subjects. Signed authorization, parental authorization, and/or child assent will be obtained from subjects, as applicable.



Complete the HIPAA Research Authorization form.

C. **Methods of Informed Consent for non-English Speakers**

1. Indicate the applicable informed consent method for non-English speakers.

Not applicable: Only individuals who can read and speak English are eligible for this study. *Scientific justification must be provided in Section 3.C.2.*

The English version of the consent form will be translated into appropriate languages for non-English speaking subjects once IRB approval is granted. *The translated consent form must be submitted to the IRB for review prior to use with human subjects. Only IRB approved consent forms (containing the IRB approval stamp) may be used to consent human subjects at UCI.*

Requesting a short form consent process.



Complete Appendix Q.

The short form process will be used for the following occasional and unexpected languages:

All non-English languages

All non-English languages except Spanish

Other languages (specify): <Type here>

2. Explain how non-English speaking subjects will be consented in their language and who will be responsible for interpreting and facilitating the informed consent discussion for the non-English speaking subjects.

At least one member of the study team is fluent in the language that will be used for communication, and that study team member(s) will be available during emergencies.



For all members of the study team responsible for obtaining informed consent from non-English speaking subjects, provide their qualifications to serve in this capacity (i.e. language fluency) in Section 2.

The study team has 24-hour access to a translation service with sufficient medical expertise to discuss the research in this study.

Other (explain): <Type here>

SECTION 6: RESEARCH METHODOLOGY/STUDY PROCEDURES

A. Study Location

Specify where the research procedures will take place (e.g. UCI Douglas Hospital – Cardiac Care Unit, UCI Main Campus Hewitt Hall, UCI Health – Pavilion II, UCI Family Health Center, Anaheim, Irvine High School).



If research activities will also be conducted at non-UCI locations (e.g., educational institutions, businesses, organizations, etc.), Complete Appendix A. Letters of Permission or other documentation may be required (e.g. Off-site Research Agreements or IRB Authorization Agreements).

The majority of all study appointments will be held at the UC Irvine Institute for Clinical and Translational Science (ICTS), the UCI Main Campus location and the UCI Orange Medical Center location. We will put both locations on the consent form due to availability changing on a weekly basis. On occasion, when the ICTS is closed, we will hold our non-medical screening appointments at the Sleep and Cognition (SaC) lab in the Social Science Research building, room 380. Subjects who remain eligible after this appointment will be scheduled for a medical history and physical appointment at the ICTS.

B. Study Design

1. Include an explanation of the study design (e.g., randomized placebo-controlled, cross-over, cross-sectional, longitudinal, etc.) and, if appropriate, describe stratification/ randomization/blinding scheme.

The research involves oral administration of zolpidem (ZOL) or placebo during sleep with EEG recording. A randomized, crossover design under double-blind conditions will be utilized. This study will employ a within-subject, crossover design, in which every subject experiences each of the following study conditions: Nap/5mg, Nap/placebo, plus an adaptation nap at the ICTS to be scheduled one week prior to the first experimental day. One condition will be tested per week, with condition order counterbalanced. The pharmacist will ensure that subjects who initially receive Zolpidem will get the placebo pill a week after and vice versa. Thus, each subject will have 2 visits (plus an adaptation nap), each separated by 5-7 days (although this may be extended based on participant availability) to ensure that the drug is completely eliminated from the body. The order of drug conditions will be randomized and counterbalanced. During the experimental phase, each drug condition will include one day in the sleep lab, two encoding test sessions, and one retrieval test session. Multiple subjects will be in the experimental phase concurrently, and multiple subjects will be tested on each day.

2. Provide precise definitions of the study endpoints and criteria for evaluation; if the primary outcomes are derived from several measurements (i.e., composite variables) or if endpoints are based composite variables, then describe precisely how the composite variables are derived.

Study endpoints will be the completion of data collection with respect of a priori decision on sample size.

C. Research Procedures

1. Provide a detailed chronological description of all research procedures.

Participants will call or email the lab if they are interested in participating in the study. Eligibility determination will occur in three steps. Initial screening of subjects will take place with screening survey. Those who are not excluded for obvious violations of eligibility criteria will then be invited to the ICTS for an in-person interview during which informed consent will be thoroughly reviewed with the subject and they will be required express their understanding of the protocol and what is being asked of them at various places throughout the informed consent.

Eligible subjects will then return for an orientation at the UCI ICTS. At orientation, subjects will experience: 1) signing of consent form, 2) a Structured Clinical Interview for DSM disorders (SCID-5) conducted by a trained research assistant, 3) an EEG-monitored adaptation nap opportunity, 4) signing of the Health Insurance Portability and Accountability (HIPAA) form to ensure ICTS can share eligibility discrepancies with appropriate research personnel, 5) cognitive testing: Digit Span Forward/Backward, Stroop task, and the Symbol Digit task.

Subjects who remain eligible after this appointment will be scheduled for a final screening appointment, which will include a medical history and physical. During this appointment, blood pressure and heart rate will be measured. Urine toxicology screens will also be taken during this

appointment and a complete drug panel will be run by the ICTS. Participants with a positive drug screen will be excluded from participation. Following the medical history and physical appointment, subjects will be invited to participate in the full study.

Prior to leaving the medical appointment, subjects will be given an actigraph, a wrist activity monitor the size of a watch that measures movement. Participants will also be asked to complete a sleep diary for 7 nights prior to their in-lab visits. The sleep diary is available via a secure online website link provided to the participant. However, paper copies of the sleep diary will be available upon request from the participant.

Participants will be asked to abstain from caffeine and alcohol 48 hours prior to and including each study session.

Subjects will be instructed to spend 8 hours time-in-bed (10pm-6am) the night before each study day. All subjects will remain in the lab for the entirety of the visit day (7am-9pm). For each visit, subjects will report to the UCI ICTS at 6:30am. From 7am-8:30am (test session 1) subjects will complete two cognitive tasks (word-pair associates and finger tapping task) described below. Subjects will have electrodes attached from 8:30am-9am, and will be provided a snack between 9am-9:30am. At 9:30am, subjects will be taken to their bed, lie down and be given a pill (ZOL (5mg) or placebo) in a double-blind fashion. We will be using 5mg in older adults, which is generally well tolerated in older adults (Langtry & Benfield, 1990). After ingesting the pill, subjects will be continuously monitored by study staff and allowed to nap for 2 hours. The two hour nap opportunity is being used in this study, contrary to the specification for treatment of insomnia suggested on the package insert suggesting a 6 hour time in bed. The reason for this discrepancy is that this is not a clinical treatment for insomnia but rather an investigation of the drug effects on the brain activity during a single cycle of sleep (approximately 90-100minutes of sleep). Following their nap, subjects are allowed to watch TV, listen to music, read, etc. but must not nap or consume any caffeine or alcohol during this time. Lunch will be served, and subjects will be offered opportunities to stretch their legs accompanied by a research assistant. Subjects will have their blood pressure taken multiple times during their down time in the lab to make sure their blood pressure is not below or above the normal range. Following their observation, subjects will complete the word-pair associates task and finger tapping task from 7pm-8:30pm (test session 2). At the end of the day, participants will go through gait testing to ensure that they are not feeling any residual effects from the medication. If participants are not experiencing adverse effects of drug, participants will be allowed to leave the lab. If participants report experiencing any adverse events or do not pass the gait examinations, they will remain in lab until symptom free. In addition, if during the experimental day the subject experiences an adverse event such as confusion, amnesia, ataxia, we will immediately terminate testing, and the on call doctor will be called. If no improvement is evident after a period of time set by the on-call doctor, we will call 911.

Subjects will be asked to have someone drive them, or we will provide taxi service between the lab and home.

2. Describe the duration of a subject's participation in the study. If there are sub-studies, include duration of participation in each sub-study.

Participants will be involved for about three weeks, but this time frame may be extended for scheduling purposes. Exact scheduling will depend on each individual subject's personal schedule and availability.

Each experimental day will require the subject to be available between 6:30AM and 9PM. Testing will occur between 7-8:30AM, and 7PM and 8:30PM, the nap will occur between 9:30AM and 11:30AM.

3. List data collection instruments (e.g., measures, questionnaires, interview questions, observational tool, etc.).



Investigator-authored, non-standardized, or un-validated measures must be submitted for review.

Polysomnography: All in-lab sleep periods are PSG-recorded and include standard electroencephalographic (EEG), electro-oculographic (EOG), electromyographic (EMG), and electrocardiographic (ECG) measures for recording sleep. Electroencephalographic (EEG) sleep recording: The EASYCAP is comfortable to wear during wake and sleep recordings. Subjects will have their nap sleep recorded electroencephalographically with standard electroencephalographic (EEG), electro-oculographic (EOG), electromyographic (EMG), and electrocardiographic (ECG) measures. 32 electrodes will be placed over the scalp using a conductive paste, after preparing the scalp area by light abrasion to reduce the scalp impedance. In this study, we will use EASYCAP GmbH from Brain Products with 32 sintered Ag/AgCl sensors, for their high signal quality and low steady electrode potentials. During wake the recorded event related potentials (ERPs) will be sampled at the rate of 500 Hz and amplified using BrainAmp amplifier. The sampled ERPs will be transferred to the acquisition computer using USB2 adapter (BUA) for monitoring while recording EEG/ERPs and for further off-line analysis. The ERP signals will be recorded using an average reference (on-line reference) and will be re-referenced to the average of the left and right mastoids for off-line analysis. Eye movements and other artifacts will be removed manually from each data set. Naps will be conducted in the Psychology Building, rooms 2124A-E. Subjects will be monitored and their sleep minutes counted to ensure consistent sleep times for each group.

We will analyze minutes and percent in each sleep stage (i.e. Stage One, Stage Two, Slow Wave Sleep, and REM); total sleep time, wake after sleep onset, sleep latency, REM latency, and sleep efficiency; power spectral analysis of specific frequency bands associated with sleep (delta 0.3-4 Hz, theta 4-8 Hz, alpha 8-12 Hz, sigma 12-16 Hz); REM density (i.e., the frequency of rapid eye movements during REM sleep); phasic and tonic REM sleep (Ernis et al., 2010).

EEG Electrode Maintenance: We use the standard procedure for cleaning and disinfecting our EEG electrodes that has been approved by the Board of Trustees of the American Society of Electroneurodiagnostic Technologists (ASET) and the Society for Psychophysiological Research's (SPR) Ad Hoc Committee who compiled a report on guidelines for reducing the risk of disease transmission in the psychophysiological laboratory (Putman et al., 1992).

The potential risk of infection for the surface electrodes used in the current proposal is of importance, as the electrodes come in contact with skin that has been purposely abraded with cleaning solution in order to reduce impedance levels. Importantly, little abrasion is needed to achieve optimal levels of impedance, and all products used to abrade the skin are sterile.

The first step in handling the EEG equipment and contacting research participants is that all technicians wash hands before and after working with the research participant. Technicians wear

sterile, latex-free, surgical gloves during skin abrasion and cleaning, as well as during electrode preparation, application and removal. Gloves are disposed of after every use.

Cleaning is accomplished before disinfection. We clean with warm water, and scrub gently with a soft brush. The electrodes are then dried with a soft cotton cloth. We disinfect the electrodes by soaking them for 15 minutes in Sekusept-Plus solution, a germicide used extensively in EEG labs and hospitals Glucoprotamin. This solution has broad spectrum microbial efficacy, is fast-acting and biodegradable. After disinfecting, the electrodes are rinsed using filtered water (i.e., drinking water quality). For drying, the electrodes are padded dry with a clean towel and then left to air dry. Any defective electrodes will be discarded.

Cognitive Tasks

Word Pair Associates Task: In this task, subjects are visually presented with nonsense word pairs (e.g. table-disboon) to maximize the novel episodic and associative declarative memory demands of the task and minimize the semantic demands of the task (Otten et al., 2007). The second word is presented under the first word to avoid lateralization effects. Subjects are presented with 48 word-pairs in the morning session. Recognition tests are assessed both immediately following the encoding session, and delayed during retrieval sessions 1 and session 2. At test, participants are presented with 40 intact word-pairs (minus the first and last four pairs to avoid primacy and recency effects), as well as 40 rearranged word-pairs (foils). Each word pair is displayed for 3000 ms followed by a response prompt asking for a discrimination of whether the two words were shown together as a pair in the study list. The discrimination is based on a standard 6-point confidence scale.

Finger Tapping Task (FTT): In this task there will be 12 blocks (each 1 minute) in which participants will be asked to type a number sequence of 5 digits (e.g. 32451) as quickly and as accurately as possible. Participants will type for 30 seconds prior to having a 30 second rest period.

Digit span Forward/Backward: In this task subjects are presented with a list of items and will be asked to repeat that with the same order or in reverse order. Items may include words, numbers or letters.

Stroop task: In this task subjects are presented with the name of a color that is printed in a color not denoted by the name and they will be asked to name the color.

Symbol digit: In this task subjects are presented with a list of digit-symbol pairs followed by a list of digits and will be asked to type the corresponding symbol under each digit as fast as possible.

Survey testing: Participants may be asked to complete a variety of questionnaires throughout the study. Questionnaires administered will include: a) the Epworth Sleepiness Scale; b) Horne-Ostberg Morningness-Eveningness Questionnaire; c) Karolinska Sleepiness Scale; d) the Pittsburgh Sleep Quality Index; e) post-nap questionnaire; f) sleep inertia questionnaire; g) Spielberger State-Trait Anxiety Index; and h) the CES-D i) STOP BANG Questionnaire. Questionnaires will be administered online via a secure survey website (www.surveymonkey.com), and paper copies will be available in the lab in the event of loss of internet connection.

Electroencephalographic (EEG) sleep recording: For sessions involving EEG recording, electrode caps will be attached following the EEG procedures described below. Participants in the nap condition will be allowed a two-hour nap opportunity to obtain either 60 or 90 minutes of total sleep time.

The **SCID-5** interview is utilized as a screening tool and participant answers will be reviewed to determine their general psychological and psychiatric well being. Participant answers will only be used to determine eligibility for the current study. The SCID-5 will not be used as a formal diagnostic tool in the current protocol.

Debriefing: At the end of the study, after all visits have been completed, subjects will be given the opportunity to ask any questions about the study and will be financially compensated.

D. UCIMC Supplementary Clinical Services

If a UCIMC clinical unit/department (e.g., phlebotomy for blood draws, pharmacy for dispensing study drug(s), radiation services for X-rays, MRIs, CT scans, and Neurology for lumbar punctures) will perform research-related procedures:

1. List the research procedure (e.g. lumbar puncture, MRI, CT Scan), and
2. Identify the unit/department that will perform the procedure.

Not applicable: This study does not involve the services of a UCIMC clinical unit/department.

1. This study will require drug dispensing and study blind set-up and maintenance by TRISHA MARIS (Hufnagel), Pharmacist Specialist at the Investigational Drug Services Pharmacy of UC Irvine Health (address: 101 The City Drive, Building #3, Room #211, Orange, CA 92868, Tel: 714-456-7833/714-456-5911, thufnage@uci.edu)

E. Privacy

Privacy is about the subject's ability to control how much others see, touch, or collect information about the subject. Indicate all of the following methods that will be used to assure subject privacy. *Violations of privacy include accessing a subject's private information without consent, asking personal sensitive information in a public setting, being audio recorded or photographed without consent.*

Research procedures (including recruitment) are conducted in a private room.

Use of drapes or other barriers for subjects who are required to disrobe.

Only sensitive information directly related to the research is collected about subjects.

When information is collected from internet sources, the internet site's privacy statement will be reviewed and followed.



Provide a copy of the Data Use Policy to the IRB.

Other (specify): <Type here>

F. Use of Existing Biological Specimens and/or Existing Information/Data

1. For studies that involve use of existing (i.e. on the shelf; currently available) specimens:
 - a. Indicate the source of the specimens and whether the specimens were originally collected for research purposes.
 - b. Explain how the existing specimens will be obtained.

Not applicable: This study does not involve use of existing biological specimens.

Source: Indicate all that apply:

UCI/UCIMC

Originally collected for research purposes: YES; UCI IRB number (i.e. HS#): <Type here>

NO; explain: <Type here>

UCIMC Pathology Biorepository will provide specimens.

Non-UCI Entity; specify: <Type here>

Originally collected for research purposes: YES



Submit a copy of the IRB Approval Notice and Consent Form for the original collection.

NO; explain: <Type here>

Other; explain: <Type here>

2. For studies that involve use of existing (i.e. on the shelf; currently available) clinical data:
- Specify the source of the clinical data.
 - Explain how the study team will access the clinical data. *Access to UCI Medical Center medical records for research purposes outside the capacity of the Honest Broker Services, such as access to physician notes, must be obtained from the Health Information Management Services.*



For investigator initiated/authored studies only, submit a data abstraction sheet that includes a complete list of data elements/information that will be collected from (existing) records or submit the case report form (CRF; eCRF).

Not applicable: This study does not involve use of existing clinical data. *Skip to Section 6.G.*

Source: Indicate all that apply:

UCI/UCIMC.

non-UCI Entity; specify: <Type here>

How Obtained: Indicate all that apply:

The study team will request specific patient information/data from UCIMC Health Information Management Services.

The study team will review their patients' records and abstract data directly from those records.

The study team will request specific patient information/data from UCI Health Honest Broker Services. Describe the following:

Cohort selection criteria (e.g., use the available Clinical Terms from the Cohort Discovery Tool such as Demographics: Gender, Diagnoses: Asthma, Procedures: Operations on digestive system): <Type here>

Expected cohort size/patient count: <Type here>

Cohort attributes or data elements (e.g., lab test values, medication, etc.): <Type here>

Other; explain: <Type here>

3. For studies that involve use of existing (i.e. on the shelf; currently available) clinical data, specify the time frame of the clinical data to be accessed (e.g. records from January 2002 to initial IRB approval).

We will review subjects' records immediately after the physician completes a medical history and physical form.

G. Collection of Photographs, or Audio/Video Recording

1. Describe all procedures involving the use and/or collection of photographs, or audio/video recording.

Not applicable: This study does not involve photographs or audio/video recording. *Skip to Section 6.H.*

<Type here>

2. Specify if photographs or audio/video recording will include subject identifiable information (e.g., name, facial image). If so, indicate which identifiers will be collected.

<Type here>

3. Explain whether the photographs or audio/video recording will be included in subsequent presentations and/or publications and, if so, whether subject identifiers will be included.

<Type here>

H. Sharing Results with Subjects

<p>1. Describe whether individual results (results of investigational diagnostic tests, genetic tests, or incidental findings) will be shared with subject or others (e.g., the subject's primary care physician). <i>Only tests ordered by a physician and conducted in a CLIA certified lab may be shared.</i></p> <p>2. Explain what information will be shared and how the results will be shared.</p>
<p><input checked="" type="checkbox"/> Not applicable: Individual results will not be shared with subjects. <Type here></p>
<p>3. Describe whether overall study results will be shared with subjects.</p> <p>4. Explain how results will be shared.</p>
<p><input checked="" type="checkbox"/> Not applicable: Final study results will not be shared with subjects. <Type here></p>

I. Statistical Considerations (*This section is required for Investigator-Authored Research*)

<p>1. Statistical Analysis Plan: Describe the statistical method(s) for the stated specific aims and hypotheses.</p> <p><i>The Biostatistics, Epidemiology and Research Design (BERD) Unit under the Institute for Clinical and Translational Science (ICTS) can assist in developing power and sample size calculation. Visit: http://www.icts.uci.edu/services/berd%20request.php for a consultation.</i></p> <p><i>Your analysis plans should match the stated study specific aims and hypotheses in Section 1.</i></p>
<p><input type="checkbox"/> Not applicable: A statistical analysis plan is not appropriate for this qualitative study design. Plan for assessing study results: <Type here> <i>Skip to Section 7.</i></p> <p>We hypothesize that older adults will show a dose-dependent increase in declarative associative verbal memory compared with placebo. In addition, we hypothesize that spindle density will increase in a dose-dependent manner, compared with placebo, and that performance will be correlated with spindle density.</p> <p>In the experimental nap, we will predict a dose-dependent increase in sleep spindle density in ZOL, compared with placebo. We predict that spindle density will be modulated equally for fast and slow frequency spindles, and no differences in spindle amplitude, frequency, or duration between drug conditions. However, we predict that declarative verbal memory, but not motor learning, will be correlated with the density of fast frequency spindles, but not slow frequency spindles. That is, ZOL will increase the amount of normally occurring fast and slow spindles, not affect spindle morphology, and only fast spindles will correlate with performance. We will examine spindles in Stage 2 and SWS separately, and NREM (Stage 2 + SWS) sleep combined. We expect Stage 2 spindles and sigma power to be topographically dominant over the central electrodes and that spindles and sigma power in deeper NREM sleep will be concentrated in frontal electrode sites. As a negative control for spindles, we will examine slow oscillations and expect no differences across drug conditions. For sleep stages, we expect that there will be increased SWS in the ZOL condition compared with placebo. Furthermore, we predict dose-dependent decreases in REM sleep with ZOL, compared with placebo. ZOL will increase sleep efficiency by decreasing wake after sleep onset and sleep latency, compared with placebo. No differences between conditions in Stage 1, Stage 2 sleep, or Total Sleep Time (which will be held constant) are predicted.</p>

2. Describe the primary statistical method(s) that will be used to analyze the primary outcome(s) or endpoints.
We will employed repeated-measures anovas to examine differences in performance across drug conditions. Linear and hierarchical regressions will be used to assess the relationship between electrophysiological variables and memory performances, controlling for confounding factors such as age, BMI, anxiety and depression levels.
3. Describe the secondary statistical method(s) that will be used to analyze the secondary outcome(s) or endpoints.
4. If appropriate describe secondary or post hoc analyses of primary outcome(s) or other exploratory analysis.
5. Sample Size Determination: Explain how the overall target sample size was determined (e.g., power analysis; precision estimation), providing justification of the effect size for the primary outcome based on preliminary data, current knowledge/literature and/or cost consideration; if appropriate, provide sample size justification for secondary outcomes. Power analysis should (at least) match the primary outcome/endpoint.
Power Analyses: We have conducted power tests (Keppel, 1991) on the results obtained from our preliminary work as well as findings from the literature. For example, the significant main effect of zolpidem on memory (a within-subjects design with 30 subjects) had 95% power with an eta squared effect size of 0.15 (us-ing $\alpha=.05$). For older adults, a recent paper examining the effects of sleep on word pair learning in healthy older adults (a within-subjects design with 46 subjects; Wilson et al., 2012) reported 90% power with an R-squared effect size of 0.23 Based on these analyses we anticipate using minimum sample sizes of 45 subjects for the current study.

SECTION 7: RISK ASSESSMENT AND POSSIBLE BENEFITS

A. Risk Assessment

1. Indicate the appropriate level of review of this study, based upon your risk assessment.
<input checked="" type="checkbox"/> This study involves greater than minimal risk to subjects and requires Full Committee review. <i>Skip to Section 7.B.</i>
<input type="checkbox"/> This study involves no more than minimal risk and qualifies as <u>Expedited research</u> .

2. If this study involves no more than minimal risk, provide justification for the level of review and for all applicable Expedited Categories you have chosen.

<Type here>

B. Risks and Discomforts

1. Describe and assess any reasonably foreseeable risks and discomforts — physical, psychological, social, legal or other. Include an assessment of their expected frequency (e.g., common – 65%, less common – 40%, unlikely – 5%, rare - <1%) and the seriousness (mild, moderate, severe). *A bullet point list is recommended. If this study will involve the collection of identifiable private information, even temporarily, for which the disclosure of the data outside of the research could reasonably place the subjects at risk, include the risk of a potential breach of confidentiality.*

2. Discuss what steps have been taken and/or will be taken to prevent and minimize any risks/potential discomforts to subjects. *Examples include: designing the study to make use of procedures involving less risk when appropriate; minimizing study procedures by taking advantage of clinical procedures conducted on the subjects; mitigating risks by planning special monitoring or conducting supportive inventions for the study; implement security provisions to protect confidential information.*

In older adults, zolpidem and other sleep aids have been shown to increase risks for falls. Due to the expanded age range of the subjects, we will take increased precautions in order to reduce this risk. These precautions include conducting the entire protocol under at the ICTS. In addition, during the naps a trained sleep technician will monitor the EMG throughout the nap for muscle movement and each subject will be closely attended throughout the study by a research assistant and nurse who will provide close monitoring and guidance for the subjects after drug administration and throughout the day. For the most common side effects (i.e., nausea, vomiting headache), a discussion with the attending nurse and on-call doctor will occur to determine appropriate treatment (i.e., treated with an over-the-counter medication (e.g., ibuprofen), or the subject will be taken to the Health Services located on the UC Irvine campus for further treatment) per Risks section of the UCI Consent.

For more serious events, 911 will be called and the study physician will be contacted immediately. Any medical care required as a result of study participation will be the financial responsibility of the researchers and will be provided to the participant at no cost to them or their third-party insurer.

In the case of an emergency, study staff will call 911 immediately. In the event of a minor adverse event, medical aid will be enlisted in the following order: 1) Primary study physician), 2) Backup study physician); 3) Health Services for University-affiliated subjects or subject's primary care provider.

During the study, research staff will monitor subjects every 15 minutes while they are in the lab. Blood pressure and pulse will be collected before drug administration, as well as every hour after drug administration until nighttime sleep.

If a subject expresses a strong wish to discontinue the study, or has any major difficulty, the protocol will be discontinued. Research staff will have a list of phone numbers for use if questions or unusual events occur during the day or night. The research staff is experienced in monitoring subjects during these types of protocols.

Adverse events, whether deemed related to drug administration or not, will be reported verbally to the UCI Office of Research within 24 hours and followed as soon as possible, but no later than 10 days, by a written report.

All files with personal information will be kept in a locked file cabinet in a locked office and only people affiliated with this study will have access to the research records. All electronic data are de-identified and stored on password-protected computers.

C. Potential Benefits

1. Describe the potential benefits subjects may expect to receive from participation in this study.
Compensation is not a benefit; do not include it in this section.

There is no direct benefit anticipated for the subjects.

No tangible benefits to the participants are expected.

2. Specify the expected potential societal/scientific benefit(s) of this study.

Benefits to society at large include a better understanding of the role sleep has on memory consolidation. This could lead to breakthrough treatments in a wide range of disorders as well as enhancement of normal cognition. The significance of this study rests on both the specific data to be collected and on the development of the experimental paradigm itself. With respect to the former, it is our ultimate aim to find a metric for implementing targeted naps for the specific behavioral needs of individuals. Previous work has shown sleep-stage-specific performance enhancements in well-rested subjects. Since real world situations involve either limited or no sleep, it becomes necessary to understand how naps can help integrate a wide variety of information under these circumstances. The knowledge derived from these data should be quickly amenable to direct transition field studies. Beyond this important contribution, though, the experimental paradigm itself holds much potential for addressing a variety of related questions. The experimental design allows for a consistent test of a variety of interventions that can occur throughout the day or night, in the context of any sleep and work schedule. Given the relatively minimal risks to participants involved and the potential benefits of understanding how daytime naps can improve memory and alertness, we believe the risk/benefit ratio is acceptable.

SECTION 8: ALTERNATIVES TO PARTICIPATION

Describe the alternatives to participation in the study available to prospective subjects. Include routine (standard of care) options as well as other experimental options, as applicable.

- No alternatives exist. The only alternative to study participation is not to participate in the study.
- There are routine standard of care alternatives available; specify: <Type here>
- There are other alternatives to study participation; specify: <Type here>

SECTION 9: SUBJECT COSTS

1. Indicate below if subjects or their insurers will be charged for study procedures. Identify and describe those costs.

- Not applicable: This study involves no interaction/intervention with research subjects. *Skip to Section 10.*
- This study involves interaction/intervention with research subjects; however there are no costs to subjects/insurers.
- This study involves interaction/intervention with research subjects, and there are costs to subjects/insurers: <Type here>

2. If subjects or their insurers will be responsible for study-related costs, explain why it is appropriate to charge those costs to the subjects or their insurers. Provide supporting documentation as applicable (e.g., study procedures include routine (standard of care) procedures; FDA IDE/HDE/IND letter that supports billing to subjects).

- Not applicable: The study involves no costs to subjects for study participation.
- Study related costs will be billed to subjects or their insurers for the following reasons: <Type here>

SECTION 10: SUBJECT COMPENSATION AND REIMBURSEMENT

1. If subjects will be compensated for their participation, explain the method/terms of payment (e.g., money; check; extra credit; gift certificate).

- Not applicable: This study involves no interaction/intervention with research subjects. *Skip to Section 11.*
- No compensation will be provided to subjects.
- Compensation will be provided to subjects in the form of cash/gift certificate.
- Compensation will be provided to subjects in the form of a check issued to the subjects through the UCI Accounting Office. The subject's name, address, and social security number, will be released to the UCI Accounting Office for the purpose of payment and for tax reporting to the Internal Revenue Service (IRS).
- Other: <Type here>

2. Specify the schedule and amounts of compensation (e.g., at end of study; after each session/visit) including the total amount subjects can receive for completing the study. *Compensation should be offered on a prorated basis when the research involves multiple visits.*

For compensation \geq \$600, subject names and social security numbers must be collected. This information must be reported to UCI Accounting for tax-reporting purposes.

Not applicable: This study involves no compensation to subjects.

Subjects will be compensated with the following schedule and amounts: Participants will receive \$300 in the form of cash for their participation in this study. They will receive compensation upon completion of the study. Compensation is broken down as follows: \$100 for each of the two nap experimental visits, \$50 for the adaptation nap, and a \$50 bonus for completing the study. If participants withdraw from the study before completion, the payment will be prorated based on the portion of the study they completed. They will not be compensated for only completing the initial interview or the medical examination.

3. Specify whether subjects will be reimbursed for out-of pocket expenses. If so, describe any requirements for reimbursement (e.g., receipt).

Not applicable: This study involves no reimbursement to subjects.

Subjects will be reimbursed; specify: Subjects will be reimbursed for costs of transportation.

SECTION 11: CONFIDENTIALITY OF RESEARCH BIOSPECIMENS/DATA

A. Biospecimens/Data Storage

1. Indicate all subject identifiers that may be included with the biospecimens or collected for the research study. *If any study-related data will be derived from a medical record, added to a medical record, created or collected as part of health care, or used to make health care decisions the HIPAA policy applies. The subject's HIPAA Research Authorization is required or a waiver of HIPAA Research Authorization must be requested by completing Appendix T.*

This study does not involve the collection of subject identifiers.

Check all the following subject identifiers will be used, created, collected, disclosed as part of the research:

- | | | |
|--|--|--|
| <input checked="" type="checkbox"/> Names | <input type="checkbox"/> Social Security Numbers | <input type="checkbox"/> Device identifiers/Serial numbers |
| <input checked="" type="checkbox"/> Dates* | <input type="checkbox"/> Medical record numbers | <input type="checkbox"/> Web URLs |
| <input checked="" type="checkbox"/> Postal address | <input type="checkbox"/> Health plan numbers | <input type="checkbox"/> IP address numbers |
| <input checked="" type="checkbox"/> Phone numbers | <input type="checkbox"/> Account numbers | <input type="checkbox"/> Biometric identifiers |
| <input type="checkbox"/> Fax numbers | <input type="checkbox"/> License/Certificate numbers | <input type="checkbox"/> Facial Photos/Images |
| <input checked="" type="checkbox"/> Email address | <input type="checkbox"/> Vehicle id numbers | <input type="checkbox"/> Any other unique identifier |
- Other (Specify all): Medical history and physical form that is completed by a physician will be shared with our research team.

* birth date, treatment/hospitalization dates

Indicate how data will be stored and secured, including electronic data as well as hardcopy data paper records, electronic files, audio/video tapes, biospecimens, etc. *If the research data includes subject identifiable data and/or Protected Health Information, the storage devices or the electronic research files must be encrypted. [For guidance on the use of cloud services, please review the [UCI OIT policy](#).]*

Electronic Data/Files (check all that apply):

- Anonymous data will be maintained; no subject identifiers
- Coded data; code key is kept separate from data in secure location.
- Data includes subject identifiable information. Provide rationale for maintaining subject identifiable info): <Type here>
- Data will be stored on secure network server.
- Data will be stored on standalone desktop computer (not connected to network/internet)
- Other (specify here): <Type here>

Hardcopy Data (Records, Recordings, Photographs) and Biospecimens (check all that apply):

- Anonymous biospecimens/data will be maintained; no subject identifiers
- Coded data; code key is kept separate from biospecimens/data in secure location.
- Biospecimens/Data includes subject identifiable information (Provide rationale for maintaining subject identifiable info): We will keep a hardcopy of identifiable information in the case we have to contact subjects after they complete their study.
- Data will be stored in locked file cabinet or locked room.
- Biospecimens will be stored in locked lab/refrigerator/freezer.
- Other (specify here): <Type here>

2. List the location(s) where the data and/or biological specimens will be stored.

Data will be stored at UCI Social Science Lab – Room 380.

3. If subject identifiable data will be transported or maintained on portable devices, explain why it is necessary use these devices. *Only the “minimum data necessary” should be stored on portable devices as these devices are particularly susceptible to loss or theft. If there is a necessity to use a portable device for the initial collection of identifiable private information, the research files must be encrypted, and subject identifiers transferred to a secure system as soon as possible.*

- Not applicable: Research data will not be transported or maintained on portable devices.
- Research data will need to be maintained on the following portable device(s) for the following reason(s): <Type here>

B. Data and/or Biological Specimens Access

Specify who will have access to subject identifiable data and/or biological specimens as part of this study.

- Not applicable: No subject identifiers will be collected.
- Authorized UCI personnel such as the research team and appropriate institutional officials, the study sponsor or the sponsor's agents (if applicable), and regulatory entities such as the Food and Drug Administration (FDA), the Office of Human Research Protections (OHRP), and the National Institutes of Health (NIH).
- Other: <Type here>

C. Data and/or Biological Specimens Retention

Indicate how long subject identifiable data and/or biological specimens, including the subject code key will be retained. *If more than one of the options below is applicable (e.g., the study involves children), records must be kept for the longer period.*

- Not applicable: No subject identifiable research data will be retained.
 - Separate code key will be destroyed or subject identifiable information will be removed from the biospecimens and/or data at the earliest convenience, consistent with the conduct of this research. Specify timeframe: <Type here>
 - Destroyed once research data is analyzed.
 - Destroyed after publication/presentation.
 - Will be maintained; specify time frame and provide the rationale: <Type here>
 - Will be stored and maintained in a repository for future research purposes.
-  **Complete Appendix M**
- Will be retained for six years as this research involves Protected Health Information (PHI) (e.g., IRB documentation, consent/assent forms – NOT the actual PHI). *Investigators must destroy PHI at the earliest opportunity, consistent with the conduct of this study, unless there is an appropriate justification for retaining the identifiers or as required by law.*
 - Will be retained for seven years after all children enrolled in the study reach the age of majority [age 18 in California] as this study includes children.
 - Will be retained 25 years after study closure as this study involves in vitro fertilization studies or research involving pregnant women.
 - Will be retained for two years after an approved marketing application, as this is a FDA regulated study. If approval is not received, the research records will be kept for 2 years after the investigation is discontinued and the FDA is notified.
 - Other: <Type here>

D. Photographs, Audio/Video Recordings Retention

1. If subject identifiable audio or video recordings will be collected, specify the timeframe for the transcription and describe retention/destruction plans.

- Not applicable: Subject identifiable audio/video recordings will not be collected.
- Audio or video recordings transcribed; specify time frame: <Type here>
- Audio or video recordings will be maintained; specify time frame: <Type here>
- Audio or video recordings maintained indefinitely; provide the rationale: <Type here>
- Audio or video recordings destroyed; specify time frame: <Type here>

2. If subject identifiable photographs will be collected, describe retention/destruction plans.

- Not applicable: Subject identifiable photographs will not be collected.
- Photographs will be maintained; specify time frame: <Type here>
- Photographs maintained indefinitely; provide the rationale: <Type here>
- Photographs destroyed; specify time frame: <Type here>

E. Certificate of Confidentiality

1. Indicate whether a Certificate of Confidentiality (COC) has been or will be requested.

- Not applicable: No COC has been requested for this study.
- A COC will be or has been requested for this study. *The COC application must be submitted to the IRB staff for review after IRB approval.*
- A COC has been obtained for this study. The expiration date of this COC is: <Type here>



Provide a copy of the COC Approval Letter.

2. Explain in what situations the UCI study team will disclose identifiable private information protected by a COC.

The Certificate of Confidentiality does not prevent researchers from voluntarily disclosing information that would identify you as a participant in the research project as required by Federal, State or local laws, and with your consent, as necessary, for your medical treatment. This includes the disclosure of information that must be released to meet the requirements of the Food and Drug Administration (FDA). No voluntary disclosures will be made