

Multicomponent Behavioral Sleep Intervention for Insomnia in Older Adults with Mild Cognitive Impairment

Protocol and Statistical Analysis Plan

IRB Protocol Number: 832826

Approval Date: 04/03/2019

Protocol Details

Basic Info

Confirmation Number: **cifhdjh**
Protocol Number: **832826**
Created By: **VARRASSE, MIRANDA S**
Principal Investigator: **VARRASSE, MIRANDA S**
Protocol Title: **Multicomponent Behavioral Sleep Intervention for Insomnia in Older Adults with Mild Cognitive Impairment**
Short Title: **MBSI-I in MCI**
Protocol Description: **This pilot randomized controlled trial will test a brief (4 week), tablet-based, personalized, multicomponent behavioral sleep intervention for insomnia (MBSI-I) in older adults with MCI, compared to a sleep education control. Study assessments will be performed at pre-treatment (baseline), post-treatment (four weeks) and at 3 month post treatment follow-up.**
Submission Type: **Social and Biological Sciences**
Application Type: **EXPEDITED Category 2 and Category 4**

Resubmission*

Yes

Study Personnel

Principal Investigator

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Training Expiration Date: **02/07/2021**
Name of course completed : **CITI Protection of Human Subjects Research Training - ORA**

Study Contacts

None

Other Investigator

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HS Training Completed:	Yes
Training Expiration Date:	04/26/2019
Name of course completed :	CITI Protection of Human Subjects Research Training - ORA

Responsible Org (Department/School/Division):

602 - Biobehavioral and Health Sciences

Key Study Personnel

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HS Training Completed:	Yes
Training Expiration Date:	12/20/2019
Name of course completed:	CITI Protection of Human Subjects Research Training - ORA

Name:	GOONERATNE, NALAKA
Department/School/Division:	DM-Geriatrics
HS Training Completed:	Yes
Training Expiration Date:	08/19/2019
Name of course completed:	CITI Protection of Human Subjects Research Training - ORA

Disclosure of Significant Financial Interests*

Does any person who is responsible for the design, conduct, or reporting of this research protocol have a **FINANCIAL INTEREST**?

No

Penn Intellectual Property*

To the best of the Principal Investigator's knowledge, does this protocol involve the testing, development or evaluation of a drug, device, product, or other type of intellectual property (IP) that is owned by or assigned to the University of Pennsylvania?

No

Certification

I have reviewed the *Financial Disclosure and Presumptively Prohibited Conflicts for Faculty Participating in Clinical Trials* and the *Financial Disclosure Policy for Research and Sponsored Projects* with all persons who are responsible for the design, conduct, or reporting of this research; and all required Disclosures have been attached to this application.

Yes

Social and Biological Sciences

Study Instruments

Discuss the particulars of the research instruments, questionnaires and other evaluation instruments in detail. Provide validation documentation and or procedures to be used to validate instruments. For well know and generally accepted test instruments the detail here can be brief. More detail may be required for a novel or new instrument. For ethnographic studies identify any study instruments to be used (i.e. for deception studies) and describe in detail where, when and how the study will be conducted and who or what are the subjects of study. Note: For more information on how to conduct ethical and valid ethnographic research, follow the link [For oral histories or interviews provide the general framework for questioning and means of data collection.](#) If interviews or groups settings are to be audio taped or video taped describe in detail the conditions under which it will take place. Include a copy of any novel or new test instruments with the IRB submission.

Sleep Measures: Consensus Sleep Diary (electronic version). We will derive sleep latency, wake after sleep onset, sleep efficiency, total sleep time, and daytime napping; Actigraphy to objectively assess variables in Table 2; Insomnia Severity Index (ISI), a widely used measure of insomnia; Pittsburgh Sleep Quality Index (PSQI), a widely used measure of sleep quality; Pre-sleep Arousal Index, this measure has been shown to change with relaxation and mindfulness training based on prior work performed by Dr. Gooneratne; 1.6) Dysfunctional Beliefs and Attitudes about Sleep (DBAS-16),^{122,123} a validated instrument to assess maladaptive beliefs regarding sleep that exacerbate insomnia, and has been shown to improve with insomnia treatment; the 16-item version will be used as it has more favorable psychometric properties than the 30-item or 10-item versions.¹²³ Quality of Life: RAND Medical Outcomes Study Short Form-36 (SF-36), one of the most widely used health-related quality of life measures,^{124,125} frequently used to measure HRQOL in older adults.¹²⁶⁻¹²⁸ It is a multidomain that measures physical and mental components of HRQOL with eight subscales. The 8 subscales contribute to two resulting component summaries: a mental component summary (MCS) and a physical component summary (PCS). Both PCS and MCS scores range from 0 to 100, representing worst to best health. Higher scores indicate better HRQOL. Physical Activity: Objective PA, characterized by mean level of physical activity (counts/minute), will be measured by Actigraphy. Subjective PA will be obtained from the Physical Activity Scale for the Elderly (PASE).^{129,130} Cognition: Montreal Cognitive Assessment (MoCA)¹⁰⁵ assesses different cognitive domains: attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. Social Activity: Participation in social activity will be recorded in the tablet. Serum inflammatory biomarkers, including cytokines (IL-6, IL-1 β , TNF-) and C-reactive protein (CRP), will be assessed at baseline, post-intervention and 3 month post intervention follow up. Approximately 20 ml of blood will be collected using standard venipuncture techniques at the mornings between 8AM to 10AM (after the baseline, post-intervention and follow-up questionnaire data collection). Blood samples will be collected by trained staff. After collection, the blood sample will be labeled, transported, and stored in a -80°C freezer until ready to be analyzed. All four biomarkers will be assayed at Laboratory of Innovative and Translational Nursing Research using the enzyme-linked immunosorbent assay (ELISA) method.¹³¹ Other information includes age, race, education, life style (tobacco and alcohol use, BMI), depression (15-item GDS-SF ^{132,133} has been validated as an assessment of depression, with a yes/no format that facilitates use), medication use (antidepressant, benzodiazepine, sleep medication), and self-reported medical conditions. This information will be collected via questionnaires.

Group Modifications

Describe necessary changes that will or have been made to the study instruments for different groups.

No modifications will be made.

Method for Assigning Subjects to Groups

Describe how subjects will be randomized to groups.

The proposed study is a randomized controlled non-crossover pilot study in which 40 subjects will be allocated in a 1:1 ratio to the MBSI-I intervention arm or an education only control arm for a treatment period of four weeks. Assignment by 1:1 simple randomization will be conducted by consecutive sealed envelope (labeled by study RA), maintained/secured at the main clinical recruitment site (Ralston House) and monitored by the site PI.

Administration of Surveys and/or Process

Describe the approximate time and frequency for administering surveys and/or evaluations. For surveys, questionnaires and evaluations presented to groups and in settings such as high schools, focus group sessions or community treatment centers explain how the process will be administered and who will oversee the process. For instance, discuss the potential issues of having teachers and other school personnel administer instruments to minors who are students especially if the content is sensitive in nature. Describe the procedure for audio and videotaping individual interviews and/or focus groups and the storage of the tapes. For instance, if audio tape recording is to be used in a classroom setting, describe how this will be managed if individuals in the class are not participating in the study. Explain if the research involves the review of records (including public databases or registries) with identifiable private information. If so, describe the type of information gathered from the records and if identifiers will be collected and retained with the data after it is retrieved. Describe the kinds of identifiers to be obtained, (i.e. names, social security numbers) and how long the identifiers will be retained and justification for use.

Baseline (pre-treatment) assessments, collected at Visit 1, include subjective sleep measures and measures of health related quality of life, physical activity, cognition, social activity, and blood samples. Intervention: A 4-week intervention (see intervention description below) will be provided to participants randomized to the intervention group. Sleep diaries will be completed and Actigraphs worn for all four weeks of treatment, in both groups. Post-intervention and Follow-up data collection (visit 2 week 5; visit 3 week 16): All baseline assessments will be repeated immediately post- intervention and at three months post-intervention follow-up (sleep measures and measures of health related quality of life, physical activity, cognition, social activity, and blood samples; one week sleep diary + actigraphy). Data on demographics and other information (age, race, education, life style (tobacco and alcohol use, BMI), depression, medication use (antidepressant, benzodiazepine, sleep medication), and self-reported medical conditions will be assessed by questionnaires at baseline, post-intervention and follow-up. All source documents (questionnaires) will be collected directly from the patient using the secure web portal that will be developed for this study. This data will be stored in the electronic clinical trials software application, REDCap. This application is compliant with FDA guidelines for clinical trials software (e.g. data encryption, electronic signatures, and internal audit trail capabilities). The application and data are stored on HIPAA compliant servers. The REDCap application also can manage study logistics to ensure timely scheduling of study visits, supports double-data entry procedures, and robust data analysis features to monitor study participant recruitment and retention rates. Physiologic data, such as the accelerometer data, will be uploaded, in a de-identified form (no personal identifiers except for an identification number), to the Actiware software on a password protected laptop on a protected server. Data collected from the tablet will be collected in de-identified form, transmitted to the same University of Pennsylvania servers, where it will be stored and backed-up. Sleep diaries will be completed by the participants via tablet using the mPhenomic application (discussed in greater detail below). No audio or video recordings will be made. Handling of Biological Samples: On data collection day, each of the 4 tubes per subject will be prepared and labeled with unique participant identifier (not linked to PHI), study number and assay for which it is assigned. Immediately upon collection, the sample will be processed and centrifuged if needed and placed in dry ice. The samples will be transported back to the respective laboratories as described in the section of this grant and placed in a -80° C freezer upon completion of the study for each subject where the samples will be logged in for future assays

Data Management

Describe how and who manages confidential data, including how and where it will be stored and analyzed. For instance, describe if paper or electronic report forms will be used, how corrections to the report form will be made, how data will be entered into any database, and the person(s) responsible for creating and maintaining the research database. Describe the use of pseudonyms, code numbers and how listing of such identifiers will be kept separate from the research data.

We will apply strict procedures to maintain confidentiality and will adhere to 2003 HIPAA Standards for Privacy of Individually Identifiable Health Information (the Privacy Rule). Each individual participant will be given a unique study identification number. Information linking the identification number to the participant will be kept in its own separate password-protected and encrypted secure file on the University of Pennsylvania server. All data will be labeled with the participants study specific identification number and uploaded to another password-protected, secure server at the University of Pennsylvania. Information will only be available the research team. All project records will reflect only the ID number of each participant. Thus, research study participants names will not appear on any forms, and instead participants will use a unique identification number. The REDCap (Research

Electronic Data Capture) system will be used as a central resource for quantitative data processing and management. REDCap is a web application and back-end database model designed to support data capture for research studies. The University of Pennsylvania has licensed its own version of REDCap that is housed on our own password-protected servers located within a data center inside the Penn firewall and therefore afforded the same network protections as other sensitive clinical systems. REDCap was developed specifically around HIPAA-security guidelines with features such as data encryption. It provides an intuitive interface for data entry with data validation, audit trails for tracking data manipulation and export procedures, automated export procedures for seamless data downloads to common statistical packages, including SAS, and procedures for importing data from external sources. We will use standard operating procedures to guide all data management activities, such as the naming and identification of variables, data cleaning and handling of missing data. All data obtained from self-report measures will be entered directly into the REDCap database on encrypted laptop computers as collected to reduce data collection time, increase accuracy, and prevent data loss. Data entry screens will be designed to incorporate range checks and concurrent checks to minimize errors. Missing fields will not be allowed. All scored data will be double entered to ensure accuracy. The software being used for this study, mPhenomic, is an application developed by the mHealth Service at Penn medicine. It has been developed under an open-source license; it is not patentable IP. Other protocols that mPhenomic has been approved for use with are protocol #816717 (Behavioral Approaches to Insomnia) and protocol #829732 mPeer2Peer. The mPhenomic application is HIPAA compliant, mobile research platform developed by the Penn Medicine mHealth Service using protected servers hosted by Penn Medicine Academic Computer Services. Data transmitted through the mPhenomic application will be encrypted in transit and at rest. To ensure HIPAA compliance, mPhenomic will be password protected and users will be given a non-identifiable username. This participant username will be used (along with a password) by the participant to log onto the software; they will not use their e-mail or other personal identifier as the username. The software will not store any personal health information or a participant's name, birthdate, sex, home address, or other personal information; it will only record tap events (time-stamped) and sleep diary times. Recorded data will be encrypted using standard protocols at rest and in transfer, leaving no point at which the raw data will be openly readable until accessed by the research team. Thus, the linkage between participant ID and participant name can only be determined from the participant's link key, which will be stored in a locked file cabinet as a paper copy and also in an encrypted file on a password-protected computer that is maintained by the University of Pennsylvania to standards acceptable for storing personal health data. Rigorous security protocols that restrict data access points will also be implemented, requiring research staff to securely authenticate their identity before accessing the data. Access to the study participants' identities will only be available to the immediate research staff.

Radiation Exposure*

Are research subjects receiving any radiation exposure (e.g. X-rays, CT, Fluoroscopy, DEXA, pQCT, FDG, Tc-99m, etc.) that they would not receive if they were not enrolled in this protocol?

No

Human Source Material*

Does this research include collection or use of human source material (i.e., human blood, blood products, tissues or body fluids)?

Yes

CACTIS and CT Studies*

Does the research involve Center for Advanced Computed Tomography Imaging Services (CACTIS) and CT studies that research subjects would not receive if they were not part of this protocol?

No

CAMRIS and MRI Studies*

Does the research involve Center for Advanced Magnetic Resonance Imaging and Spectroscopy (CAMRIS) and MRI studies that research subjects would not receive if they were not part of this protocol?

No

Cancer Related research not being conducted by an NCI cooperative group*

Does this protocol involve cancer-related studies in any of the following categories?

No

Medical Information Disclosure*

Does the research proposal involve the use and disclosure of research subject's medical information for research purposes?

Yes

CTRC Resources*

Does the research involve CTRC resources?

No

If the answer is YES, indicate which items is is provided with this submission:

Modified research informed consent document that incorporates HIPAA requirements

Use of UPHS services*

Does your study require the use of University of Pennsylvania Health System (UPHS) services, tests or procedures*, whether considered routine care or strictly for research purposes?

No

Primary Focus*

Clinical Trial (prospectively assigning subjects to health-related interventions to evaluate outcomes)

Protocol Interventions

- Sociobehavioral (i.e. cognitive or behavioral therapy)
 - Drug
 - Device - therapeutic
 - Device - diagnostic (assessing a device for sensitivity or specificity in disease diagnosis)
 - Surgical
 - Diagnostic test/procedure (research-related diagnostic test or procedure)
 - Obtaining human tissue for basic research or biospecimen bank
 - Survey instrument
 - None of the above

The following documents are currently attached to this item:

There are no documents attached for this item.

Sponsors

Business Administrator

Name:	LIU, CHIU-FANG
Dept / School / Div:	631 - Office of Nursing Research
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Pager:	
Email:	chiufang@nursing.upenn.edu

Department budget code

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Funding Sponsors

Funding sponsors billing address

If you have selected a commercial or industry sponsor, please provide the appropriate address and contact information for the Sponsor for the purposes of billing for IRB review fees (initial review, continuing review and convened modification fees apply here). If the Sponsor is not industry/commercial, this information is not necessary to provide with your application.

Funding sponsors gift

Is this research being funded by a philanthropic gift?

Regulatory Sponsor

IND Sponsor

none

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Industry Sponsor

None

Project Funding*

Is this project funded by or associated with a grant or contract?

Pending

Sponsor Funding

Is this study funded by an industry sponsor?

No

Status of contract

The following documents are currently attached to this item:

Grant Application (k23grant-science.pdf)

Multi-Center Research

Penn as lead

1. Is this a multi-center study where Penn is serving as the Lead Site or the Penn PI is serving as the Lead Investigator?

No

Management of Information for Multi-Center Research

Penn irb of record

2. Is this a multi-center study where the Penn IRB will be asked to serve as the IRB of Record for other external study sites?

No

Other Sites

No other sites

Protocol

Abstract

Insomnia symptoms in older adults with mild cognitive impairment represent a significant public health burden in terms of impaired quality of life, risks from untreated insomnia, and risks from pharmaceutical insomnia treatment. To address the limitations in the most effective non-pharmacological treatments for insomnia in older adults with mild cognitive impairment, a randomized pilot study will be conducted to test a brief (4 week), tablet-based, personalized, multicomponent behavioral sleep intervention for insomnia, compared to a sleep education control, in this at-risk group. The findings of the proposed project will inform future, larger scale clinical trials and may provide a novel and innovative way for older adults with mild cognitive impairment to achieve better sleep and health-related quality of life outcomes.

Objectives

Overall objectives

1) Determine the preliminary immediate (one month) and sustained efficacy (3 months) of MBSI-I compared to sleep education on sleep related outcomes. 2) Determine the preliminary immediate (one month) and sustained efficacy (3 months) of MBSI-I compared to sleep education on health related quality of life. 3) Exploratory Aim: To explore the mechanisms by which MBSI-I affects sleep and health related quality of life

Primary outcome variable(s)

Sleep latency: measured at baseline, immediately post intervention (4 weeks) and 3 months post-intervention (16 weeks). Sleep latency will be derived from subjective sleep diaries and refers to the time it takes a person to fall asleep, starting from the first intention to sleep. Health-related quality of life, measured at baseline, immediately post intervention (4 weeks) and 3 months post-intervention (16 weeks). Health related quality of life is a multi-dimensional concept that includes domains related to physical, mental, emotional and social functioning. We will use the RAND Medical Outcomes Study Short Form-36 (SF-36), one of the most widely used health-related quality of life measures frequently used to measure HRQOL in older adults. It is a multidomain that measures physical and mental components of HRQOL with eight subscales. The 8 subscales contribute to two resulting component summaries, a mental component summary (MCS) and a physical component summary (PCS). Both PCS and MCS scores range from 0 to 100, representing worst to best health. Higher scores indicate better HRQOL.

Secondary outcome variable(s)

Additional sleep outcomes include wake after sleep onset, total sleep time, sleep efficiency, sleep quality and insomnia symptoms, measured with Actigraphy, sleep diary and other validated sleep questionnaires. These variables are measured at baseline, immediately post intervention (4 weeks) and 3 months post-intervention (16 weeks). We will explore the mechanisms by which the intervention affects sleep and health related quality of life measures via standardized questionnaires and inflammatory biomarkers.

Background

Healthy sleep is critical for optimizing health related quality of life, including physical, social, emotional, and cognitive domains while untreated sleep disturbances can result in physical, psychological, social, and economical impairments. Insomnia is the most common sleep disturbance in older adults and is characterized by difficulty initiating or maintaining sleep, awakening too early, and next day consequences such as difficulty concentrating. Epidemiological studies of older adults have reported insomnia prevalence of 10-40%;⁸ yet, less than 15% of patients with insomnia consult a healthcare provider or receive treatment. Furthermore, it is estimated that 7% to 20% of older adults have mild cognitive impairment (MCI) and 60% of people with MCI have some sleep disturbances. MCI is a degenerative condition characterized by cognitive decline; insomnia symptoms are bidirectionally linked to cognitive decline. Insomnia is often managed with pharmacologic agents which can be associated with adverse medical complications; memory impairments make treating insomnia even more challenging. Cognitive behavioral therapy is the most widely used

nonpharmacological treatment for insomnia and although efficacious in older adults has potential challenges in people with MCI. Thus, it is critical to develop and test interventions that are brief and accessible to improve insomnia in this growing at-risk population.

Study Design

Phase*

Phase I

Design

The proposed study is a randomized controlled non-crossover pilot study in which 40 subjects will be allocated in a 1 to 1 ratio to the MBSI-I intervention arm or an education only control arm for a treatment period of four weeks. All study consents, questionnaires and education regarding the intervention will take place in a private room at Ralston House. Ralston House has free parking and is close to public transportation.

Study duration

The study protocol will be conducted over a three year period, with the first three months devoted to establishing study databases, study operating procedures (SOP) and other logistic study initiation steps. Subject recruitment will begin in month four and continue during year 2, concluding in month 10 of year 3 (a total of two and a half years of subject recruitment, which is adequate to enroll 40 subjects). The final 3 months of year 3 will be devoted to data analysis and manuscript writing. The project will begin once we have IRB approval. Participants will be in the study for a total of 17 weeks, including baseline visit, intervention, post-intervention and three month follow-up.

Resources necessary for human research protection

Describe research staff and justify that the staff are adequate in number and qualifications to conduct the research. Describe how you will ensure that all staff assisting with the research are adequately informed about the protocol and their research related duties. Please allow adequate time for the researchers to conduct and complete the research. Please confirm that there are adequate facilities for the research.

The study team includes Dr. McPhillips, PhD, RN, a postdoctoral research fellow at the University of Pennsylvania and her mentoring team: 1) Primary mentor: Dr. Nancy A. Hodgson, PhD, RN, FAAN (NH) is an Associate Professor in the Department of Biobehavioral Health and the Anthony Buividas Endowed Term Chair in Gerontology at the Penn School of Nursing. She is an expert in clinical trials and the development and translation of biobehavioral sleep interventions to ease symptom burden for cognitively frail older adults and the study of the physiologic mechanism underlying the effect of behavioral interventions to reduce symptom distress. 2) Co-mentor: Dr. Nalaka S. Gooneratne, M.D, M.Sc. (NG) is an Associate Professor at the Penn School of Medicine, Division of Geriatric Medicine and the Center for Sleep and Respiratory Neurobiology, Associate Director of the Masters in Translational Research program, and Director of the mHealth mobile app development service. He is an expert in geriatric sleep research and mobile device technology. 3) Co-mentor: Dr. Allan Pack, MBChB, PhD, FRCP (AP) is a Professor of Medicine at Penn, Director of the Center for Sleep and Circadian Neurobiology (CSCN), and Chief of the Division of Sleep Medicine. Dr. Pack is a leader in the field of sleep medicine and has a primary focus on sleep, chronobiology and biomarker research. All investigators have a certificate of completion for required education on the protection of human research participants and meet the NIH criteria for continued training in responsible conduct of research. Dr. McPhillips will be responsible for all research related activities, prior to hiring a Research Assistant. Once a Research Assistant is hired, a modification for the IRB will be submitted. Under Dr. McPhillips' supervision, the RA will be responsible for developing and executing procedures and processes of study implementation including day-to-day operations (e.g. meeting coordination, meeting minutes), preparing Data/Safety monitoring reports, ongoing reports, database development, recruitment and retention, payments, data collection, and budget oversight. S/he will work closely with the PI to ensure that data collection is conducted on schedule. Any research staff that will be directly involved in data collection will have one on one training sessions with Dr. McPhillips. Dr. McPhillips has a research office at Ralston House, with locked cabinets for storing secure data. The Penn School of Nursing has a secure research server for online data storage. We also have a secure research laptop for data collection. We are confident we have appropriate space and resources for conducting this study.

Characteristics of the Study Population

Target population

Older adults with insomnia and mild cognitive impairment

Subjects enrolled by Penn Researchers

40

Subjects enrolled by Collaborating Researchers

0

Accrual

ACCESS TO THE POPULATION We plan to recruit 40 participants from two sources: 1) Division of Geriatric Medicine Division Ralston House clinic: There are currently 2,864 active patients, with 40% having mild cognitive impairment (MCI), yielding a potential 1,145 patients with MCI. We will use EPIC to generate a list of eligible participants coming in for clinic visits each week. Staff will introduce patients to the study team for further screening. 2) PennSeek search of MCI and insomnia yielded 870 potential participants. After obtaining permission to contact from their provider and completing a telephone screening call, consent and research visits will be set up at Ralston House. We currently have a private room that is available and parking is free. Given the concern of having people come to Ralston House and then not meeting MoCA inclusion, we will add the Telephone Interview for Cognitive Status (TICS) as part of the screening process for the PennSeek group. We are confident our two recruitment strategies will be successful, based off current experiences in on-going clinical trials. **ANALYSIS** Power Analysis: Power estimates are based on the primary sleep related outcomes using two type I error rates, a traditional alpha of 0.05 and an alpha of 0.20 typically used in pilot studies. Based on published means for sleep outcomes from a pilot randomized controlled trial comparing a six-session, adapted version of a cognitive behavioral therapy with an active control in 28 older adults with insomnia and mild cognitive impairment, 138 power for sample sizes of 20 per group at each timepoint were estimated using hypothesized differences and standard deviations interpolated to 1 and 3 months. Table 3 below provides power estimates for various sleep outcomes. As an example, group sample sizes of 20 each (total N=40) achieve 99% power to detect a difference between 88.04 vs 82.30 in sleep efficiency means with a standard deviation of 4.0 for both groups and with a significance level of 0.05 using a two-sided two-sample equal-variance t-test.

Key inclusion criteria

Must meet inclusion criteria of: 1) age 65 and older; 2) mild cognitive impairment [Montreal Cognitive Score (MoCA) less than 26], 3) have subjective sleep diary evidence of insomnia, with an average sleep latency greater than 30 min or wakefulness after sleep onset of greater than 60 min during the one week pre-treatment assessment; 4) live in the community; 5) speak English as primary language (most of the study questionnaires only have validated English-language versions).

Key exclusion criteria

Exclusion Criteria include 1) Presence of moderate to severe cognitive impairment defined as MoCA score less than 17; 2) Visual or manual dexterity impairment that prevents them from pressing yes/no buttons, or selecting a number at 24 point font. 3) Current sedative-hypnotic or other sleep aid use on a regular or as needed schedule within the prior three months; 4) The presence of an acute medical or psychiatric condition (such as acute congestive heart failure at high likelihood of imminent hospitalization) which, in the judgement of the research team, would interfere with the subjects ability to realistically follow the study protocol

Vulnerable Populations

Children Form

Pregnant women (if the study procedures may affect the condition of the pregnant woman or fetus) Form

Fetuses and/or Neonates Form

Prisoners Form

Other

None of the above populations are included in the research study

The following documents are currently attached to this item:

There are no documents attached for this item.

Populations vulnerable to undue influence or coercion

N/A

Subject recruitment

We plan to recruit 40 participants from two sources: 1) Division of Geriatric Medicine Division Ralston House clinic and 2) PennSeek. 1) Division of Geriatric Medicine Division Ralston House clinic: We will use EPIC to generate a list of eligible participants coming in for clinic visits each week. Staff will introduce patients to the study team for further screening. 2) PennSeek: After obtaining permission to contact potential participants from their provider and completing a telephone screening call, consent and research visits will be set up at Ralston House. We have included the Telephone Interview for Cognitive Status (TICS) as part of the screening process for the PennSeek group to minimize the number of people who come to Ralston House and then do not meet MoCA inclusion criteria.

Will the recruitment plan propose to use any Penn media services (communications, marketing, etc.) for outreach via social media avenues (examples include: Facebook, Twitter, blogging, texting, etc.) or does the study team plan to directly use social media to recruit for the research?

No

The following documents are currently attached to this item:

There are no documents attached for this item.

Subject compensation*

Will subjects be financially compensated for their participation?

Yes

The following documents are currently attached to this item:

There are no documents attached for this item.

If there is subject compensation, provide the schedule for compensation per study visit or session and total amount for entire participation, either as text or separate document

Participants will be compensated for their time completing all research related activities, with a maximum compensation of \$200. The compensation will be in the form of gift card, and broken down into three payments: 1) Payment 1: \$50 at the end of Visit 1 (day 1; week 1) 2) Payment 2: \$100 at the end of Visit 2 (post-intervention; week 5) 3) Payment 3: \$50 at the end of Visit 3 (12 weeks post intervention; week 16)

Study Procedures

Suicidal Ideation and Behavior

Does this research qualify as a clinical investigation that will utilize a test article (ie- drug or biological) which may carry a potential for central nervous system (CNS) effect(s)?

No

Procedures

Study Procedures: A) Subjects: The target study population is older adults with mild cognitive impairment who have insomnia. B) Recruitment and Screening: We will recruit 40 eligible participants from two sources: 1) Division of Geriatric Medicine Division Ralston House clinic and 2) PennSeek. After consent, subjects will be screened for key inclusion criteria. First, they must answer yes to the insomnia screening question and score within the MCI range on the MoCA. Next, they will be sent home with tablet-based sleep diary and actigraphy for one week. Once insomnia inclusion criteria are confirmed, participants will set up Visit 1 at Ralston House. C) Randomization: All retained participants will be randomly allocated (1:1) to either intervention or control arm. D) Baseline (pre-treatment) assessments, collected at Visit 1, include sleep measures and measures of health related quality of life, physical activity, cognition, social activity, and blood samples. E) Intervention: A 4-week intervention (see intervention description below) will be provided to subjects randomized to the intervention group. Sleep diaries will be completed and Actigraphs worn for all four weeks of treatment, in both groups. F) Post-intervention and Follow-up data collection (visit 2 week 5; visit 3 week 16): All baseline assessments will be repeated immediately post- intervention and at three months post-intervention follow-up (sleep measures and measures of health related quality of life, physical activity, cognition, social activity, and blood samples; one week sleep diary + actigraphy). G) Demographics: Data on demographics and other information (see measurement section) will be assessed by questionnaires at baseline, post-intervention and follow-up. Intervention: The intervention will include a meaningful activity protocol during the day and Assistive Relaxation Therapy at night. The personalized meaningful activity protocol will be developed based on the individuals factors contributing to insomnia, typical daily circadian profile, functional status, and preference for activity. The individuals typical circadian profile will be calculated from the one-week baseline Actiwatch accelerometer data using algorithms previously developed by Dr. Gooneratne (co-mentor) and research team. The intervention will be broken into: 1) Sleep Hygiene Education, including content on routine, stimulus control principles, food/drink/substance intake (caffeine, alcohol, etc.), activity, naps, etc; 2) Meaningful Activity Modules a) Physical Activity, including content from the Go4Life Campaign (NIA) on endurance, strength, balance, and flexibility b) Cognitive Activity including various cognitively stimulating games and exercises such as cross-word puzzles and c) Social engagement including identifying social support persons, group activities in the area and using technology to stay connected; 3) Assistive Relaxation Therapy (ART), a breath-based relaxation application that is coupled with a physical anchoring task. After reviewing baseline assessments to determine etiological risk factors contributing to the insomnia, each participant and the PI will construct their meaningful activity plan. Thus, study participants in the intervention arm will receive (1) tablet computer with mPhenomic software which will include sleep diary, sleep education material, meaningful activity modules, and ART; (2) Actiwatch-2 wrist watch device. They will be instructed how to use the tablet and encouraged to view the installed educational content, which will be tracked using the treatment fidelity component of the software. They will be asked to complete the daily sleep diary on the tablet, use the activity modules daily as pre-determined times personalized to the participant, use ART when they get in bed and if they awake during the night to help them with their insomnia symptoms for a four-week period. They will be asked to wear the actiwatch on the non-dominant wrist to monitor sleep/wake patterns. Participants will have biweekly phone consultation with the PI to receive guidance and adjustment on activity plans. Based on previous research, physical, social, or cognitive activity has shown significant improvement in sleep in 2-4 weeks and ART therapy has improved sleep latency in just two weeks. Thus, we feel confident that a 4 week intervention period is sufficient and justified. As per NIH guidelines, we are providing additional details related to the intervention relevant for assessing Human Subjects Safety. The following components which will be used for the four-week intervention period. Android OS v5.1 tablet computer (Samsung Galaxy Tab E 8 inch) connected by wireless cell phone data link. Tablet-enabled sleep diary: The Sleep Diary will be administered via the mPhenomic platform optimized for use by older adults. Data will be accessed via an API interface to the secure web portal below. Sleep Education Information: Sleep education/sleep hygiene information will also be loaded to the mPhenomic platform. Meaningful Activity Modules: There will be three modules related to physical, social and cognitive stimulating

activity. These will be loaded to the tablet on an application developing using the mPhenomic platform. Assisted Relaxation Therapy (ART) will also be loaded onto the tablet via the mPhenomic platform. We will ask the study participant to engage in an anchoring task (finger tap) on the tablet screen at the exhalation point of the breathing cycle while they are lying in bed trying to sleep. Study participants will be asked to use the ART intervention every night as they are trying to fall asleep, or when they wake up at night. They will use it every night for four weeks. For ART intervention to work, it must be used on a nightly basis when in bed. It will be administered via the tablet. These technologies do not constitute a medical device as per FDA guidance related to mobile device technologies. Secure web portal to allow study participant to view educational material; can be accessed from the Android tablet. It will include only sleep education information for the control arm. Actiwatch-2 device: Each participant will be given an Actiwatch-2 device (Koninklijke Philips, N.V.), a piezoelectric accelerometer worn on the non-dominant wrist. Movement data are sampled at a rate of 32 Hz, and activity counts are recorded in 60-second epochs. Additionally, the Actiwatch-2 has Silicon photodiode light sensors, and a button that enables participants to signal when they first try to fall asleep and when they get out of bed in the morning. The button can also be used to signal naps. Periods of activity and inactivity are analyzed in order to estimate sleep/wake status. Computer programs are used to derive levels of activity/inactivity, rhythm parameters and daytime naps. Wrist actigraphy monitoring has been shown to be a reliable way to objectively monitor sleep-wake cycles. Control arm: The control arm will consist of sleep education which will be provided to the study participant on the tablet. They will be asked to complete a tablet-enabled sleep diary and wear an Actiwatch-2 device on the non-dominant wrist. See attached for protocol table.

The following documents are currently attached to this item:

Procedures (k23_irb_mbsi-i_studyvisitbreakdown.docx)

Deception

Does your project use deception?

No

International Research

Are you conducting research outside of the United States?

No

Analysis Plan

Power Analysis for Sample Size described previously under "Accrual". Descriptive Analyses: Descriptive statistics will be used to characterize the sample, with measures of central tendency and variation for continuous measures, and frequencies and percentages for dichotomous and categorical variables. All variables will be assessed for normality. Descriptive estimates will be generated for all subjects at each of the observed time points, and by intervention group within each time point. Outliers will be assessed via visual inspection of distributions and checked for accuracy. To identify relationships demonstrating multicollinearity and/or possibly areas requiring statistical adjustment, bivariate analyses via two-sample t-tests and Fishers exact tests will be used to compare continuous and categorical variables by intervention group, respectively. For comparisons involving continuous variables, homoscedasticity will be evaluated using Levenes tests, and normality will be assessed using Shapiro-Wilk tests. Should violations emerge, transformations will be applied, or non-parametric tests used. Aim 1 and 2 Analyses: We will determine the preliminary immediate (1 month) and sustained efficacy (3 month post-intervention) of MBSI-I compared to sleep education on sleep related outcomes (sleep latency, wake after sleep onset, total sleep time, sleep efficiency, sleep quality and insomnia symptoms) and health related quality of life. H1: MBSI-I will significantly improve subjective sleep latency compared to the control group at 1 month. H1b: These results will be sustained at 3 months. H2: MBSI group will have significant improvements in subjective health related quality of life, measured via SF-36, compared to the control group at 1 month. H2b: Results will be sustained at 3 months. The intervention groups will initially be compared at 1 and 3 months by sleep related outcomes and health related quality of life outcomes using two-sample t-tests or non-parametric Wilcoxon statistics, depending on whether normality appears to be in question. Levenes tests will be used to assess homogeneity of variance. In the presence of chance imbalances between intervention groups at baseline, multivariable general linear models will be used. To obtain measures of effect for larger studies, additional analyses will include examining changes in the sleep related and health related quality of life outcomes over time (baseline, 1 month, 3 months). These longitudinal profiles will be examined using a linear mixed effects framework with SAS Proc Mixed. Separate mixed effects

regression models will be generated for each of the sleep related and health related quality of life outcomes. Both random slopes and random intercepts will be modeled to represent deviations from the average, or fixed-effect, slope over time and intercept, respectively. Restricted maximum likelihood will be used for parameter estimation and the most appropriate covariance structure will be examined. Scores will be analyzed as repeated observations, with mean-centered baseline outcome scores serving as a covariate. Other predictor variables will include group, assessment time, and the interaction of group and time (primary effect of interest). Baseline measures and group will be analyzed as time-independent covariates. The evaluation of differences in outcome profiles over time according to group will rely on the group (MBSI-I vs. sleep education control) x time interaction terms. Statistical significance for individual intervention contrasts will be evaluated for each outcome, applying the Benjamini & Hochberg¹³⁹ method to control for the type I error rate at 5%. Time-specific contrasts will be estimated to evaluate differences in outcome within groups at 1 and 3 months using the SLICE option in SAS. The Akaike information criterion (AIC) will be used to evaluate overall model fit and to select the best-fitting longitudinal change pattern. We expect groups to be balanced on baseline characteristics due to randomization; however, imbalances that occur by chance will be adjusted for in all analyses. Primary analyses will be performed within the full intent-to-treat (ITT) sample, which consists of all subjects randomized to MBSI-I or sleep education control. In addition, we will perform analyses within a per-protocol (PP) sample that includes all randomized participants able to adhere to intervention fidelity. Aim 3 Analyses: We will explore the mechanisms by which MBSI-I affects sleep and health related quality of life measured via standardized questionnaires and inflammatory biomarkers. To examine the effect of the intervention on changes in pre-arousal, DBAS, and inflammatory biomarkers, two-sample t-tests or non-parametric Wilcoxon tests, as appropriate, will be used at 1 and 3 months. As described for Aims 1 and 2, additional analyses will include examining changes in the outcomes over time according to group using a linear mixed effects framework and will rely on the group x time interaction terms. Statistically significant findings will be concluded on the basis of a two-sided 0.05 level of significance, recognizing these analyses are exploratory in nature and findings will be used to generate hypotheses.

The following documents are currently attached to this item:

There are no documents attached for this item.

Data confidentiality

- x **Paper-based records will be kept in a secure location and only be accessible to personnel involved in the study.**
- x **Computer-based files will only be made available to personnel involved in the study through the use of access privileges and passwords.**
- x **Prior to access to any study-related information, personnel will be required to sign statements agreeing to protect the security and confidentiality of identifiable information.**
- x **Wherever feasible, identifiers will be removed from study-related information.**

A Certificate of Confidentiality will be obtained, because the research could place the subject at risk of criminal or civil liability or cause damage to the subject's financial standing, employability, or liability.

A waiver of documentation of consent is being requested, because the only link between the subject and the study would be the consent document and the primary risk is a breach of confidentiality. (This is not an option for FDA-regulated research.)

- x **Precautions are in place to ensure the data is secure by using passwords and encryption, because the research involves web-based surveys.**

Audio and/or video recordings will be transcribed and then destroyed to eliminate audible identification of subjects.

Subject Confidentiality

We will apply strict procedures to maintain confidentiality and will adhere to 2003 HIPAA Standards for Privacy of Individually Identifiable Health Information (the Privacy Rule). Each individual participant will be given a unique study identification number. Information linking the identification number to the participant will be kept in its own separate password-protected and encrypted secure file on the University of Pennsylvania server. All data will be labeled with the participants study specific

identification number and uploaded to another password-protected, secure server at the University of Pennsylvania. Information will only be available the research team. All project records will reflect only the ID number of each participant. Thus, research study participants names will not appear on any forms, and instead participants will use a unique identification number. To ensure HIPAA compliancy, the mPhenomic application on the tablet will be password protected and users will be given a non-identifiable username. This participant username will be used (along with a password) by the subject to log onto the application; they will not use their e-mail or other personal identifier as the username. The mPhenomic software on the tablet will not store any personal health information or a participants name, birthdate, sex, home address, or other personal information; it will only record tap events (time-stamped) and sleep diary times. Recorded data will be encrypted using standard protocols at rest and in transfer, leaving no point at which the raw data will be openly readable until accessed by the research team. The linkage between participant ID and participant name can only be determined from the participants link key, which will be stored in a locked file cabinet as a paper copy and also in an encrypted file on a password-protected computer that is maintained by the University of Pennsylvania to standards acceptable for storing personal health data. Rigorous security protocols that restrict data access points will also be implemented, requiring research staff to securely authenticate their identity before accessing the data. Access to the study participants identities will only be available to the immediate research staff. This data will be abstracted and entered directly into REDCap. Rigorous security protocols that restrict data access points will also be implemented, requiring research staff to securely authenticate their identity before accessing the data. This database is housed in HIPAA-compliant space within the University of Pennsylvania and meets FDA guidelines for research data management, including internal audit trail and data encryption features for secure data transmission. The University of Pennsylvania Health System (UPHS) also has guidelines in place for mobile devices and software. These include documentation of information security controls, incident response program, compliance certifications (OWASP, etc.), privacy practices, physical data security, and subcontractors. All tablets from the research team will contain remote monitoring software to track the units in case they are lost/stolen, perform remote data wipes, will be locked to prevent unauthorized use and can do remote software uploads when necessary to ensure that the app remains compliant with the latest patches and updates. These approaches have been used previously by our group for mobile device research and have been reviewed by the University of Pennsylvania IRB. Access to the study participants identities will only be available to the immediate research staff. The tablet app falls within the category of motivating patient behaviors, which according to the latest FDA guidance is considered within the category of enforcement discretion, therefore it does not require prior FDA review and approval. The app does not carry significant risk to research study participants (it is not implanted and does not expose the body to significant external energy for diagnostic or treatment purposes), thus it is within the category of FDA IDE device exemption. Prior research conducted by the mHealth service using similar exercise/behavioral intervention apps has been approved as an FDA IDE device exempt app. All data will be coded with a study specific identifying number and all data will be de-identified. The identifying number will be kept on a password-protected, secure server as described previously. All study data will be transmitted using encryption, and stored on secure servers as noted previously. The majority of data will be collected electronically via the REDCap system and minimal data will be obtained on paper Information will be compiled from all the participants in the study and, when published, data will be reported in aggregate form. As a result of aggregation, no individual participants will be identifiable from the written materials. Data will be saved for seven years and securely deleted after. The REDCap (Research Electronic Data Capture) system will be used as a central resource for quantitative data processing and management. REDCap is a web application and back-end database model designed to support data capture for research studies. The University of Pennsylvania has licensed its own version of REDCap that is housed on our own password-protected servers located within a data center inside the Penn firewall and therefore afforded the same network protections as other sensitive clinical systems. REDCap was developed specifically around HIPAA-security guidelines with features such as data encryption. It provides an intuitive interface for data entry with data validation, audit trails for tracking data manipulation and export procedures, automated export procedures for seamless data downloads to common statistical packages, including SAS, and procedures for importing data from external sources. We will use standard operating procedures to guide all data management activities, such as the naming and identification of variables, data cleaning and handling of missing data. All data obtained from electronic medical record review and self-report measures will be entered directly into the REDCap database on encrypted laptop computers as collected to reduce data collection time, increase accuracy, and prevent data loss. Data entry screens will be designed to incorporate range checks and concurrent checks to minimize errors. Missing fields will not be allowed. All scored data will be double entered to ensure accuracy. If tablets are lost or stolen, the

users password can be changed on the administrative end. This will cause the account to automatically log-out and will require the new credentials to be input into the fields in order to access the mPhenomic user interface.

Sensitive Research Information*

Does this research involve collection of sensitive information about the subjects that should be excluded from the electronic medical record?

No

Subject Privacy

Privacy refers to the person's desire to control access of others to themselves. Privacy concerns people, whereas confidentiality concerns data. Describe the strategies to protect privacy giving consideration to the following: The degree to which privacy can be expected in the proposed research and the safeguards that will be put into place to respect those boundaries. The methods used to identify and contact potential participants. The settings in which an individual will be interacting with an investigator. The privacy guidelines developed by relevant professions, professional associations and scholarly disciplines (e.g., psychiatry, genetic counseling, oral history, anthropology, psychology).

The researchers will be introduced to potential participants by staff at the Geriatric Clinic (with participant approval). For those identified via PennSeek, researchers will obtain provider permission prior to contacting participants by phone. Scientific environments must be safe for both the researcher and the research subjects, and also protect participant privacy, confidentiality, and autonomy. Research visits will take place Ralston House in private rooms, scheduled a time that is convenient for the participants. There is free parking for patients at Ralston House.

Data Disclosure

Will the data be disclosed to anyone who is not listed under Personnel?

No

Data Protection*

- Name**
- Street address, city, county, precinct, zip code, and equivalent geocodes**
- All elements of dates (except year) for dates directly related to an individual and all ages over 89**
- Telephone and fax number**
 - Electronic mail addresses**
 - Social security numbers**
- Medical record numbers**
 - Health plan ID numbers**
 - Account numbers**
 - Certificate/license numbers**
 - Vehicle identifiers and serial numbers, including license plate numbers**
 - Device identifiers/serial numbers**
 - Web addresses (URLs)**
 - Internet IP addresses**
 - Biometric identifiers, incl. finger and voice prints**
 - Full face photographic images and any comparable images**
 - Any other unique identifying number, characteristic, or code**
- None**

Does your research request both a waiver of HIPAA authorization for collection of patient information and involve providing Protected Health Information ("PHI") that is classified as a "limited data set" (city/town/state/zip code, dates except year, ages less than 90 or aggregate report for over 90) to a recipient outside of the University of Pennsylvania covered entity?

No

Tissue Specimens Obtained as Part of Research*

Are Tissue Specimens being obtained for research?

Yes

Tissue Specimens - Collected during regular care*

Will tissue specimens be collected during regulator clinical care (for treatment or diagnosis)?

No

Tissue Specimens - otherwise discarded*

Would specimens otherwise be discarded?

No

Tissue Specimens - publicly available*

Will tissue specimens be publicly available?

No

Tissue Specimens - Collected as part of research protocol*

Will tissue specimens be collected as part of the research protocol?

Yes

Tissue Specimens - Banking of blood, tissue etc. for future use*

Does research involve banking of blood, tissue, etc. for future use?

Yes

Genetic testing

If genetic testing is involved, describe the nature of the tests, including if the testing is predicative or exploratory in nature. If predictive, please describe plan for disclosing results to subjects and provision of genetic counseling. Describe how subject confidentiality will be protected Note: If no genetic testing is to be obtained, write: "Not applicable."

Not applicable

Consent

1. Consent Process

Overview

An employee of the participating setting (Ralston House) will initiate contact with eligible participants, as required by HIPAA regulations. Persons who agree to be contacted will have the study explained to them in the screening process. If participant is recruited via PennSeek, their provider will give us permission to contact them. In order to ensure that the participant truly understands what the research study entails and that his/her participation is voluntary, written informed consent (HIPAA authorization will be included in the informed consent document) will be obtained from all patients by the principle investigator. The investigator will go over the informed consent document with each subject at Ralston House in a private room and he/she will have the opportunity to ask questions. Potential participants will be fully informed regarding the intensity and length of data collection required of them. The specific types and methods of data to be collected will be described in detail. The informed consent will include disclosure of the purpose and duration of the study, risks and benefits, alternatives to participating, confidentiality, and contact information for the principal investigator in case further questions arise. The subjects will be made aware that the research study is voluntary, and if they choose not to be in the study or to be in the study but to stop at a later date, there will be no penalty or loss of benefits to which they are entitled. This will help to address any role conflict or coercion, so the participant does not feel he/she has to participate in the study or will otherwise lose the benefits of the University of Pennsylvania Health System. Participants will also have the opportunity to think about whether or not he/she would like to participate in the study. If a participant would like more time, they will have the opportunity to call the researcher back to set up another appointment. In order to ensure that the participant truly understands what the research study entails and that his/her participation is

voluntary, participants will be asked five questions: What is the purpose of the study? What are the risks to the study? What are the benefits of the study? How to contact me, the principle investigator? How to withdraw from the study? Assessing older adults capacity to provide consent is an important step in the informed consent process. Older adults who can verbally provide 4 out of 5 answers correctly will be considered capable of providing their own consent. I will again answer any questions they may have about the study. If they continue to agree to participate, then they will be asked to sign the last page of the consent form designating their consent to participate in the study. If the subject chooses to consent, he/she will be sent home with a copy of the consent form, a copy will be scanned to the electronic medical record and the original paper copy will be stored in a locked filing cabinet in the PIs locked office at the University of Pennsylvania, Ralston House. For older adults who have given oral assent to participate in the study but cannot verbally provide 4 answers correctly (demonstrating the lack of cognitive ability to provide consent), they will not be included in this study for two reasons. First, there is no caregiver component to the intervention that would permit us to use proxy-reported informed consent and second, this study is looking at mild cognitively impairment people that should be able to give informed consent if they meet the inclusion criteria of the MoCA.

Children and Adolescents

Not applicable

Adult Subjects Not Competent to Give Consent

All adult subjects must be competent to give informed consent.

2. Waiver of Consent

Waiver or Alteration of Informed Consent*

No Waiver Requested

Minimal Risk*

Impact on Subject Rights and Welfare*

Waiver Essential to Research*

Additional Information to Subjects

Written Statement of Research*

No

If no written statement will be provided, please provide justification

The following documents are currently attached to this item:

There are no documents attached for this item.

Risk / Benefit

Potential Study Risks

We do not believe there are any major risks associated with the proposed protocol. There is minimal risk associated with blood draws, physical activity, and study burden. We will explain associated risk to the participants. Other potential risks to participants are fatigue from data collection, stress in response to self-report instruments or concerns related to confidentiality. In addition, the participant may experience discomfort from sleeping with the wrist watch device, but that usually subsides after the first night. If the participant cannot tolerate the watch, he/she will be instructed that removal of the watch is allowed. Participant burden, specifically fatigue, is the most likely risk related to this study. To minimize fatigue during data collection, we chose only the most relevant self-report instruments. However, given that this is an older adult population with cognitive impairment; we will offer the participant the opportunity to take breaks. It is possible that some participants may become anxious or stressed during data collection because of the questions asked, the burden of data collection, or for other personal reasons. Stress is judged to be low likelihood because the instrument questions are not highly

intrusive or sensitive. However, should this occur, the participant will be asked if they would like to terminate or delay data collection. Loss of confidentiality is considered very low likelihood given the protections we will have in place and our experience in systems of protecting private information. Intervention: The study poses minimal risks to subjects beyond standard clinical care for insomnia. Sleep hygiene is a standard clinical recommendation for insomnia, and thus does not pose any additional risks to the subject beyond standard clinical care. Furthermore, the relaxation intervention component can reduce the risk of falls or daytime sleepiness associated with the standard of care treatment, conventional CBT-I. The tablet screen background is black for the sleep diary to avoid excessive light exposure at night, and the tablet screen is set to black when using the ART intervention in bed. The tablets are locked to prevent use of other applications. Plan to address risk: Venipuncture for blood samples might result in occasional bruising, pain, or local reaction. All blood samples will be taken by a trained research assistant and certified phlebotomist using sterile methods. Further, the risk of a vaso-vagal episode following venipuncture will be minimized by conducting this procedure in a phlebotomy chair in which the subject can quickly be laid flat in the case that a vaso-vagal episode may occur. Physical Activity: In very rare occasions, the subject may fall or get injured during physical activities. These adverse events should be minimized by using personalized physical activity plans, which will be developed/designed based on the subjects personal features by the PI to be most suitable for the subject. The activity intervention will be based on an existing NIH-funded activity protocol for older adults. Any occurrence of adverse events will be immediately reported to the IRB at the University of Pennsylvania. Wrist watch discomfort: The subject may experience discomfort from sleeping with the wrist watch device, but that usually subsides after the first night. If the subject cannot tolerate the watch, he/she will be instructed that removal of the watch is allowed. Fatigue: We estimate screening and consent to take 30 minutes, quantitative data collection 20 minutes; instructions for actigraphy and sleep diary 5-10 minutes; blood draws 5 minutes. We anticipate developing the meaningful activity plan to take 30 minutes to one hour. Stress: As the PI, I will be collecting the data. I am a registered nurse with a masters degree specialized in the care of older adults and a PhD. Thus, I am well trained to be supportive and helpful to the participants should they become anxious or stressed in response to survey questions. If participants do become stressed, data collection will be delayed to tend to the participants emotional needs. Data collection will resume if and when the participant is ready to proceed.

Potential Study Benefits

For society in general, the study offers benefits in that it develops a new treatment option for insomnia in older adults with mild cognitive impairment, a group that has difficulty participating in traditional CBT-I and is at increased risk for side effects from pharmacotherapy for insomnia. In general, we feel that this study represents a minimal risk to participants. The treatments that they will undergo are similar to standard care for insomnia, thus pose minimal additional risk above standard medical care. It is possible that while these study results may benefit older adults in the future, participants in this study may not realize an immediate or direct benefit from participating. It is also possible that the participants gain a heightened awareness of their sleep habits and patterns after completing the sleep diary. Additionally, those randomized to the intervention group may have benefits from the intervention. As the study involves very little risk and there is significant potential for benefit, the risk / benefit ratio is favorable.

Alternatives to Participation (optional)

The alternative to participation in the study is to decline participation and continue with routine clinical care for the study participants insomnia. Refusal to participate in the study will in no way adversely affect the clinical care the study participants would otherwise receive at the University of Pennsylvania Health System.

Data and Safety Monitoring

Trial monitoring will be done by the PI and the primary mentor (Dr. Hodgson). They will evaluate the progress of the study on a monthly basis, including periodic assessments of data quality (safety and integrity) and timeliness, recruitment, accrual and retention, participant risk versus benefit, and other factors that can affect study outcome; consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the trial; review study performance; and discuss the resolution of problems. Furthermore, the PI and primary mentor will monitor adverse events (AEs), including serious adverse events (SAEs) and unanticipated problems (UPs). An Adverse Event is any untoward medical occurrence in a patient or clinical investigation participant and which does not necessarily have a causal

relationship with this treatment. Participants will be queried regarding any changes in their health and medications at each contact. The informed consent document will list the daytime and after hours contact information for the site Principal Investigator. All AE and SAE reporting will be done in adherence with IRB guidelines; the PI will notify the IRB within 48 hours of any serious possible or potentially study-related AEs. The report will include the description of the AEs and any actions taken by the PI. SAEs in this population include, but are not limited to death, hospitalization, evidence of abuse, suicidal ideation, and medical emergencies. The PI will also keep a log of all AEs. Any deviations related to the protocol will be reported to the IRB using a deviation form immediately upon the discovery of the deviation. Given the non-invasive nature of the intervention, the team does not anticipate AEs beyond the average rate of these events in this population. The literature in the field will be continually appraised by the team. If any team member uncovers new information that would impact the safety of the participants or the ethics of our study, the PI and entire mentoring team will discuss the issues. At this time, given the low risk of the intervention, there is no plan for interim analyses or any stopping rules.

The following documents are currently attached to this item:

There are no documents attached for this item.

Risk / Benefit Assessment

We believe that the benefits far outweigh the risks to participants in this study. We feel this study is minimal risk.

General Attachments

The following documents are currently attached to this item:

Cover Letter (2019_03_26_irb_response_cover_letter.pdf)

Informed consent form (2019_03_26_k23_irb_consent_tracked.docx)

Informed consent form (2019_03_26_k23_irb_consent_clean.docx)