CPAP Randomized Controlled Trial

Treating Sleep Apnea to Improve Cognitive Function, Alzheimer's Disease Pathology, and Astrocyte Activation in Older Adults with Cognitive Impairment: A Multi-Centre Randomized Controlled Trial

Protocol Number: CTO 5040

Version Number: *1.2 dated November 10, 2024*

Principal Investigator: *Dr. Andrew Lim*
Regulatory Sponsor: Sunnybrook Research Institute

Funding Agency: Weston Family Foundation

PROTOCOL SIGNATURE PAGE

I have read this protocol in its entirety and its appendices. I agree to comply with the requirements of the study protocol and procedures for data recording/reporting and acknowledge my responsibility for the well-being of each research participant, and to ensure that all persons involved in study activities are adequately informed about the protocol, the investigational product, and their trial-related duties. The signature below constitutes the agreement to conduct this study in accordance with the REB approved protocol, GCP and applicable regulatory requirements, including confidentiality, ethical guidelines and regulations regarding the conduct of research in humans.

Qualified Investigator:

Name:
(Print) _____

Title & Institution:
(Print) _____

Signature: _____

Date of signature:
(yyyy-mmm-dd) _____

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LIST OF ABBREVIATIONS

The following abbreviations describe terms, documents and study personnel used in the conduct of this study protocol.

AE	Adverse Event/Adverse Experience
AD	Alzheimer's disease
AHI	Apnea hypopnea index
BHP	Brain Health Pro
CC	Coordinating Centre
CCNA	Canadian Consortium on Neurodegeneration in Aging
CPAP	Continuous Positive Airway Pressure
CRF	Case Report Form
EC	Ethics Committee
EEG	Electroencephalography
IB	Investigator's Brochure
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
eCRF	Electronic Case Report Form
pCRF	Paper Case Report Form
GCP	Good Clinical Practice
GFAP	Glial Fibrillary Acidic Protein
HSAT	Home sleep apnea test
ICF	Informed Consent Form
MCI	Mild Cognitive Impairment
MOCA	Montreal Cognitive Assessment
MRI	Magnetic Resonance Imaging
ODI	Oxygen Desaturation Index
OSA	Obstructive Sleep Apnea
PET	Positron Emission Tomography
PHI	Personal Health Information
PI	Principal Investigator
PSG	Polysomnography
PVS	Perivascular Space
QI	Qualified Investigator
REB	Research Ethics Board
RCT	Randomized Controlled Trial

REM	Rapid Eye Movement
SAE	Serious Adverse Event/Serious Adverse Experience
SDMT	Symbol Digit Modalities Test
SOP	Standard Operating Procedure
SRI	Sunnybrook Research Institute
SUADR	Serious and Unexpected Adverse Drug Reaction
TMF	Trial Master File

PROTOCOL SUMMARY

Protocol Title (Short Title)	Treating Sleep Apnea to Improve Cognitive Function, Alzheimer's Disease Pathology, and Astrocyte Activation in Older Adults with Cognitive Impairment: A Multi-Centre Randomized Controlled Trial (CPAP Randomized Controlled Trial)
Protocol Number	CTO 5040
Phase	II
Study Design	Single-blinded randomized controlled trial
Study Duration	3 years
Setting	Community-dwelling older adults who respond to recruitment initiatives and advertisements, or patients attending dementia prevention clinics, memory clinics, or sleep clinics throughout the Greater Toronto Area
Sample Size	206 participants randomized to either: **Early CPAP group**: Brain Health Support PRO sleep modules (BHP-sleep; a web-based sleep education intervention) and Continuous Positive Airway Pressure (CPAP) for 8 months; or **Later CPAP group**: BHP-sleep for first 4 months, then BHP-sleep and CPAP for remaining 4 months of participation. Target sample size for each group is 103.
Main Inclusion Criteria	Older adults with mild cognitive impairment (MCI) and previously untreated obstructive sleep apnea (OSA)
Primary Outcome(s):	This trial tests the hypothesis that in older adults with MCI and previously untreated OSA, 4 months of web-based sleep education and CPAP will improve cognitive function more than web-based sleep education alone. This trial also tests the hypothesis that 8 months of CPAP will improve cognitive function more than 4 months of CPAP. The primary outcome of this study will be change in the Symbol Digit Modalities Test (SDMT). The SDMT is a test of speeded executive function that is predictive of clinically significant improvement in patients with MCI. Additional cognitive measures that supplement the primary outcome of this study will be: attention and executive function (Trail Making Test A & B), working memory (Digit Span and Letter-Number Sequencing), verbal learning and memory (Hopkins Verbal Learning Test), and severity of cognitive impairment (Alzheimer's Disease Assessment Scale – Cognitive Subscale; ADAS-Cog-13).

Secondary Outcome(s):	This trial will also assess change in 1) Magnetic Resonance Image (MRI) quantified brain perivascular spaces (PVS) 2) plasma glial fibrillary acidic protein (GFAP) and 3) plasma pTau-181. This trial will also aim to identify features of sleep physiology that mediate the impact of CPAP on cognitive function. An exploratory subset of 28 participants (14 per group) will be invited to participate in a sub-study with its own protocol and informed consent process where changes in microglial activation will be assessed by [^{18}F]FEPPA Positron Emission Tomography (PET).
Planned Treatment	**Early CPAP group**: Participants randomized to this group will start BHP-sleep and CPAP simultaneously and continue both for 8 months. BHP-sleep consists of the sleep modules of the Canadian Consortium on Neurodegeneration in Aging's (CCNA) online Brain Health PRO platform covering sleep physiology, healthy sleep habits, and information about sleep disorders like sleep apnea. Participants will receive a study-provided auto-titrating CPAP device, with settings set by one of the study sleep medicine physicians according to current clinical practice parameters. Participants will undergo an in-person mask fitting, and then will be supported by a sleep technologist with extensive clinical experience with CPAP. **Later CPAP group**: Participants randomized to this group will start BHP-sleep without CPAP for first 4 months, followed by BHP-sleep and CPAP simultaneously for remaining 4 months of participation.
Statistical Analysis:	For our primary analysis, this trial will model performance on the SDMT as a function of time (baseline vs. 4 months) and study group (Early CPAP vs. Later CPAP). In secondary analyses, we will consider a series of models replacing the SDMT with our secondary cognitive endpoints. We will repeat the analyses above, considering the change between baseline and 8 months. We will also conduct a mixed-effect analysis including both the 4-month and 8-month time points. We will again repeat the analyses above, replacing our cognitive outcomes with a) plasma GFAP b) plasma pTau-181 and c) MRI PVS burden. Finally, we will use mediation analysis to examine the extent to which the effect of CPAP on change in SDMT is mediated by specific changes in sleep physiology.

1 KEY ROLES AND CONTACT INFORMATION

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2 INTRODUCTION

This study document is the protocol for research involving human participants. This study is to be conducted according to Canadian and international standards, and in compliance with the protocol, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice E6 (GCP), World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Participants, as well as applicable regulatory and institutional requirements and research policies.

2.1 Background

Sleep disruption and cognitive impairment frequently coexist. Several forms of sleep disruption, including sleep apnea (1), are associated with more rapid cognitive decline and Alzheimer's disease (AD) related brain changes. However, observational studies, particularly those in older adults, cannot determine whether sleep disruption contributes to or is a consequence of AD-related brain changes. Indeed, there has been a lack of randomized controlled trials (RCT) demonstrating an impact of any sleep intervention on cognitive decline or key AD-related brain changes.

Of particular interest is obstructive sleep apnea (OSA), a disorder characterized by repetitive obstruction of the upper airway in sleep leading to hypoxia, sleep fragmentation, and disrupted slow wave sleep. OSA is seen in up to 50% of patients with mild cognitive impairment (MCI) (Figure 1) and associated with more rapid cognitive decline (1). It is effectively treated by continuous positive airway pressure (CPAP); the application of positive airway pressure to splint open the upper airway preventing collapse. Observational studies suggest CPAP use is associated with improved cognitive function (Figure 2) and reduced perivascular space (PVS) burden (Figure 3).

This study will address residual knowledge gaps left by other observational studies of CPAP in MCI patients. The randomized design of this study will allow greater causal certainty than observational studies and may support a change in practice. This study may support screening for and treatment of OSA in individuals with MCI to improve cognition. There will be much deeper mechanistic dissection, particularly of microglial activation and perivascular biology (assessed using a neural network MRI segmentation tool we developed called SynthSegCSVD) (Figure 4). This will provide therapeutic targets for addressing the adverse effects of OSA on MCI-related outcomes in the individuals who cannot tolerate CPAP. This study will also use wearable sensors to assess the role of changes in sleep physiology in mediating the link between CPAP and MCI-related outcomes.

This study may provide evidence that for the ~50% of patients with MCI who have OSA, treatment with CPAP can improve cognition, and reduce key pathophysiological contributors to dementia including neurofibrillary tangle pathology (Figure 5), astrocyte (Figure 6) and microglial activation (Figure 7), and enlargement of perivascular spaces. This will support widespread treatment of OSA in patients with cognitive impairment to slow cognitive decline and reduce dementia-related brain changes. Moreover, it will identify the key sleep changes mediating these effects, which can then be specifically targeted by other interventions.

Our four key end users are 1) patients with MCI, sleep apnea, or both 2) sleep and dementia physicians who care for them 3) allied health practitioners supporting these patients and who would support CPAP adherence and 4) public health officials who would fund screening and treatment of sleep apnea.

2.2 Pre-Clinical and Clinical Data to Date

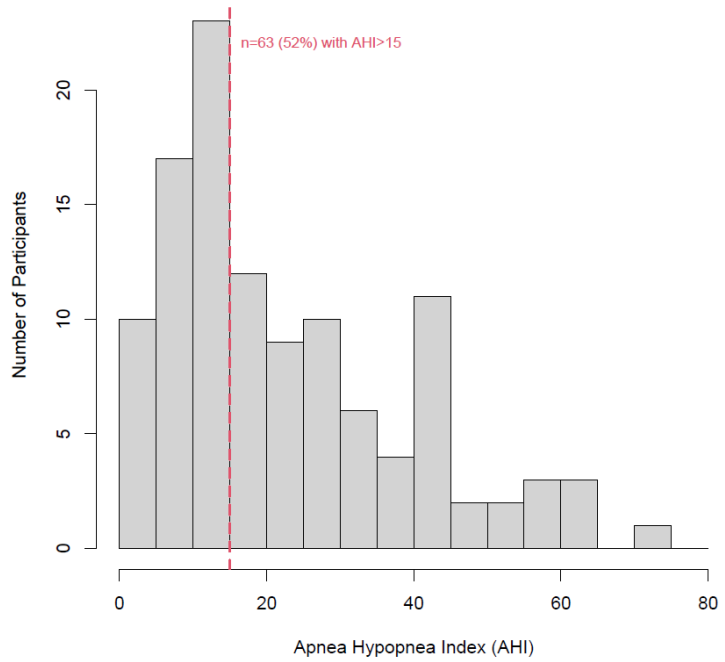

Figure 1: Sleep apnea is common in adults with MCI. We measured sleep apnea in 121 adults with MCI in the Memory and Aging Project using the WatchPAT wearable sensor. 61 participants (52%) had at least moderate sleep apnea.

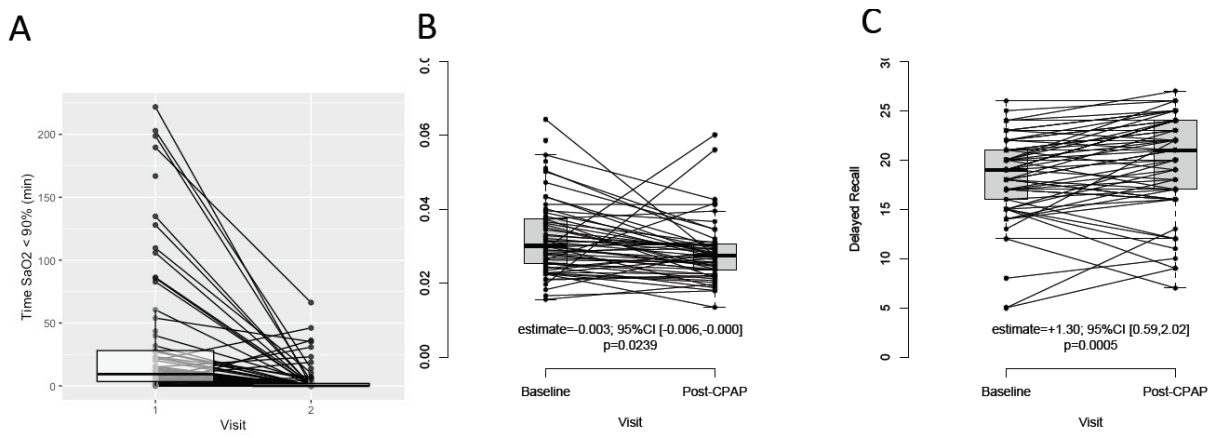

Figure 2: CPAP improves hypoxia, sleep fragmentation and cognitive function in patients with sleep apnea. We treated 66 patients with newly diagnosed moderate sleep apnea (AHI>15; Apnea hypopnea index) with 4 months of CPAP. We measured oxygen saturation with pulse oximetry. We measured sleep fragmentation with 10 days of wrist actigraphy. Cognition was measured with the Toronto Cognitive Assessment. 4 months of CPAP was associated with dramatically reduced hypoxia (time with SpO2<90%, panel A) and sleep fragmentation (kRA, panel B), and improved delayed memory performance (panel C).

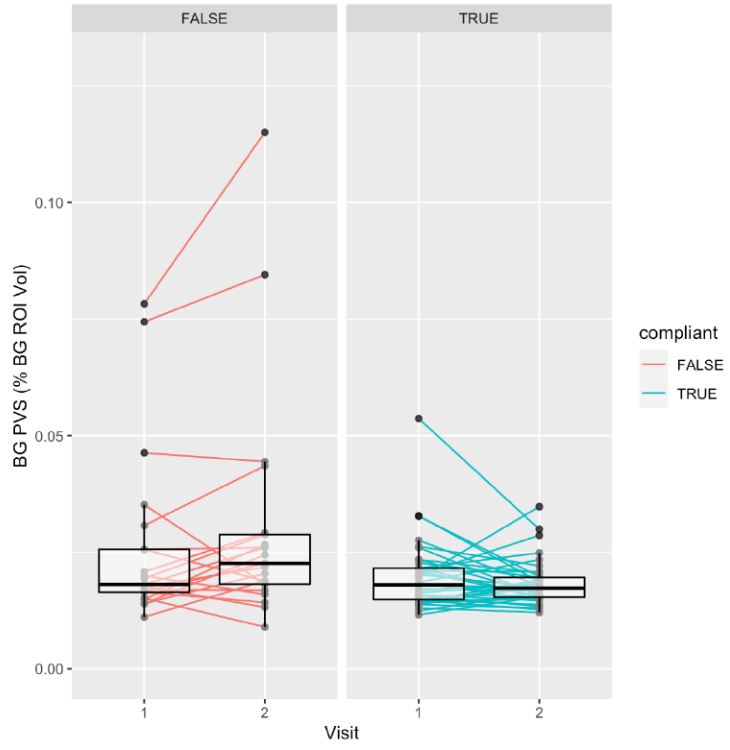

Figure 3: CPAP use stabilizes MRI-visible perivascular space volumes. We treated 66 patients with newly diagnosed moderate (AHI>15) sleep apnea with 4 months of CPAP. We measured MRI-visible perivascular space volumes, which are thought to be a key contributor to cognitive impairment. ~50% of participants used CPAP >4 hours a day. In those not adherent with CPAP, PVS volumes increased over 4 months. However, CPAP adherence was associated with stabilisation of PVS volumes.

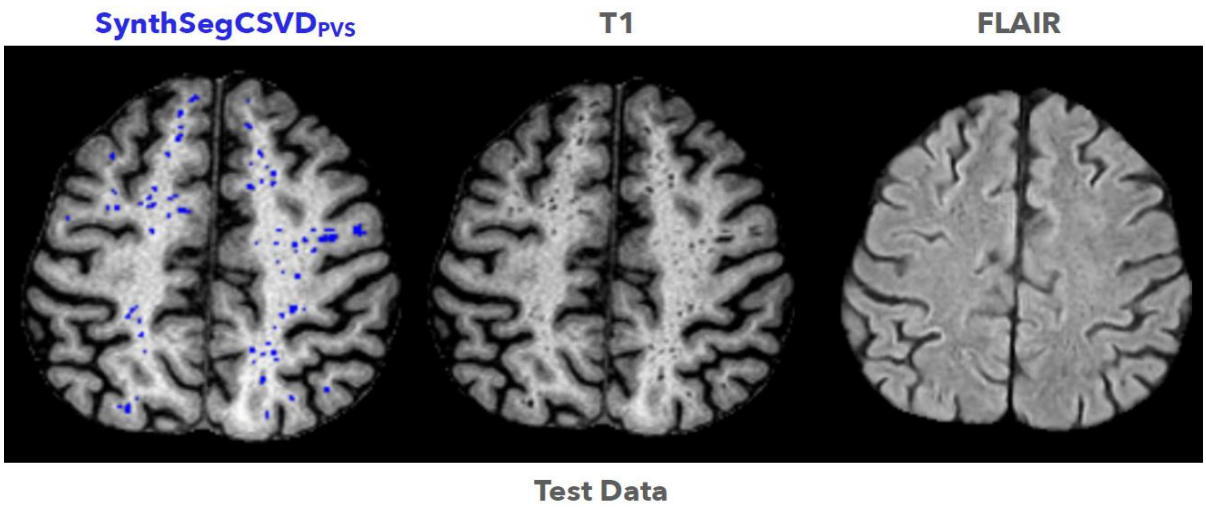

Figure 4: SynthSegCSVD, a new Convolutional Neural Network-Based Tool for Segmentation of Perivascular Spaces. We have developed and validated SynthSegCSVD for rapid automated segmentation of PVS from heterogeneous MRI datasets. This panel shows example SynthSegCSVD output showing PVS segmentation.

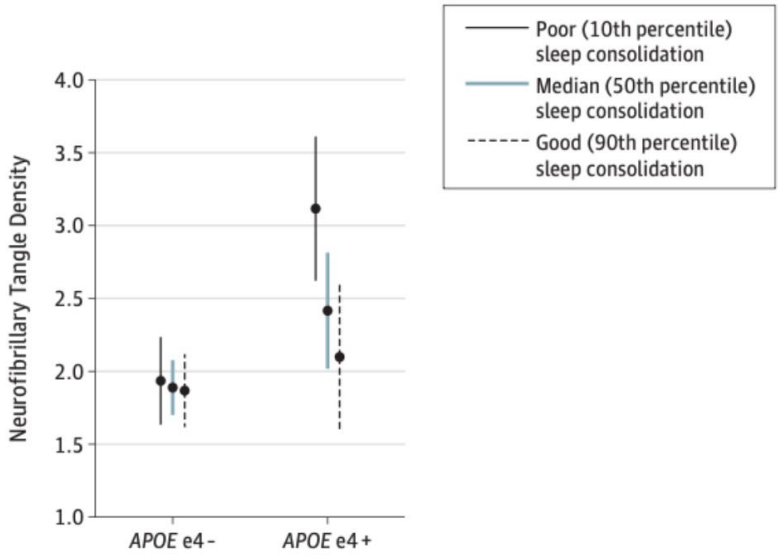

Figure 5: Better sleep consolidation is associated with lower neurofibrillary tangle density in genetically at risk adults. (interaction estimate, −0.42; SE, −0.17; P= .02) (2).

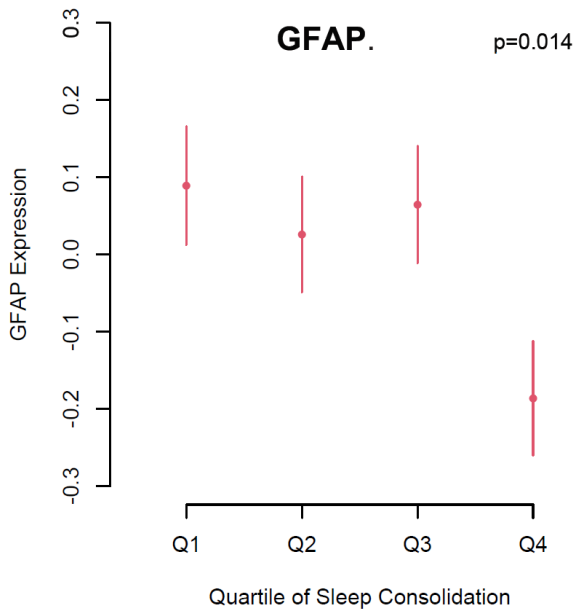

Figure 6: More consolidated (less fragmented) sleep is associated with lower expression of plasma glial fibrillary acidic protein (GFAP), a marker of astrocyte activation. In 415 older adults, we assessed gene expression in the dorsolateral prefrontal cortex by RNAseq and related this to sleep consolidation assessed by wrist accelerometry. Better sleep consolidation (lower sleep fragmentation) was associated with lower expression of GFAP.

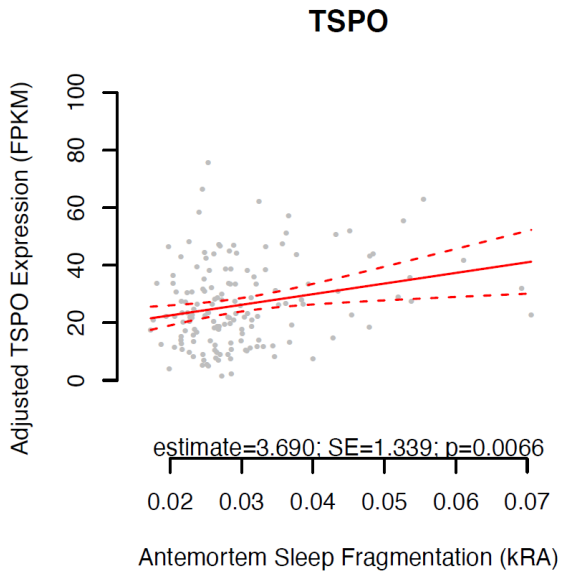

Figure 7: More fragmented sleep is associated with higher expression of TSPO, a marker of microglial activation. In 152 older adults, we assessed gene expression in the dorsolateral prefrontal cortex by RNAseq and related this to sleep fragmentation assessed by wrist accelerometry. Higher sleep fragmentation was associated with greater expression of TSPO.

2.3 Anticipated Benefits and Rationale

This study will provide class I evidence that CPAP, in combination with an online sleep optimization program, will improve memory and concentration, reduce Alzheimer's associated proteins, prevent brain blood vessel damage, and reduce brain inflammation, in adults with OSA and MCI. This will suggest that large scale screening for and treatment of OSA may be an effective means of preventing and potentially improve dementia-related outcomes. Moreover, it would be the first proof that improving sleep can in principle prevent dementia and open the door to trials of other interventions to improve sleep to prevent dementia.

3 STUDY OBJECTIVES

The overall goal of this randomized controlled trial is to test the hypothesis that in older adults with MCI and previously untreated OSA, 4 months of web-based sleep education and CPAP will improve cognitive function more than web-based sleep education alone. Secondarily, this trial will test the hypothesis that 8 months of CPAP will improve cognitive function more than 4 months of CPAP. Moreover this trial will test several mechanistic hypotheses, namely that 4 months of CPAP will 1) stabilize the growth of MRI-quantified brain perivascular spaces, a key correlate of cognitive impairment, 2) reduce plasma glial fibrillary acidic protein, a marker of astrocyte activation, 3) reduce plasma pTau-181, a marker of neurofibrillary tangle pathology – one of the pathological hallmarks of Alzheimer's disease, and 4) identify features of sleep physiology that mediate the impact of CPAP on cognitive function.

An exploratory subset of 28 participants (14 per group) will be invited to participate in a sub-study with its own protocol and informed consent process aimed to assess change in microglial activation assessed by [^{18}F]FEPPA Positron Emission Tomography (PET).

3.1 Primary Objective

The specific primary objectives are:

(1) Cognitive Function: Test the hypothesis that in adults with MCI and previously untreated moderate-severe OSA, 4 months of web-based sleep education and CPAP will improve cognitive function (or slow cognitive decline) as measured by the Symbol Digit Modalities Test (SDMT) more than web-based sleep education alone.

(2) Treatment Duration: Test the hypothesis that 8 months of CPAP will improve cognitive function (or slow cognitive decline) as measured by SDMT more than 4 months.

3.2 Secondary Objective(s)

The specific secondary objectives are:

(3) Neurobiological Mechanisms: Test the hypothesis that 4 months of web-based sleep education and CPAP will reduce a) astrocyte activation (plasma GFAP) b) neurofibrillary tangle burden (plasma pTau181) and c) MRI-visible perivascular space burden more than web-based sleep education alone.

(4) Sleep Physiology: Identify features of sleep physiology (i.e. decreased hypoxic burden and fragmentation, increased slow-wave power and REM sleep) that mediate the impact of CPAP on cognitive function.

4 STUDY DESIGN

4.1 General Design

The general design of this study is a single-blinded randomized controlled trial of 206 adults randomized into two groups:

Early CPAP group: Participants randomized to this group will start BHP-sleep and CPAP simultaneously and continue both for 8 months. BHP-sleep consists of the sleep modules of the Canadian Consortium on Neurodegeneration in Aging's (CCNA) online Brain Health PRO platform covering sleep physiology, healthy sleep habits, and information about sleep disorders like sleep apnea. Participants will receive a study-provided auto-titrating CPAP device, with settings set by one of the study sleep medicine physicians according to current clinical practice parameters. Participants will undergo an in-person mask fitting, and then will be supported by a sleep technologist with extensive clinical experience with CPAP.

Later CPAP group: Participants randomized to this group will start BHP-sleep without CPAP for first 4 months, followed by BHP-sleep and CPAP simultaneously for remaining 4 months of participation.

4.2 Primary Outcomes

The primary outcome of this study will be change in the Symbol Digit Modalities Test (SDMT). The SDMT is a test of speeded executive function that is predictive of clinically significant improvement in patients with MCI with a well-defined minimal clinically significant change (2) and that is responsive to CPAP in observational studies (3).

Additional cognitive measures that supplement the primary outcome of this study will be: attention and executive function (Trail Making Test A & B), working memory (Digit Span and Letter-Number Sequencing), verbal learning and memory (Hopkins Verbal Learning Test), and severity of cognitive impairment (Alzheimer's Disease Assessment Scale – Cognitive Subscale; ADAS-Cog-13).

4.3 Secondary Outcomes

Vascular risk factors and AD-biomarkers: Plasma pTau181 (for AD pathology) and GFAP (for astrocyte activation) will be assessed. pTau181 has been shown to be strongly predictive of both amyloid and tau pathology as measured by PET (4,5) while plasma GFAP correlates strongly with ^{18}F-SMBT-1 PET, a marker of brain reactive astrocytes (6). This protocol does not include plasma amyloid beta 42 as recent studies suggest that pTau181 alone has similar performance to a larger panel of biomarkers in discriminating between levels of a PET proxy of AD pathology (4) and our previous work showed a stronger association between sleep fragmentation and burden of tau pathology than burden of amyloid pathology (7).

Aliquots will be sent to and analysed in the Toronto laboratory of Co-I Dr. Tartaglia on the Quanterix SIMOA platform, a semi-automated digital ELISA platform. Analysis will include quantification of plasma p-tau-181 using the ptau-181 V2.1 Advantage assay, and GFAP using the GFAP discovery assay.

Remaining aliquots will be retained for future studies.

Blood levels of various fats, sugars, and proteins (like cholesterol or glucose) will be assessed.

Participants will undergo MRI using the Canadian Dementia Imaging protocol consisting of a 3D T1, interleaved 3mm PD/T2, 3D FLAIR, T2*, DTI, and resting state BOLD. Perivascular spaces and white matter hyperintensities will be quantified with the SynthSegCSVD algorithm developed and validated in our laboratory, a robust neural network based tool (Figure 4).

Sleep physiology will be assessed using wearable sensors: at-home sleep apnea testing apparatus (for oximetry metrics including AHI, ODI, mean SpO2, hypoxia burden, and time with O2<92%), EEG headband (sleep staging, including % slow wave sleep, % REM sleep, total EEG sleep time, and NREM slow wave power), and wrist-worn accelerometry (for total sleep time and sleep fragmentation).

5 PARTICIPANT SELECTION AND WITHDRAWAL

Community-dwelling older adults who respond to recruitment initiatives and advertisements, or patients attending dementia prevention clinics, memory clinics, or sleep clinics throughout the Greater Toronto Area. Target sample size is 206 adults over the age of 55 with MCI and previously untreated OSA.

5.1 Inclusion Criteria

Each participant must meet all of the following inclusion criteria to participate in this study:

1) Informed consent obtained and signed.
2) Age >55
3) MCI: Participants will undergo a video-based screening, including a clinical interview, Logical Memory II, MoCA, and Lawton-Brody Instrumental Activities of Daily Living Scale Score. A participant will be considered to have MCI if they have:
    a. MoCA score of 13-24, and
    b. Logical Memory II Score ≤ 8 (>=16 years of education), ≤ 4 (8-15 years of education) or ≤ 2 (0-7 years of education), and
    c. Lawton-Brody IADL Score >14/23, and
    d. do not meet DSM IV criteria for dementia, and
    e. have a change in self-perceived cognition from previous
4) Moderate-severe OSA: Participants who screen positive for MCI will be mailed an at-home sleep apnea testing device (Apnealink, ResMed, San Diego, California, USA), an FDA-approved self-administered 3-channel portable device that assesses for sleep apnea based on airflow as assessed using an intra-nasal pressure transducer, pulse oximetry assessed using a finger probe, and respiratory effort using a band around the chest.. Participants with ODI$\geq$5 will undergo in-lab polysomnography (PSG) for confirmation and characterization of sleep apnea. A participant will be considered to have moderate-severe OSA if they have on PSG:
    a. AHI$\geq$15, and
    b. ODI$\geq$10, and
    c. central apneas<10% of all apneas, and
    d. periodic limb movement index <15.

5.2 Exclusion Criteria

All potential participants meeting any of the following exclusion criteria will be excluded from participation in this study:

1) drowsiness-related driving accidents or near misses in the past 12 months
2) drives as their primary occupation
3) unable to complete cognitive evaluation in English
4) unable to participate in video-based cognitive assessment
5) not a resident of Ontario
6) contraindications to MRI

7) contraindications to CPAP or unwilling to start CPAP
8) no available study partner to support CPAP
9) previously treated for sleep apnea
10) clinically significant insomnia (ISI > 15), restless legs syndrome, or shift work
11) taking disease modifying agents for MCI

5.3 Participant Recruitment

We estimate that we will need to enroll 206 participants with MCI and sleep apnea in order to have 80% power to detect a minimal clinically significant change in the SDMT of 3.8 points assuming CPAP adherence of 62% and loss-to-follow-up of 10%. In our data, the prevalence of moderate or greater OSA among patients with MCI is ~50% (Figure 1). Assuming that of these ~25% will already be on CPAP, this would require identifying ~550 adults with MCI who would be willing to participate in the study. In or to reach ~550 of these individuals, we will use a combination of the following recruitment strategies:

1) **Geotargeted mailings.** We will send geotargeted mailings to adults In the GTA over the age of 55, inviting those with cognitive concerns and symptoms compatible with sleep apnea to go to our study website. A similar approach was used in the Canadian Consortium on Neurodegeneration in Aging Can Thumbs Up Brain Health Support Program (CTU-BHSP) study. In CTU-BHSP, one participant enrolled for every 130 postcards mailed, of which 1/3 had MCI. We plan to send out up to 40,000 postcards, which should yield ~100 interested potential participants with MCI. We will retain the option to scale up as needed to increase enrolment.
2) **Online advertisements.** We will produce geotargeted ads to run through Instagram and Facebook. A similar approach was used in the CTU-BHSP study, where $500 spent on geotargeted Facebook and Instagram advertising to reach 39,000 adults resulted in 18 enrolled participants with MCI. We plan to run an advertising campaign with double the reach of CTU-BHSP, which should yield ~40 interested potential participants with MCI. We will retain the option to scale up as needed to increase enrolment.
3) **Clinic-based recruitment.** We will recruit from Toronto Dementia Research Alliance affiliated clinics at the Toronto Western Hospital, Baycrest Hospital, and Sunnybrook hospital. Collectively, these clinics see ~80 patients with MCI per month. Between these three clinics, we anticipate recruiting up to 10 adults with MCI per month over 24 months. This should yield ~240 interested potential participants with MCI. Flyers will be placed in clinic rooms and/or bulletin boards and will also be available for potential participants to take home. Potential participants may also be approached by a member of their care team who can provide them with a study flyer which will contain contact information for the study. Potential participants will be given the opportunity to verbally agree with their clinic care team to share contact information (name, phone, email) with study staff so that they may be contacted to discuss interest in participating in this study. If applicable, potential participants may also consent for clinical information relevant to this protocol (i.e. MCI diagnosis, cognitive test results) to be shared with the study team.
4) **Baycrest Centre.** The Baycrest Centre offers a number of recruitment sources, including but not limited to:

a. **Rotman Database:** The Rotman Research Institute manages a database of research volunteers, with >16,000 active participants. Some of these individuals have received a diagnosis of MCI.
b. **Cogniciti.** The Cogniciti Brain Health Registry (*www.cogniciti.com*), based at Baycrest, includes >10,000 individuals in the GTA who have undergone online cognitive testing and who have also indicated their desire to be contacted about clinical trials. We anticipate based on pilot work that we will find 1,200 adults with MCI. An already established pipeline is in pl ace in Dr. Chertkow's lab (co-PI of this protocol) to screen these individuals by videoconferencing for MCI. This should yield ~300 interested potential participants with MCI, with option to scale up as needed to increase enrolment. Potential participants may also be provided a study flyer which will contain contact information for the study. Potential participants will be given the opportunity to verbally agree to share contact information (name, phone, email) with study staff so that they may be contacted to discuss interest in participating in this study. If applicable, potential participants may also consent for clinical information relevant to this protocol (i.e. MCI diagnosis, cognitive test results) to be shared with the study team.
c. Kimel Family Centre for Brain Health. The Kimel Centre (*https://kimelcentre.baycrest.org/*) is enrolling 2,000 individuals aged 50 or over interested in dementia prevention, all of whom are screened cognitively prior to entry in programs. These individuals are entered into the Rotman database at Baycrest and given the opportunity to indicate their desire to be contacted about clinical trials. We anticipate of these 2,000 participants, 600 will have MCI based on their cognitive evaluations. Through Dr. Chertkow (co-PI of this protocol and Scientific Director of the Kimel Centre, and also Dr. Nicole Anderson, Associate Scientific Director of the Kimel Centre), this should yield ~400 interested potential participants with MCI, with an option to scale up as needed to increase enrolment. Kimel Centre participants will be reached through 5 mechanisms: 1) through the Rotman database 2) through physical flyers placed in Kimel Centre spaces 3) through regular email newsletters sent out by the Kimel Centre 4) in person by Kimel centre staff during Kimel clinic visits, and 5) the study PI will conduct a series of in-person education sessions at the Kimel centre addressing sleep more broadly and also this study more specifically**.**. For 1) Kimel Centre staff will identify Kimel Centre participants who are already part of the Rotman database who have already consented to recontact and will provide their contact information (name, phone, email) to our study staff. For 2) the physical flyers will direct participants to the study website / study email address / study phone. For 3) the newsletters will direct potential participants to the study website / study email address / study phone. For 4) Kimel Centre staff will a) provide participants with a study flyer and b) obtain consent from potential participants to share contact information with our study staff. For 5) at the conclusion of in-person education sessions hosted by the study PI, attendees will be provided the physical flyer for the study, directing them to the study website / study email address / study phone. If applicable, potential participants may also consent for

clinical information relevant to this protocol (i.e. MCI diagnosis, cognitive test results) to be shared with the study team. Finally,

d. **Baycrest cognitive neurology clinics:** Flyers will be placed in clinic rooms and/or bulletin boards and will also be available for potential participants to take home. Potential participants may also be approached by a member of their care team who can provide them with a study flyer which will contain contact information for the study. Potential participants will be given the opportunity to verbally agree with their clinic care team to share contact information (name, phone, email) with study staff so that they may be contacted to discuss interest in participating in this study. If applicable, potential participants may also consent for clinical information relevant to this protocol (i.e. MCI diagnosis, cognitive test results) to be shared with the study team.

5.4 Participant Screening

Potential participants, irrespective of the recruitment source, will be required to proceed to the study website where they will fill out a short REDCap-hosted online questionnaire. The questionnaire will include collection of basic demographics and subjective sleep and cognitive information, limited to information necessary for determining eligibility. This includes email address, phone number, and implied consent to be contacted by study staff for additional screening.

Potential participants who fill out the REDCap-hosted online questionnaire will be contacted by study staff to assess eligibility. This includes:

1) An in-depth video-conference to establish a diagnosis of MCI and to confirm all inclusion/exclusion criteria. This will consist of a clinical interview, Logical Memory II, MoCA, and Lawton-Brody Instrumental Activities of Daily Living Scale Score, as well as screening for clinically significant insomnia (Insomnia severity index>15) or restless legs syndrome (Cambridge Hopkins questionnaire). 2) If MCI confirmed, participants will be mailed a home-based sleep apnea test (HSAT), namely the Apnealink which will be self-administered. With our community-based recruitment model, using a HSAT is necessary to minimize the number of participants without sleep apnea who need to undergo polysomnography. The Apnealink is considered a Type 4 sleep monitor by the American Academy of Sleep Medicine and has been validated against polysomnography. 3) Individuals who screen positive for OSA on the HSAT will meet with a study physician by video call or in person prior to in-lab PSG. The study physician will confirm inclusion and exclusion criteria, including positive results for both MCI and OSA, and will perform a standard clinical assessment to ensure clinical appropriateness of and eligibility for CPAP. The participant will then be scheduled for an in-lab PSG. 4) Participants that meet the criteria for MCI and OSA, and satisfy all other inclusion/exclusion criteria, will have a video-conference with study staff to discuss the final determination of eligibility, obtain informed consent, and to unlock their randomization assignment.

5.5 Screen Failures

Participants that do not meet the criteria for MCI or OSA, or do not meet all of the inclusion criteria or have at least one of the exclusion criteria at any stage of the screening process are deemed as screen failures and will have a video-conference with study staff to discuss their

reason for not being eligible. These participants who have failed the screening criteria are ineligible for participation and will be informed that they do not meet the study's inclusion criteria and they will be thanked for their time. They will be encouraged to try to participate in future studies for which they may be eligible, and they will have an opportunity to ask questions pertaining to their screening for this study. Screen information will be retained as part of the trial for further analyses.

5.6 Randomization and Blinding

Participants will be randomized 1:1 to one of the following groups:

Early CPAP group: Brain Health Support PRO sleep modules (BHP-sleep; a web-based sleep education platform) and Continuous Positive Airway Pressure (CPAP) for 8 months; or

Later CPAP group: BHP-sleep for first 4 months, then BHP-sleep and CPAP for remaining 4 months of participation.

From the beginning of month 5 until the end of month 8, both groups will be receiving CPAP.

Randomization will be performed using an instance of the OxMAR software package hosted on a Sunnybrook Research Institute computer. Randomization will be carried out in blocks of 2 and stratified such that equal numbers from each recruitment type (i.e. clinic, community) will be in each group.

Research personnel not involved in assessments or interventions will access the randomization list to allocate participants in each group. Personnel performing outcome assessments and methodologists performing analyses will be blinded to group allocation. Randomization will be completed by a dedicated analyst, who will distribute randomization codes (using a random number generator) to determine the treatment arm to which each participant is allocated. Assessors and Research Assistants administering the interventions will be blinded and as such, only the analyst overseeing randomization will have access to the password-protected randomization list.

5.7 Participant Withdrawal and Discontinuation of Study Procedures

At their own discretion, participants may withdraw from the study at any time and for any reason. Study participants may also be withdrawn from the study at the discretion of an investigator for reasons such as, but not limited to safety, participant compliance or behavioral concerns.

Participants withdrawing from the study should be contacted by the study research team requesting a final visit and to follow up with any unresolved adverse events. Once withdrawn from the study, no further study procedures or evaluations should be performed, or additional study data collected. However, every effort should be made to obtain permission to document the reason for withdrawal and to collect participant outcomes, such as survival data up to the protocol-described end of participant follow up period, where possible. Any data collected prior to the withdrawal of consent may be retained and used by the sponsor.

6 INTERVENTIONS

6.1 Continuous positive airway pressure (CPAP)

Participants randomized to the Early CPAP group will receive a study-provided auto-titrating CPAP device, with settings set by one of the study sleep medicine physicians according to current clinical practice parameters (9). Participants will undergo an in-person mask fitting at their baseline study visit, and then will be supported by a sleep technologist with extensive clinical experience with CPAP who will contact participants by telephone or video call. Masks, tubing, chin straps, and other equipment necessary to optimize CPAP adherence will be provided by the study as necessary to optimize adherence, which will be tracked through participants' CPAP devices.

At the start of the 5th month, participants in the Later CPAP group will receive a study-provided auto-titrating CPAP device following the same protocol.

6.1.1 Acquisition

This study will use only CPAP devices that are clinically approved for the treatment of sleep apnea in Canada, and will be purchased by the study directly from the manufacturer.

6.1.2 Receipt of Device

Upon receipt of the CPAP equipment, an inventory will be performed and a receipt log filled out and signed by the research team member accepting the shipment. Designated study staff will count and verify that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable product in a given shipment will be documented in the study files. We will notify the manufacturer of any damaged or unusable product that was supplied to the site.

6.1.3 Administration of CPAP Intervention

The CPAP intervention will be overseen by one of the study physicians (Dr. Boulos, Dr. Lim, Dr. Murray, or Dr. Bradley, with Dr. Bradley playing principally a consultative role) assisted by a full-time sleep technologist.

To initiate CPAP, participants will come in-person to the study centre to meet with the sleep technologist, who will oversee initial mask fitting and selection, CPAP teaching, and set-up under the direction of the sleep physicians. The technologist will contact participants by telephone or video call according to the study schedule. Calls will address a) anticipation and troubleshooting of common CPAP barriers (mask leak, mask fit, bloating, claustrophobia, etc.) b) education around the OSA physiology and consequences c) motivational enhancement and d) engagement of study partners, following principles shown to be effective at achieving high levels of CPAP adherence in adults with MCI (10). Between scheduled calls, the technologist will be available during business hours as needed for both remote and in-clinic visits. Participants will be provided an auto-titrating CPAP device. CPAP adherence and technical efficacy will be assessed by remotely interrogating participants' CPAP machines. Should high

residual AHI persist, participants may be brought in for an in-lab CPAP titration at the discretion of the study physician.

We will compute several measures of adherence including: 1) % of days adherent, defined as use over 4 hours, for months 0-4 and 5-8, 2) mean nightly usage in hours for months 0-4 and 5-8, and 3) cumulative number of days used >4h since entry into the study (a measure of the total cumulative duration of CPAP adherence). A participant will be considered adherent if they used CPAP for >4h on >80% of nights over the 4-month period.

Risks and side effects related to CPAP are minor and may include: congestion or runny nose, dry mouth, nostrils, eyes, facial pain or skin irritation, claustrophobia. CPAP is not an experimental device and is being used in this study according to its intended use. In the unlikely event of an emergency related to CPAP use, participants will receive the same care as they would in usual care pathways. That is, participants are encouraged to contact the sleep technologist for the study during business hours. If the emergency is more urgent, participants are encouraged to use local emergency services, and then contact the sleep technologist for the study during business hours.

6.2 Brain Health PRO platform (BHP)

The BHP web-based education platform (11) is a 45-week, multidomain, web-based formal educational program designed to increase dementia literacy, foster engagement, and convey best available evidence for lifestyle changes that can mitigate dementia risk. The program was developed as a collaborative effort by CCNA investigators with recognized expertise in the program's content areas, along with input from older-adult citizen advisors. The program was refined and updated based on feedback from focus-groups and a 3-month pilot study to assess usability and accessibility.

This protocol will utilize the sleep modules of the BHP platform covering sleep physiology, healthy sleep habits, and information about sleep disorders like sleep apnea.

6.2.1 Administration of BHP Intervention

Participants in both groups will register at baseline on the BHP website and obtain a personal password. Participants will need to provide a valid e-mail address and password in order to login and participate in BHP. Participants will also be asked to enter a preferred name (this can be a first name or nickname), which they will be referred to as throughout their participation in the program. Name and e-mail address will not be included in the study data set. All data from BHP will be de-identified and linked to participant study ID prior to being included in our dataset. Registration will also include viewing a brief video explaining the program.

The program content consists of 24 chapters discussing the following topics. Participants will be invited to read the content at their own pace and will be given the opportunity to discuss with research staff at scheduled check-in calls. Specific chapters are:

1) What is sleep?

2) How do we sleep?

3) Measuring sleep
4) Why do we sleep – Emotional health and well-being
5) Why do we sleep – Physical health
6) Why do we sleep – To strengthen memory
7) How much sleep do you need?
8) Dreams
9) Sleep changes across adulthood and factors that may disturb sleep
10) Insomnia
11) Insomnia 2
12) Daytime sleepiness
13) Sleep apnea: Definition, symptoms, causes
14) Sleep apnea: Treatments
15) Restless legs syndrome
16) Movements during sleep
17) REM sleep behavior disorder (RBD)
18) Disrupted sleep: when to be concerned
19) Sleep in Alzheimer's disease
20) Sleep in Parkinson's Disease
21) Lighting up the aging brain: the effects of light
22) Sleep and physical activity
23) Recommendations for better sleep
24) Sleep and sex differences

We will track adherence through metadata from the BHP platform that can be exported by the study team and includes: participant ID, date an account was created, and date specific chapters are read.

7 STUDY SCHEDULE AND PROCEDURES

7.1 Overview of Study Schedule

An overview of the study schedule can be found in Appendix B.

7.2 Study Instruments

Copies of each study instrument can found in Appendix D.

7.2.1 Eligibility Screening and Basic Information

Screening Checklist for Eligibility: The screening checklist for eligibility is a simple document with inclusion and exclusion criteria. All inclusion criteria and no exclusion criteria must be met to be eligible (video conference). See Appendix C-1.

Demographic and Medical Information: Basic demographic and medical information include age, sex, education, and past/present medications and medical comorbidities. (video conference). See Appendix C-2.

7.2.2 Sleep Disorders and Patient Reported Sleep Outcomes

Sleep Apnea: As an initial screen for sleep apnea, we will use the STOP-Bang questionnaire competed on an online form (12). See Appendix C-3.

Insomnia Severity Index (ISI): A 7-item questionnaire assessing sleep onset, sleep maintenance, sleep satisfaction, and sleep problems. Each item is rated on a scale ranging from 0-4 with total scores ranging from 0 to 28 and higher scores suggesting more severe insomnia (13). The ISI is administered as a questionnaire which can be administered via any interphase (face-to-face or video conferencing). We will administer it via video conferencing. See Appendix C-4.

Restless Legs. RLS will be assessed using the 8-item Cambridge Hopkins Questionnaire (14) administered by video conference. See Appendix C-5.

REM Sleep Behaviour Disorder RBD will be assessed using a single question from the Mayo sleep questionnaire: “Have you ever been told, or suspected yourself, that you seem to ‘act out your dreams’ while asleep (for example, punching, flailing your arms in the air, making running movements, etc.)?” (15). See Appendix C-6.

Self-Report Sleep Quality: We will use the PROMIS Sleep Disturbance and PROMIS Sleep Related Impairment short form questionnaires to assess subjective sleep quality (16). See Appendix C-7.

Sleep Diary: We will use a 10-day sleep diary to complement the accelerometry data. See Appendix C-8.

7.2.3 Cognitive Evaluation

Montreal Cognitive Assessment: The Full MoCA via Audio-Visual Conference consists of a 30-point test assessing the following items: short term memory recall, visuospatial abilities,

executive functioning, phonemic fluency, verbal abstraction, attention, concentration, working memory, language, and orientation (17). The remote version of the MoCA will be administered using the validated online full MoCA (version 8.1) via audio-visual conference (18). See Appendix C-9.

Logical Memory: Logical Memory I & II (Story A) from the Wechsler memory scale assesses memory and free recall (19). This test will be completed via video conferencing in which the participant will be instructed to listen to a story and repeat it back after it has been read to the best of his/her ability. The participant will then be asked to recall the story approximately 30 minutes later. Because this test is an auditory test to begin with (i.e., it does not require visual stimuli such as paper and pencil questionnaires), it can be administered using any modality (face-to-face or via video conference). We will conduct it via video conferencing. See Appendix C-10.

Geriatric Depression Scale: The GDS Short Form is a brief, 15-item questionnaire in which participants are asked to respond by answering yes or no in reference to how they felt over the past week (20). See Appendix C-11.

Symbol Digit Modalities Test (SDMT): Our primary outcome measure is the total score on the SDMT, a, a test of speeded executive function. A recent study estimated a minimal clinically important difference in the SDMT in a sample of adults with MCI of -3.8 points, corresponding to an effect size of -0.42 (2). An observational study of CPAP in adults with MCI found a similar effect size of CPAP (6-month effect size 0.46) on a very similar test, the Digit Symbol Substitution Test subtest of the Wechsler Adult Intelligence Scale (3). The test-retest correlation for the SDMT in clinically stable individuals with MCI over a mean follow-up of 19 months is 0.78 (2). See Appendix C-12.

Trail Making Test A&B: The TMT A & B is a two-part test that assesses attention speed, and mental flexibility and has been widely used in clinical settings for assessing deficits in attention and executive functioning (21). See Appendix C-13.

Digit Span: The digit span forward and backward from the WAIS-III will be administered as an assessment of working memory (21). See Appendix C-14.

Letter Number Sequencing: The Letter Number Sequencing Test (23) is a test of working memory.

The Hopkins Verbal Learning Test-Revised (HVLT-R): A brief, multicomponent word-list learning task that was developed by Brandt and Benedict (24) to assess verbal learning and memory. The HVLT-R consists of three free recall learning trials, a delayed recall trial and a recognition task, and yields a number of raw and calculated scores including total recall score, delayed recall score, percentage retention and a recognition discrimination index (RDI). See Appendix C-15.

ADAS-Cog: The ADAS-Cog-13 consists of 13 brief cognitive tests assessing memory, language, attention, concentration, and praxis. Scores range from 0 to 85 with higher scores indicating increased severity of cognitive impairment. See Appendix C-16.

7.2.4 Functional Status

IADL: The Lawton-Brody Instrumental Activities of Daily Living (IADL) scale measures participant's ability to engage in instrumental activities of daily living via questionnaire assessing activities such as preparing meals and managing personal finances (25). Responses range from

0 (normal ability) to 3 (dependent for functioning) with total scores ranging from 0 to 23. This assessment of functional independence is collected via questionnaire, which can be administered via any interface (face-to-face or video conferencing). We will administer it via video conferencing. See Appendix C-17.

7.2.5 Sleep Physiology

Sleep Apnea: At screening baseline, 16 weeks, and 32 weeks, participants will undergo 1 night of Apnealink from which we will extract oximetry metrics including ODI, AHI, mean SpO2, hypoxia burden, and time with SpO2<92%. An entry requirement will be ODI≥5 OR time with SpO2<92% of >10 minutes. The ApneaLink is an FDA-approved self-administered 3-channel portable device that assesses for sleep apnea based on airflow as assessed using an intra-nasal pressure transducer, pulse oximetry assessed using a finger probe, and respiratory effort using a band around the chest. It is considered a Type 4 sleep monitor by the American Academy of Sleep Medicine and has been validated against polysomnography (26).

EEG: At baseline, 16 weeks and 32 weeks, participants will undergo 3 nights of home EEG using a wearable headband (MUSE-S, Interaxon, Toronto) which will undergo automated sleep staging using a random forest based model developed by our lab based on 308 MUSE-S recordings with simultaneous in-lab PSG. To develop our own model, we divided our set of n=308 recordings with simultaneous PSG-MUSE EEG recordings randomly into n=215 training and n=93 test recordings. The MUSE-S provides four-channel EEG, triaxial accelerometer (ACC), and PPG data. After segmentation into 30-second epochs and normalization of each channel within each epoch, we extract statistical and morphological features are extracted from each epoch. EEG signals undergo bandpass filtering to isolate frequency components, enabling the extraction of power spectral density (PSD) across different frequency bands (Delta, Theta, Alpha, Beta, Gamma). Similarly, PPG data is filtered and denoised before features such as PSD, dominant frequency, heart rate variability, and respiratory rate are extracted. For sleep stage classification, a 1-D Convolutional Neural Network (CNN) architecture is employed. Ground truth labels were obtained from visual analysis of simultaneously recorded full PSG. Extracted features from MUSE EEG, accelerometer, and PPG data are fed into the model, which consists of Conv1D layers with ReLU activation, followed by MaxPooling1D layers. The hierarchical features extracted by the CNN are then flattened and passed through densely connected layers with ReLU activation. The output layer employs softmax activation to output class probabilities. The model is trained using categorical cross-entropy loss and the Adam optimizer, with a learning rate of 0.001, over 10 epochs with a batch size of 32. For sleep vs wake classification, a Decision Tree classifier is used. This classifier is configured with specific parameters controlling its complexity and generalization ability, such as with a Gini impurity criterion for splitting, limiting the maximum depth of the tree to 50, and setting minimum samples per leaf to 5 and minimum samples for splitting to 5. Post-processing involves applying majority voting on predicted sleep stages to smooth transitions and enhance the coherence of the sleep architecture. Finally, the performance of the trained models, whether binary or multiclass, is evaluated using appropriate metrics such as accuracy, sensitivity, specificity, and F1-score. Sleep metrics such as total recording time, total sleep time, sleep latency, and time spent in different sleep stages (N1, N2, N3, and REM) are calculated over all test subjects to assess the efficacy of the classification pipeline. . In the n=93 test set, we saw improved performance compared to the manufacturer provided model, correctly classifying a much larger proportion of epochs of slow wave sleep (72% vs. 56%), REM sleep (89% vs. 71%), and wake (94% vs. 71%).

Accelerometry The AX3 is an accelerometer used to detect detecting movement, vibrations, and orientation changes. The AX3 will be mailed to participants and a sponsor site study steam member will instruct the participant on the proper application and use of the device through videoconference. The participant will be given a copy of the instruction script, in addition to an instruction card containing contact information of research staff should they have any questions. The participant will be shown how to place the device on their non-dominant wrist by research staff, and participants will be instructed to wear the devices continuously for 10 days, even when bathing or swimming. During the 10 days, participants will be asked to track their work and sleep hours in a diary. At the end of 10 days, participants will return the device to the sponsor site using a pre-paid parcel system. This procedure will be repeated at 4 months and 8 months

7.2.6 CPAP Adherence

CPAP adherence will be automatically logged by the CPAP devices for the duration of the study period, and accessible remotely from the study centre. We will compute several measures of adherence including: 1) % of days adherent, defined as use over 4 hours, for months 0-4 and 5-8. 2) mean nightly usage in hours for months 0-4 and 5-8 3) cumulative number of days used >4h since entry into the study (a measure of the total cumulative duration of CPAP adherence).

7.2.7 MRI Brain

Participants will be imaged using the Canadian Dementia Imaging protocol consisting of a 3D T1, interleaved 3mm PD/T2, 3D FLAIR, T2*, DTI, and resting state BOLD. Perivascular spaces and white matter hyperintensities will be quantified with the SynthSegCSVD algorithm developed and validated in our laboratory, a robust neural network based (i.e. applies an AI deep learning method) tool. The $SegCSVD_{PVS}$ segmentation model employs a convolutional neural net (CNN) based on the UNet architecture and incorporates several advanced machine learning techniques to ensure accurate and robust PVS segmentation. Central to the development of $SegCSVD_{PVS}$ was the curation of a diverse dataset consisting of T1-weighted images sourced from several multi-site studies spanning a wide range of patient populations. Ground truth PVS labels for this dataset were generated using a semi-automated procedure consisting of: “RORPO” filtering to identify small tubular structures on the T1; false positive minimization using the FreeSurfer segmentation output; and manual refinement by a trained image analyst to correct any remaining errors.

7.2.8 Plasma Samples

Collection: Blood samples (10 ml) will be collected in plasma vacutainer tubes and centrifuged at 1000×g for 10 minutes. Plasma will be separated and preserved in a freezer at -80^{o}C in a secure freezer. All samples will be de-identified and preserved at -80^{o}C and assayed together in a batch after the collection of the last sample

Vascular Risk Factors: Classical vascular risk factors will also be assessed (lipid profile including LDL, HDL, and triglycerides; fasting glucose; haemoglobin A1C)

Plasma AD Biomarkers: We will assess plasma pTau181 (for AD pathology) and GFAP (for astrocyte activation). pTau181 has been shown to be strongly predictive of both amyloid and tau pathology as measured by PET (4,5) while plasma GFAP correlates strongly with ^{18}F-SMBT-1 PET, a marker of brain reactive astrocytes (6).

7.3 Premature Withdrawal

Participants may be withdrawn or be discontinued from the study for any of the following reasons:

1. At the participant's request (withdrawal of consent)
2. At the discretion of the investigator, if deemed appropriate, for any reason
3. If an intolerable or life-threatening adverse event occurs

Participant data collected to the date of discontinuation or withdrawal will be included in the analysis.

7.4 Study Close-Out

At the close of the study, participants will be able to keep their CPAP equipment. Clinical care will initially continue with the study physician, but arrangements will be made to transfer clinical care to another physician if desired by the study participant. Ongoing CPAP support would be transitioned to local CPAP suppliers.

7.5 Protocol Deviations

It is the responsibility of the investigator to ensure that only investigative procedures, as outlined in this protocol are performed on study participants; the occurrence of deviations from the protocol or SOPs are limited; and compliance with the regulations is maintained. Planned deviations from the protocol must not be implemented without prior agreement from the sponsor and approval from the local REB, as required, unless to eliminate an immediate hazard to a participant.

Planned or unplanned deviations may occur on the part of the participant, the investigator, or study research team. In resolution to a deviation, corrective/preventative actions are to be developed and implemented in a timely manner. Protocol deviations will be documented and reported as required and assessed where necessary during analysis.

8 ASSESSMENT OF SAFETY

The safety of research participants is foremost and should always be considered throughout the conduct of research.

8.1 Definitions

8.1.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a participant that occurs from the time of enrollment and up to 30 days after study participation has ended. For the purposes of reporting, an AE is defined as any unfavourable or unintended sign (e.g., including an abnormal laboratory finding), symptom, or disease associated with study procedures that are both non-serious and either temporally or causally related to study procedures. Pre-existing conditions, which increase in frequency or severity or worsen in nature during, or as a consequence of, a study procedure, may also be considered an AE if it meets the definition of being both non-serious and related to a study procedure.

An AE does not include:

- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion).
- The condition that leads to the procedure is the AE.
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions).
- Worsening of symptoms associated with expected decline in memory or an associated co-morbid condition and not related to a study procedure.
- Those medical or surgical adverse events that are not related to the study procedures

8.1.2 Serious Adverse Events

A serious adverse event (SAE) or reaction is any untoward occurrence related to study procedures that:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or in significant disability/incapacity,
- Is a congenital abnormality or a birth defect.

The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

8.1.3 Unexpected Adverse Event

An unexpected adverse event is any AE that is not identified in nature, severity or frequency in the relevant safety document(s) or is not identified as a possible risk in the study protocol or the

informed consent form.

8.2 Assessment of an Adverse Event

8.2.1 Relationship (Causality/Relatedness)

The causality assessment is the determination, according to the investigator's clinical judgment, of the existence of a reasonable possibility that study procedures caused or contributed to an adverse event.

If the investigator or delegated sub-investigator is unsure about whether or not study procedures caused or are related to the event, then the event will be handled as "related" to study procedures for reporting purposes of the trial. If the causality assessment is "unknown but not related", this should be clearly documented in the source documents.

8.2.2 Expectedness

Events are classified as unforeseen or unexpected if the nature, severity or frequency is not consistent with the risk information set out in the relevant safety document(s).

8.2.3 Seriousness

Events are classified as serious if associated with effects threatening the life or physiological functions of a participant. Refer to the definition for "Serious Adverse Events" in section 8.1.2.

8.2.4 Severity

The term "severe" is often used to describe the intensity (severity) of a specific event (e.g. mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on participant/event outcome or action criteria usually associated with events that pose a threat to a participant's life or functioning. The terms "serious" and "severe" are not synonymous. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

To assess the severity of an adverse event the investigators will use the following:

Severity	**Definition**
Mild	Awareness of event but easily tolerated
Moderate	Discomfort enough to cause interference with usual activity
Severe	Inability to carry out usual activity, incapacitating, requires medical intervention

8.3 Adverse Event Recording

All AEs both non-serious and either temporally or causally related to study procedures (i.e., a new event or an exacerbation of a pre-existing condition) that occur from the time of enrollment and up to 30 days after study participation has ended will be recorded as an AE. The Investigator must follow all AEs until the AE resolves, or until the Investigator determines the event is chronic or clinically stable. If an AE remains unresolved at the conclusion of the AE reporting period, the Investigator will make a clinical assessment to determine whether continued follow-up of the AE is warranted. The Investigator should attempt to establish a diagnosis of the event based on signs, symptoms and/or other clinical information. In such cases, the diagnosis should be documented as the AE and not the individual signs/symptoms.

The following are not considered AEs and therefore do not require recording:

- Pre-existing diseases or conditions identified and recorded at screening/baseline unless, at the discretion of the investigator, the disease or condition worsens in severity or frequency

- At the discretion of the investigator, events considered likely manifestations of the underlying disease or that commonly occur in the study population independent of study procedures

- Elective medical or surgical procedures.

8.4 Reporting of SAEs and Unanticipated Events

8.4.1 Investigator reporting: Notifying the REB

Serious adverse events and unanticipated events should be recorded and reported to the REB in accordance with local reporting requirements and timelines.

8.4.2 Investigator reporting: Notifying the Sponsor

The investigator is responsible for reporting serious adverse events and unanticipated events to the sponsor in accordance with applicable regulations and reporting requirements and timelines.

Events that are assessed to be **serious and unexpected and related or cannot be ruled out as related** to the study procedures are reportable. Reporting should include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. The minimum information required includes at least one identifiable participant, one identifiable reporter, one serious reaction, and one suspect procedure.

8.4.3 Sponsor Reporting of SAEs and Unanticipated Events: Notifying Health Canada

In the event of an incident related to a failure of the device used in this protocol or deterioration in its effectiveness, or any inadequacy in its labelling or in its directions for use that leads to the death or a serious deterioration in the state of health of a patient, user or other person, or could do so were it to recur, the sponsor of this study will report the incident to Health Canada. The

sponsor will report the incident and the circumstances surrounding it to the Minister and to the manufacturer or importer of the device within 72 hours after it comes to the attention of the qualified investigator.

8.5 Reporting and Entry Timelines

Study investigators will report SAEs to the sponsor within the following timelines:

- All deaths and immediately life-threatening events, whether related or unrelated, will be recorded and reported to the sponsor within 24 hours of site awareness.
- Serious adverse events other than death and immediately life-threatening events, regardless of relationship, will be reported to the sponsor within 72 hours of site awareness.

Adverse event information will be entered into the CRF in a timely manner and **no later than 15 days** from the time the investigator becomes aware of the event.

Serious adverse event information will be entered into the CRF in a timely manner and **within 72 hours** from the time the investigator becomes aware of the event.

9 STATISTICAL CONSIDERATIONS

9.1 Study Hypotheses

This RCT will test the hypothesis that treatment of OSA with CPAP in patients with MCI will slow cognitive decline and prevent accumulation of astrocyte activation, PVS burden, and biomarkers of brain AD pathology.

9.2 Sample Size Considerations

Our primary outcome measure is the total score on the Symbol Digit Modalities Test (SDMT), a, a test of speeded executive function, at 4 months. A recent study estimated a minimal clinically important difference in the SDMT in a sample of adults with MCI of -3.8 points, corresponding to an effect size of -0.42 (2). An observational study of CPAP in adults with MCI found a similar effect size of CPAP (6-month effect size 0.46) on a very similar test, the Digit Symbol Substitution Test subtest of the Wechsler Adult Intelligence Scale (3). The test-retest correlation for the SDMT in clinically stable individuals with MCI over a mean follow-up of 19 months is 0.78 (2). In a recent study of adults with MCI, overall CPAP adherence was ~70% (10). In order to account for this, we will design our study to detect a smaller effect size of 0.26. Assuming a test-retest correlation of 0.78, and a 2-tailed type I error rate of 0.05 in a 2-group ANCOVA model, we estimate that a total sample size of 184 will provide 80% power to detect an effect estimate of 0.26. To account for an estimated 10% drop out, we will aim to recruit a total sample size of 206 participants (103 per group).

9.3 Stopping Rules

This study will be stopped prior to its completion if: 1) the intervention is associated with adverse events that call into question the safety of the intervention; 2) difficulty in study recruitment or retention will significantly impact the ability to evaluate the study endpoints; 3) any new information becomes available during the trial that necessitates stopping the trial; or 4) other situations occur that might warrant stopping the trial.

9.4 Final Analysis Plan

Our primary analysis will be an intent-to-treat (ITT) analysis comparing difference on the SDMT at 4 months as a function of assigned treatment group (CPAP vs. web education alone), adjusted for baseline SDMT. The analysis will use linear regression, adjusted for baseline SDMT, age, sex, years of education and recruitment source (direct from community vs. hospital/clinic). Participants will be analyzed in the treatment group to which they were assigned irrespective of their actual treatment adherence. Intention to treat analyses preserve the benefits afforded by randomization (most importantly, the elimination of selection bias in treatment assignment), and are conservative in their estimates of treatment effect. As a secondary analysis, we will carry out a “per protocol” analysis where participants will be classified based on actual CPAP usage with participants considered CPAP users if they used CPAP >4h per night >80% of days over the preceding four months, and non-users if less than that.

Further analysis will be an intent-to-treat analysis comparing difference on the SDMT at 8 months, adjusted for baseline SDMT, as a function of assigned treatment group (CPAP 4 months vs. CPAP 8 months). The analysis will use linear regression, adjusted for baseline SDMT, age, sex, years of education and recruitment source (direct from community vs. memory clinic). As a secondary analysis, we will carry out a “per protocol” analysis where participants will be classified based on actual CPAP usage with participants considered CPAP users if they used CPAP >4h per night >80% of days in the four months leading up to cognitive evaluation.

We plan to repeat our initial analyses replacing our cognitive outcomes with a) plasma GFAP b) plasma pTau-181 and c) MRI PVS burden.

In exploratory analyses we will use a linear mixed effect models to model the effect of CPAP dose on the SDMT at 4 and 8 months in a time-dependent manner. CPAP dose will be defined in two ways; (a) cumulative dose, defined as total number of days since randomization where CPAP was used for more than 4 hours, (b) average dose, defined as the average number of hours CPAP was used per day over the previous four months. In each of the models, an interaction between dose and time will be fit to estimate the time-specific dose effects. Additionally, the models will adjust for baseline SDMT, age, sex, education, and recruitment source, with individual-specific random intercepts. Since only two time-points are being used, they will be considered discrete variables and so random slopes do not apply.

In further exploratory analyses, we will use mediation analysis to examine the extent to which the effect of CPAP on SDMT is mediated by sleep physiology (e.g. slow wave sleep). Slow wave sleep percentage will be our primary mediator but we will consider in secondary analyses the other sleep parameters estimated from our wearable sensors. We plan to repeat these analyses replacing our cognitive outcomes with a) plasma GFAP b) plasma pTau-181 and c) MRI PVS burden. An additional sub-group analysis will be done for recruitment source.

In lieu of propensity score matching, we will include as covariates in our non ITT models factors reported to predict CPAP adherence in a recent observation study of patients with MCI (baseline OSA severity, race (10)), and health behaviours and risk factors that may plausibly correlate with CPAP adherence and affect cognitive function (objectively measured physical activity from actigraphy, smoking, alcohol consumption, body habitus measured by BMI, depressive symptoms measured by the Geriatric Depression Scale, conscientiousness and neuroticism measured by the Big Five Inventory, vascular risk factors including measured blood pressure, and years of education).

10 DATA HANDLING AND RECORD KEEPING

10.1 Confidentiality

Information about study participants will be kept confidential and managed according to the requirements of the Personal Health Information Protection Act of 2004 (PHIPA) and the Research Ethics Board. PHIPA outlines the rules for the collection, use and disclosure of personal health information. The Act requires each participant to consent to the collection, use and access of personal health information (PHI), unless consent is waived by the REB. Where consent is required, each participant must be informed of the following:

- What PHI will be collected during this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research participant to revoke their authorization for use of their PHI.

In the event that a participant revokes authorization to collect or use PHI, the investigator may use all information collected prior to the revocation of participant authorization. For participants that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the participant is alive) at the end of their scheduled study period.

10.2 Source Documents

Source data/documents are original documents, data and records in a clinical study that are necessary for the reconstruction and evaluation of the study. Examples of these original documents and data records include, but are not limited to:

- Worksheets
- hospital records
- medical records
- memorandum
- participants' diaries or evaluation checklists
- pharmacy dispensing records
- recorded data from automated instruments (i.e. ECGs)
- copies or transcriptions certified after verification as being accurate and complete
- participant files and records kept at the pharmacy
- entries entered directly into the printed CRF

Each participating site will maintain appropriate medical and research records for this study, in addition to regulatory and institutional requirements for the protection of confidentiality of participants. If electronic source data documents is printed it should be signed and dated by the investigator to confirm content and filed with other source documents.

The investigator(s) and research team members listed on the Task Delegation Log (TDL) will have access to participant medical records and will collect only the information needed for the study. Sponsor delegated monitors, representatives of institutional committees and regulatory authority representatives of the country in which the study is being conducted will also have access to examine records for the purposes of quality assurance reviews, audits and evaluation of study safety and progress.

10.3 Data Management Responsibilities

Data collection and accurate documentation are the responsibility of the study personnel under the supervision of the investigator. All source documents and applicable laboratory reports should be reviewed as needed and used to ensure that data collected for the purposes of the study are accurate and complete. Contemporaneous review of laboratory results and the assessment of clinical significance for those results considered out of range should be documented by means of dated signature by the reviewing investigator. Study personnel, including data entry team members, should use source documents to complete case report forms (CRFs).

As part of the safety plan for this study, the investigator will review individual study participant records to ensure that appropriate mechanisms to protect the safety of study participants are being followed, that protocol requirements are being adhered to, and that data is accurate, complete, and secure. Participant records include, but are not limited to: consent forms, case report forms, data forms, laboratory specimen records, inclusion/exclusion forms, and medical charts. All study data will be collected by a member of the study research team and recorded in accordance with applicable procedures.

10.4 Data Capture

10.4.1 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. Electronic/Paper case report forms (eCRFs/pCRFs) will be used to collect data for this study. CRFs are to be completed by data capture personnel and signed off by the investigator in a timely manner. Good documentation practices should be implemented according to standard operating procedures. All data requested on the CRF must be recorded and verifiable by source document.

10.5 Records Retention

Primary source data will be stored using on networked servers in locked rooms at Sunnybrook Health Sciences Centre to which only study staff will have access, as well as on Sunnybrook REDCap servers. Hard copies of any data collection forms will be stored in locked cabinets located at the workplaces of study research staff and accessible only by study staff.

10.6 Clinical Trial Registration

In accordance with Health Canada's Notice "Registration and Disclosure of Clinical Trial Information, November 30, 2007", this trial will be registered on clinicaltrials.gov.

11 QUALITY CONTROL AND QUALITY ASSURANCE

Data validation and quality control checks will be defined and implemented. Inconsistent and questionable data detected during the data entry or data validation process will be queried.

12 ETHICS CONSIDERATIONS

12.1 Ethical Standard

The investigator will ensure that this study is conducted in accordance with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Participants of Research, and codified in the Tri-Council Policy Statement and/or the ICH E6.

12.2 Research Ethics Board (REB)

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the REB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the REB before the changes are implemented in the study, unless to eliminate an immediate hazard.

12.3 Ethical Concerns Surrounding Randomization

CPAP is an established treatment for sleep apnea that is effective at improving sleepiness in some patients. However, there is a lack of class I evidence for its efficacy in preventing most important clinical outcomes including cardiovascular disease and dementia. Thus, randomized controlled trials of CPAP vs. usual care continue to be ethically performed in myriad patient populations including survivors of stroke (e.g. Sleep SMART Trial clinicaltrials.gov NCT03812653). To address ethical consideration pertaining to potential randomization of participants with severe sleep apnea to usual care we will a) exclude participants who have had a sleepiness related traffic accident or near-miss within the last 12 months and b) we will limit the period of randomized treatment to 4 months, after which all participants will receive CPAP. This reflects the fact that in local patterns of care, time from referral for a PSG to final receipt of CPAP is generally more than 4 months, and so even participants on the web-based education arm will receive CPAP no later than usual patterns of clinical care. These considerations are discussed in further depth in a letter of support from the chair of the Sunnybrook Research Ethics Board, which we have included in the supplementary material.

We opted for a duration a) long enough to see effects on cognition and biomarkers while b) short enough to maintain high adherence, c) and ethically/practically allow randomization of more severe patients. Even a few days of sleep manipulation can alter CSF/plasma tau (3, 4) and 1-4 months of CPAP can modify CSF AD biomarkers (5) and PVS burden (Figure 3). Meanwhile, others have shown that adherence declines beyond 3 months (6) but that intensive support can maintain high adherence in individuals with MCI for at least 3 months (7). Moreover, ethical considerations make it difficult to randomize symptomatic individuals to non-CPAP beyond 4 months. As discussed above, to mitigate these ethical risks, this protocol includes a 4 month extension period during which both arms will receive CPAP to evaluate the effects of up to 8 months of treatment.

CPAP RCTs often have low adherence (6). Longer RCTs have excluded participants with significant sleepiness, who are the most likely to adhere to CPAP. Our relatively shorter duration (4 months) allows us to ethically randomize individuals with relatively severe symptoms, who are more likely to adhere. Secondly, longer RCTs have shown better adherence in early stages of the trial than later stages. By limiting randomization to 4 months, we maximize adherence. Further, recent studies have shown that a high-contact high-support approach can achieve

overall adherence levels at 3 months exceeding 70% (7). We will implement a similar high-contact high-support approach in this protocol.

12.4 Consent

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation. A consent form describing in detail the study procedures and risks will be reviewed with and given to each participant. Consent forms will be REB-approved, and the participant is required to read and review the document or have the document read to him or her. The investigator or designee will explain the research study to the participant and answer any questions that may arise. The participant will sign the informed consent document prior to any study-related assessments or procedures. Participants will be given the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. They may withdraw consent at any time throughout the course of the study. A copy of the signed informed consent document will be given to participants for their records.

Prior to involvement in any study-related activities, consent must be obtained in writing for each participant using the current REB approved informed consent from. It is the responsibility of the investigator to ensure that all advertisements and written information, including the informed consent form, disseminated to participants has been approved by the local REB prior to use. The ethics approved Informed Consent Form (ICF) and any other written information, must be provided to each participant, allowing ample time to ask and have answered any questions prior to making a decision regarding participation. Neither the investigator nor study staff should unduly influence or coerce a participant to participate in the study.

The ICF will be signed and dated by the participant and individual obtaining consent. The consent process will be documented in the clinical or research record.

The original ICF, in its entirety, will be maintained by the site, and a complete copy of the signed ICF provided to the participant. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their clinical care will not be adversely affected if they decline to participate in this study.

The provision of consent is an ongoing process and should be maintained throughout the duration of the study. Participants may withdraw consent at any time throughout the course of the study.

12.5 Participant Compensation

Participants will be compensated $50 for each in-person study visit (screening PSG, initial visit with physician, and study visits at 0, 4, and 8 months), which is intended to cover the costs of parking and meals. In addition, participants completing the at home screening process (video assessment + sleep wearable sensors) will be compensated $10. Finally, participants will be able to keep the CPAP study apparatus at the end of the study.

13 LITERATURE REFERENCES

1. Yaffe K, Laffan AM, Harrison SL, Redline S, Spira AP, Ensrud KE, et al. Sleep-disordered breathing, hypoxia, and risk of mild cognitive impairment and dementia in older women. JAMA. 2011 Aug 10;306(6):613-9. PubMed PMID: 21828324. Epub 2011/08/11. Eng.
2. Borland E, Edgar C, Stomrud E, Cullen N, Hansson O, Palmqvist S. Clinically Relevant Changes for Cognitive Outcomes in Preclinical and Prodromal Cognitive Stages: Implications for Clinical Alzheimer Trials. Neurology. 2022 Sep 13;99(11):e1142-e53. PubMed PMID: 35835560. PMCID: PMC9536741. Epub 2022/07/15.
3. Richards KC, Gooneratne N, Dicicco B, Hanlon A, Moelter S, Onen F, et al. CPAP Adherence May Slow 1-Year Cognitive Decline in Older Adults with Mild Cognitive Impairment and Apnea. J Am Geriatr Soc. 2019 Mar;67(3):558-64. PubMed PMID: 30724333. PMCID: PMC6402995. Epub 2019/02/07.
4. Jack CR, Wiste HJ, Algeciras-Schimnich A, Figdore DJ, Schwarz CG, Lowe VJ, et al. Predicting amyloid PET and tau PET stages with plasma biomarkers. Brain. 2023 May 2;146(5):2029-44. PubMed PMID: 36789483. PMCID: PMC10151195. Epub 2023/02/16.
5. Mielke MM, Hagen CE, Xu J, Chai X, Vemuri P, Lowe VJ, et al. Plasma phospho-tau181 increases with Alzheimer's disease clinical severity and is associated with tau- and amyloid-positron emission tomography. Alzheimer's & dementia : the journal of the Alzheimer's Association. 2018 Aug;14(8):989-97. PubMed PMID: 29626426. PMCID: PMC6097897. Epub 2018/04/08.
6. Chatterjee P, Dore V, Pedrini S, Krishnadas N, Thota R, Bourgeat P, et al. Plasma Glial Fibrillary Acidic Protein Is Associated with 18F-SMBT-1 PET: Two Putative Astrocyte Reactivity Biomarkers for Alzheimer's Disease. J Alzheimers Dis. 2023;92(2):615-28. PubMed PMID: 36776057. PMCID: PMC10041433. Epub 2023/02/14.
7. Lim AS, Yu L, Kowgier M, Schneider JA, Buchman AS, Bennett DA. Modification of the Relationship of the Apolipoprotein E epsilon 4 Allele to the Risk of Alzheimer Disease and Neurofibrillary Tangle Density by Sleep. JAMA neurology. 2013;In Press. Epub October 21, 2013
8. Yalamanchali S, Farajian V, Hamilton C, Pott TR, Samuelson CG, Friedman M. Diagnosis of obstructive sleep apnea by peripheral arterial tonometry: meta-analysis. JAMA otolaryngology-- head & neck surgery. 2013 Dec;139(12):1343-50. PubMed PMID: 24158564.
9. Morgenthaler TI, Aurora RN, Brown T, Zak R, Alessi C, Boehlecke B, et al. Practice parameters for the use of autotitrating continuous positive airway pressure devices for titrating pressures and treating adult patients with obstructive sleep apnea syndrome: an update for 2007. An American Academy of Sleep Medicine report. Sleep. 2008 Jan;31(1):141-7. PubMed PMID: 18220088. PMCID: PMC2225554. Epub 2008/01/29.
10. Richards KC, Lozano AJ, Morris J, Moelter ST, Ji W, Vallabhaneni V, et al. Predictors of Adherence to Continuous Positive Airway Pressure in Older Adults With Apnea and Amnestic Mild Cognitive Impairment. J Gerontol A Biol Sci Med Sci. 2023 Oct 9;78(10):1861-70. PubMed PMID: 37021413. Epub 2023/04/07
11. Feldman HH, Belleville S, Nygaard HB, Montero-Odasso M, Durant J, Lupo JL, et al. Protocol for the Brain Health Support Program Study of the Canadian Therapeutic Platform

Trial for Multidomain Interventions to Prevent Dementia (CAN-THUMBS UP): A Prospective 12-Month Intervention Study. J Prev Alzheimers Dis. 2023;10(4):875-85. PubMed PMID: 37874110. PMCID: PMC10258470. Epub 2023/10/24

12. Chung, F., H. R. Abdullah and P. Liao (2016). "STOP-Bang questionnaire: a practical approach to screen for obstructive sleep apnea." Chest **149**(3): 631-638.
13. Bastien, C. H., A. Vallieres and C. M. Morin (2001). "Validation of the Insomnia Severity Index as an outcome measure for insomnia research." Sleep Med **2**(4): 297-307.
14. Allen, R. P., B. J. Burchell, B. MacDonald, W. A. Hening and C. J. Earley (2009). "Validation of the self-completed Cambridge-Hopkins questionnaire (CH-RLSq) for ascertainment of restless legs syndrome (RLS) in a population survey." Sleep medicine **10**(10): 1097-1100.
15. Boeve, B. F., J. R. Molano, T. J. Ferman, G. E. Smith, S.-C. Lin, K. Bieniek, W. Haidar, M. Tippmann-Peikert, D. S. Knopman and N. R. Graff-Radford (2011). "Validation of the Mayo Sleep Questionnaire to screen for REM sleep behavior disorder in an aging and dementia cohort." Sleep medicine **12**(5): 445-453.
16. Lan Yu,Daniel J. Buysse,Anne Germain,Douglas E. Moul,Angela Stover,Nathan E. Dodds,Kelly L. Johnston &Paul A. Pilkonis (2011). “Development of Short Forms From the PROMIS™ Sleep Disturbance and Sleep-Related Impairment Item Banks.” Behavioral Sleep Medicine 10(1).
17. Nasreddine, Z. S., N. A. Phillips, V. Bedirian, S. Charbonneau, V. Whitehead, I. Collin, J. L. Cummings and H. Chertkow (2005). "The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment." J Am Geriatr Soc **53**(4): 695-699
18. Chapman, J. E., D. A. Cadilhac, B. Gardner, J. Ponsford, R. Bhalla and R. J. Stolwyk (2019). "Comparing face-to-face and videoconference completion of the Montreal Cognitive Assessment (MoCA) in community-based survivors of stroke." J Telemed Telecare: 1357633X19890788
19. Doppelt, J. E. and W. L. Wallace (1955). "Standardization of the Wechsler adult intelligence scale for older persons." J Abnorm Psychol 51(2): 312-330.
20. J A Yesavage, T L Brink, T L Rose, O Lum, V Huang, M Adey, V O Leirer (1982). “Development and validation of a geriatric depression screening scale: a preliminary report.” J Psychiatr Res. 17(1):37-49.
21. Esther Strauss, O. S. (1998). Trail Making Tests. New York, Oxford University Press.
22. Wechsler D. *WAIS-III Administration and Scoring Manual*. The Psychological Corporation; 1997].
23. Wechsler D. The Psychological Corporation; 1997. WMS-III Administration and Scoring Manual.
24. Benedict RHB, Schretlen D, Groninger L, & Brandt J (1998). Hopkins Verbal Learning Test – Revised: Normative Data and Analysis of Inter-Form and Test-Retest Reliability. The Clincal Neuropsychologist, 12(1), 43–55.
25. Lawton, M. P. and E. M. Brody (1969). "Assessment of older people: self-maintaining and instrumental activities of daily living." Gerontologist **9**(3): 179-186
26. Crowley KE, Rajaratnam SM, Shea SA, Epstein LJ, Czeisler CA, Lockley SW. Evaluation of a single-channel nasal pressure device to assess obstructive sleep apnea risk in laboratory and home environments. J Clin Sleep Med. 2013; **9**(2): 109-16

27. Onder, N. S., M. E. Akpinar, O. Yigit and A. P. Gor (2012). "Watch peripheral arterial tonometry in the diagnosis of obstructive sleep apnea: influence of aging." Laryngoscope **122**(6): 1409-1414.
28. Hedner, J., D. P. White, A. Malhotra, S. Herscovici, S. D. Pittman, D. Zou, L. Grote and G. Pillar (2011). "Sleep staging based on autonomic signals: a multi-center validation study." J Clin Sleep Med 7(3): 301-306.

SUPPLEMENTAL MATERIALS

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April 11 2024

Dear Review Committee.

I am the chair of the Sunnybrook Research Ethics Board, and a practising sleep physician who routinely cares for patients with severe sleep apnea.

In follow-up to my original letter of December 5, 2023, I would like to express my continued support for this important and carefully designed project, including the plan to extend the period of randomization to 4 months. Practically speaking, clinical access to diagnosis and treatment for sleep apnea in our health care system, from symptom identification by primary care practitioners through specialist consultation, diagnostic testing, and initiation of continuous positive airway pressure (CPAP), is considerably longer than 4 months. Therefore, this study can reasonably be thought of as randomization to expedited versus routine access to CPAP within a 4 month study time frame, which is arguably better than standard operationalization of care in this population. This design remains appropriate to definitively answer the question of CPAP benefit for this patient population, for which there remains clinical equipoise.

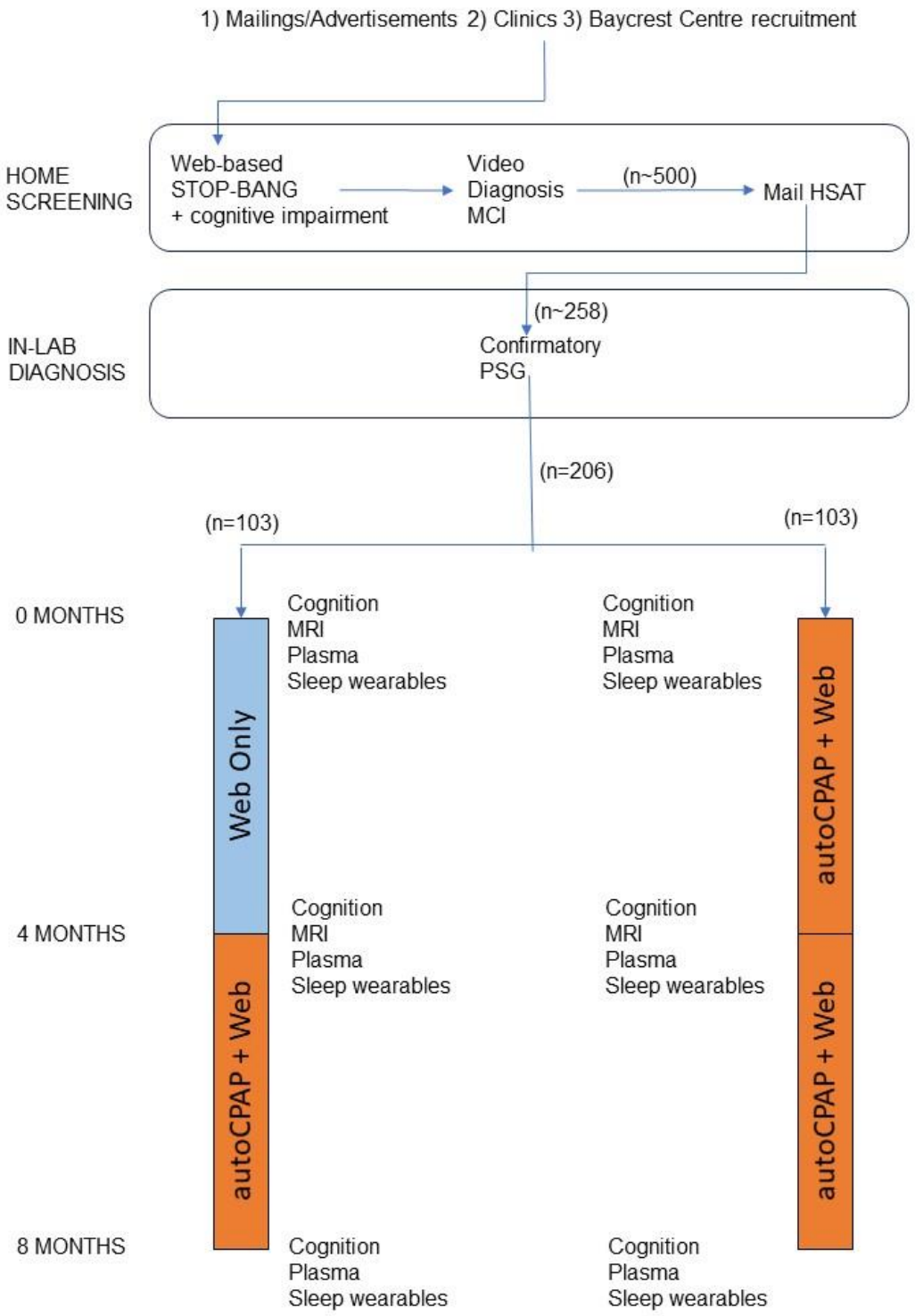
To reiterate, there are two factors should be considered when assessing the ethics of expedited versus standard treatment start times in sleep apnea - vascular factors and attentional considerations. There remains equipoise on the cardiovascular implications of treating sleep apnea. Large studies acknowledge this equipoise and continue to recruit patients with sleep apnea for treatment with CPAP versus no therapy. Secondly, attention is strongly influenced by disrupted sleep which could theoretically lead to accidents, though at a low rate. Cautious efforts have been implemented in this protocol to prevent individuals from enrolling who may be susceptible to injury such as those in high-risk driving situations. Full disclosure to participants of the expedited versus routine treatment start will be ensured. Most of these participants would not have reached treatment consideration in the first place, and this study will help get research participants to appropriate therapy in either study arm.

As such, I think the ethics of the protocol are appropriate. Thank you for your consideration of this important project.

Brian J. Murray MD FRCPC FAAN FAASM

APPENDICES

APPENDIX A: SCHEDULE OF EVENTS



APPENDIX B: OVERVIEW OF STUDY SCHEDULE

Date	Venue	Staff	Activities	Compensation
Pre-Baseline	Online Form	None	Online Screening Questionnaire - STOP-BANG - presence of cognitive difficulties - collect contact information	None
Pre-Baseline	Video (1 hour)	Coordinator / RA	- informed consent - exclusion criteria: driving, non-resident of Ontario, CPAP contraindicated or unwilling to start, no study partner, shift work, Insomnia Severity Index, Cambridge-Hopkins RLS, MRI contraindications - inclusion criteria: decline in cognition from previous, Lawton-Brody IADL - cognitive screening: video MoCA, Logical Memory II - Sleep wearables: Apnealink	$10 upon completion of home sleep assessment
Pre-Baseline	Video (1 hour)	Sleep Physician + RA	- clinical sleep assessment + information necessary to prescribe CPAP	$50
Pre-Baseline	In-Person (overnight)	RA	- in-lab PSG	$50 upon completion of PSG
Pre-Baseline	Video (30min)	Coordinator / RA	- discuss final determination of eligibility + randomization	None
Week 0	In-Person (2-3 hours)	Coordinator / RA	- phlebotomy - cognitive evaluation (SDMT, Trails A&B, Digit Span Forward and Backward, Letter-Number, Hopkins Verbal Learning, ADAS-Cog) - BH-PRO training - CPAP mask fitting + teaching (early CPAP group) - MRI Sleep wearables: MUSE-EEG, Actigraphy	$50
Weeks 0-16	Video/Phone	Coordinator / RA	- Week 0 days 1, 2, 5, 7; weeks 1, 2, 3, 4, 6,8, 10, 12, 16 (early CPAP group): calls with study staff to support CPAP	None
Week 16	In-Person (2-3 hours)	Coordinator / RA	- phlebotomy - cognitive evaluation (SDMT, Trails A&B, Digit Span Forward and Backward, Letter-Number, Hopkins Verbal Learning, ADAS-Cog) - CPAP mask fitting + teaching (later CPAP group) - MRI - Sleep wearables on CPAP: Apnealink, MUSE-EEG, Actigraphy	$50
Weeks 16-32	Video/Phone	Coordinator / RA	- Week 16 days 1, 2, 5, 7; weeks 17, 18, 19, 20, 22, 24, 28, 32 (later CPAP group): calls with study staff to support CPAP	None
Week 32	In-Person (2-3 hours)	Coordinator / RA	- phlebotomy - cognitive evaluation (SDMT, Trails A&B, Digit Span Forward and Backward, Letter-Number, Hopkins Verbal Learning, ADAS-Cog) - Sleep wearables on CPAP: Apnealink, MUSE-EEG, Actigraphy	$50

APPENDIX C-1: INCLUSION/EXCLUSION LIST

INCLUSION CRITERIA	CRITERIA MET? (Should be Yes)		SUPPORTING SOURCE DOCUMENT	
			NAME OR LOCATION	DATE (mm-dd-yy)
Informed consent obtained and signed	☐ Yes	☐ No		
Age > 55	☐ Yes	☐ No		
MoCA score 13-24	☐ Yes	☐ No		
Logical Memory II score: ≤ 8 (if ≥ 16 years of education) ≤ 4 (if 8-15 years of education) ≤ 2 (if ≥ 0-7 years of education)	☐ Yes	☐ No		
Lawton-Brody IADL score >14	☐ Yes	☐ No		
DSM IV criteria for dementia not met	☐ Yes	☐ No		
Change in self-perceived cognition from previous	☐ Yes	☐ No		
Apnealink ODI ≥ 5	☐ Yes	☐ No		
PSG AHI ≥ 15	☐ Yes	☐ No		
PSG ODI ≥ 10	☐ Yes	☐ No		
PSG central apneas <10% of all apneas	☐ Yes	☐ No		
PSG periodic limb movement index <15	☐ Yes	☐ No		

EXCLUSION CRITERIA	CRITERIA MET?	SUPPORTING SOURCE DOCUMENT

	(Should be No)		NAME OR LOCATION	DATE (mm-dd-yy)
Drowsiness-related driving accidents or near misses in the past 12 months	☐ Yes	☐ No		
Drives as their primary occupation	☐ Yes	☐ No		
Unable to complete cognitive evaluation in English	☐ Yes	☐ No		
Unable to participate in video-based cognitive assessment	☐ Yes	☐ No		
Not a resident of Ontario	☐ Yes	☐ No		
Contraindications to MRI	☐ Yes	☐ No		
Contraindications to CPAP or unwilling to start CPAP	☐ Yes	☐ No		
No available study partner to support CPAP	☐ Yes	☐ No		
Previously treated for sleep apnea	☐ Yes	☐ No		
Clinically significant insomnia (ISI > 15)	☐ Yes	☐ No		
Restless Legs Syndrome	☐ Yes	☐ No		
Shift Work	☐ Yes	☐ No		
Taking disease modifying agents for MCI	☐ Yes	☐ No		

APPENDIX C-2: DEMOGRAPHICS & MEDICAL INFORMATION

Question	Response
1. What is your date of birth?	
2. What is your current age?	
3. What sex was originally listed on your birth certificate?	
4. What is your gender/do you think of yourself as: Female Male Transgender woman/trans woman/male to female (MTF) Transgender man/trans man/ female to male (FTM) Genderqueer/gender non-conforming neither exclusively male nor female Additional gender category (or other) Don't know	
5. People living in Canada come from many different cultural and racial backgrounds. Are you… (Choose all that apply): White Chinese South Asian Black Filipino Latin American Southeast Asian Arab West Asian Japanese Korean First Nations	

Inuit Metis Other Don’t Know	
6. What is your handedness?	
7. Please indicate your highest level of education: Fewer than 12 years of formal education High school Undergraduate degree (bachelor's, associate) Graduate degree (master's, doctorate, professional degrees)	
8. What is your household income?	
9. List the medications you are currently taking.	
10. List the medications that you are not currently taking but were taking in the past 2 years.	
11. List any previous diagnosis or major health concerns.	

APPENDIX C-3: STOP-BANG

Updated STOP-Bang Questionnaire

Yes ○ No ○ **S**noring?
Do you **Snore Loudly** (loud enough to be heard through closed doors or your bed-partner elbows you for snoring at night)?

Yes ○ No ○ **T**ired?
Do you often feel **Tired, Fatigued, or Sleepy** during the daytime (such as falling asleep during driving or talking to someone)?

Yes ○ No ○ **O**bserved?
Has anyone **Observed** you **Stop Breathing** or **Choking/Gasping** during your sleep?

Yes ○ No ○ **P**ressure?
Do you have or are being treated for **High Blood Pressure**?

Yes ○ No ○ **B**ody Mass Index more than 35 kg/m^2?

Yes ○ No ○ **A**ge older than 50 year old?

Yes ○ No ○ **N**eck size large? (Measured around Adams apple)
For male, is your shirt collar 17 inches/43 cm or larger?
For female, is your shirt collar 16 inches/41 cm or larger?

Yes ○ No ○ **G**ender = Male?

Scoring Criteria:

For general population

Low risk of OSA: Yes to 0-2 questions

Intermediate risk of OSA: Yes to 3-4 questions

High risk of OSA: Yes to 5-8 questions

or Yes to 2 or more of 4 STOP questions + male gender

or Yes to 2 or more of 4 STOP questions + BMI > 35 kg/m^2

or Yes to 2 or more of 4 STOP questions + neck circumference

(17"/43cm in male, 16"/41cm in female)

Modified from: Chung F et al. Anesthesiology 2008; 108:812-21; Chung F et al. Br J Anaesth 2012, 108:768–75; Chung F et al. J Clin Sleep Med 2014;10:951-8.

APPENDIX C-4: ISI

Insomnia Severity Index (ISI)

The Insomnia Severity Index has seven questions. The seven answers are added up to get a total score. When you have your total score, look at the 'Guidelines for Scoring/Interpretation' below to see where your sleep difficulty fits.

For each question, please CIRCLE the number that best describes your answer.

1-3: Please rate the CURRENT (i.e. LAST 2 WEEKS) SEVERITY of your insomnia problem(s).

Insomnia Problem	**None**	**Mild**	**Moderate**	**Severe**	**Very Severe**
1. Difficulty falling asleep	0	1	2	3	4
2. Difficulty staying asleep	0	1	2	3	4
3. Problems waking up too early	0	1	2	3	4

4. How SATISFIED/DISSATISFIED are you with your CURRENT sleep pattern?

Very Satisfied	Satisfied	Moderately Satisfied	Dissatisfied	Very Dissatisfied
0	1	2	3	4

5. How NOTICEABLE to others do you think your sleep problem is in terms of impairing the quality of your life?

Not at all Noticeable	A Little	Somewhat	Much	Very Much Noticeable
0	1	2	3	4

6. How WORRIED/DISTRESSED are you about your current sleep problem?

Not at all Worried	A Little	Somewhat	Much	Very Much Worried
0	1	2	3	4

7. To what extent do you consider your sleep problem to INTERFERE with your daily functioning (e.g. daytime fatigue, mood, ability to function at work/daily chores, concentration, memory, mood, etc.) CURRENTLY?

Not at all Interfering	A Little	Somewhat	Much	Very Much Interfering
0	1	2	3	4

<u>Guidelines for Scoring/Interpretation:</u>

Add the scores for all seven items (questions 1 + 2 + 3 + 4 + 5 +6 + 7) =_____ your total score
Total score categories:
0–7 = No clinically significant insomnia
8–14 = Subthreshold insomnia
15–21 = Clinical insomnia (moderate severity)
22–28 = Clinical insomnia (severe)

Please indicate if: ☒ Completed ☐ Test not administered ☐ Test not completed
If either not administered or not completed, code reason:

Completed by: _____; _____/_____/_____
Initial DD MM YYYY

APPENDIX C-5: CAMRBRIDGE-HOPKINS

1. Do you have, or have you had, recurrent uncomfortable feelings or sensations in your legs while you are sitting or lying down? • Yes • No
2. Do you, or have you had, a recurrent need or urge to move your legs while you were sitting or lying down? • Yes • No
3. Are you more likely to have these feelings when you are resting (either sitting or lying down) or when you are physically active? • Resting • Active
4. If you get up or move around when you have these feelings do these feelings get any better while you actually keep moving? • Yes • No • Don't know
5. Which times of day are these feelings in your legs *most* likely to occur? *(Please circle one or more than one)* • Morning • Mid-day • Afternoon • Evening • Night • About equal at all times
6. Will simply changing leg position by itself *once* without continuing to move usually relieve these feelings? • Usually relieves • Does *not* usually relieve •Don't know

7a. Are these feelings *ever* due to muscle cramps? • Yes • No • Don't know

7b. If so, are they *always* due to muscle cramps? • Yes • No • Don't know

---

Scoring:

Definite RLS: 1 yes, 2 yes, 3 resting, 4 yes, 5 NOT equal or morning, 6 does not usually relieve, 7 a as No OR b as No.

APPENDIX C-6: MAYO SLEEP QUESTIONNAIRE (Q1 ONLY)

Have you ever been told that you seem to “act out your dreams” while sleeping (punched or flailed arms in the air, shouted, or screamed?	☐ No ☐ Yes

APPENDIX C-7: PROMIS

PROMIS Sleep–Related Impairment and Sleep Disturbance

PROMIS Bank v1.1 - SF

Please respond to each item by marking one box per row.

SLEEP–RELATED IMPAIRMENT

In the past 7 days...	Not at all	A little bit	Somewhat	Quite a bit	Very much
1. I had a hard time getting things done because I was sleepy...	1	2	3	4	5
2. I felt alert when I woke up...	5	4	3	2	1
3. I felt tired...	1	2	3	4	5
4. I had problems during the day because of poor sleep...	1	2	3	4	5
5. I had a hard time concentrating because of poor sleep...	1	2	3	4	5
6. I felt irritable because of poor sleep...	1	2	3	4	5
7. I was sleepy during the daytime...	1	2	3	4	5
8. I had trouble staying awake during the day...	1	2	3	4	5

SLEEP DISTURBANCE

In the past 7 days...	Not at all	A little bit	Somewhat	Quite a bit	Very much
1. My sleep was restless...	1	2	3	4	5
2. I was satisfied with my sleep...	5	4	3	2	1
3. My sleep was refreshing...	5	4	3	2	1
4. I had difficulty falling asleep...	1	2	3	4	5

In the past 7 days...	Never	Rarely	Sometimes	Often	Always
5. I had trouble staying asleep...	1	2	3	4	5
6. I had trouble sleeping...	1	2	3	4	5
7. I got enough sleep...	5	4	3	2	1

In the past 7 days...	Very poor	Poor	Fair	Good	Very good
8. My sleep quality was...	5	4	3	2	1

Version 1.0_RevisionDate: 5/07/2015

APPENDIX C-8: SLEEP DIARY

General Instructions

What is a Sleep Diary? A sleep diary is designed to gather information about your daily sleep pattern.

How often and when do I fill out the sleep diary? It is necessary for you to complete your sleep diary every day. If possible, the sleep diary should be completed within one hour of getting out of bed in the morning.

What should I do if I miss a day? If you forget to fill in the diary or are unable to finish it, leave the diary blank for that day.

What if something unusual affects my sleep or how I feel in the daytime? If your sleep or daytime functioning is affected by some unusual event (such as an illness, or an emergency) you may make brief notes on your diary.

What do the words "bed" and "day" mean on the diary? This diary can be used for people who are awake or asleep at unusual times. In the sleep diary, the word "day" is the time when you choose or are required to be awake. The term "bed" means the place where you usually sleep.

Will answering these questions about my sleep keep me awake? This is not usually a problem. You should not worry about giving exact times, and you should not watch the clock. Just give your best estimate.

Sleep Diary Item Instructions

Use the guide below to clarify what is being asked for each item of the Sleep Diary. Date.: Write the date of the morning you are filling out the diary.

1. ***Yesterday, I took a nap for _____ minutes.*** A nap is a time you decided to sleep during the day, whether in bed or not in bed. Count all the times you napped at any time from when you first got out of bed in the morning until you got into bed again at night. Count how many minutes you napped during each nap and add them up to obtain the total time you napped in minutes.
2. ***I went to bed at _____.*** Write the time that you got into bed. This may not be the time you began "trying" to fall asleep.
3. ***I was able to go to bed at my preferred time (as early or late as desired)*** Respond YES or NO if you were able or not to go to bed at your preferred time.
4. ***I turned off the lights at _____.*** Write the time that you turned the lights off with the intention to sleep.
5. **Once the lights went out, I fell asleep in about _____ minutes**. Write the time in minutes that it took you to fall asleep, after the lights were turned off.
6. **During the night, I woke up for about _____ minutes.** Count all the times you woke up at any time from the time you first fell asleep and your final awakening, not counting your final awakening. Count how many minutes you were awake during each awake time and add them up to obtain the total time you were awake. For example, if you woke 3 times for 30 minutes first time, 20 minutes second time, and 5 minutes third time, add them all up (30+20+5= 55 min)
7. ***This morning I woke up at _____.*** Record the last time you woke up in the morning.
8. ***I got up at _____.*** Record the time you got out of bed for the day with no further attempt at sleeping. This may be different from your final awakening time (e.g. you may have woken up at 6:35 a.m. but did not get out of bed to start your day until 7:20 a.m.)
9. ***I woke up spontaneously (i.e. without an alarm clock or any external noise or light) yes/no.*** Respond YES or NO, if you were woken up by an alarm clock or any other external noise such as traffic, sirens, pets or noise created by other members of your household.

10. ***I find that my sleep has been:*** Record the number that best describes your sleep quality: 1 = very relaxing; 2 = restful; 3 = neutral; 4 = not very relaxing; 5 = not restful at all.

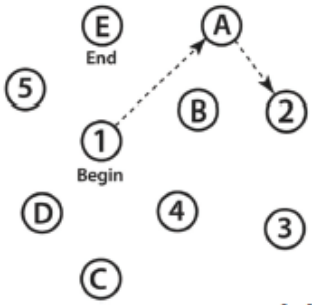
	Sample	Day 1	Day 2	Day 3	Day 4	Day 5
Today's Date	04-05-19					
1. Yesterday, I took a nap for _____ minutes. (Indicate the total length of all your naps in minutes. Here is an example: 15 minutes the first nap + 10 minutes the second nap = 25 minutes total.)	25 min.					
2. I went to bed at _____.	22h00					
3. I was able to go to bed at my preferred time (as early or late as desired)	YES					
4. I turned off the lights at _____.	22h30					
5. Once the lights went out, I fell asleep in about ___min.	30 min.					
6. During the night, I woke up for about _____ min. Here is an example: 30 minutes the first time I woke up + 20 minutes the second time I woke up + 5 minutes the third time I woke up = 55 minutes in total)	55 min.					
7. This morning I woke up at _____.	7h00					
8. I got up at _____. (Indicate the time you got out of bed.)	7h30					
9. I woke up spontaneously (i.e. without an alarm clock or any external noise or light) yes/no	NO					
10. I find that my sleep has been: 1 = very relaxing 2 = restful 3 = neutral 4 = not very relaxing 5 = not restful at all (Indicate the number that best describes your sleep).	3					

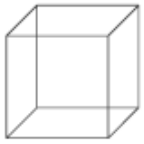
	Sample	Day 6	Day 7	Day 8	Day 9	Day 10
Today's Date	04-05-19					
1. Yesterday, I took a nap for _____ minutes. (Indicate the total length of all your naps in minutes. Here is an example: 15 minutes the first nap + 10 minutes the second nap = 25 minutes total.)	25 min.					
2. I went to bed at _____.	22h00					
3. I was able to go to bed at my preferred time (as early or late as desired)	YES					
4. I turned off the lights at _____.	22h30					
5. Once the lights went out, I fell asleep in about ___min.	30 min.					
6. During the night, I woke up for about _____ min. Here is an example: 30 minutes the first time I woke up + 20 minutes the second time I woke up + 5 minutes the third time I woke up = 55 minutes in total)	55 min.					
7. This morning I woke up at _____.	7h00					
8. I got up at _____. (Indicate the time you got out of bed.)	7h30					
9. I woke up spontaneously (i.e. without an alarm clock or any external noise or light) yes/no	NO					
10. I find that my sleep has been: 1 = very relaxing 2 = restful 3 = neutral 4 = not very relaxing 5 = not restful at all (Indicate the number that best describes your sleep).	3					

APPENDIX C-9: MOCA ONLINE V8.1

MONTREAL COGNITIVE ASSESSMENT (MOCA®) ID:
Version 8.1 English DATE:

VISUOSPATIAL/EXECUTIVE — POINTS



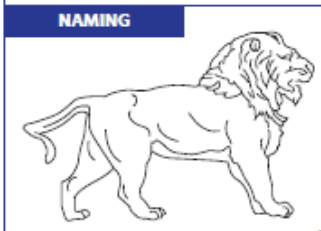


Copy cube [ ] [ ]

Draw CLOCK (Ten past eleven) (3 points)

[ ] Contour [ ] Numbers [ ] Hands __/5

NAMING



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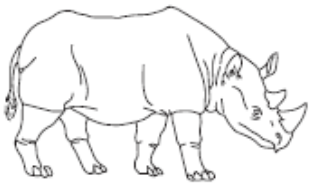

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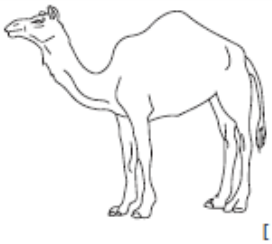


[ ] __/3

MEMORY Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1ST TRIAL					
2ND TRIAL					

NO POINTS

ATTENTION Read list of digits (1 digit/ sec.). Subject has to repeat them in the forward order. [ ] 2 1 8 5 4
Subject has to repeat them in the backward order. [ ] 7 4 2 __/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors
[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B __/1

Serial 7 subtraction starting at 100. [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65
4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0** __/3

LANGUAGE Repeat: I only know that John is the one to help today. [ ]
The cat always hid under the couch when dogs were in the room. [ ] __/2

Fluency: Name maximum number of words in one minute that begin with the letter F. [ ] _____ (N≥11 words) __/1

ABSTRACTION Similarity between e.g. orange - banana = fruit [ ] train - bicycle [ ] watch - ruler __/2

DELAYED RECALL Memory Index Score (MIS)

		FACE	VELVET	CHURCH	DAISY	RED	Points for UNCUED recall only
(MIS) X3	Has to recall words WITH NO CUE	[ ]	[ ]	[ ]	[ ]	[ ]	
X2	Category cue						MIS =____/15
X1	Multiple choice cue						

__/5

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City __/6

www.mocatest.org
Administered by: _____
Training and Certification are required to ensure accuracy

MIS: /15
(Normal ≥ 26/30)
Add 1 point if ≤ 12 yr edu

TOTAL __/30

APPENDIX C-10: LOGICAL MEMORY

Logical Memory IA – Immediate Recall (Story A)

[Say]: "I am going to read to you a little story of just a few lines. Listen carefully and try to remember it just the way I say it, as close to the same words as you can remember. When I am through I want you to tell me everything I read to you. You should tell me all you can remember even if you are not sure. Are you ready?"

"Anna Thompson of South Boston, employed as a cook in a school cafeteria, reported at the City Hall Station that she had been held up on State Street the night before and robbed of fifty-six dollars. She had 4 small children, the rent was due, and they had not eaten for two days. The police, touched by the woman's story, took up a collection for her."

[Say]: "Now what did I read to you? Tell me everything and begin at the beginning."

Record the participant's responses between the lines of the story below. To simplify the recording, make a check mark (√) by any units of the story that are repeated unchanged (i.e., verbatim), and write in any units that are reported, but **NOT** verbatim.

Story A - Immediate Recall	Score
Anna / Thompson / of South / Boston, / employed / as a cook /	_____ (0 - 6)
in a school / cafeteria, / reported / at the City Hall / Station /	_____ (0 - 5)
that she had been held up / on State Street / the night before /	_____ (0 - 3)
and robbed / of fifty-six dollars. / She had four / small children, /	_____ (0 - 4)
the rent was due, / and they had not eaten / for two days. /	_____ (0 - 3)
The police, / touched by the woman's story, /	_____ (0 - 2)
took up a collection / for her. /	_____ (0 - 2)

Total number of story units recalled (verbatim & acceptable non-verbatim): _____/25

Always permit the participant to include additional information by prompting with, **"Anything else?"**

Logical Memory IA – Immediate Recall

After the participant appears to recall no more of the story, then:

[Say]: "Later on I will ask you to tell me this story again, so try not to forget it."

Interviewer Note: Logical Memory IIA - Delayed Recall should be administered at least 30 minutes, but no more than 40 minutes, after this test. Note that if the 30-40 minute period has elapsed and another test is being administered, interrupt that test and administer the Logical Memory IIA - Delayed Recall.

Time ended (24-hour clock):_____: _____

Method of Administration: Telephone: ☐ Video-Call: ☐

Please indicate if: ☐ test not administered ☐ test not completed If either, code reason: _____

Logical Memory IIA – Delayed Recall (Story A)

Time began (24-hour clock):_____:_____ | Time elapsed since Logical Memory I:_____min

(Note: The interval between immediate and delayed recall should be 30-40 minutes.)

The following instructions are to be read verbatim.

[Say]: "Do you remember the little story I read to you a few minutes ago? Now I want you to tell me the story again. Tell me everything; begin at the beginning."

Record the participant's story on this form between the lines of the text below. To simplify the recording, make a check mark (√) by any units of the story that are repeated unchanged (i.e., verbatim), and write in any units that are reported, but **NOT** verbatim.

If the participant does not recall the story, it is permissible to offer a reminder as follows: **"The story was about a woman who was robbed"**, but do not give any further help other than general encouragement. Note at the bottom of this form whether a reminder was given, and do not credit the participant for that item (i.e., "robbed") when scoring.

Story A - Delayed Recall	Score	
Anna / Thompson / of South / Boston, / employed / as a cook /	_____	(0 - 6)
in a school / cafeteria, / reported / at the City Hall / Station /	_____	(0 - 5)
that she had been held up / on State Street / the night before /	_____	(0 - 3)
and robbed / of fifty-six dollars. / She had four / small children, /	_____	(0 - 4)
the rent was due, / and they had not eaten / for two days. /		(0 - 3)
The police, / touched by the woman's story, /	_____	(0 - 2)
took up a collection / for her. /	_____	(0 - 2)

Total number of story units recalled (verbatim & acceptable non-verbatim): _____/25

After the participant has recalled the story, prompt with **"Anything else?"**

Was a reminder given? YES ☐ NO ☐

Method of Administration: Telephone: ☐ Video-Call: ☐

Please indicate if: ☐ test not administered ☐ test not completed If either, code reason: ___

APPENDIX C-11: GERIATRIC DEPRESSION SCALE (SHORT FORM)

Geriatric Depression Scale (short form)

Instructions: Circle the answer that best describes how you felt over the past week.

1.	Are you basically satisfied with your life?	yes	no
2.	Have you dropped many of your activities and interests?	yes	no
3.	Do you feel that your life is empty?	yes	no
4.	Do you often get bored?	yes	no
5.	Are you in good spirits most of the time?	yes	no
6.	Are you afraid that something bad is going to happen to you?	yes	no
7.	Do you feel happy most of the time?	yes	no
8.	Do you often feel helpless?	yes	no
9.	Do you prefer to stay at home, rather than going out and doing things?	yes	no
10.	Do you feel that you have more problems with memory than most?	yes	no
11.	Do you think it is wonderful to be alive now?	yes	no
12.	Do you feel worthless the way you are now?	yes	no
13.	Do you feel full of energy?	yes	no
14.	Do you feel that your situation is hopeless?	yes	no
15.	Do you think that most people are better off than you are?	yes	no

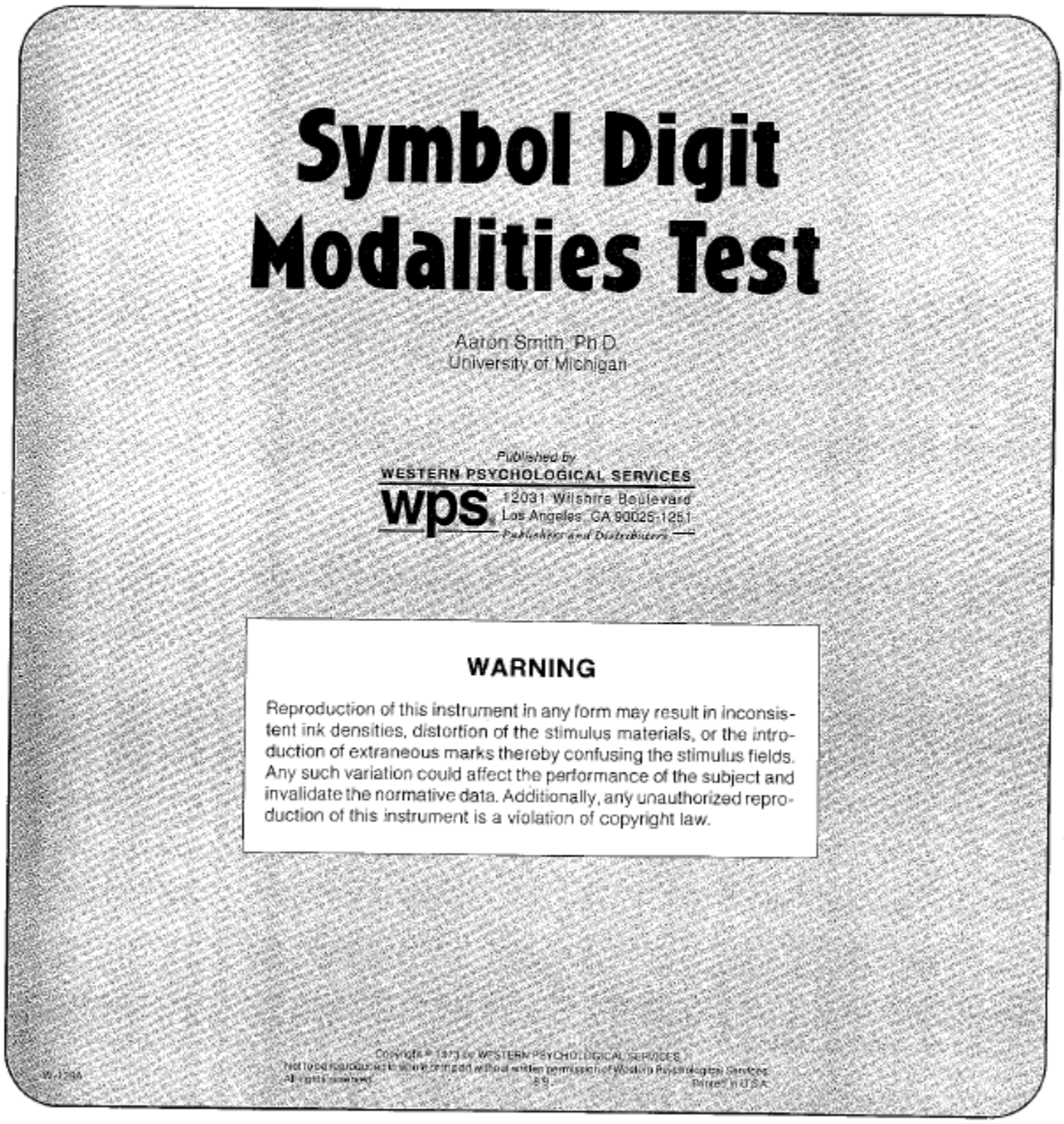
Total Score _____

APPENDIX C-12: SDMT

Hand Used: ☐ Left ☐ Right

ID: _____

Date: _____



Symbol Digit Modalities Test

Aaron Smith, Ph.D.
University of Michigan

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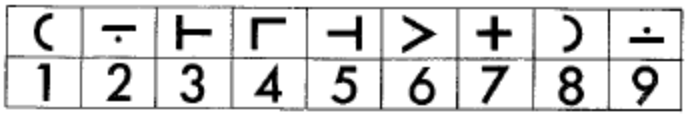

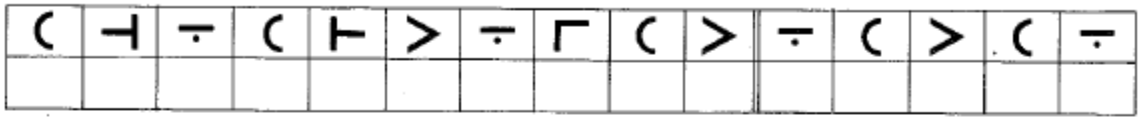

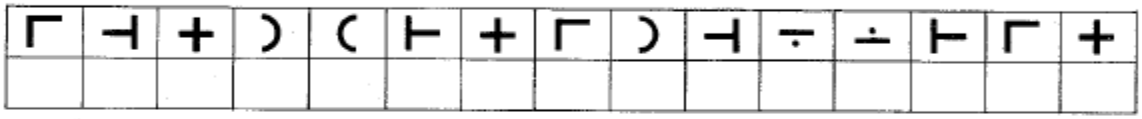

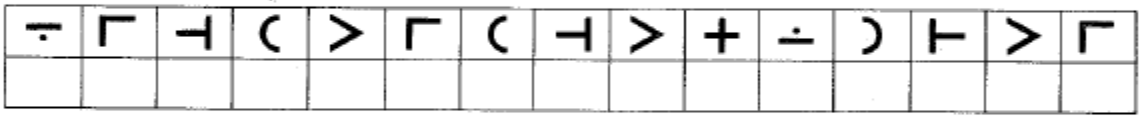

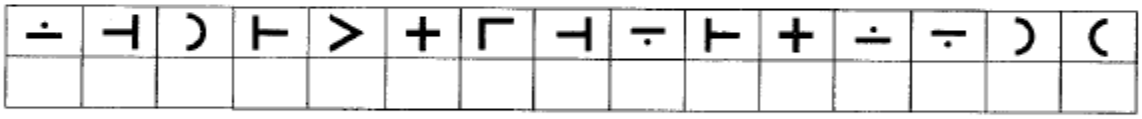

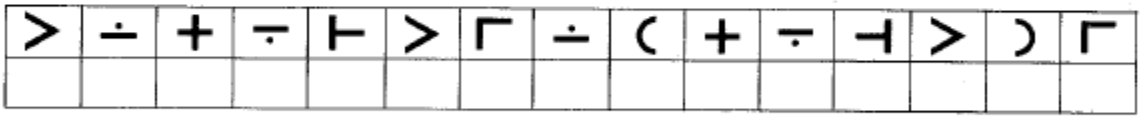

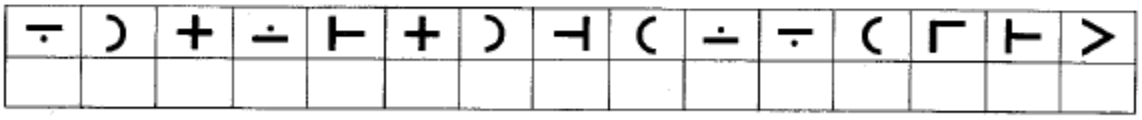

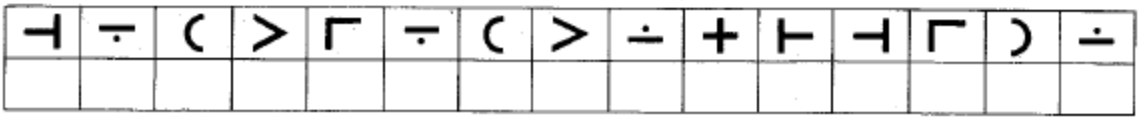


Written Score
Oral Score
2 1 6 1 2
Item Numbers → 1 2 3 4 5
4 6 1 2 5 6 3 4 1 2 6 9 4 3 8
6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
4 5 7 8 1 3 7 4 8 5 2 9 3 4 7
21 22 23 24 25 26 27 28 29 30 31 32 33 34 35
2 4 5 1 6 4 1 5 6 7 9 8 3 6 4
36 37 38 39 40 41 42 43 44 45 46 47 48 49 50
9 5 8 3 6 7 4 5 2 3 7 9 2 8 1
51 52 53 54 55 56 57 58 59 60 61 62 63 64 65
6 9 7 2 3 6 4 9 1 7 2 5 6 8 4
66 67 68 69 70 71 72 73 74 75 76 77 78 79 80
2 8 7 9 3 7 8 5 1 9 2 1 4 3 6
81 82 83 84 85 86 87 88 89 90 91 92 93 94 95
5 2 1 6 4 2 1 6 9 7 3 5 4 8 9
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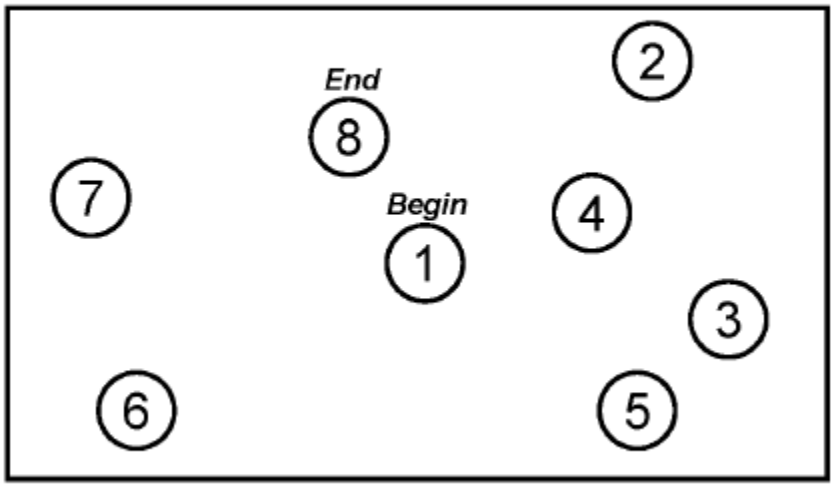
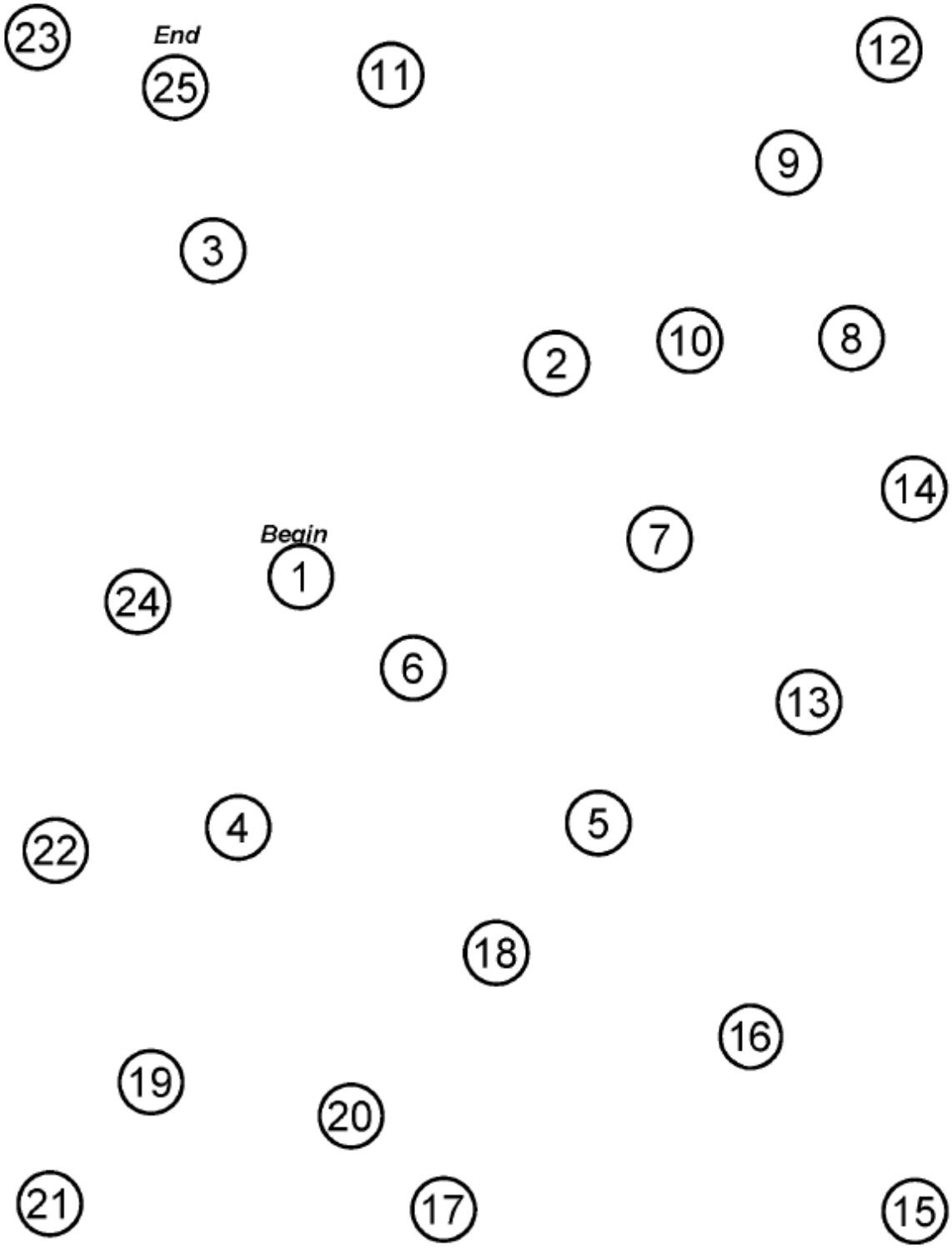
APPENDIX C-13: TRAILS A+B

SAMPLE




23
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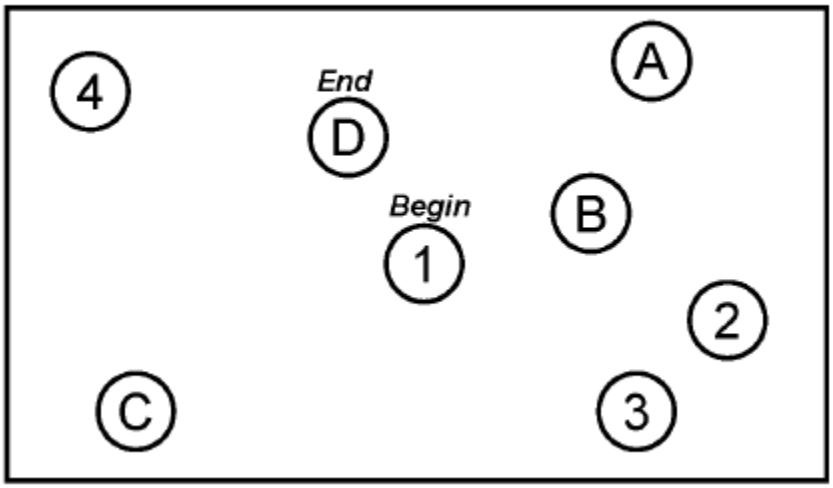
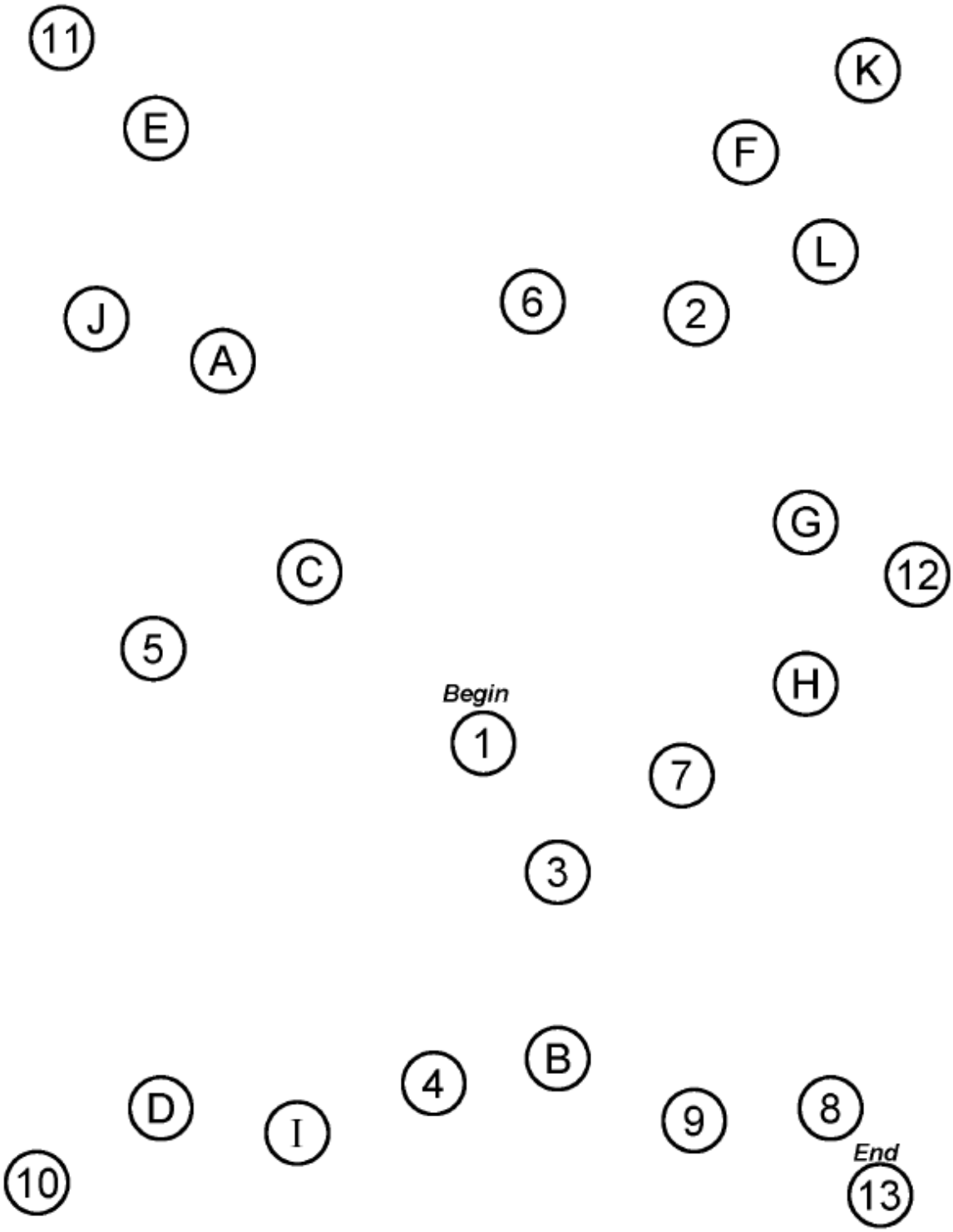
SAMPLE

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APPENDIX C-14: DIGIT SPAN

WAIS-IV Digit Span

Digit Span Forward

"Now I'm going to say some numbers. Listen carefully, I can only say them one time. When I am through, I want you to say them back to me in the same order. Just say what I say."

Item	Trial	Response	Trial Score	Item Score
1	9 – 7		0 1	0 1 2
	6 – 3		0 1	
2	5 – 8 – 2		0 1	0 1 2
	6 – 9 – 4		0 1	
3	7 – 2 – 8 – 6		0 1	0 1 2
	6 – 4 – 3 – 9		0 1	
4	4 – 2 – 7 – 3 – 1		0 1	0 1 2
	7 – 5 – 8 – 3 – 6		0 1	
5	3 – 9 – 2 – 4 – 8 – 7		0 1	0 1 2
	6 – 1 – 9 – 4 – 7 – 3		0 1	
6	4 – 1 – 7 – 9 – 3 – 8 – 6		0 1	0 1 2
	6 – 9 – 1 – 7 – 4 – 2 – 8		0 1	
7	3 – 8 – 2 – 9 – 6 – 1 – 7 – 4		0 1	0 1 2
	5 – 8 – 1 – 3 – 2 – 6 – 4 – 7		0 1	
8	2 – 7 – 5 – 8 – 6 – 3 – 1 – 9 – 4		0 1	0 1 2
	7 – 1 – 3 – 9 – 4 – 2 – 5 – 6 – 8		0 1	
Longest Digit Span Forward: (Maximum = 9)			Digit Span Forward Total Raw Score: (Maximum = 16)	

Digit Span Backward

"Now I am going to say some more numbers, but this time when I stop, I want you to say the numbers backward. If I say 7 – 1, what would you say?"

✓ Correct response [1 – 7]: That's right. *Proceed to Trial 2.*

X Incorrect response: That's not quite right. I said 7 – 1, so to say them backward, you should say 1 – 7. *Proceed to Trial 2.*

Trial 2: Let's try another one. Remember to say them backwards. 3 – 4.

✓ Correct response [4 – 3]: That's right. Let's try some more. *Proceed to Item 1.*

X Incorrect response: That's not quite right. I said 3 – 4, so to say them backward, you should say 4 – 3. Let's try some more. *Proceed to Item 1.*

Item	Trial	Correct Response	Response	Trial Score	Item Score
S	7 – 1	1 – 7			
	3 – 4	4 – 3			
1	3 – 1	1 – 3		0 1	0 1 2
	2 – 4	4 – 2		0 1	
2	4 – 6	6 – 4		0 1	0 1 2
	5 – 7	7 – 5		0 1	
3	6 – 2 – 9	9 – 2 – 6		0 1	0 1 2
	4 – 7 – 5	5 – 7 – 4		0 1	
4	8 – 2 – 7 – 9	9 – 7 – 2 – 8		0 1	0 1 2
	4 – 9 – 6 – 8	8 – 6 – 9 – 4		0 1	
5	6 – 5 – 8 – 4 – 3	3 – 4 – 8 – 5 – 6		0 1	0 1 2
	1 – 5 – 4 – 8 – 6	6 – 8 – 4 – 5 – 1		0 1	
6	5 – 3 – 7 – 4 – 1 – 8	8 – 1 – 4 – 7 – 3 – 5		0 1	0 1 2
	7 – 2 – 4 – 8 – 5 – 6	6 – 5 – 8 – 4 – 2 – 7		0 1	
7	8 – 1 – 4 – 9 – 3 – 6 – 2	2 – 6 – 3 – 9 – 4 – 1 – 8		0 1	0 1 2
	4 – 7 – 3 – 9 – 6 – 2 – 8	8 – 2 – 6 – 9 – 3 – 7 – 4		0 1	
8	9 – 4 – 3 – 7 – 6 – 2 – 1 – 8	8 – 1 – 2 – 6 – 7 – 3 – 4 – 9		0 1	0 1 2
	7 – 2 – 8 – 1 – 5 – 6 – 4 – 3	3 – 4 – 6 – 5 – 1 – 8 – 2 – 7		0 1	
Longest Digit Span Backward: (Maximum = 8)			Digit Span Backward Total Raw Score: (Maximum = 16)		

Digit Span Sequencing

"Now I'm going to say some more numbers. After I say them, I want you to tell me the numbers in order, starting with the lowest number. If I say 2 – 3 – 1, what would you say?"

- ✓ Correct response [1 – 2 – 3]: **That's right.** *Proceed to Trial 2.*
- X Incorrect response: **That's not quite right. I said 2 – 3 – 1, so to say them in order from lowest to highest, you should say 1 – 2 – 3.** *Proceed to Trial 2.*

Trial 2: **Let's try another one. 5 – 2 – 2.**

- ✓ Correct response [2 – 2 – 5]: **That's right. Let's try some more.** *Proceed to Item 1.*
- X Incorrect response: **That's not quite right. I said 5 – 2 – 2, so to say them in order from lowest to highest, you should say 2 – 2 – 5. Let's try some more.** *Proceed to Item 1.*

Item	Trial	Correct Response	Response	Trial Score	Item Score
S	2 – 3 – 1 5 – 2 – 2	1 – 2 - 3 2 – 2 - 5			
1	1 – 2 4 – 2	1 - 2 2 - 4		0 1 0 1	0 1 2
2	3 – 1 – 6 0 – 9 – 4	1 – 3 – 6 0 – 4 - 9		0 1 0 1	0 1 2
3	8 – 7 – 9 – 2 4 – 8 – 7 – 1	2 – 7 – 8 – 9 1 – 4 – 7 – 8		0 1 0 1	0 1 2
4	2 – 6 – 9 – 1 – 7 3 – 8 – 3 – 5 – 8	1 – 2 – 6 – 7 – 9 3 – 3 – 5 – 8 – 8		0 1 0 1	0 1 2
5	2 – 1 – 7 – 4 – 3 – 6 6 – 2 – 5 – 2 – 3 – 4	1 – 2 – 3 – 4 – 6 – 7 2 – 2 – 3 – 4 – 5 – 6		0 1 0 1	0 1 2
6	7 – 5 – 7 – 6 – 8 – 6 – 2 4 – 8 – 2 – 5 – 4 – 3 – 5	2 – 5 – 6 – 6 – 7 – 7 - 8 2 – 3 – 4 – 4 – 5 – 5 – 8		0 1 0 1	0 1 2
7	5 – 8 – 7 – 2 – 7 – 5 – 4 – 5 9 – 4 – 9 – 7 – 3 – 0 – 8 – 4	2 – 4 – 5 – 5 – 5 – 7 – 7 – 8 0 – 3 – 4 – 4 – 7 – 8 – 9 – 9		0 1 0 1	0 1 2
8	5 – 0 – 1 – 1 – 3 – 2 – 1 – 0 – 5 2 – 7 – 1 – 4 – 8 – 4 – 2 – 9 – 6	0 – 0 – 1 – 1 – 1 – 2 – 3 – 5 – 5 1 – 2 – 2 – 4 – 4 – 6 – 7 – 8 – 9		0 1 0 1	0 1 2
Longest Digit Span Sequence: (Maximum = 9)			Digit Span Sequencing Total Raw Score: (Maximum = 16)		

Digit Span Total Raw Score: (Maximum = 48)	

APPENDIX C-15: HOPKINS VERBAL

HVLT-R™

Form 4

Test Booklet

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Ralph H. B. Benedict, PhD

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Learning Trial Instructions

Trial 1

Say the following:

> **I am going to read a list of words to you. Listen carefully, because when I'm through, I'd like you to tell me as many of the words as you can remember. You can tell them to me in any order. Are you ready?**

- Repeat or paraphrase the instructions if necessary.
- Read the words at the rate of approximately one word every 2 seconds.
- If the individual does not spontaneously begin reporting words after the last word is read, say the following:

> **OK. Now tell me as many of those words as you can remember.**

Record the responses verbatim (including repetitions and intrusions) in the Trial 1 column. When the individual indicates no more words can be recalled, proceed to Trial 2.

Trial 2

Say the following:

> **Now we are going to try it again. I am going to read the same list of words to you. Listen carefully, and tell me as many of the words as you can remember, in any order, including all the words you told me the first time.**

Use the same procedure as in Trial 1 to record the responses in the column for Trial 2. Then proceed to Trial 3.

Trial 3

Say the following:

> **I am going to read the list one more time. As before, I'd like you to tell me as many of the words as you can remember, in any order, including all the words you've already told me.**

Record the responses in the column for Trial 3 using the same procedure as in the previous trials.

NOTE: *Do not tell the respondent that recall of the words will be tested later.*

Delayed Recall Trial Instructions

After the 20-25 minute delay, say the following:

> **Do you remember that list of words you tried to learn before?**

If the response is "No," remind the individual that you read the list three times and that he or she was asked to recall the words each time. Say the following:

> **Tell me as many of those words as you can remember.**

ID:

Form 4

Semantic Categories: Birds, Articles of Clothing, Carpenter's Tools

Examiner _____ Date ___/___/___

Word List	Learning Trials			Delayed Recall (20-25 min.)
	Trial 1	Trial 2	Trial 3	Trial 4
CANARY				
SHOES				
EAGLE				
BLOUSE				
NAILS				
CROW				
BLUEBIRD				
SCREWDRIVER				
PANTS				
CHISEL				
SKIRT				
WRENCH				
Total correct responses =				

Completion Time Start Time

Trial 3 _____ Trial 4 _____

Delayed Recognition Instructions

The Delayed Recognition (Forced Choice) trial is administered immediately after the Delayed Recall trial. Say the following:

> **Now I am going to read a longer list of words to you. Some of them are words from the original list, and some are not. After I read each word, I'd like you to say "Yes" if it was on the original list, or "No" if it was not.**

Read the words of the Delayed Recognition trial list in numerical order. Allow the individual as much time as needed to respond. You may use the prompt, **"Was <u>bluebird</u> on the list? Yes or no?"** The individual must give you a response for every word. If the individual is not sure, ask for a guess.

Delayed Recognition (Forced Choice)			
1. BLUEBIRD Y N	7. chapel Y N	13. NAILS Y N	19. CANARY Y N
2. shirt Y N	8. SCREWDRIVER Y N	14. socks Y N	20. apple Y N
3. CHISEL Y N	9. CROW Y N	15. child Y N	21. SKIRT Y N
4. EAGLE Y N	10. sparrow Y N	16. SHOES Y N	22. saw Y N
5. chocolate Y N	11. WRENCH Y N	17. hair Y N	23. silver Y N
6. robin Y N	12. PANTS Y N	18. hammer Y N	24. BLOUSE Y N

Total number of true-positive responses ("hits"): _____ **/12** (no shading)

Semantically-related false-positive errors: _____ /6 (light shading)

Semantically-unrelated false-positive errors: _____ /6 (darker shading)

Total number of false-positive errors: _____ **/12**

	Raw score	*T* score
Total Recall (sum of total correct responses for Trials 1, 2, & 3)		
Delayed Recall (Trial 4)		
Retention (%) [(Trial 4 ÷ Higher score of Trials 2 and 3) x 100]		
Recognition Discrimination Index (Total no. of true-positives) – (Total no. of false-positives)		

Normative table (Appendix A): _____

APPENDIX C-16: ADAS-COG-13

54 pages, located here: https://www.fda.gov/media/122843/download

APPENDIX C-17: LAWTON BRODY IADL

LAWTON - BRODY
INSTRUMENTAL ACTIVITIES OF DAILY LIVING SCALE (I.A.D.L.)

Scoring: For each category, circle the item description that most closely resembles the client's highest functional level (either 0 or 1).

A. Ability to Use Telephone		**E. Laundry**	
1. Operates telephone on own initiative-looks up and dials numbers, etc.	1	1. Does personal laundry completely	1
		2. Launders small items-rinses stockings, etc.	1
2. Dials a few well-known numbers	1	3. All laundry must be done by others	0
3. Answers telephone but does not dial	1		
4. Does not use telephone at all	0		
B. Shopping		**F. Mode of Transportation**	
1. Takes care of all shopping needs independently	1	1. Travels independently on public transportation or drives own car	1
2. Shops independently for small purchases	0	2. Arranges own travel via taxi, but does not otherwise use public transportation	1
3. Needs to be accompanied on any shopping trip	0	3. Travels on public transportation when accompanied by another	1
4. Completely unable to shop	0	4. Travel limited to taxi or automobile with assistance of another	0
		5. Does not travel at all	0
C. Food Preparation		**G. Responsibility for Own Medications**	
1. Plans, prepares and serves adequate meals independently	1	1. Is responsible for taking medication in correct dosages at correct time	1
2. Prepares adequate meals if supplied with ingredients	0	2. Takes responsibility if medication is prepared in advance in separate dosage	0
3. Heats, serves and prepares meals, or prepares meals, or prepares meals but does not maintain adequate diet	0	3. Is not capable of dispensing own medication	0
4. Needs to have meals prepared and served	0		
D. Housekeeping		**H. Ability to Handle Finances**	
1. Maintains house alone or with occasional assistance (e.g. "heavy work domestic help")	1	1. Manages financial matters independently (budgets, writes checks, pays rent, bills, goes to bank), collects and keeps track of income	1
2. Performs light daily tasks such as dish washing, bed making	1	2. Manages day-to-day purchases, but needs help with banking, major purchases, etc.	1
3. Performs light daily tasks but cannot maintain acceptable level of cleanliness	1	3. Incapable of handling money	0
4. Needs help with all home maintenance tasks	1		
5. Does not participate in any housekeeping tasks	0		
Score		**Score**	
		Total score_____	
A summary score ranges from 0 (low function, dependent) to 8 (high function, independent) for women and 0 through 5 for men to avoid potential gender bias.			