Informed Consent Form for Participation in a Research Study

Study 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

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INTRODUCTION

You are being invited to participate in a clinical trial (a type of study that involves research). You are invited to participate in this trial because you are over the age of 55 and have self-reported sleep symptoms and cognitive concerns. This consent form provides you with information to help you make an informed choice. Please read this document carefully and ask any questions you may have. All your questions should be answered to your satisfaction before you decide whether to participate in this research study.

Please take your time in making your decision. You may find it helpful to discuss it with your friends and family.

Taking part in this study is voluntary. You have the option to not participate at all or you may choose to leave the study at any time. Whatever you choose, it will not affect the usual medical care that you receive outside the study.

IS THERE A CONFLICT OF INTEREST?

There are no conflicts of interest to declare related to this study.

WHAT IS THE BACKGROUND INFORMATION FOR THIS STUDY?

Obstructive sleep apnea (OSA) - a sleep disorder characterized by difficulty breathing in sleep resulting in repeated awakenings, and daytime fatigue and sleepiness – is experienced by

>20% of older adults and ~50% of adults with mild cognitive impairment (memory and thinking problems beyond what is expected based on participant's age, but not significant enough to interfere with activities of daily living). Studies have shown that older adults with sleep apnea are more likely to develop cognitive impairment and Alzheimer's disease or related dementias, and do so at an earlier age, than those without sleep apnea. Moreover, adults with sleep apnea have a higher burden of brain amyloid plaques and neurofibrillary tangles – the abnormal proteins that are characteristic of Alzheimer's disease.

The standard or usual treatment for OSA is Continuous Positive Airway Pressure (CPAP). CPAP is effective at improving sleepiness in most patients. CPAP is a system comprised of a face mask connected by tubing to a machine that applies positive pressure to keep the upper airway open during sleep.

In addition, simple lifestyle modifications like weight loss, sleeping on one's side instead of one's back, and healthy sleep habits more generally can be effective at improving sleep symptoms in adults with sleep apnea.

Recent studies at Sunnybrook have shown that among patients with mild cognitive impairment and sleep apnea who are prescribed CPAP, those that use CPAP consistently have a slower rate of cognitive decline than those who don't. Moreover, among patients with newly diagnosed sleep apnea who are prescribed CPAP, those who use CPAP consistently (>4 hours a night >5 nights a week) are able to prevent further damage to the brain perivascular spaces – the drainage channels through which the brain is thought to clear toxic proteins. However, correlation is not proof and we still do not have proof that CPAP or any other intervention can prevent or reverse dementia-associated brain changes or slow or reverse cognitive decline in patients with sleep apnea and mild cognitive impairment (MCI). Moreover, we do not know what treatment or combination of treatments (for instance, educational interventions to promote healthy sleep habits, CPAP, or both) are most effective at achieving this.

The purpose of this study is to definitively answer whether 1) treatment of sleep apnea with CPAP can prevent or reverse dementia-associated brain changes and cognitive impairment, in adults with mild cognitive impairment and 2) what combination of CPAP and education to improve healthy sleep habits is most effective at achieving this.

If you are eligible and choose to participate in this study, you will be screened for both OSA and MCI. If you do not screen positive for both OSA and MCI, you will not be eligible to continue in this study. Those that screen positive for both moderate-severe OSA and MCI will be randomized into one of two groups: 1) Early CPAP group where you will simultaneously receive a web-based sleep education intervention aimed at improving sleep habits, along with expedited CPAP (sooner than would be typical in standard clinical care pathways) for 8 months or 2) Later CPAP group where you will first receive the web-based sleep education intervention for the first 4 months, followed by both web-based sleep education and CPAP for the next 4 months.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to find out what effects CPAP has on you and your cognitive function and AD-related brain changes and determining what is the best approach to delivering CPAP in combination with sleep educational interventions.

WHAT OTHER CHOICES ARE THERE?

You do not have to take part in this study in order to receive treatment or care. Other options (in

addition to the standard or usual treatment described above) may include, but are not limited to:

- CPAP through standard local clinical care pathways
- oral appliances, behavioural/lifestyle changes, or surgery
- no therapy at this time
- other research studies may be available if you do not take part in this study

Please talk to your usual doctor or the study doctor about the known benefits and risks of these other options before you decide to take part in this study. Your usual doctor or the study doctor can also discuss with you what will happen if you decide not to undertake any treatment at this time.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

It is anticipated that about 206 people will take part in this study from the Greater Toronto Area (GTA) communities or patients attending dementia prevention clinics, memory clinics, or sleep clinics located in the GTA.

This study should take 3 years to complete and the results should be known in about 6 months after study completion.

WHAT WILL HAPPEN DURING THIS STUDY?

ASSIGNMENT TO A GROUP

If you decide to participate, you will be "randomized" into one of the groups described below. Randomization means that you are put into a group by chance (like flipping a coin). There is no way to predict which group you will be assigned to. You will have equal chance of being placed in either group. Neither you, the study staff, nor the study doctors can choose what group you will be in.

You will be told which group you are in. Study staff who are administrative in nature (for example, research coordinator or project manager) will also know which group you are in. The study staff responsible for data collection will be blinded to which group you are in.

WHAT IS THE STUDY INTERVENTION?

Group 1 (Early CPAP group):

If you are randomized to this group you will receive a study-provided CPAP device at your baseline visit, with settings set by one of the study sleep medicine physicians according to current clinical practice parameters. You will undergo an in-person mask fitting and then will be supported by a study sleep technologist with extensive clinical experience with CPAP who will contact you by telephone or video call at set intervals. Masks, tubing, chin straps, and other equipment necessary to optimize CPAP adherence will be provided by the study. Adherence will be monitored through downloads from the CPAP device. You will be asked to use CPAP nightly during your participation in this study.

In addition to CPAP, you will simultaneously participate in web-based sleep education through the Brain Health Pro (BHP) platform. BHP is a formal educational program designed to increase dementia literacy, foster engagement, and convey best available evidence for lifestyle changes

that can mitigate dementia risk. You will be guided through the registration process by study staff. You will need to provide a valid e-mail address and will need to enter a preferred name (this can be a first name or a nickname). All data from BHP will be de-identified and linked to a study ID. 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

Group 2 (Later CPAP group):

If you are randomized to this group, you will receive the web-based sleep educational intervention first for 4 months, to give you a chance to optimize your sleep prior to starting CPAP. Then at the beginning of month 5, which is around the time you would have received CPAP through standard clinical care pathways, you will receive a study-supplied CPAP device as in group 1, along with all the CPAP supports described for group 1 above.

WHAT ELSE DO I NEED TO KNOW ABOUT THE STUDY INTERVENTION?

In usual patterns of clinical care, time from OSA diagnosis to final receipt of CPAP is generally more than 4 months, and so even participants in Group 2 (Later CPAP group) will receive CPAP no later than usual patterns of clinical care.

WHAT ARE THE STUDY PROCEDURES?

The following tests will be done as part of this study. Some of these tests may be done as part of your standard care, in which case the results may be used. Some of these tests may be done more frequently than if you were not taking part in this study and some may be done only for the purpose of the study. If the results show that you are not able to continue participating, the study doctor(s) will let you know.

Both treatment groups will receive the assessments as follows at in person visits at Sunnybrook, lasting approximately 2.5 hours each at baseline and month 4 and 1.5 hours at month 8:

Memory, concentration, and mood assessment: various paper/pen and computer tasks.

MRI (baseline and month 4 only): An MRI is a test that uses a magnetic field and radio waves to create detailed pictures of the brain. MRI is a safe and non-invasive diagnostic imaging test. The scan involves lying still on a bed that moves into the centre of the main magnetic field. MRI technologists at Sunnybrook will execute all MRI scans and are trained to address participant needs and maximize comfort. You will be able to communicate with the MRI technologists and study investigators at all times.

Blood samples: Blood samples will be taken by inserting a needle into a vein in your arm. These will be taken at the same time as your study related tests whenever possible, by study staff trained in blood draws. These samples serve several purposes. 1) Samples will be tested for various fats, sugars, and proteins (like cholesterol or glucose). 2) Samples will be sent to the laboratory of a co-investigator on this study at University Health Network (UHN) where they will be examined for the purposes outlined in this research protocol only. 3) Samples will be frozen and stored for future analysis in future studies related to sleep, cognitive impairment, and dementia, which may include testing for as-of-now unspecified genetic markers of health outcomes or other physiological traits. We may also test your blood for specific proteins or genetic- or bio-markers to determine eligibility for additional optional research (if you agree to be contacted about additional optional research related to this study later in this consent form). Under no circumstances will your blood samples be used for commercial use.

Amount of blood to be taken: approximately 45mL, equivalent to 3 tablespoons.

Safety and invasiveness: blood collection can sometimes cause bruising, pain, or very rarely,

loss of consciousness. In all cases, these side effects should be short-lived and temporary.

Measures employed to protect the privacy of and minimize risks to you: to protect your identity, the information that will be on your samples will be limited to study ID and date of collection. Despite protections being in place, there is a risk of unintentional release of information. Due to technological advances in genetics, there may be a risk that the genetic information in the samples could be linked back to you.

The length of time the samples will be kept, how they will be preserved, the location of storage, and the process for disposal: samples will be frozen and stored at Sunnybrook Research Institute (2075 Bayview Avenue, Toronto, Ontario, Canada, M4N 3M5). The sample freezer room is a shared space with other researchers at Sunnybrook Research Institute, with protocols in place to restrict access to study staff who require access only. The samples sent to UHN will be used in full for the purposes of this trial, and any remaining that was sent to UHN will be destroyed.

I agree to allow my samples to be stored for future analysis in future studies related to sleep, cognitive impairment, and dementia, including studies of unspecified biomarkers and testing for as-of-now unspecified genetic markers of health outcomes or other physiological traits:

☐ Yes or ☐ No (Initials: _____)

I understand if I check “No” above, I can still participate in this study.

The samples not sent to UHN, but instead kept at Sunnybrook for future analysis in future studies as above, will be kept, preserved, and stored as above, and retained until used in said future studies, up to a maximum of 10 years, at which point any remaining samples will be destroyed according to local regulatory requirements.

Incidental findings: if the study investigator determines that any of their findings from your blood draws are medically significant or might change your treatment, the study doctor will share these medical findings with you so you may discuss potential treatment or follow-up options with your family doctor/health care provider.

If you no longer want your samples to be used in this research, you should tell the study coordinator, who will ensure the samples are returned to Sunnybrook and destroyed according to local regulatory requirements. If tests have already been done on your sample(s) it will not be possible to withdraw those results. However, no further testing will be done.

At the end of your in-person visits at baseline, 4 months, and 8 months, we will send you home to complete the following assessments and will include return packaging to return the devices:

MUSE EEG headband (3 nights at your own home): 3 nights of home EEG using a wearable headband. EEG measures brain waves – it does not produce any stimulation or uncomfortable sensations. The headband is commercially available and made of a soft band to be worn during sleep. You will be provided an iOS or Android device, with the MUSE app already installed, to facilitate data collection. De-identified data is live-streamed via Bluetooth, then sent to a cloud server provided by Interaxon Inc (located in Toronto, manufacturer of the headband). Data sent to the cloud server is automatically converted to a file type that research staff can download and analyze (file type: edf). Once downloaded by study staff, data is deleted from the company servers.

Wristworn accelerometer (10 consecutive days): A wristwatch-like device to measure activity and sleep. You will be asked to fill out a sleep diary while wearing this device.

Apnealink home sleep apnea test (1 night at your own home, month 4 and month 8 only): the Apnealink consists of a belt worn around your chest with a finger probe and nasal cannulas, to measure your breathing and oxygen levels during sleep.

Optional Research: The Researchers doing this study are interested in doing additional optional research. If you are willing to be contacted about additional optional research related to this study, please check the box below and initial beside it. If you agreed above to allow your blood samples to be stored for future studies, we may test your blood for specific proteins or genetic- or bio-markers to determine eligibility for additional optional research. You may decide not to participate in the optional research and still participate in this main study.

I agree to be contacted about additional option research related to this study:

☐ Yes or ☐ No (Initials: _____)

WHAT ARE THE RESPONSIBILITIES OF STUDY PARTICIPANTS?

If you choose to participate in this study, you will be expected to:

- Comply with the requirements of the study (e.g. attend scheduled sessions, participate in web-based education) to facilitate completion of the study procedures described above;
- Tell the study doctor about your current medical conditions;
- Tell the study doctor about any past diagnosis or treatment of sleep apnea; and
- Tell the study doctor if you are thinking about participating in another research study

HOW LONG WILL PARTICIPANTS BE IN THE STUDY?

The study intervention will last for about 8 months, with Group 1 (early CPAP) receiving CPAP for 8 months and Group 2 (later CPAP) receiving CPAP for the last 4 months of their participation.

CAN PARTICIPANTS CHOOSE TO LEAVE THE STUDY?

You can choose to end your participation in this research (called withdrawal) at any time without having to provide a reason. If you choose to withdraw from the study, you are encouraged to contact the study doctor or study staff.

You may be asked questions about your experience with the study intervention.

You may withdraw your permission to use information that was collected about you for this study at any time by letting the study doctor know. However, this would also mean that you withdraw from the study.

If you decide to leave the study, you can ask that the information that was collected about you not be used for the study. Let the study doctor know if you choose this.

CAN PARTICIPATION IN THIS STUDY END EARLY?

The study doctor may stop your participation in the study early, and without your consent, for reasons such as:

- You are unable to tolerate the study intervention
- You are unable to complete all required study procedures
- New information shows that the study intervention is no longer in your best interest
- The study doctor no longer feels this is the best option for you
- The Sponsor decides to stop the study
- The Regulatory Authority/ies (for example, Health Canada) or research ethics board withdraw permission for this study to continue
- Your group assignment becomes known to the study staff responsible for data collection

If this happens, it may mean that you would not receive the study intervention for the full period described in this consent form.

If you are removed from this study, the study doctor will discuss the reasons with you and plans will be made for your continued care outside of the study.

WHAT ARE THE RISKS OR HARMS OF PARTICIPATING IN THIS STUDY?

You may experience side effects from participating in this study. Some side effects are known and are listed below, but there may be other side effects that are not expected. You should discuss these with the study doctor.

The study doctor will watch you closely to see if you have side effects.

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

Risks and side effects related to other study procedures are minor and may include:

- Discomfort or skin irritation from wearing a wristwatch-like accelerometer
- Minor disturbance of your usual sleep on the night you are wearing the Apnealink device or the MUSE headband
- Bruising, pain, or very rarely, loss of consciousness during blood collection
- Rarely, people experience temporary and mild tingling sensation during the MRI. You may also experience temporary stress/anxiety or claustrophobia during the MRI.

You may learn something about yourself that you were unaware of, including being told if you have MCI or OSA, which could cause some anxiety or discomfort.

The CPAP intervention will be overseen by one of the study physicians assisted by a full-time sleep technologist. The sleep technologist will oversee initial mask fitting and selection, CPAP

teaching, and set-up under the direction of the study physicians. The sleep technologist will contact participants by telephone or video call according to a set schedule. Calls will address a) anticipation and troubleshooting of common CPAP barriers (mask leak, mask fit, bloating, claustrophobia, etc.) b) education around sleep apnea physiology and consequences and c) motivational enhancement. Between scheduled calls, the technologist will be available during business hours as needed for both remote and in-clinic visits.

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.

WHAT ARE THE BENEFITS OF PARTICIPATING IN THIS STUDY?

All participants will receive web-based sleep education that they would not otherwise receive. The participants in the Early CPAP group will obtain CPAP faster than usual care pathways.

You will receive a study-provided auto-titrating CPAP device and the necessary masks, tubing, chin straps, and other equipment to optimize CPAP adherence. You will receive CPAP either at baseline or at the beginning of your 5th month in the study, depending on which group you are randomized. While using CPAP in this study, you will be supported by a sleep technologist with extensive clinical experience with CPAP. At the end of your participation, you will get to keep the CPAP device and equipment obtained throughout your participation, but sleep technologist support will end. The study doctor can help you identify standard CPAP support available in community clinics, or you can discuss ongoing support with your family doctor.

In addition to the above, you will get access to an online sleep educational intervention developed by the Canadian Consortium for Neurodegeneration and Aging aimed at optimizing sleep habits for dementia prevention.

We hope the information learned from this study will help other people with MCI and sleep apnea in the future. Our key end users are 1) patients with MCI and sleep apnea; 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. This study, if successful and a positive result, would support widespread treatment of OSA in patients with cognitive impairment to slow cognitive decline and reduce AD-related brain changes, and identify how best to combine treatments (i.e. sleep education, CPAP) to achieve this. Further, this study will identify key sleep changes that can be targeted by other interventions, like web-based educational platforms.

HOW WILL PARTICIPANT INFORMATION BE KEPT CONFIDENTIAL?

If you decide to participate in this study, the study doctors and study staff will only collect the information they need for this study.

Records identifying you at this centre will be kept confidential and, to the extent permitted by the applicable laws, will not be disclosed or made publicly available, except as described in this consent document.

Authorized representatives of the following organizations may look at your original (identifiable)

medical/clinical study records at the site where these records are held, to check that the information collected for the study is correct and follows proper laws and guidelines.

- The research ethics board who oversees the ethical conduct of this study in Ontario
- This institution and affiliated sites, to oversee the conduct of research at this location

Information that is collected about you for the study (called study data) may also be sent to the organizations listed above. Representatives of Clinical Trials Ontario, a not-for-profit organization, may see study data that is sent to the research ethics board for this study. Your name, address, email, or other information that may directly identify you will not be used. The records received by these organizations may contain your participant code, initials, sex, and date of birth.

The following organizations may also receive study data:

- Site research groups affiliated with this study for the research purposes explained in this consent form
- Interaxon Inc. located in Toronto, ON, Canada and the manufacturer of the MUSE headband, to facilitate data analyses for the research purposes explained in this consent form. Information sent to Interaxon Inc. will be de-identified and in a file format proprietary to Interaxon Inc. so that it is only accessible by the intended recipient.

Communication via e-mail is not absolutely secure. We do not recommend that you communicate sensitive personal information via e-mail.

If the results of this study are published, your identity will remain confidential. It is expected that the information collected during this study will be used in analyses and will be published/ presented to the scientific community at meetings and in journals.

Even though the likelihood that someone may identify you from the study data is very small, it can never be completely eliminated.

WILL FAMILY DOCTORS/HEALTH CARE PROVIDERS KNOW WHO IS PARTICIPATING IN THIS STUDY?

Your family doctor/health care provider will not be informed by the study team that you are taking part in the study. You can choose to let your family doctor/health care provider know, if you like.

Most tests done in research studies are only for research and have no clear meaning for health care. Occasionally, an unexpected finding comes up in the course of assessing a participant that may require further medical attention. For instance, learning that a participant has an abnormal MRI finding, or depression, which should be treated. If the study investigator determines that any of their findings from your study examinations are medically significant or might change your treatment, the study doctor will share these medical findings with you so you may discuss potential treatment or follow-up options with your family doctor/health care provider.

WILL INFORMATION ABOUT THIS STUDY BE AVAILABLE ONLINE?

A description of this clinical trial will be available on http://www.clinicaltrials.gov and www.sunnybrook.ca. These websites will not include information that can identify you. You can search these websites at any time.

You can request to be notified if the results of this study are published in scientific journals or presented at scientific conferences.

WHAT IS THE COST TO PARTICIPANTS?

The CPAP device and associated masks, tubing, and equipment for its operation will be supplied at no charge while you take part in this study. You will also receive support from a sleep technologist at no charge while you take part in this study.

You may keep the CPAP device and equipment obtained throughout your participation after your participation in the study is completed. However, sleep technologist support will end at the conclusion of your study participation.

Taking part in this study may result in added costs to you. For example:

- There may be costs associated with hospital visits. For example, parking or transportation, or snacks/meals during your stay. The payments outlined below should offset these costs.
- You may miss work as a result of participation in this study.

ARE STUDY PARTICIPANTS PAID TO BE IN THIS STUDY?

If you decide to participate in this study, you will receive compensation that varies depending on the extent of study participation, as follows:

- Each in-person assessment visit (3 total): $50

The above will be paid at the conclusion of each study visit. A study participant completing all study procedures would receive a total compensation of $260 ($110 during screening activities prior to enrolling in the study, plus $150 for in-person assessment visits after enrolling).

If you decide to leave the study, you will not receive payment for future assessment visits that do not happen.

In the case of research-related side effects or injury, medical care will be provided by your doctor or you will be referred for appropriate medical care.

WHAT ARE THE RIGHTS OF PARTICIPANTS IN A RESEARCH STUDY?

You will be told, in a timely manner, about new information that may be relevant to your willingness to stay in this study.

You have the right to be informed of the results of this study once the entire study is complete. If you would like to be informed of the results of this study, please let the study doctor know.

Your rights to privacy are legally protected by federal and provincial laws that require safeguards to ensure that your privacy is respected.

By signing this form you do not give up any of your legal rights against the study doctor, sponsor or involved institutions for compensation, nor does this form relieve the study doctor, sponsor or their agents of their legal and professional responsibilities.

You will be given a copy of this signed and dated consent form prior to participating in this study.

WHOM DO PARTICIPANTS CONTACT FOR QUESTIONS?

If you have questions about taking part in this study, or if you suffer a research-related injury, you can talk to your study doctor, or the doctor who is in charge of the study at this institution. That person is: Dr. Andrew Lim, (416) 480-6100 x5753.

If you have questions about your rights as a research participant or any ethical issues related to this study that you wish to discuss with someone not directly involved with the study, you may call the **Chair of the Sunnybrook Research Ethics Board at (416) 480-6100 ext. 688144.**

SIGNATURES

- All of my questions have been answered,
- I understand the information within this informed consent form,
- I allow access to medical records and related personal health information as explained in this consent form
- I allow linkage to Public Health databases, health records, and administrative health data for purposes of future studies, for example measuring long term health outcomes
- I do not give up any legal rights by signing this consent form
- I agreeto participate in this research study

Signature of Participant	PRINTED NAME	Date
Signature of Person Conducting the Consent Discussion	PRINTED NAME & ROLE	Date