Protocol Title:

The Canadian Therapeutic Platform Trial for Multidomain Interventions to Prevent Dementia: Brain Health Support Program Intervention

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CCNV
Consortium canadien en neurodégénérescence associée au vieillissement

CCNA
Canadian Consortium on Neurodegeneration in Aging

CAN Thumbs Up

Protocol Title:	The Canadian Therapeutic Platform Trial for Multidomain Interventions to Prevent Dementia: Brain Health Support Program Intervention
Protocol Acronym:	CAN-THUMBS UP or CTU: BHSP
Sponsor:	The Canadian Consortium for Neurodegeneration in Aging
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Study Summary

Title	Canadian Therapeutic Platform Trial for Multidomain Interventions to Prevent Dementia (CAN-THUMBS UP or CTU): Brain Health Support Program Intervention
Background & Rationale	In Canada, it is estimated that there are currently over 500,000 older adults living with dementia [1]. It has been estimated that close to a third of dementia cases could be prevented by addressing modifiable risk factors including; physical inactivity, depression, and social isolation, metabolic and vascular risk factors, sensory loss, sleep problems, cognitive inactivity and poor diet [2]. Prior studies have also reported that even in the early stages of AD, older adults can benefit from formal educational programs about dementia [3]. Furthermore, web-based programs focusing on risks and protective factors have been found to improve dementia-related protection/risk profiles in middle-aged adults [4]. Participating in an online educational program could potentially increase participants' dementia literacy, empowerment, general self-efficacy and engagement regarding ways to promote their brain health. The Canadian Therapeutic Platform Trial for Multidomain Interventions to Prevent Dementia (CAN-THUMBS UP, or CTU) is a comprehensive and innovative program aimed to develop, implement and evaluate an interactive and compelling online educational Brain Health Support Program (BHSP) intervention, called Brain Health PRO (BHPro), with potential to positively influence dementia literacy, lifestyle risk factors, and scale-up to reach the broader Canadian public; enroll and retain a community-dwelling Platform Trial Cohort (PTC) of individuals at risk of dementia; and support an open platform trial to test a variety of multidomain interventions that might further benefit individuals at risk of dementia. BHPro is a 45-week, multidomain web-based formal educational program which has been designed to increase dementia literacy, convey best available evidence for lifestyle changes that can mitigate dementia risk, and foster engagement toward one's own brain health. 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. Furthermore, this study will employ mobile technology, such as remote testing of cognitive function and wearable devices that track changes in activity and sleep patterns, to more readily evaluate compliance and effects of lifestyle interventions. Implementation of a fully remote online research protocol will provide an accessible approach to research in a setting where restrictions to in-person evaluations may continue to be imposed by COVID-19 and would allow research progress towards the goal of dementia prevention during challenges such as COVID-19. In addition to reaching more potential participants who can more easily join the program, this will help us achieve the important goal of reaching a broader geography with recruitment of participants across Canada irrespective of where they live.

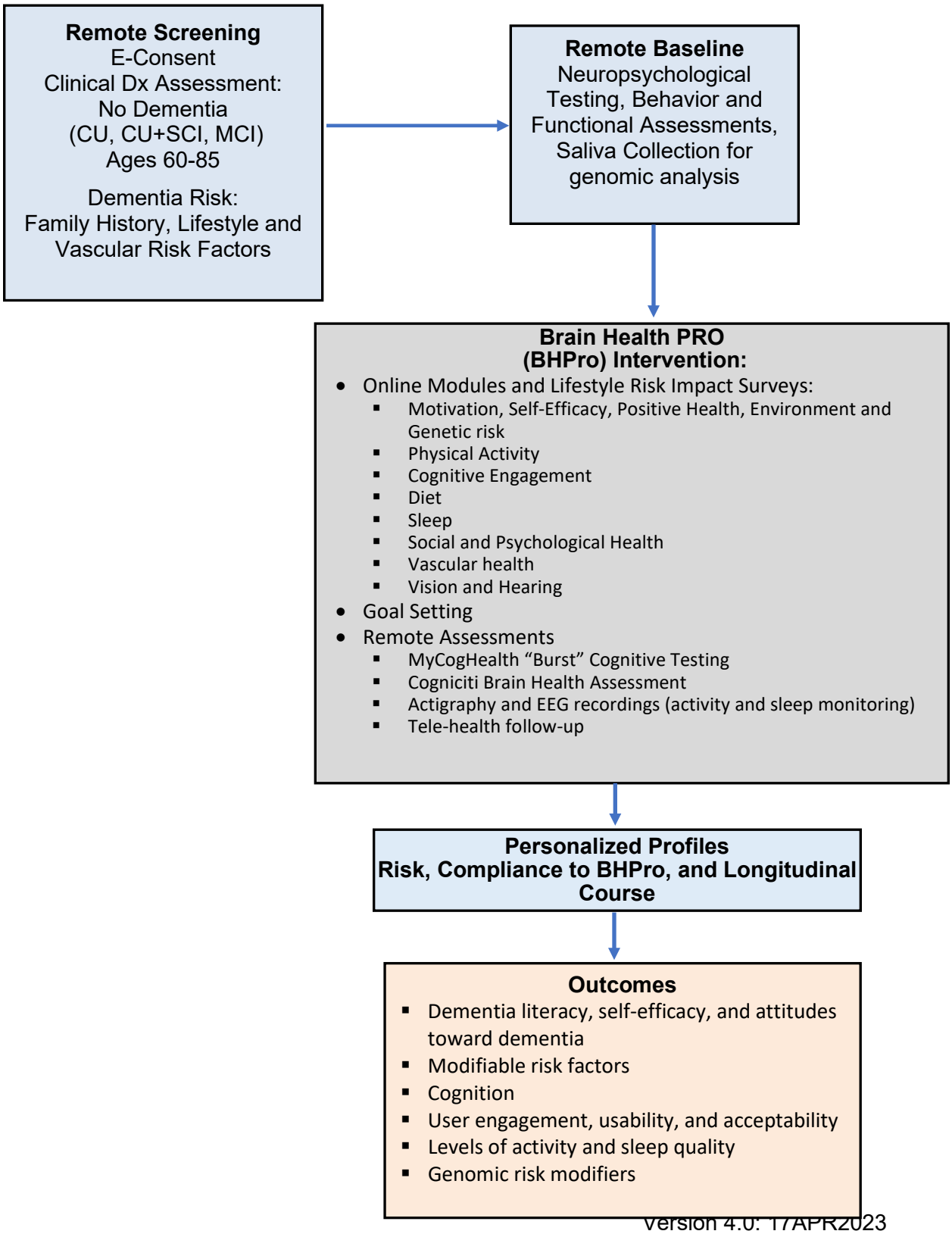
Target Population	**All Participants**: • Ages 60-85 • Meets criteria for **No Dementia** and one of the following (according to CCNA criteria): ▪ Cognitively Unimpaired (CU) ▪ Cognitively Unimpaired plus Subjective Cognitive Impairment (CU + SCI) ▪ Mild Cognitive Impairment (MCI) • **AND** Classified as being at **increased risk of dementia** based on **at least one of the following**: ▪ First-degree family history of dementia ▪ Self-Reported or documented current and/or history at midlife (45-60) on any of the following risk factors: ○ Hypertension (documented Systolic Blood Pressure > 140 mm Hg; OR physician diagnosis of hypertension; OR treatment for hypertension; OR other approaches to treatment (e.g. diet, exercise)) ○ Hypercholesterolemia (documented total cholesterol > 6.5 mmol/L; OR physician diagnosis of hypercholesterolemia; OR treatment for hypercholesterolemia; OR other approaches to treatment (e.g. diet, exercise)) ◦ Body Mass Index > 30 kg/m^2 (derived from NIH Metric BMI Calculator) ◦ Physical Inactivity (active is defined as engaging in a minimum of 20- 30 min of physical activity causing sweating and breathlessness, at least 2 times a week)
Number of Participants	**n = up to 350** (enrolled from across Canada using centralized recruitment)
Study Goal and Aims	**Overall Goal:** To develop and evaluate a 45-week web-based Brain Health Support Program (BHSP) intervention, called Brain Health PRO (BHPro), focused on dementia literacy, self-efficacy and modifiable lifestyle risk factors. Participants will subsequently be part of a PTC and may be evaluated for eligibility to participate in interventional dementia prevention trials under separate protocols. **Aims:** **A.** Our primary aim is to evaluate within-person change in dementia literacy following participation in BHPro. **B.** To evaluate within-person change following participation in BHPro, including change in: i. Self-efficacy and attitudes towards dementia and its screening ii. Individuals' modifiable risk factors iii. Cognition

	iv. Physical activity and sleep quality as measured by actigraphy and electroencephalogram (EEG) wearable devices **C.** To evaluate BHPro in relationship to: i. Levels of engagement (i.e., number of chapters completed), thresholds of compliance, ratings of satisfaction, and dropout rates from the intervention ii. Levels of engagement in the program as a function of individual characteristics and risk profile iii. Levels of engagement as a moderator of within person change in outcomes. iv. Association between change in modifiable risk factors and change in cognition **D.** To develop a successful comprehensive national recruitment plan to fully enroll the PTC with engagement stakeholder groups including participants, citizen advisors, and community partners.
Outcome Measures	**Primary Outcome Measure:** **A.** The primary outcome will be change in dementia literacy following participation in the study, as measured by the Alzheimer's Disease Knowledge Scale. **Secondary Outcome Measures:** **A.** Change in self-efficacy following participation in the study, as measured by the General Self-Efficacy Scale (GSE). **B.** To evaluate BHPro, as measured by: i. Engagement using the online program (e.g., percentage of chapters completed) ii. User satisfaction ratings and evaluation of usability and acceptance (System Usability Scale and Technology Acceptance Model Questionnaire) **Exploratory Outcome Measures:** **A.** Change in attitudes toward dementia following participation in the study as measured by Sections B and D of the Perceptions Regarding Investigational Screening for Memory in Primary Care (PRISM-PC). **B.** Change in modifiable risk factors following participation in the study, as measured by BHPro Lifestyle Risk Questionnaires. **C.** Cognition

	i. Change in global cognition based on a composite score using the Neuropsychological Test Battery (calculated as average Z scores standardized to the baseline mean and standard deviation). ii. Change in the subdomains of memory, processing speed, and executive functions based on composite scores derived from the Neuropsychological Test Battery (calculated as average Z scores standardized to the baseline mean and standard deviation). iii. Change in performance based on "Burst" Cognitive Testing that addresses: o Within-person change in asymptote, daily variation and within-burst practice effects of "burst" cognitive testing o Between- and within-person factors including self-rated emotional reactivity and its association with variation in cognitive performance over the BHPro intervention iv. Change in performance based on online self-administered cognitive testing with the Cogniciti Brain Health Assessment v. Change in modifiable risk factors and relationship to change in cognition **D.** National recruitment success will be measured by: i. Enrollment rates per month and year across regions with centralized and local recruitment strategies ii. Screen fail rate and reasons iii. Projected enrollment rates vs actual enrollment rates **E.** Change in levels of physical activity and sleep quality, as measured by actigraphy and EEG wearable devices. **F.** Saliva sample collection, to characterize the distribution of age adjusted polygenic hazard scores within the BHSP study group.
Study Design & Statistical Approach	This initial phase (Phase A) of CTU will be a prospective 12-month multi-center longitudinal intervention study to evaluate a web-based educational BHSP, called BHPro, focused on dementia literacy, self-efficacy, and modifiable lifestyle risk factors. Participants will be individuals who are either cognitively unimpaired or have MCI with increased risk related to lifestyle risk factors. At the conclusion of the BHSP intervention, participants will continue in the PTC with the opportunity to consent and enroll in further multidomain intervention trials. **Sample Size & Power:**

	With an initial t1 sample size of 350 participants and an anticipated 20-30% range of drop-out rates, we will have between 245 (with 30% dropout) and 280 (with 20% dropout) completed participants at t2 (end of intervention). All calculations are for 80% power and 5% two-tailed alpha. We considered small (d=0.2) and medium (d=0.5) Effect Sizes for 4 different t1-t2 correlations (r_{t1-t2}) in the primary outcome variable: r=0.2, 0.3, 0.4 and 0.5. A final sample of n=280 will allow us to detect an ES ≥0.2 if r_{t1-t2}≥0.3. A final sample of n=245 will allow us to detect an ES ≥0.2 if r_{t1-t2}≥0.4. We are aiming to recruit 50% women to allow for later stratification of analyses to assess for sex differences. **Statistical Approach:** In our one-group pretest-posttest design the major interest is within-person change in the primary and secondary outcomes over time (response variables) in the presence of one or more explanatory variables that are categorical or continuous. The data will be analyzed using a mixed model for repeated measures approach (MMRM). This approach will treat sites and participants as random effects, while observational time and their characteristics such as sex and age as fixed effects. Potential effect modifications will be examined using this MMRM approach with variable selection based on Akaike/Bayesian information criterion. A more detailed and formal statistical analytic plan (SAP) will be developed and finalized during the study. The SAP will include detailed descriptions for evaluating our study outcomes including BHPro, cognition, physical activity and sleep, and recruitment metrics.

STUDY SCHEMATIC
Phase A: Platform Trial Cohort and Brain Health Support Program Intervention



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LIST OF ABBREVIATIONS:

AD	Alzheimer's Disease
ADKS	Alzheimer's Disease Knowledge Scale
AE	Adverse Event
BHA	Cogniciti Brain Health Assessment
BHPro	Brain Health PRO
BHSP	Brain Health Support Program
BMI	Body Mass Index
BNT	Boston Naming Test
BVMT-R	Brief Visuospatial Memory Test-Revised
CAIDE	The Cardiovascular Risk Factors, Aging, and Incidence of Dementia
CCNA	Canadian Consortium for Neurodegeneration in Aging
CDR	Clinical Dementia Rating
COMPASS-ND	The Comprehensive Assessment of Neurodegeneration and Dementia
CRF	Case Report Form
CTU	CAN-THUMBS UP
CU	Cognitively Unimpaired
CWIT	Color-Word Interference Test
DCF	Data clarification form
DKEFS	Delis-Kaplan Executive Function System
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSPC	Data Sharing and Publications Committee
ECG	Electrocardiogram
EEG	Electroencephalogram
GAD-7	Generalized Anxiety Disorder 7-Item Scale
GCP	Good Clinical Practice
GDS	Geriatric Depression Scale
HIPAA	Health Insurance Portability & Accountability Act
IADL	Instrumental Activities of Daily Living
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICMJE	International Committee of Medication Journal Editors
IRB	Institutional Review Board
LMM	Linear Mixed Model
LORIS	Longitudinal Online Research and Imaging System
MBI-C	Mild Behavioral Impairment Checklist
MCI	Mild Cognitive Impairment
MMRM	Mixed Model for Repeated Measures
MoCA	Montreal Cognitive Assessment
MRI	Magnetic Resonance Imaging
MTP	Master Trial Protocol
NACC	National Alzheimer's Coordinating Center
NTB	Neuropsychological Test Battery
OPT	Open Platform Trial
PC	Primary Care

PHS	Polygenic Hazard Score
PI	Principal Investigator
PIPEDA	Personal Information Protection and Electronic Documents Act
PRISM	Perceptions Regarding Investigational Screening for Memory
RBD	REM Sleep Behaviour Disorder
RCT	Randomized Controlled Trial
REB	Research Ethics Board
RLS	Restless Leg Syndrome
SAE	Serious Adverse Event
SAP	Statistical Analytic Plan
SCI	Subjective Cognitive Impairment
SFTP	Secure File Transfer Protocol
SRI	Sunnybrook Research Institute
SUS	System Usability Scale
SYNERGIC	Synchronizing Exercises, Remedies in Gait and Cognition

1.0 INTRODUCTION

1.1 Background

The opportunity to delay or prevent up to 30% of dementia cases through the active management of modifiable risk factors, notably vascular, diet, activity, sensory, cognitive and social engagement, prior to dementia onset, is increasingly recognized as the most tractable and immediate approach to finding effective treatment and prevention with an enormous public health impact [5]. Furthermore, even a modest delay of one year in the onset of dementia has been projected to save the Canadian health care system $120 billion over the next 3 decades [6]. Priorities for public health and lifestyle interventions have included those that promote brain resilience and address modifiable risk factors, an approach that will be directed by personalized host profiles [7, 8]. To address this, the Canadian Therapeutic Platform Trial for Multidomain Interventions to Prevent Dementia (CAN-THUMBS UP or CTU) has been designed as a comprehensive and innovative program aimed to develop an interactive and compelling online Brain Health Support Program (BHSP) intervention, called Brain Health PRO (BHPro), with potential to positively influence dementia literacy, lifestyle risk factors, and scale-up to reach the broader Canadian public; enroll and retain a community-dwelling Platform Trial Cohort (PTC) of individuals at risk of dementia; and support an open platform trial to test a variety of multidomain interventions that might further benefit individuals at risk of dementia.

Addressing long-term outcomes with combined interventions that address risk factor modification and potentially promote brain resilience, could advance the important goal of acquiring evidence to guide public health policy for dementia prevention [5, 9-11]. Our focus in this study addresses many of these elements including understanding personalized risk profiles and the role of education and training. As well, we create a framework that will enable ongoing testing of combination and multidomain interventions for dementia prevention with novel approaches and with legacy contributions for the Canadian public.

The Role of Education and Engagement in Dementia Prevention

Prior studies have reported that even in the early stages of Alzheimer's disease (AD), older adults can benefit from formal educational courses on dementia and that they can improve their knowledge of the disease, with beneficial effects on their mood and self-efficacy [3]. Furthermore, web-based educational programs focusing on risks and protective factors have been found to improve dementia-related protection/risk profiles in middle-aged adults [4]. Engaging in an educational program could potentially increase participants' dementia literacy, empowerment, general self-efficacy and engagement regarding ways to promote their brain health. Based on prior studies, this could have a positive risk reduction effect on its own while also improving participants' readiness to change and increasing motivation to participate in further prevention of dementia studies.

Personalized Risk Profiles and Remote Assessments

In considering the path to successful multidomain lifestyle interventions key issues include tailoring approaches to personalized risk profiles, addressing individual preferences, and compliance with and fidelity to the intervention. It is now increasingly possible to mobilize technology to more readily evaluate compliance and effects of lifestyle interventions, through the incorporation of wearable devices that track changes in activity levels and sleep patterns, and through app-based remote testing of cognitive function using paradigms of 'burst' cognitive testing and/or self-administered online cognitive testing. These measurement approaches should be very informative in evaluating how interventions are being taken up and also in

assessing whether there is an early and subtle slope of decline. Such early detection of decline can be used to design more powerful, personalized trials where those at the highest predicted risk would be included and those at lower risk excluded. There is emerging evidence that lifetime cognitive activity can mitigate or forestall AD pathology specifically in genetically susceptible individuals, suggesting that tailoring cognitive training according to genetic risk is warranted in trying to achieve best outcomes [12]. Additionally, there is evidence that the intensity and supervision of lifestyle interventions, including exercise and cognitive training, contributes in part to their potential efficacy. Given the inherent cost and infrastructure needed for more intensive lifestyle interventions, including personal trainers, coaches and trained staff compared to self-administration [13, 14] it is important to enrich the targeted population to those at higher risk. Employing technology for remote data collection provides a timely opportunity to engage with participants and continue to advance research in dementia prevention in the context of current restrictions to traditional research conduct during the global novel coronavirus (COVID-19) pandemic.

Dementia Risk Scores
Significant progress has been made in identifying those at high risk of dementia with aging through testing that can be quite simply and readily undertaken. The Cardiovascular Risk Factors, Aging, and Incidence of Dementia (CAIDE) Score provides an age, metabolic, and vascular factor risk score and is a validated tool to predict late-life dementia risk [15]. The Polygenic Hazard Score (PHS) is derived from analysis of a 31 single-nucleotide polymorphism (SNP) panel that has been demonstrated to reliably identify individuals at risk of AD at any age, and provides a continuous measure of increased risk of AD with increasing score and younger age of onset [16].

Novel and Better Design of Trials
There is a compelling need to more readily and efficiently test available and emerging candidate interventions, within a rigorous clinical trial framework, in order to secure a strong scientific evidence base upon which to advance development of potentially beneficial treatments for those at increased risk of dementia. Current trial approaches vary within and across countries, use disparate inclusion criteria and outcome measures, and lack interoperability. This limits the potential for head to head comparisons of effect sizes and limits the acquisition of converging evidence. A vital issue to address is improving approaches to risk stratification to enrich prevention clinical trials and allow for the most efficient use of resources for such trials in determining sample sizes and effect sizes.

Open platform trials (OPT), which include Master Protocols that have key shared design components, common inclusion and exclusion criteria, and common outcome measures, provide a novel and attractive approach to the conduct of randomized controlled trials (RCTs), with potential application to dementia prevention [17]. Rather than relying on a traditional trial design with a single hypothesis to test a single intervention within a homogeneous group of patients, platform trials have the ability to test multiple interventions within the same indication, to select and adaptively randomize participants to those treatment arms with the highest probability of success, and to reduce opportunity cost through futility analyses which allow the early discontinuation of interventions that are unlikely to be successful [18]. Recruiting and engaging a pre-randomized Platform Trial Cohort (PTC) of individuals at increased risk of dementia shifts the recruitment paradigm away from its current model which is resulting in severe challenges and trial slowdown [19]. Furthermore, the pre-randomized data obtained from

the PTC can serve to help validate the inclusion criteria, study design, and development of the Master Trial Protocol (MTP) of the OPT.

1.2 Rationale

There currently exists no medication or combination of medications to halt, reverse, or delay AD, or any other related neurodegenerative dementias. The necessary elements are now available, however, to make dramatic headway in dementia prevention. To address this, the CAN-THUMBS UP (CTU) study is a comprehensive and innovative program aimed to enroll and retain a Platform Trial Cohort (PTC) of individuals at risk of dementia, develop an interactive, and compelling online educational intervention, and to support an open platform trial with which to test a variety of multidomain interventions that might further benefit individuals at risk of dementia. Large-scale prevention studies require the sustained engagement of thousands of individuals willing to dedicate their time and effort into a program they believe will improve their lives. Therefore, during the initial phase of the CTU program, a community enrolled PTC of individuals who are cognitively unimpaired or have mild cognitive impairment (MCI) and with increased risk of dementia related to lifestyle risk factors will be recruited. The PTC will be engaged in a 45-week educational online Brain Health Support Program (BHSP) intervention, called Brain Health PRO (BHPro), aimed to increase dementia literacy, engagement, and convey best available evidence for lifestyle changes that can mitigate dementia risk.

Compliance and evidence of BHPro's impact, will be comprehensively evaluated and if successful, could culminate in a program disseminated for public use. The outcome data acquired from BHPro, will serve in the development of a separate Master Trial Protocol (MTP; Phase B). The MTP will create the framework for an open platform trial design, where participants from the PTC who have participated in BHPro will be evaluated for eligibility to enroll in RCTs testing multidomain lifestyle interventions.

Through BHPro, individuals will be engaged in an innovative, accessible and multimodal platform conveying evidence-based information and guidance on lifestyle risk factors including, vascular, dietary, sleep, physical activity, cognition and social engagement. Furthermore, this study will employ mobile technology to more readily evaluate compliance and effects of lifestyle interventions, through the incorporation of wearable devices that track changes in activity levels and sleep patterns, and through app-based remote testing of cognitive function using paradigms of 'burst' cognitive testing and/or self-administered online cognitive testing. We expect these remotely acquired data will establish user acceptance and compliance with these methods. These results could be stage-setting for conducting more of the CTU's evaluations remotely and with less disruption to participants, saving clinic visits and lowering trial costs that would in turn enable more interventions to be evaluated. Virtual clinical trials that might be performed completely remotely would allow research progress towards the dementia prevention goal during challenges such as COVID-19. Implementation of a fully remote online research protocol will provide an accessible approach to research, reaching a broader geography with recruitment of participants across Canada, which will help us to enroll more potential participants who can more easily join the program.

Furthermore, identifying those with a declining cognitive trajectory during this phase of CTU would support precision-based trials to be undertaken with greater power and smaller sample sizes. Engaging the PTC in the BHPro intervention will provide an unprecedented opportunity to determine personalized profiles in this population, by collecting data on multiple variables such as sleep, diet, and social and physical activities, and obtaining cognitive slope data for up to 12

months. Thereafter we can tailor the specific intervention and study population for those that have a personalized profile of interest.

2.0 STUDY DESIGN

This initial phase (Phase A) of CTU will be a prospective 12-month multi-center longitudinal intervention study to evaluate a web-based educational BHSP, called BHPro, focused on dementia literacy, self-efficacy, and modifiable lifestyle risk factors. Participants will be individuals who are either cognitively unimpaired or have MCI with increased risk related to lifestyle risk factors. At the conclusion of the BHSP intervention, participants will continue in the PTC with the opportunity to consent and enroll in further multidomain intervention trials.

3.0 STUDY GOAL AND AIMS

3.1 Overall Goal

To develop and evaluate a 45-week web-based Brain Health Support Program (BHSP) intervention, called Brain Health PRO (BHPro), focused on dementia literacy, self-efficacy and modifiable lifestyle risk factors. Participants will subsequently be part of a PTC and may be evaluated for eligibility to participate in interventional dementia prevention trials under separate protocols.

3.2 Aims

A. Our primary aim is to evaluate within-person change in dementia literacy following participation in BHPro.

B. To evaluate within-person change following participation in BHPro, including change in:

i. Self-efficacy and attitudes towards dementia and its screening
ii. Individuals' modifiable risk factors
iii. Cognition
iv. Physical activity and sleep quality as measured by actigraphy and EEG wearable devices

C. To evaluate BHPro in relationship to:

i. Levels of engagement (i.e., number of chapters completed), thresholds of compliance, ratings of satisfaction, and dropout rates from the intervention
ii. Levels of engagement in the program as a function of individual characteristics and risk profile
iii. Levels of engagement as a moderator of within person change in outcomes.
iv. Association between change in modifiable risk factors and change in cognition.

D. To develop a successful comprehensive national recruitment plan to fully enroll the PTC with engagement stakeholder groups including participants, citizen advisors, and community partners

4.0 OUTCOME MEASURES

4.1 Primary Outcome Measure:

A. The primary outcome will be change in dementia literacy following participation in the study, as measured by the Alzheimer's Disease Knowledge Scale.

4.2 Secondary Outcome Measures:

A. Change in self-efficacy following participation in the study, as measured by the General Self-Efficacy Scale (GSE).

B. To evaluate BHPro, as measured by:

i. Engagement using the online program (e.g., percentage of chapters completed)

ii. User satisfaction ratings and evaluation of usability and acceptance (System Usability Scale and Technology Acceptance Model Questionnaire)

4.3 Exploratory Outcome Measures:

A. Change in attitudes toward dementia following participation in the study as measured by Sections B and D of the Perceptions Regarding Investigational Screening for Memory in Primary Care (PRISM-PC).

B. Change in modifiable risk factors following participation in the study, as measured by BHPro Lifestyle Risk Questionnaires.

C. Cognition

i. Change in global cognition based on a composite score using the Neuropsychological Test Battery (calculated as average Z scores standardized to the baseline mean and standard deviation).

ii. Change in the subdomains of memory, processing speed, and executive functions based on composite scores derived from the Neuropsychological Test Battery (calculated as average Z scores standardized to the baseline mean and standard deviation).

iii. Change in performance based on Burst Cognitive Testing that addresses:
- Within-person change in asymptote, daily variation and within-burst practice effects of "burst" cognitive testing
- Between- and within-person factors including self-rated emotional reactivity and its association with variation in cognitive performance over the BHPro intervention

iv. Change in performance based on online self-administered cognitive testing with the Cogniciti Brain Health Assessment

v. Change in modifiable risk factors and relationship to change in cognition

D. National recruitment success will be measured by:

i. Enrollment rates per month and year across regions with centralized and local recruitment strategies

ii. Screen fail rate and reasons

iii. Projected enrollment rates vs actual enrollment rates

E. Change in levels of physical activity and sleep quality, as measured by actigraphy and EEG wearable devices.

F. Saliva sample collection, to characterize the distribution of age adjusted polygenic hazard scores within the BHSP study group.

5.0 ETHICS AND REGULATORY CONSIDERATIONS

5.1 Good Clinical Practice

The current study will be conducted in compliance with the protocol, International Conference on Harmonization Good Clinical Practice (ICH-GCP) and the applicable regulatory requirements.

Study personnel involved in conducting this study will be qualified by education, training and experience to perform their respective task(s) in accordance with GCP.

5.2 Institutional Review Board (IRB) / Research Ethics Board (REB)

All relevant documents for this study will be submitted to an appropriate Institutional Review Board (IRB) or Research Ethics Board (REB) for review. A signed and dated letter documenting IRB/REB approval must be obtained prior to entering participants at the site. IRBs and REBs must be constituted and their authority delegated through the institution's normal process of governance according to applicable regulatory requirements for each participating site. Each participating institution must provide for the review and approval of this protocol and the associated informed consent documents and relevant participant materials by an appropriate IRB/REB. For each participating site, the protocol and associated informed consent and relevant participant materials will be submitted for approval to the designated IRB/REB, as per site local regulatory policies and procedures. The study will not commence at any site until initial approval is obtained from the designated IRB/REB and an approval to enroll notification is released to the site by the CTU central coordinating team.

The investigator must obtain approval from the IRB/REB for all protocol amendments and, when warranted, changes to the informed consent document and/or participant materials. Protocol and informed consent form amendments can be made only with the prior approval from the CTU central coordinating team. The investigator may not implement any protocol deviation except where necessary to eliminate an immediate hazard to study participants, or

when change(s) involve only logistical or administrative aspects of the trial, i.e., change of monitor(s) or telephone number(s) (ICH 4.5.2). The investigator shall notify the IRB/REB of deviations from the protocol or serious adverse events occurring at the site, in accordance with local policy.

5.3 Electronic Informed Consent Process

For the purposes of this study, the consent process will be completed remotely through the electronic Informed Consent Process (e-Consent).

5.3.1 *E-Consent Process*

A site team member will schedule a phone or video call with the participant where they will walk through the key elements of consent with the participant and allow time for questions before sending them the e-mail link to complete the e-Consent online. Each participant will be sent a unique URL link by e-mail to access the consent form electronically. The electronic consent process will include a user-friendly screen, in which participants can access each section of the consent through a series of virtual “doors” presented on the screen. Participants must successfully complete the consent process by going through each section and correctly answering 1-2 quiz questions per section to assess comprehension. Participants will be required to open and review the full pdf version of the Informed Consent Form (ICF) prior to providing consent, which will be available to download and save to a personal computer for the participants’ own records. Participants will then be presented with a statement of consent followed by two options in the form of radio buttons: “I agree” and “I disagree”. The participant will choose one of these options to activate a submit button. The database will store the date and time of page submission as a record of consent. Participants will also be able to log back into the e-Consent platform at any time throughout the study to review the e-Consent information and to see a record of their consent. A hard copy of the ICF may also be mailed/e-mailed to the participant by site staff if the participant prefers/requests it.

For any participating sites whose designated IRB/REB requires a wet signature, a hard copy of the ICF may be mailed/e-mailed to the participant by site staff. Participants will sign the ICF and return a signed copy to the study site by e-mail or mail, according to site policy and/or participant preference. A copy of the final signed ICF with both participant and site study team signature will also be provided back to the participant once complete.

If a study partner is available, they will also participate in the consenting process and be informed of their role and responsibilities in the study. They may also be asked to complete a study partner e-consent or sign and return a study partner ICF according to site policy and all applicable regulatory requirements. The method of obtaining and documenting the informed consent and the contents of the consent must comply with ICH-GCP and all applicable regulatory requirement(s).

It will be made clear to each potential participant, and study partner (if applicable), that informed consent may be withdrawn at any time without needing to give a reason and that such withdrawal will not compromise the relationship between the participant and the Investigator nor the participant’s future treatment.

The ICF must be in a language fully comprehensible to the prospective participants and ample opportunity must be given to inquire about the details of the study.

The ICF will include consent to access stored data for future analyses. Consent forms will specify that saliva samples are for research purposes only; the tests on the saliva samples are not diagnostic in nature and participants will not receive results.

5.4 Participant Confidentiality

The Longitudinal Online Research and Imaging System (LORIS) [20] will house the data from participating institutions. LORIS is a web-based database solution for neuroimaging and other research data that is physically located at McGill University in Montreal. It will store data that has been processed to remove any direct identifiers of an individual study participant. Study subjects will be assigned a unique coded study identification number (LORIS Project Study Center ID (PSCID)) at the time of study enrollment that will be used to store their data.

Local study sites will be responsible for storing all participant identifying information (name, contact, e-mail addresses) in secured encrypted databases and to maintain the master file that links the participant to their unique LORIS PSCID.

Participant data collected by external sources including BHPro, Cogniciti Brain Health Assessment, MyCogHealth app, actigraphy device and the EEG Muse app will be de-identified and linked to the LORIS PSCID prior to being merged with the CTU dataset. Please also see section 13.0 Recording and Data Collection and Appendix 5 (CTU Flow of Data Figures) for additional information on temporary storage locations and secure transfer of various data sources into LORIS.

The investigator will grant monitor(s) and auditor(s) from the Canadian Consortium for Neurodegeneration in Aging (CCNA) and regulatory health authorities' access to the participant's original medical records for verification of the data gathered and to audit the data collection process. The participant's confidentiality will be maintained. Information about study participants will be made publicly available to the extent permitted by the applicable laws and regulations. In publications, only group data will be reported.

In cases where participant identification is required (e.g. when an incidental finding is uncovered on coded data), the recruiting site study investigator for the participant will be given access to only the minimum identifying information required to link the participant to the incidental finding and move it towards a resolution.

5.5 Potential Risks and Benefits Associated with this Study

5.5.1 *Potential Risks*

Risks associated with study participation are minimal and include risks related to the process of undergoing neuropsychological and remote cognitive testing, which may lead to fatigue and/or frustration associated with participating in cognitively demanding testing. Questionnaires on mood and lifestyle risk may increase negative affect. There may be minimal discomfort or disruption of sleep with the application and removal of the actigraph device and EEG headband. There may be risks associated with a breach in confidentiality. Strict privacy and confidentiality procedures have been implemented (see section 5.4 Participant Confidentiality) to minimize this risk to the extent possible.

5.5.2 ***Potential Benefits***

Participants in this study may experience benefits from participating in a web-based educational program including increased knowledge and engagement regarding ways to promote their brain health, and possible positive reduction in their risk profiles, though such improvement cannot be predicted with any certainty. This study is expected to benefit the general community in the future by promoting public interest, literacy, and engagement in lifestyle interventions for brain health and dementia prevention through dissemination of BHPro to the broader public.

6.0 RECRUITMENT

A centralized recruitment and site management approach will be utilized. There will be up to 7 regional sites set up across Canada, all of whom will have full time, dedicated coordinators to receive participants. We will implement a nationwide recruitment campaign varying from geotargeted mailing to targeted social media and digital advertising with a goal to bring awareness of the study to more Canadians. Recruitment efforts using existing national and clinic registries and societies may also be utilized. Potential participants learning about the study through our advertising methods will be invited to visit a dedicated study website, available in both English and French, where they can express their interest about the study through a form that will help establish initial eligibility. The form will collect participant details such as name, age, preferred language, province of residence, first three letters/numbers from postal code, and contact information. Potential participants will be assigned to the site closest to them and each site will contact the potential participants that fall within their jurisdiction. Central recruitment will keep in close contact with the sites to adjust efforts as needed throughout the recruitment period.

7.0 PATIENT SELECTION

7.1 Inclusion Criteria

Participants must meet all of the following inclusion criteria to be eligible for enrollment:

1. Completion and documentation of the electronic Informed Consent Process (from the participant)
2. Sufficient proficiency in English or French to undergo remote clinical and neuropsychological assessment and participate in an online educational program.
3. Technical ability to participate in an online educational program and remote assessments (i.e. computer and internet access; ability to send and receive emails; ability to complete remote assessments)
4. Sufficient vision and hearing to participate in online educational program and to undergo remote clinical and neuropsychological testing
5. Ability to sit comfortably for a period of about 30 minutes
6. Ages 60-85
7. Meets criteria for **No Dementia** and meet criteria (according to CCNA Criteria, Appendix 1) of one of the following:
   - Cognitively Unimpaired (CU)
   - Cognitively Unimpaired plus Subjective Cognitive Impairment (CU + SCI)
   - Mild Cognitive Impairment (MCI)
8. **AND** Classified as being at **increased risk** of dementia based on **at least one of the following**:
   - First-degree family history of dementia

- Self-Reported or documented current and/or history at midlife (45-60 years) on any of the following lifestyle risk factors:
  - Hypertension (documented Systolic Blood Pressure > 140 mm Hg; OR physician diagnosis of hypertension; OR treatment for hypertension; OR other approaches to treatment (e.g. diet, exercise))
  - Hypercholesterolemia (documented total cholesterol > 6.5 mmol/L; OR physician diagnosis of hypercholesterolemia; OR treatment for hypercholesterolemia; OR other approaches to treatment (e.g. diet, exercise)
  - Body Mass Index > 30 kg/m^2 (derived from NIH Metric BMI Calculator)
  - Physical Inactivity (active is defined as engaging in a minimum of 20- 30 min of physical activity causing sweating and breathlessness, at least 2 times a week)

9. Participant has a family physician or other healthcare provider and agrees to have the provider notified of participation in the study and incidental or other findings that may be clinically significant

7.2 Exclusion Criteria

1. Participants who, in the opinion of the investigator, are not able to complete trial procedures remotely or adhere to the schedule of study assessments will be excluded from study participation.
2. Individuals where English or French is not sufficiently proficient for remote clinical assessment, neuropsychological testing and participation in an online educational program.
3. Participants who do not have sufficient vision and hearing for remote clinical assessment, neuropsychological testing participation in an online educational program
4. Individuals who do not have the technical ability to participate in an online educational program. Technical ability is defined as having computer and internet access; ability to send and receive emails; ability to participate in remote assessments
5. Individuals who have a clinical diagnosis of Dementia
6. Clinical Dementia Rating (CDR; telephone/video-conference administration) Score of ≥1
7. Total Score on the Montreal Cognitive Assessment (MoCA; video-conference administration) <13

8.0 STUDY PROCEDURES

8.1 Study Visits

The schedule of study visits and procedures to be performed at each visit are outlined below and summarized in the Schedule of Events table (Appendix 2). A detailed description of study procedures is located in section 9.0. and a detailed description of study instruments is located in section 10.0.

8.1.1 *Technology for Remote Study Visits*

Screening and Baseline visits should be conducted using video-conference technology. Follow-up study calls (Month 3, Month 6, and Month 9) can be completed by telephone. All remote study procedures administered over video-conference must be conducted on a secure platform (e.g. Zoom) that is compliant with Canadian Data Protection regulations, including the Personal Information Protection and Electronic Documents Act (PIPEDA). If a participant experiences technological difficulty (e.g. disruption in internet access) during a remote visit, any remaining

study procedures may be completed by telephone to the extent possible. Attempts should be made to re-schedule the video-conference visit to complete any measures that can only be completed by video within the allowed time frame prior to the next visit. Neuropsychological test battery administration at Screening, Baseline, and Month 12 conducted by video-conference technology will be recorded to assist with rater scoring, to ensure standard administration and scoring, and to help inform the study on feasibility of remote administration of the study assessments.

8.1.2 *Video Conference Screening (within 21 days prior to baseline)*

Participants who the Investigator considers to be appropriate for the study will complete the e-consent process according to the process described in section 5.3 Electronic Informed Consent Process. Prior to the participant completing informed consent, the Investigator or his/her designee will schedule a phone or video call with the participant to explain the details of this study and allow participants sufficient time to study this information and the opportunity to ask any questions they wish, prior to continuing with the screening procedures.

Informed consent must be obtained before any study-related activities are conducted.

8.1.2.1 Study Partner (Optional)

If the participant has a study partner available, he/she will be invited to participate in the study, be involved in the consenting process, and complete a Study Partner ICF. However, not having a study partner/informant available does not exclude the participant from joining this study. The role of the study partner will be to answer questions about the participant and his/her health, memory, daily functioning and behavior. If available, the study partner will provide input on completion of the following assessments:

- Clinical Dementia Rating (CDR) at Screening
- Mild Behavioral Impairment Checklist (MBI-C) at Baseline

8.1.2.2 Video-Conference Screening Procedures

The following procedures will be conducted remotely via secure video-conference technology during the screening period (Estimated Time to Complete: 3.0-3.5 hours). Screening procedures may be completed over multiple days as long as all procedures are completed within 21 days prior to the first scheduled baseline video-call visit. Procedures and instruments will be adapted for remote administration (see section 9.0 Study Procedure Descriptions and section 10.0 Study-Specific Instruments).
:

- Review of inclusion/exclusion criteria
- Consent for medical record review
- Documentation of demographics, medical history (including past medical procedures), medications
- Hearing and Vision assessment
- CAIDE Score (derived score based on self-report and/or medical record review)

- Clinical Dementia Rating (CDR; if a study partner is not available, the CDR score will be decided by site-level research team consensus based on all other available information and utilizing best clinical judgement.)
- Logical Memory 1 & 2 from Wechsler memory scale
- Montreal Cognitive Assessment (MoCA)
- Lawton Brody Instrumental Activities of Daily Living (IADL)
- Brief Remote Neurological Exam (completed by Site Principal Investigator or qualified medical professional)

8.1.2.3 Confirmation of Study Eligibility by Site Principal Investigator (or designated Co-Investigator)

Following completion of the screening assessments above, the Site Principal Investigator (or Co-Investigator) will be responsible for confirming participant diagnosis and eligibility to be enrolled in the study.

8.1.3 ***Remote Baseline Visit (+/- 2 weeks)***

8.1.3.1 Video-Conference Baseline Procedures

Participants who are enrolled in the study will complete the following baseline procedures remotely via video-conference with a member of the study team. (Estimated Time to Complete: 2.5-3.0 hours)

Participants may complete screening and baseline assessments at the same remote visit as long as the participant (and study partner if applicable) have provided consent prior to initiating any study-specific procedure and the site Study Investigator has confirmed study eligibility. Baseline procedures may also be completed over multiple days as long as all procedures are completed within 14 days of the first baseline video-call visit.

- Neuropsychological Test Battery (adapted for remote administration; see section 10.1.4 for test descriptions and information on remote administration; estimated time to complete is 1.0-1.5 hours)
    - Craft Story 21 Immediate and Delayed Recall
    - ADAS-Cog word recall, delayed recall, orientation
    - Brief Visuospatial Memory Test-Revised (BVMT-R)
    - Delis-Kaplan Executive Function System (DKEFS) Verbal Fluency
    - Oral Trail Making Test A and B
    - DKEFS Color-Word Interference Test
    - Oral Symbol Digit Substitution Test
    - Boston Naming Test (BNT) 15-Item
    - “Burst” Cognitive Testing (training session)

- Self-report height and weight
- Body Mass Index (BMI) calculation (based on self-report current height and weight)
- Saliva sample collection for genomics testing (Polygenic Hazard Score; with at-home collection kit)
- Instructions on how to complete “Burst” Cognitive Testing and completion of training testing session

- Instructions on how to complete the Cogniciti Brain Health Assessment
- Instructions and application of wearables for actigraphy and EEG recordings (see section 9.3)
- Instructions on how to register and participate in BHPro (see section 8.3)

8.1.3.2 Baseline Functional and Behavioral Assessments

Participants will receive a unique URL link by e-mail to complete the following functional and behavioral assessments electronically through the LORIS survey tool. Site study staff may also be available by phone/video-call to assist participants in completion of these questionnaires if preferred. Paper versions of the questionnaires may also be sent to participants by mail to complete at home and return to the site if preferred or requested by the participant. (Total estimated time: 30 minutes):

- Geriatric Depression Scale (GDS)
- Generalized Anxiety Disorder 7-Item Scale (GAD-7)
- Sleep Disorders Questionnaire
- COVID-19 Impact Survey
- Research Satisfaction Survey

The following questionnaire will be completed by study partner (if available).

- Mild Behavioral Impairment Checklist (MBI-C) (estimated time: 10-15 minutes)

8.1.4 ***Additional Remote Baseline Testing***

Following completion of the baseline procedures above, participants will also complete the following assessments remotely within approximately 2 weeks:

- BHPro registration and completion of lifestyle risk questionnaires and goal setting (estimated time to complete is 1.0 hour; see section 8.3)
- Weekly participation in BHPro (approximately 40 minutes/week)
- "Burst" Cognitive Testing (5-10 minutes/day for 6 consecutive days following initial testing at Baseline Visit)
- Cogniciti Brain Health Assessment (estimated time to complete is 20 minutes)
- Actigraphy recording (continuous recording for 14 consecutive days)
- EEG recording (nightly recordings for 3 consecutive nights)

8.1.5 ***Month 3 Remote Follow-Up and Testing***

Participants will receive a follow-up phone call from a site study team member at approximately month 3 following baseline to assess continued interest in BHPro participation and satisfaction with BHPro.

Participants will also receive notifications to complete the following activities remotely at month 3:

- Notification via the MyCogHealth app will be sent to participant to complete "Burst" Cognitive Testing (estimated time: 5-10 minutes/day for 7 consecutive days)
- Lifestyle risk questionnaires and goal setting within BHPro (estimated time: 20-30 minutes; see section 8.3)

8.1.6 *Month 6 Remote Follow-Up and Testing*

Participants will receive a follow-up phone call from a site study team member at approximately month 6 following baseline to assess continued interest in BHPro participation, and review any medical, lifestyle and diagnostic changes that have occurred since the baseline visit. The phone call will take an estimated 0.5-1.0 hours to complete.

Participants will also complete the following cognitive assessments remotely:

- Notification via the MyCogHealth app will be sent to participant to complete "Burst" Cognitive Testing (estimated time: 5-10 minutes/day for 7 consecutive days)
- Study coordinator will send participant an email that contains a personalized link to complete the Cogniciti Brain Health Assessment (estimated time: 20 minutes)
- BHPro outcome assessments (program usability and acceptability, dementia literacy, self-efficacy, attitudes toward dementia; see section 8.3). These will be completed online within BHPro (estimated time: 30-45 minutes)
- Lifestyle risk questionnaires and goal setting within BHPro (estimated time: 20-30 minutes)

8.1.7 *Month 9 Remote Follow-Up and Testing*

Participants will receive a follow-up phone call from a site study team member at approximately month 9 following baseline to assess continued interest in participation and satisfaction with BHPro.

Participants will also receive notifications to complete the following activities remotely at month 9:

- Notification via the MyCogHealth app will be sent to participant to complete "Burst" Cognitive Testing (estimated time: 5-10 minutes/day for 7 consecutive days)
- Lifestyle risk questionnaires and goal setting within BHPro (estimated time: 20-30 minutes)

8.1.8 *Month 12 Remote Visit*

Participants will complete the following procedures remotely via video-conference with a member of the study team at approximately Month 12 for a remote re-assessment.

Study participants will undergo the following procedures (Estimated Time to Complete: 4.0-5.0 hours):

- Documentation of changes to medical history (including medication changes and any medical procedures) that have occurred since the time of the last assessment
- Self-report weight
- Body Mass Index (BMI) calculation (based on self-report current height and weight)
- Brief Remote Neurological Exam (completed by Site Principal Investigator or qualified medical professional)
- Lawton Brody IADL
- MoCA
- CDR (if a study partner is not available, the CDR score will be decided by site-level research team consensus based on all other available information and utilizing best clinical judgement.)
- Neuropsychological Test Battery (see section 10.1.4)
- Instructions and application of wearables for actigraphy and EEG recordings (see section 9.3)

8.1.8.1 Month 12 Functional and Behavioral Assessments

Participants will receive a unique URL link by e-mail to complete the following functional and behavioral assessments electronically through the LORIS survey tool. Site study staff may also be available by phone/video-call to assist participants in completion of these questionnaires if preferred. Paper versions of the questionnaires may also be sent to participants by mail to complete at home and return to the site if preferred or requested by the participant. (Total estimated time: 30 minutes):

- Geriatric Depression Scale (GDS)
- Generalized Anxiety Disorder 7-Item Scale (GAD-7)
- Sleep Disorders Questionnaire
- COVID-19 Impact Survey
- Research Satisfaction Survey

The following questionnaire will be completed by study partner (if available).

- Mild Behavioral Impairment Checklist (MBI-C) (estimated time: 10-15 minutes)

8.1.8.2 Month 12 Remote Testing

Participants will also complete the following assessments remotely within approximately 2 weeks:

- "Burst" Cognitive Testing (estimated time: 5-10 minutes/day for 7 consecutive days)
- Cogniciti Brain Health Assessment (estimated time: 20 minutes)
- Actigraphy recording (continuous recording for 14 consecutive days)
- EEG recording (nightly recordings for 3 consecutive nights)
- BHPro outcome assessments (program usability and acceptability, dementia literacy, self-efficacy, attitudes toward dementia). These will be completed online within BHPro (estimated time: 30-45 minutes)
- Lifestyle risk questionnaires and goal setting within BHPro (estimated time: 20-30 minutes)

8.1.9 End of Study Remote Visit (Early Discontinuation)

Participants who have logged in and completed the registration process for BHPro but choose to withdraw and/or discontinue participation (see also: section 11.0 Early Discontinuation Procedures) in the BHPro Intervention for any reason will have the opportunity to complete further study visits per protocol up to the end of the study with their ongoing consent. Their continued participation should be encouraged to address the impact of early discontinuation compared to completion of the BHPro Intervention. If a participant declines to complete further study visits per protocol, an End of Study Remote Visit will be completed as close as possible to the time of study discontinuation. Ideally, the End of Study Remote visit will include all of the procedures and assessments described in the Month 12 Remote Visit (section 8.1.8). If the participant is not willing to complete all of the procedures and assessments, the BHPro outcome assessments (program usability and acceptability, dementia literacy, self-efficacy, attitudes toward dementia) should be prioritized. These will be completed online within BHPro (estimated time: 30-45 minutes). An additional priority is completion of the Lifestyle risk questionnaires and goal setting within BHPro (estimated time: 20-30 minutes). For further detail please refer to the Study Procedures Manual.

8.2 Platform Trial Cohort (PTC)

All participants who meet CTU eligibility criteria (see sections 7.1 and 7.2) will be enrolled in the PTC and will participate in the BHSP study with monitoring of their engagement over the course of 12-months. Data collected during the BHSP study will be used to model the Open Platform Trial (OPT) to conduct future RCTs utilizing participants from the PTC (Phase B of CTU). Once participation in the BHSP study has ended, participants may be offered potential participation in future multidomain intervention RCTs of the CTU program under separate protocols. For participants who are interested and meet inclusion criteria for specific RCTs within the OPT, a separate informed consent will be signed prior to participation.

8.3 Brain Health Pro (BHPro) Intervention

The BHPro Intervention 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.

Participants will receive instructions on how to register and participate in the program at the remote baseline study visit.

8.3.1 *Program Content*

Participants will register on the BHPro 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 BHPro. 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 BHPro will be de-identified and linked to the LORIS PSCID prior to being included in the CTU database. Registration will also include viewing a brief video explaining the program, demographic questions and lifestyle questionnaires including general questions related to socio-demographic profile, health, and lifestyle.

BHPro is organized into the following 8 content modules:

1	Motivation, self-efficacy, positive health, dementia, environment vs genetic risk, cognitive aging and healthy lifestyle, medication
2	Physical activity
3	Cognitive engagement
4	Diet
5	Sleep
6	Social and Psychological Health
7	Vascular health
8	Vision and hearing

The program content is provided progressively to deliver new weekly content (i.e. module chapters) of approximately 40 minutes. Participants will have access to new content on 4 modules each week (10 minutes/module; alternating every 2 weeks) through an email push notification, as an approach to maintain interest. Participants will be invited to visit the web site at their own rate but encouraged to spend a minimum of 40 minutes/week on the program.

Information is organized as chapters within the modules, which contain scientific evidence, explanation of principles and mechanisms that underlie positive effects, specific recommendations (e.g., type and dose of prescribed physical exercises), suggestions to improve behavior in everyday life and typical barriers and tips to circumvent them. Content format will include visual and auditory text, pictures, animations, quizzes, questionnaires and interactive exercises.

8.3.2 *Personalized Profiles on Modifiable Lifestyle Risk Factors*

Participants will be asked to complete brief online lifestyle risk questionnaires approximately every 3 months (see Appendix 3 for descriptions of the BHPro Lifestyle Risk Questionnaires). Questions will be related to the content in the program modules (e.g. sleep, diet, physical activity, cognitive engagement, social and psychological health, sensory). A personalized profile will be developed for each participant based on their responses to the lifestyle questionnaires. Participants will also be asked to set goals based on their risk profile and to re-visit and update their goals every three months. Participants will be encouraged to focus on the content modules that are related to their risk profile. Although participants will have access to all content modules within the program, modules that are suggested to the participant based on their risk profile will be highlighted.

8.3.3 *BHPro Outcome Variables and Data Collection*

The following data and assessments will be collected directly through BHPro. For more detailed information on the specific instruments see section 10.0. (Study Specific Instruments):

Outcome	**Measure/Data Collected**	**Frequency**
Engagement using BHPro	Direct monitoring of several parameters that could include: - Dates and time of program use - % completion of chapters at regular intervals - % completion of questionnaires - Other parameters may be added to this list as the studies goes on	Weekly/monthly
Acceptability (usefulness and ease of use) of BHPro	Adapted version of the Technology Acceptance Model questionnaire	Every 6 months
Usability of the BHPro	Adapted web-based version of the System Usability Scale (SUS)	Every 6 months
Dementia Literacy	Alzheimer Disease Knowledge Scale (ADKS)	Every 6 months
Participant Self-Efficacy	General Self-Efficacy Scale (GSE)	Every 6 months

Outcome	Measure/Data Collected	Frequency
Attitudes towards dementia and dementia screening	Sections B and D from The Perceptions Regarding Investigational Screening for Memory in Primary Care (PRISM-PC) Questionnaire	Every 6 months

9.0 STUDY PROCEDURE DESCRIPTIONS

9.1.1 *Sociodemographics*

Sociodemographic data (sex, gender identity, age, handedness, languages, marital/partner status, living circumstances, reproductive history, education, employment history) will be captured.

9.1.2 *Medical/Surgical/Family History*

Relevant medical and surgical history will be captured as well as relevant medical history of first-degree relatives. A list of current medications will also be documented.

9.1.3 *Hearing and Vision Assessment*

Hearing and vision will be assessed at baseline. Vision and hearing ability will be assessed by questions on perceived visual and auditory ability and an inventory of aids used. Participants must have relatively sufficient vision (with corrective lenses or other aids) so that they can identify symbols, stimuli and text presented on a computer screen in front of them. Participants must also have sufficient hearing (corrected with hearing aids or other voice amplification devices) to be able to follow spoken instructions and information that is presented only verbally.

9.1.4 *CAIDE Score*

The CAIDE Dementia Risk Score is a validated tool to predict late-life dementia risk (20 years later), based on midlife vascular risk factors [15]. Its components are age, education, sex, systolic blood pressure, body mass index, total cholesterol and physical activity. Participants will be asked about current vascular risk factors and history at mid-life (40-60 years old) to capture both a current and mid-life CAIDE Score. Since this remote study does not include an actual measure of blood pressure nor is there a blood draw for total cholesterol, the rating of these components will be based either on medical record review (if available) or on participant self-report (i.e. confirmation of physician diagnosis, medical treatment, other approaches to treatment). Physical activity is defined as engaging in a minimum of 20- 30 min of physical activity causing sweating and breathlessness, at least 2 times a week. BMI will be captured using the NIH BMI Metric Calculator (https://www.nhlbi.nih.gov/health/educational/lose_wt/BMI/bmi-m.htm).

9.1.5 *Saliva Sample for Genomics Testing (Polygenic Hazard Score)*

A saliva sample collection kit (OG-500 kit, DNA Genotek, Kanata, Ontario) will be sent to each participant for extraction of DNA. Study staff at SRI will be responsible for mailing the kits to the

participant's home. The at-home kit will include detailed instructions on how to collect the sample and a study team member will provide guidance to the participant on how to properly collect and ship the sample during the Baseline video-call visit. A total of 2 mls of saliva will be collected by passive drool in 1 tube. Participants will be instructed not to eat, drink, smoke, or chew gum for 30 minutes prior to giving the sample. The samples will be collected, handled, stored and shipped according to established standard operating procedures. Instructions for collection, handling and shipping of saliva samples for DNA testing will also be provided in the Study Procedures Manual.

De-identified samples will be sent to the Clinical Genomics Centre in the Mount Sinai Hospital, 600 University Ave, Toronto, ON M5G 1X5, Canada and will be processed under the guidance of Dr. Kathy Siminovitch. Samples will be stored for the duration of the study and until all planned analyses are complete, after which they will be properly destroyed according to established lab procedures.

A Polygenic Hazard Score (PHS) will be derived from a planned panel of single nucleotide polymorphisms that describes age of onset and ADD risk [16] . Both raw and processed data will be posted to the LORIS server.

9.1.6 ***Remote Neurological Exam***

A brief neurological examination will be conducted during screening by the site principal investigator or a designated medically qualified professional. The examination will be completed by a telemedicine visit using secure PIPEDA compliant video-conference technology (e.g. Zoom). The exam will be conducted following guidance from the American Academy of Neurology (AAN) and the Telemedicine and COVID-19 Implementation Guide (https://www.aan.com/siteassets/home-page/tools-and-resources/practicing-neurologist--administrators/telemedicine-and-remote-care/20-telemedicine-and-covid19-v103.pdf) and will include assessment of mental status, language, calculations, memory, cranial nerves, gate, motor, sensory, and cerebellar function.

9.2 ***Online Cognitive Testing***

Participants will be asked to complete cognitive testing remotely throughout the duration of the study. Participants will be provided with detailed instructions on each remote assessment at the baseline video-conference with a study team member. The following online cognitive assessments will be completed (see Schedule of Events (Appendix 2) for timing of assessments):

9.2.1 ***Cogniciti Brain Health Assessment***

The Cogniciti Brain Health Assessment (BHA) is a self-administered validated computerized cognitive assessment comprised of four tests (Spatial Working Memory, Stroop Interference, Face-Name Association, and Number-Letter Alternation). Total time to complete testing is approximately 20 minutes. Cogniciti technology allows for secure, remote, unsupervised assessment of participants using a web-based system and is compatible with any desktop and laptop device that has web browser capability and an internet connection. Participants will receive instructions from a study team member on how to complete testing at Baseline, Month 6, and Month 12 (see section 10.1.5 for full description of cognitive measures included in the Cogniciti BHA).

9.2.2 *MyCogHealth App "Burst" Cognitive Testing*

MyCogHealth is an iOS/Android app for self-administered cognitive assessments and customizable surveys of health behaviors, risk factors, and patient-reported outcomes. The MyCogHealth app currently supports iPhones from version 6 and up (running iOS 11 and up). The app also supports Android 6 and up. The software is built on Health Insurance Portability & Accountability Act (HIPAA)-compliant scheduling and data management server-side software that permits individually tailored assessment protocols and scheduling. The platform is user-friendly and was developed for use with older adults. Based on available data pertaining to smartphone use and ownership in this age population, we anticipate that the majority of participants will have a personal smartphone that is compliant with this program. With assistance from a study team member, each participant will install the mobile application software on their personal mobile device. For individuals lacking a compliant smartphone, CTU will provide up to 150 participants with Android devices, including training. Participants will be oriented to the application software during the baseline remote video-conference, and will complete a training session on the mobile battery with the study team member present via video-conference to answer questions and trouble-shoot any issues that may arise. Ongoing technical support may also be provided to participants, over the duration of their participation in the 12-month BHSP, as needed through Dr. Scott Hofer's CogTech Group at the University of Victoria. For the purposes of providing technical support, participant contact information (name, telephone number, email address) and study ID may be sent by encrypted email to study staff at the CogTech Group at the University of Victoria.

"Burst" cognitive testing using the MyCogHealth app will consist of five measurement "bursts" over approximately 12 months, at Baseline, Month 3, 6, 9 and 12. Each measurement burst will involve two mobile assessment sessions per day for seven consecutive days, with sessions that take approximately 5-10 minutes to complete. Each session includes 3 cognitive tests, Symbol Match, Dot Memory, and Trail-Making A and B, as well as several brief questions assessing state factors at the time of testing (e.g., mood, fatigue, subjective impression of cognitive ability). See section 10.1.6 for full description of cognitive measures.

9.3 *Physical Activity and Sleep Monitoring*

Participants will be asked to participate in at-home physical activity and sleep monitoring throughout the duration of this study through the application of Actigraphy and EEG headband devices. Participant contact information (name, telephone number, email address, mailing address) and study ID will be sent by encrypted email to study staff at Sunnybrook Research Institute (SRI, University of Toronto, Ontario), a participating CTU site. Devices will be centrally distributed from SRI to participants and detailed instructions on application and use of devices will be provided to participants along with guidance from an SRI study team member via video-conference. For participants enrolled at French-speaking sites, a study team member from that site may assist SRI with participant communications.

Participants may also be invited in a sub-study, based at SRI (Appendix 6), which will add 24-hours of cardiopulmonary monitoring for sleep apnea and its physiological consequences using a pair of adhesive band-aid like sensors. The optional sub-study will be conducted under a separate study protocol with a separate consent form.

CTU will provide the Actigraphy devices, EEG headbands, and iPods to be used for the duration of this study, which should allow for all participants to participate in recordings at Baseline and Month 12. As described earlier, EEG recordings will be captured on the Muse app installed on the iPod.

9.3.1 Actigraphy

Physical activity and sleep monitoring using actigraphy (Axivity AX3) will be assessed at Baseline and Month 12. The Axivity is an accelerometer used to detect movement, vibrations, and orientation changes. The Axivity device will be mailed to participants. After study equipment and materials are shipped to and received by the participant, study staff will instruct the participant on the proper application and use of the Axivity over remote video-conference. The participant will be given an instruction card containing contact information of study staff should they have any questions. The participant will be shown how to place the device on their non-dominant wrist by study staff, and participants will be instructed to wear the devices continuously for 14 days, even when bathing or swimming. During the 14 days, participants will be asked to track their work and sleep hours in a diary. At the end of 14 days, participants will return the device to SRI using a pre-paid, pre-addressed package. This procedure will be repeated at the Month 12 remote visit.

9.3.2 ***EEG Recording***

Overnight EEG recording will be assessed at Baseline and Month 12 using the MUSE S Headband (Interaxon Inc, Toronto, Ontario, Canada). The MUSE S Headband is a commercially-available consumer headband that has 5 sensors, 2 on the forehead, 2 behind the ears, plus 1 reference sensors, to detect and measure EEG signals. The EEG headband and iPod with Muse app installed will be mailed to participants. After study equipment and materials are shipped to and received by the participant, study staff will instruct the participant on the proper application and use of the Muse over remote video-conference. Participants will use the iPod with the Muse app to capture EEG sleep recordings. Study coordinators will use a pseudo email and password, which will be linked to a central study e-mail address (provided by the sleep team at SRI) to initially sign-up for the app prior to mailing the study iPod to participants. Recordings will be linked to the associated Muse headband device number only and will not include any PHI.

The participant will be given an instruction card containing contact information of study staff should they have any questions. On the night after the baseline visit, participants will wear the headband, start the recording using the provided iPod, and stop the recording the following morning. They will repeat this for an additional 2 nights (3 consecutive nights total), charging the devices in-between each recording according to the instructions provided, and then return the EEG headband, iPod, and the Axivity device described above, after 14 days of actigraphy. Participants will be provided with a pre-paid, pre-addressed package. Data is uploaded automatically from the iPod to a manufacturer-supported cloud server. Raw data will be downloaded from the cloud server, processed by the study team at SRI, and then will be uploaded to LORIS. This procedure will be repeated at the Month 12 visit.

9.4 Data Collection from other CCNA Studies

A subset of CTU: BHSP participants may be recruited from those participating in other CCNA studies such as COMPASS-ND and SYNERGIC-2. If participants consent to have their data

from other CCNA studies shared with CTU: BHSP, the following data will be accessible (via LORIS) for use within BHSP:

- Clinical Data
- Neuropsychological Testing
- Biospecimen

10.0 STUDY-SPECIFIC INSTRUMENTS

10.1 Cognitive Measures

10.1.1 *Clinical Dementia Rating (CDR)*

The CDR is a validated 5-point composite scale used in longitudinal AD research to characterize cognitive and global function performance applicable to AD and related dementias [21]. Information is obtained through a semi-structured interview of the patient and a reliable informant or collateral source (e.g. family member). The three cognitive domains include memory, orientation, and judgment/problem solving and the three functional domains include community affairs, home and hobbies and personal care. The five possible scores for each domain [0, 0.5, 1, 2, and 3] represent a range of impairment (e.g. score of 0 represents no impairment and a score of 3 represents severe impairment). If an informant is not available, the CDR score will be decided by site-level research team consensus based on all other available information and utilizing best clinical judgement.

10.1.2 *Logical Memory I and II*

Logical Memory I and II (Story A) from the Wechsler memory scale [22] will be completed during remote screening by tele/video-conference. The participant will be instructed to listen to a story and repeat it back after it has been read. They will then be asked to recall the story approximately 30 minutes later.

10.1.3 *Montreal Cognitive Assessment (MoCA)*

The MoCA is a 10-minute test that provides a global assessment of cognition, covering domains of memory, language, attention, visuospatial, and executive functioning [23]. An audiovisual version of the full MoCA has been validated for remote administration by video-conference[24]. Instructions for administration of full MoCA by video-conference can be found at https://www.mocatest.org/remote-moca-testing/.

10.1.4 **Neuropsychological Test Battery (NTB)**

The NTB will be administered remotely at baseline and Month 12 by video-conference. The sessions will be audio recorded to facilitate rater scoring and for quality control. Full details on rater training and the administration for remote testing will be provided in the Study Procedures Manual.

Participants will receive all necessary testing materials by mail ahead of the testing session. The battery requires approximately 1.0-1.5 hours to administer.

Tests that have been administered clinically in the past 12 months will not be repeated (unless there is a discrepancy between test versions). Consent forms for each site will include a statement asking participants to allow for their clinical results from tests overlapping with the CTU battery to be entered into the CTU case report form. If a patient was assessed using a different version of the same test used in the CTU neuropsychological battery, the test will be repeated using the version consistent with the study.

Domain	**Test**	**Description**	**Time (Mins)**
Memory & Orientation	Craft Story 21 Immediate and Delayed Recall	Story learning and Recall	10-15
	ADAS-Cog Immediate & Delayed Word Recall	Word List Learning and Recall	10-15
	ADAS-Cog Orientation	Orientation	2-3
	Brief Visuospatial Memory Test - Revised	Figure learning and Recall	10-15
Attention, Processing Speed	Digit Symbol Modalities Test-Oral Version	Attention and Processing speed	5
	Oral Trail Making Test (Part A)	Visual and Motor Processing Speed	2-3
	DKEFS Color-Word Interference Test- Color Naming & Word Reading	Attention and Processing Speed	5
Executive Function	DKEFS Verbal Fluency	Phonemic (letter) fluency, Semantic (category) fluency, Category Switching	2
	Oral Trail Making Test (Part B	Switching attention	3-5
	DKEFS Color-Word Interference Test- Inhibition	Inhibition	5-10
Visuoperceptual & Construction	Brief Visuospatial Memory Test-Revised Copy	Visuoconstruction	3
Speech & Language	Boston Naming Test-15 Item	Confrontational Naming	5-10

10.1.4.1 ADAS-Cog (Word Recall, Delayed Recall, Orientation)

The ADAS-Cog administration will be restricted to the Word Recall and Orientation subtests, as these have demonstrated to have the greatest sensitivity to change in MCI [25]. For Word Recall, participants are given three trials to learn a list of 10 high-frequency, high imagery nouns presented one at a time in block letters on white cards. Immediate recall is assessed after each presentation trial. Delayed recall is assessed after approximately 5 minutes. Orientation for person, time and place is assessed with 10 examiner-administered questions.

10.1.4.2 Boston Naming Test (BNT) – 15-item

This is an abbreviated version of the Boston Naming Test and will be administered to assess visual confrontation naming [26]. Participants are asked to identify (i.e., name) line drawings of objects.

10.1.4.3 Brief Visuospatial Memory Test-Revised (BVMT-R)

On this task, participants are presented with a 2 x 3 array of six line drawings for ten seconds. After the display is taken away, participants are asked to draw each figure accurately and in its correct location on the page. There are three learning trials, a 25-minute delayed recall trial, a delayed recognition memory trial and a copy trial [27].

10.1.4.4 Craft Story 21 Immediate and Delayed Recall

This test assesses the ability to recall a story[28]. Participants are read a story and are immediately asked to recall what they can remember. After a 20-minute delay, participants are asked again to recall the story.

10.1.4.5 Digit Symbol Modalities Test-Oral Version

This is a timed task that gives participants 120 seconds to orally match geometric figures with specific numbers according to a defined key (specifying which symbols are assigned to which numbers) that is provided at the top of the stimulus page [29].

10.1.4.6 DKEFS Color-Word Interference Test (CWIT)

This timed task requires participants to (1) name a series of colors, (2) read a series of words and then (3) name the color of the ink of dissonant color words (i.e., must say “green” when the word red is written in green ink) [30]. The latter task is a measure of response inhibition as participants must inhibit an overlearned verbal response of reading the particular word (red) in favor of generating a conflicting response of naming the different ink color (green). For the fourth trial, participants must alternate between naming the ink color of dissonant color words and simply reading the word and ignoring the ink color (inhibition and switching). The score is total time it takes to complete each trial. The maximum time for the color naming and word reading trials is 90 seconds and the maximum time for the inhibition and inhibition switching trials is 180 seconds.

10.1.4.7 DKEFS Verbal Fluency

This verbal fluency test includes phonemic (letter) fluency, semantic (category) fluency and category switching [30]. For the phonemic fluency task, the participant is asked to generate words that begin with a particular letter as quickly as possible, within a 60 second time period. Three trials are given, each with a different letter. The semantic fluency task asks participants to verbally generate as many words as they can according to specific categories (animals and boys names) with a 60 second time period. The category switching task asks participants to alternate between saying words from two different semantic categories (fruits and furniture) with a 60 second time period.

10.1.4.8 Oral Trail Making Test

The oral version of the Trail Making Test provides an assessment of sequential set-shifting without the motor and visual demands of the written Trail Making Test [31]. For Part A, participants are asked to count from 1 to 25 as quickly as possible. For Part B, participants are asked to switch between number and letter in sequential order (e.g. 1-A, 2-B, 3-C) until the number 13 is reached. Scoring is the total time to complete each part.

10.1.5 ***Cogniciti Brain Health Assessment***

The Cogniciti Brain Health Assessment (BHA) is a self-administered online assessment of memory and executive function, comprised of four cognitive tests [32]. The Cogniciti BHA also includes a demographic and health questionnaire. The four cognitive tests included in the Cogniciti BHA are:

1) **Spatial Working Memory** is a test of visuospatial working memory. This task requires participants to match several pairs of hidden shapes across three trials and to avoid unnecessarily returning to previously searched locations. Number of responses across three trials is measured.
2) **Stroop Interference** is a speeded test of response inhibition. Participants are required to identify the number of words shown on each trial. During interference trials, the number of words is incongruent with the meaning of the word (e.g. the word “two” is written one time). Median reaction time on incongruent trials is measured.
3) **Face-Name Association** is a test of associative recognition. The participant is shown various faces paired with names and then completes a recognition task. Recognition accuracy is measured.
4) **Number-Letter Alternation** is a test of alternating attention. Participants are required to alternate sequencing numbers and letters in ascending order as quickly as possible. Time to completion is measured.

10.1.6 ***“Burst” Cognitive Testing***

Participants will undergo five intensive measurement bursts, spaced approximately three months apart, over 12 months (at Baseline, Months 3, 6, 9, and 12) using the MyCogHealth mobile application. Each measurement burst will involve two mobile assessments per day for seven consecutive days. Each assessment session will take approximately 5-10 minutes to complete, and will include the 3 cognitive tests included in the current MyCogHealth battery (i.e., Symbol Match, Dot Memory, and Trail-Making A and B), as well as several brief questions assessing state factors at the time of testing (e.g., mood, fatigue, subjective cognitive ability).

Cognitive Tasks

Each cognitive task in the mobile battery takes 1-2 minutes to complete, ensuring feasibility for use in intensive measurement studies that include multiple sessions within a day.

Symbol Match assesses attention and information processing speed. Participants are shown a row of three symbol pairs at the top of the screen, and are simultaneously presented with two symbol pairs at the bottom of the screen. Stimuli are presented until a response is provided. The task is to decide, as quickly as possible, which of the two pairs presented at the bottom of the screen matches one of the pairs at the top of the screen. Participants complete 12 trials of this task. The dependent variable is median response time of correct trials.

Dot Memory assesses visual short-term memory. Each trial consists of 3 phases: Encoding, distraction, and retrieval. During the encoding phase, the participant is asked to remember the locations of 3 red dots on a 5 x 5 grid. After a 3-second study period, the grid is removed and the distraction phase begins, during which the participant is required to locate and touch all the F's among an array of E's. After performing the distraction task for 8 seconds, an empty 5 x 5 grid re-appears on the screen, and participants are prompted to recall the locations of the initially presented 3 dots. Participants complete 4 trials of this task (encoding, distractor, retrieval), with a 1-second delay between trials.

Digital Trail Making Test assesses complex attention/controlled sequential processing. It is a digital analogue of the classic neuropsychological task.

Survey

As part of each mobile assessment participants will be asked to complete a series of single-item questions that assess state factors that can affect cognition (e.g. mood, fatigue, physical activity, subjective cognitive ability).

10.2 Behavioral and Functional Measures

Participants will complete the following behavioral and functional measures remotely through the LORIS survey tool. Each survey form is generated with a unique URL. This survey link URL can be emailed directly to respondents for survey completion from home. Participants will be provided with contact information for site study staff for any questions, concerns or if they experience any technical difficulties with completing the assessments.

10.2.1 ***COVID-19 Impact Survey***

This is a 14-item questionnaire developed by the National Alzheimer's Coordinating Center (NACC) to assess the impact that the COVID-19 pandemic has had on older adults. Questions include symptoms, testing, social isolation, loneliness and disruption to everyday life [33].

10.2.2 ***Generalized Anxiety Disorder 7-Item Scale (GAD-7)***

Anxiety symptoms will be assessed with the GAD-7 [34]. The participant is asked how frequently they felt the way that is described in a given item over the last two weeks (choices are "Not at all sure", "Several days", "Over half the days" & "Nearly every day"). If any of the items are indicated to have been experienced several days or more, there is a follow-up question on how much difficulty this created in being able to work, take care of things at home, or get along with other people. The score is based on the frequency of each experienced item with "Not at all sure" =0 points, "Several days" =1 point, "Over half the days" =2 points, and "Nearly every day" =3 points. A score greater or equal to 10 suggests generalized anxiety.

10.2.3 ***Geriatric Depression Scale (GDS)***

Depressive symptoms will be assessed with the 15-item Geriatric Depression Scale [35]. This is a 15-item scale of Yes/No questions where each point represents a depressive answer. A score over 10 suggests depression and a score over 15 suggests major depression.

10.2.4 ***Lawton Brody Instrumental Activities of Daily Living (IADL) Scale***

This is a 10-15-minute scale that can be completed by self-report or by informant (if available) and captures functional ability on 8 instrumental activities of daily living (telephone use, shopping, food preparation, housekeeping, laundry, transportation, medication management, and ability to handle finances) [36]. Each activity has a series of levels of capability described, ranging from full capability to no capability. A total score out of 23 is derived from the levels of capability for each activity with a higher score representing better functional capacity.

10.2.5 ***Mild Behavioral Impairment Checklist (MBI-C)***

The MBI-C is a 32-item scale that assesses severity of behavioral symptoms in 5 domains: impaired drive/motivation (apathy); emotional dysregulation (mood/anxiety symptoms); impulse dyscontrol (agitation/aggression/abnormal reinforcement and reward salience); social inappropriateness (impaired social cognition); and abnormal thoughts/perception (psychotic symptoms) [37]. The MBI-C will be completed by a study partner/informant (if available). The study partner will be asked to select "Yes" only to each behavior that has been present for at least 6 months and is a change from the participant's longstanding behavior.

10.2.6 ***Research Satisfaction Survey***

A brief Research Satisfaction Survey will be administered to the participant at Baseline, Month 6 and Month 12 to evaluate satisfaction with this study. The survey may reveal specific aspects of the study that participants dislike, which can inform efforts to improve the experience for participants in the future.

10.2.7 ***Sleep Disorders Questionnaire***

This brief self-report questionnaire will be used to assess Sleep Apnea, REM Sleep Behaviour Disorder and Restless Leg Syndrome (RLS). Sleep Apnea will be assessed using questions from the Stop-Bang Questionnaire [38]. 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.)?"[39]. RLS will be assessed using the 8-item Cambridge Hopkins Questionnaire [40].

10.3 BHPro Outcome Measures

The following assessments will be completed online directly through BHPro. Participants will receive an e-mail notification to login into BHPro to complete the following assessments.

10.3.1 ***Alzheimer's Disease Knowledge Scale (ADKS)***

The Alzheimer's Disease Knowledge Scale is a 30-item, true/false scale that was designed to assess knowledge about Alzheimer's disease among laypeople, patients, caregivers, and professionals. It covers risk factors, assessment and diagnosis, symptoms, course, life impact, caregiving, and treatment and management [41]. This scale will be completed online within BHPro to measure changes in dementia literacy.

10.3.2 ***The General Self-Efficacy Scale (GSE)***

Self-Efficacy is a concept that refers to one's global confidence in their ability to cope with demanding or novel situations. The General Self-Efficacy scale is a 10-item, 4-point scale which measures one's perceived competence in dealing with a range of stressful or challenging situations [42]. The scale will be completed online within BHPro.

10.3.3 *Perceptions Regarding Investigational Screening for Memory in Primary Care (PRISM-PC)*

Sections B and D of the PRISM-PC questionnaire will be used to assess attitudes toward dementia and dementia screening and will be completed online within BHPro. The PRISM-PC questionnaire captures participants' acceptance, perceived harms, and perceived benefits of dementia screening [43].

10.3.4 *System Usability Scale (SUS)*

The SUS [44] is a simple scale giving a global view of subjective assessments of usability. An adapted 11-item version of the SUS will be used to measure usability of BHPro.

10.3.5 *Technology Acceptance Model Questionnaire*

A web-based adapted version of the Technology Acceptance Model Questionnaire [45] will be used to evaluate user acceptance of BHPro. Questions include attitude, perceived usefulness and perceived ease of use of the technology.

11.0 EARLY DISCONTINUATION PROCEDURES

Participants are free to withdraw from study participation at any time, for any reason, and without prejudice.

Study Discontinuation for an individual participant may occur in the following circumstances:

1. Withdrawal of informed consent by the participant. If a study partner withdraws his/her willingness to participate, attempts will be made to find a replacement. If a replacement study partner is not identified, the participant will continue to be followed in the study and assessments completed to the extent possible.

2. Adverse event or other significant medical condition which, in the opinion of the Investigator, render it necessary to remove the individual from study participation.

3. Any other occurrence that, in the Investigator's opinion, makes continued participation contrary to the participant's best interests.

If the site investigator or CCNA Co-Principal Investigator (Co-PI) leadership team discovers sufficient reasonable cause for the premature termination of the study, the terminating party will provide written notification documenting the reason for study termination. The appropriate regulatory agencies and IRB/REB must be notified.

12.0 ADVERSE EVENTS

An adverse event (AE) is any untoward medical occurrence in a participant that occurs from the time of the baseline visit and up to 30 days after study participation has ended. For the purposes of reporting on the CTU study, 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

12.1 Evaluation and Reporting of Adverse Events

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 baseline visit and up to 30 days after study participation has ended will be recorded as an AE in LORIS. Adverse events that occur prior to the baseline visit will be documented as medical history. 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 participation in the BHSP, 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.

12.2 Assessment of Adverse Events

All AEs both non-serious and either temporally or causally related to study procedures will be assessed by the Investigator and documented in LORIS. Details of the event must include the dates of onset and resolution, severity, relationship to study procedures, seriousness, whether the event caused the participant to withdraw from the study, and outcome.

Severity: Severity should be graded and recorded according to the table below.

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

Relationship: The relationship of the AE to study procedures will be determined by the Investigator, and assessed using the following definitions:

Relatedness	Description
Not Related	There is no evidence of a causal relationship and a causal relationship cannot be reasonably attributed to the study procedures. The event is clearly due to non-study causes.
Unlikely Related	A poor temporal relationship exists between the event onset and study procedures. The event could easily be explained by the participant's clinical state, intercurrent illness, or concomitant therapies.
Possibly Related	A relationship between event onset and study procedures cannot be ruled out with certainty and the event may be related. There is some evidence to suggest a causal relationship but the influence of other factors may have contributed to the event, such as the participant's clinical condition or concomitant treatment.
Probably Related	The event is likely related to study participation. There is evidence to suggest a causal relationship, such as reasonable temporal sequence from procedure. The influence of other factors is unlikely.
Definitely Related	The event is clearly related to study participation. There is clear evidence to suggest a causal relationship. The influence of other factors can be ruled out.

These criteria, in addition to good clinical judgment, should be used as a guide for determining the causal assessment.

12.3 Collection and Reporting of Serious Adverse Events (SAEs)

All SAEs thought to be **unanticipated and related to study procedures** must be collected from the time of the baseline visit and up to 30 days after study participation has ended. SAEs will be promptly assessed by the Investigator and documented in LORIS as described below.
In order to meet the requirements for reporting as an SAE in LORIS, an event **must meet all three criteria** as defined below:

1) **Serious**
    a. Untoward occurrence that results in death, is a life-threatening situation, requires inpatient hospitalization or prolongation of existing hospitalization, results in significant disability/incapacity or is a congenital anomaly
2) **Unanticipated**
    a. An AE that is not identified in nature, severity, or frequency in the relevant safety documents(s) or is not identified as a possible risk in the study protocol or the informed consent form
3) **Related to study procedures** in the judgement of the Principal Investigator taking into account all aspects of the event

If the Investigator believes that an SAE is related to a study procedure, this should be specified in the narrative section of the SAE report.

SAEs meeting the above definition must be reported in LORIS **promptly, but no later than 10 business days** of the Investigator becoming aware of the event.

In addition, Investigators must report SAEs to their local IRB/REB according to local safety reporting guidelines for submission of SAEs.

SAE information including event term, start/stop dates, severity, relationship to study procedures, whether the event caused the participant to withdraw from the study, and outcome will be entered into LORIS as specified in the Study Procedures Manual.

If only limited information on the SAE is initially available, follow-up reporting is required. If an ongoing SAE changes in its intensity or relationship to study procedures or if new information becomes available, a follow-up SAE report should be entered into LORIS within 10 days of the Investigator becoming aware of the updated information using the same procedure used for the transmission of the initial SAE and the same event term should be used. All SAEs should be followed to resolution or stabilization. For any questions relating to SAEs, please contact the CCNA coordinating center via telephone or email at the number listed in the Study Procedures Manual.

13.0 STATISTICAL CONSIDERATIONS

13.1 Sample Size and Power

With a baseline (t1) sample size of 350 participants and an anticipated 20-30% range of drop-out rates, we will have between 245 (with 30% dropout) and 280 (with 20% dropout) completed participants at t2 (end of intervention). All calculations are for 80% power and 5% two-tailed alpha. We considered small (d=0.2) and medium (d=0.5) Effect Sizes for 4 different t1-t2 correlations ($r_{t1\text{-}t2}$) in the primary outcome variable: r=0.2, 0.3, 0.4 and 0.5. A final sample of n=280 will allow us to detect an ES $\geq$0.2 if $r_{t1\text{-}t2} \geq 0.3$. A final sample of n=245 will allow us to detect an ES $\geq$0.2 if $r_{t1\text{-}t2} \geq 0.4$ (please see Table 1 for required sample sizes, and Appendix 4 for supporting formulae).

Table 1: Required sample size to detect ES = 0.2 or 0.5 across a range of $r_{t1\text{-}t2}$ with statistical power = 0.8 and two-tailed alpha error = 0.05.

Effect Size (ES)	$r_{t1\text{-}t2}$	*n*
0.2 (small)	0.2	316
	0.3	277
	0.4	238
	0.5	198
0.5 (medium)	0.2	53
	0.3	46
	0.4	40
	0.5	34

It is estimated that approximately 50% of participants will own a smartphone with internet access appropriate for use of the MyCogHealth mobile cognitive assessment (n=175) and an additional 150 will be provided with Android devices (total approx. n = 325).

CTU will provide 120 Axivity devices and 60 EEG headbands to be used for the duration of this study, which should allow for all participants to participate in recordings at Baseline and Month 12. Devices will be centrally distributed from SRI to participants.

13.2 Analysis Plan

In our one-group pretest-posttest design the major interest is within-person change in the primary and secondary outcomes over time (response variables) in the presence of one or more explanatory variables that are categorical or continuous. The data will be analyzed using a mixed model for repeated measures approach (MMRM). This approach will treat sites and participants as random effects, while observational time and their characteristics such as sex and age as fixed effects. Potential effect modifications will be examined using this MMRM approach with variable selection based on Akaike/Bayesian information criterion.

A more detailed and formal statistical analytic plan (SAP) will be developed and finalized during the study. The SAP will include detailed descriptions for evaluating our study outcomes including BHPro, cognition, physical activity and sleep, and recruitment metrics.

13.2.1 *Sex and Gender Analysis*

Sex-stratification will be used in analyses as appropriate. Where appropriate and available, sex-specific normative data will be used in the scoring of cognitive tests. In assessing the psychometric properties of composites, the cohort will be divided into groups based on sex.

14.0 RECORDING AND COLLECTION OF DATA

14.1 Case Report Form

See Appendix 5 for the Flow of Data Figure.

14.1.1 *Standardized Subject Demographic and Clinical-Research Meta-Data*

Demographic, clinical, and remote assessment data will be entered into the LORIS system.

The Investigator and local site study personnel will be trained on case report form (CRF) and electronic case report form (eCRF) completion and data entry into the LORIS system. The investigator is responsible for all entries in the CRF/eCRF for completeness, accuracy and clarity. The investigator or designee should complete the CRF/eCRF as soon as possible after the information is collected. The investigator is responsible to endorse all the information recorded in the CRF/eCRF and will provide formal approval of the final submitted data.

14.1.2 *Recordings of Remote Study Visits*

The neuropsychological test battery administration at Screening, Baseline, and Month 12 conducted by video-conference technology (e.g. Zoom) will be recorded to assist with rater

scoring, to ensure standard administration and scoring, and to help inform the study on feasibility of remote administration of the study assessments. Raters will ask the participant for permission to record the testing session prior to initiating the recording. If the participant does not provide the rater permission to record, the neuropsychological test battery administration will proceed without recording. If video recordings are permitted per local site policy, files will only be kept for the minimum amount of time required (but no longer than 60 days from the date of recording) to allow for review of the files by local site research members and the study Supervising Neuropsychologist to ensure accuracy of scoring, completion of study CRFs and entry of study data into LORIS. Only the audio-recording file from the recorded sessions will be saved and securely stored within the LORIS system. Audio-recordings will be labelled by LORIS PSCID and be accessible to study research personnel only for the purposes described above. Once analyses for the study are complete, audio recordings will be permanently deleted from LORIS. A copy of the de-identified audio-recording will be saved on external hard drive (unlinked to the internet) and retained by the study site for the duration required according to local IRB/BEB policy and/or other applicable regulatory requirements for storage of study files.

14.1.3 ***BHPro***

The BHPro website will be hosted on a secure server. De-identified data (linked to LORIS PSCID) will be uploaded (API and/or csv.format), processed, and included in the CTU dataset for long-term maintenance and secure storage on the LORIS servers.

14.1.4 ***Online Cognitive Testing***

Results from the MyCogHealth “burst” cognitive testing will be automatically uploaded to a secure server maintained by McGill University (and hosted by LORIS) for data management. Data will be downloaded by study staff from The Institute on Aging and Lifelong Health (University of Victoria, BC) for cleaning and processing. Processed data will be uploaded again into LORIS for inclusion in the CTU dataset (See Appendix 5 Figure 2. MyCogHealth Data Flow) and for long-term maintenance and secure storage. The MyCogHealth platform will use and be maintained by LORIS system administrators with interoperability with the LORIS system for secure access to CCNA investigators.

Web servers for the Cogniciti Brain Health Assessment are hosted in Azure App Service, including firewalls and secure data transfer between client and server. Results from the Cogniciti Brain Health Assessment will be uploaded (csv.format), processed, and included in the CTU dataset for long-term maintenance and secure storage on the LORIS servers.

14.1.5 ***Actigraphy and EEG Recordings***

Actigraphy data will be downloaded from the Axivity devices by study staff for cleaning and processing, and then will be uploaded to LORIS servers to be included in the CTU dataset for analysis (See Appendix 5 Figure 5. Actigraphy Data Flow), and long-term maintenance and secure storage.

EEG data stored on the CTU-provided iPod will be automatically uploaded to a manufacturer-supported cloud server at the end of each day’s recording. Data scripts will automatically download data files from the manufacturer-supported server to a server at SRI for cleaning and processing. Processed data will be uploaded into LORIS to be included in the CTU dataset for

analysis (See Appendix 5 Figure 6. EEG Data Flow), and long-term maintenance and secure storage.

14.1.6 ***Genomics***

Raw data from genomic analysis and associated sample and experiment metadata will be de-identified and uploaded to the LORIS molecular database subsystem for long-term maintenance and secure storage and sharing.

14.2 Study Files and Patient Source Documents

Participant confidentiality is strictly held in trust by the participating investigators, research staff, and the sponsoring institution and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Authorized representatives of the sponsoring institution may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records (office, clinic or hospital) for the participants in this study. The participating site will permit access to such records. Any data, specimens, forms, reports, and other records that leave the site will be identified only by a participant identification number to maintain confidentiality.

ICH-GCP guidelines require independent inspection of clinical program activities. Such inspections may be performed at any time - before, during and/or after the study. The Investigator and study staff are responsible for maintaining the site regulatory file containing all study-related regulatory documentation that will be suitable for inspection at any time by CCNA and/or its designees. The Investigator understands and agrees to give access to the necessary documentation and files. These documents include Investigators' Study Files, original participant clinical source documents generated at the study site, original participant electronic documents or completed source document worksheets. The term "original" means the first recording of the data.

Participant clinical source documents may include, but are not limited to, participant hospital/clinic records, physicians' and nurses' notes, appointment books, laboratory reports, Electrocardiograms (ECGs), Magnetic Resonance Imaging (MRI) images, pathology and special assessment reports. The Investigator must assure that all original source documents are available to support monitoring activities.

The Investigator will ensure the site regulatory files are maintained, including essential documents such as the study protocol and its amendments, IRB/REB and regulatory approvals with associated correspondence, informed consents, staff curriculum vitae, correspondence, and other appropriate documents.

14.3 Rater Training

Site staff delegated to administer the remote cognitive, functional and behavioral measures will be trained on the assessments and certified on these study specific measures that are described in Sections 9.0 and 10.0. Additional details of the rater training and certification process will be provided to participating sites and outlined in the Study Procedures Manual.

14.4 Retention of Data

After the notification of the IRB/REB regarding the end of the study, the investigator must retain all study records (paper and electronic) according to local IRB/REB policy or other applicable regulatory requirements. If the investigator retires, relocates or withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility. The CTU leadership team must be notified in writing if a custodial change occurs.

14.5 Quality Assurance/Quality Control

Study data will be entered in the eCRF in LORIS by trained site study personnel. Data validation edit checks will be defined and implemented. Inconsistent and questionable data detected during the data entry or data validation process will be queried.

14.6 Incidental Findings

Incidental findings that are identified as being medically significant will be addressed by participating site Principal Investigators. Any incidental findings identified during data entry into LORIS will be flagged for follow-up to the Investigator or site study staff where the participant was seen. The site study staff will link the participant code to his or her identity and the finding will be passed on to the site Investigator of the participant in question within 24 hours. The site Investigator or site physician will be responsible for determining the significance of the finding, arranging appropriate follow-up and informing the primary care physician or other health care provider (designated by the participant during screening) in writing of the follow-up. The finding and its follow-up will be documented and monitored until it has been resolved or as long as the participant remains in the study.

15.0 PUBLICATIONS POLICY AND SHARING OF DATA

In order to access the data generated in this study, researchers must agree to abide by the CCNA Publication and Data Access Committee policy, a document prepared by the CCNA Publication and Data Access Committee (PDAC), available for download at www.ccna-ccnv.ca. The PDAC consists of a Chair and up to 10 CCNA members. The PDAC members list is available upon request. Access to and analyses of CTU-acquired data, stored in LORIS, may be granted to qualified persons 12 months (quarantine period) after the principal paper(s) answering primary research questions is/are published. A list of CTU protected planned projects and publications to be undertaken by the CTU Co-PIs, co-investigators or SC members will be posted in the LORIS publication module. Any CTU investigator who worked on the project and wishes to analyze and subsequently publish data related to a question already listed in the “Protected planned projects and publications” will have priority on said project. Any other researcher must receive approval to join the designated writing group for that project to avoid duplication of the aims and methods of another CTU publication or wait until the “quarantine period” has passed. Requests for use of CTU datasets may be made on the LORIS publications module and via email to CCNA; Central Administration [ccna.admin@ladydavis.ca]. Investigators will only be granted access to data related to the project outlined in the data access request.

Prior to submission for publication or for presentation of any data or results obtained in this study, notification to the PDAC is required. Draft manuscripts, abstracts and presentations should be submitted to the PDAC for administrative review. The participating sites will retain the

ownership of their data obtained in this study. No researcher shall include identifiable personal health information in any publication or presentation. Authorship of publications resulting from this study should accurately reflect the academic contribution of individuals to the design and implementation of the trial, analysis of the data and preparation of the manuscript. Funding of CTU and CCNA by CIHR and other funding partners must be acknowledged. All publications that arise from the use of CTU data will give acknowledgement, attribution, or co-authorship as appropriate in accordance with the International Committee of Medication Journal Editors (ICMJE) standards and any rules established by the PDAC.

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17.0 APPENDICES

17.1 APPENDIX 1: CLINICAL DIAGNOSTIC CRITERIA

Appendix 1A: Clinical Diagnostic Criteria for Cognitively Unimpaired (CU) Individuals:

1. Normal age-, sex-, and education-adjusted performance on standardized cognitive tests	Global CDR Score = 0
	Logical Memory II Score= ≥ 9 for 16 or more years of education ≥ 5 for 8-15 years of education ≥ 3 for 0-7 years of education
	MoCA Total Score ≥ 25
2. No Subjective Memory Complaint	Answer “no” to one or both of the following questions: “Do you feel like your memory or thinking is becoming worse?” and “Does this concern you?”
3. Does not meet clinical diagnostic criteria for Dementia	DSM-IV

Appendix 1B: Clinical Diagnostic Criteria for Subjective Cognitive Impairment (SCI):

1. Normal age-, sex-, and education-adjusted performance on standardized cognitive tests	Global CDR Score = 0
	Logical Memory II Score= ≥ 9 for 16 or more years of education ≥ 5 for 8-15 years of education ≥ 3 for 0-7 years of education
	MoCA Total Score ≥ 25
2. Subjective Memory Complaint: Self-experienced persistent decline in cognitive capacity in comparison with a previously normal status and unrelated to an acute event	Answer “yes” to both of the following questions: “Do you feel like your memory or thinking is becoming worse?” and “Does this concern you?”
3. Does not meet clinical diagnostic criteria for Dementia	DSM-IV

Appendix 1C: Clinical Diagnostic Criteria for Mild Cognitive Impairment (MCI):

1. Concern regarding a change in cognition	Report from participant and/or informant
2. Impairment in one or more cognitive domains	Global CDR Score = 0.5
	Logical Memory II Score = ≤ 8 for 16 or more years of education ≤ 4 for 8-15 years of education ≤ 2 for 0-7 years of education
	MoCA Total Score 13-24 inclusive
3. Preservation of independence in functional abilities	Lawton-Brody IADL Score > 14/23
4. Does not meet clinical diagnostic criteria for Dementia	DSM-IV Global CDR Score < 1.0

17.2 APPENDIX 2: SCHEDULE OF EVENTS

PROCEDURES	**SCREENING (within 21d of baseline)**	**BASELINE (+/- 2 weeks)**	**MONTH 3 (+/- 2 weeks)**	**MONTH 6 (+/- 2 weeks)**	**MONTH 9 (+/- 2 weeks)**	**MONTH 12 (+/- 2 weeks)**
TELE/VIDEO-CONFERENCE REMOTE PROCEDURES[1]						
INFORMED CONSENT	X					
SOCIODEMOGRAPHICS	X					
MEDICAL /SURGICAL/FAMILY HISTORY	X			X		X
HEIGHT / WEIGHT / BMI[2]	X					X
CLINICAL DEMENTIA RATING (CDR)[3]	X					X
LAWTON BRODY INSTRUMENTAL ADLs	X					X
HEARING AND VISION ASSESSMENT	X					
CAIDE SCORE	X					X
REMOTE NEUROLOGICAL EXAM[4]	X					X
FOLLOW-UP PHONE CALL (continued interest, satisfaction with BHPro, medical and diagnostic changes[5])			X	X	X	
NEUROPSYCHOLOGICAL TEST BATTERY[6]						
MONTREAL COGNITIVE ASSESSMENT	X					X
LOGICAL MEMORY 1 and 2	X					
CRAFT STORY 21 Immediate and Delayed Recall AND DELAYED RECALL		X				X
ADAS-COG word recall, delayed recall, orientation		X				X
BRIEF VISUOSPATIAL MEMORY TEST-REVISED (BVMT-R)		X				X
ORAL SYMBOL DIGIT MODALITITES TEST		X				X
ORAL TRAIL MAKING TEST A AND B		X				X
DKEFS COLOR-WORD INTERFERENCE TEST		X				X
DKEFS VERBAL FLUENCY		X				X
BOSTON NAMING TEST (BNT), 15-item		X				X

PROCEDURES	SCREENING (within 21d of baseline)	BASELINE (+/- 2 weeks)	MONTH 3 (+/- 2 weeks)	MONTH 6 (+/- 2 weeks)	MONTH 9 (+/- 2 weeks)	MONTH 12 (+/- 2 weeks)
BURST COGNITIVE TESTING[7]		X	X	X	X	X
COGNICITI BRAIN HEALTH ASSESSMENT (BHA)[8]		X		X		X
ONLINE FUNCTIONAL AND BEHAVIORAL ASSESSMENTS[9]						
GERIATRIC DEPRESSION SCALE (GDS)		X				X
GENERALIZED ANXIETY DISORDER 7-ITEM SCALE (GAD-7)		X				X
MILD BEHAVIORAL IMPAIRMENT CHECKLIST (MBI-C) [10]		X				X
SLEEP DISORDERS QUESTIONNAIRE		X				X
COVID-19 QUESTIONNAIRE		X				X
RESEARCH SATISFACTION SURVEY		X		X		X
OTHER REMOTE DATA COLLECTION AND MONITORING						
ACTIGRAPHY APPLICATION AND DATA COLLECTION[11]		X				X
EEG WEARABLE INSTRUCTIONS AND DATA COLLECTION[11]		X				X
SALIVA SAMPLE COLLECTION[12]		X				
ONLINE BHPro ASSESSMENTS[13]						
SELF-EFFICACY (The General Self-Efficacy scale, GSE)		X		X		X
DEMENTIA LITERACY (The Alzheimer's Disease Knowledge Scale, ADKS)		X		X		X
ATTITUDE TOWARDS DEMENTIA AND DEMENTIA SCREENING (Parts B and D of the PRISM-PC Questionnaire)		X		X		X
USABILITY (web-based version System Usability Scale-adapted)				X		X
ACCEPTABILITY (Technology Acceptance Model questionnaire-adapted)				X		X
BHPro LIFESTYLE RISK QUESTIONNAIRES[14]		X	X	X	X	X

[1]Procedures and assessments completed by telephone or video-conference between participant, study partner (if applicable) and study site team member.
[2] Height will not be collected at Month 12.

[3] If no study partner/informant available the Global CDR score will be determined by research team consensus using all other available information and best clinical judgement .

[4]To be completed by site Principal Investigator or other medically qualified professional following the recommended Telemedicine guidelines for neurological exams provided by AAN.

[5]Medical and diagnostic changes only to be completed at Month 6 follow-up phone call.

[6]Neuropsychological Test Battery to be completed by video-conference between participant and trained rater. Instructions and administration adapted for remote use and provided in Study Procedures Manual.

[7]Instructions and initial testing for "Burst" Cognitive Testing will be completed during remote baseline video-conference. Participants will receive notification by smartphone (for "burst" cognitive testing) and by email to complete other timepoints remotely. The Neuropsychological Test Battery should be completed prior to the start of "Burst" Cognitive Testing at Baseline and Month 12.

[8]Participants will receive a personalized link sent by the study coordinator to complete the Cogniciti BHA. "Burst" Cognitive Testing should be completed prior to the Cogniciti BHA at Baseline, Month 6 and Month 12.

[9]Participants will receive a personalized link sent through the LORIS survey tool to complete the behavioral and functional self-report measures.

[10]The MBI-C will be completed by Study Partner/Informant if available.

[11]Devices and user instructions will be sent to participants from SRI by mail. Application and Instructions on use and duration of Axivity device, and EEG headband will be provided by video-conference between participant and SRI study team member. At the conclusion of the specified recording period, devices will be returned by mail. The same procedure will be followed for Month 12.

[12]A saliva sample with at-home collection kit will be provided for genomics testing (PHS) and analysis.

[13]These assessments will be completed online through the BHPro website.

[14]Brief questionnaires based on BHPro content modules that will be completed every 3 months within the online program to evaluate changes in lifestyle risk (e.g. sleep, diet, physical activity, vascular risks, social engagement, cognition, vision and hearing; see Appendix 3 for questionnaire descriptions).

17.3 APPENDIX 3: BHPro LIFESTYLE RISK QUESTIONNAIRES

BHPro Module	Questionnaire Description
Physical Activity	The International Physical Activity Questionnaire -Short Form[1] is a brief 7-item self-report measure that captures types of and intensity of physical activity and sitting time daily over the last 7 days.
Cognitive Engagement	Participants will complete a 6-item questionnaire assessing types and duration of cognitive activities[2] (e.g. read, watch T.V., socialize).
Diet	Participants will complete a shorter version of the Eating Pattern Self-Assessment Questionnaire developed by CCNA Team 5, which asks participants about foods and servings typically consumed over the last 30 days.
Sleep	Brief 10-item self-report questionnaire developed by BHPro Sleep Module content leads that assesses sleep duration, sleep patterns and difficulties and daytime fatigue over the past 3 months.
Social and Psychological Health	An 8-item questionnaire comprising 1 item on loneliness adapted from CLSA, 1 item on ageism adapted from the European Social Survey[3], 1 item on subjective age adapted from the MIDUS study[4], 1 item on essentialist beliefs of aging from Weiss et al., 2019[5], and 4 items on depression, anxiety, stress, and social support from STOP-D[6].
Vascular Health	12-item self-report questionnaire developed by the BHPro Vascular Health team based on the American Heart Association's Life's Simple Seven checklist of the main risk factors for heart disease and stroke. https://www.heart.org/en/healthy-living/healthy-lifestyle/my-life-check--lifes-simple-7
Vision and Hearing	10-item questionnaire developed by BHSP Vision and Hearing Module content leads that assesses perceived visual and auditory ability and actions taken to address potential vision/hearing difficulties.

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17.4 APPENDIX 4: SAMPLE SIZE CALCULATION FOR ONE-GROUP PRE-TEST POST-TEST DESIGN

Sample size/power calculation was done based on effect size for one-group pre-/post design. According to Becker [46], the effect size (ES) for such a design should be defined as, assuming SD at pre- and post-test are equal,

$$\text{ES}=\frac{\text{mean change}}{\text{SD baseline}}=\frac{\text{mean change}}{\text{SD change}/\sqrt{2(1-r)}}$$

where *r* is correlation between pre- and post-scores. Note that

$$\text{var}(\text{mean change})=2\text{var}(\text{baseline})(1-\text{r})$$

Sample size can then be done based on the following test statistic

$$T=\frac{\text{mean change}}{\text{SD change}/\sqrt{n}}=\frac{\text{ES}}{\sqrt{2(1-r)/n}}$$

i.e., The corresponding sample size formula for 80% power at 5% significance level is given by:

$$n=\frac{(1.96+0.84)^2}{(\text{mean change/SD change})^2}+2=\frac{(1.96+0.84)^2}{\text{ES}^2/[2(1-r)]}+2$$

Note that plus 2 $(\approx 2\times 1.96^2)$ is to approximate the Z-test with a sample size calculated for the t-test [47].

Therefore, the sample sizes for detecting small and moderate magnitudes of ES 3 at 2-sided 5% significance level with 80% power are given below for values of correlation r

ES	*r*	*n*
0.2 (small)	0.2	316
	0.3	277
	0.4	238
	0.5	198
0.5 (medium)	0.2	53
	0.3	46
	0.4	40
	0.5	34

17.5 APPENDIX 5: CTU FLOW OF DATA FIGURES

Figure 1. Overview of CTU Flow of Data into LORIS

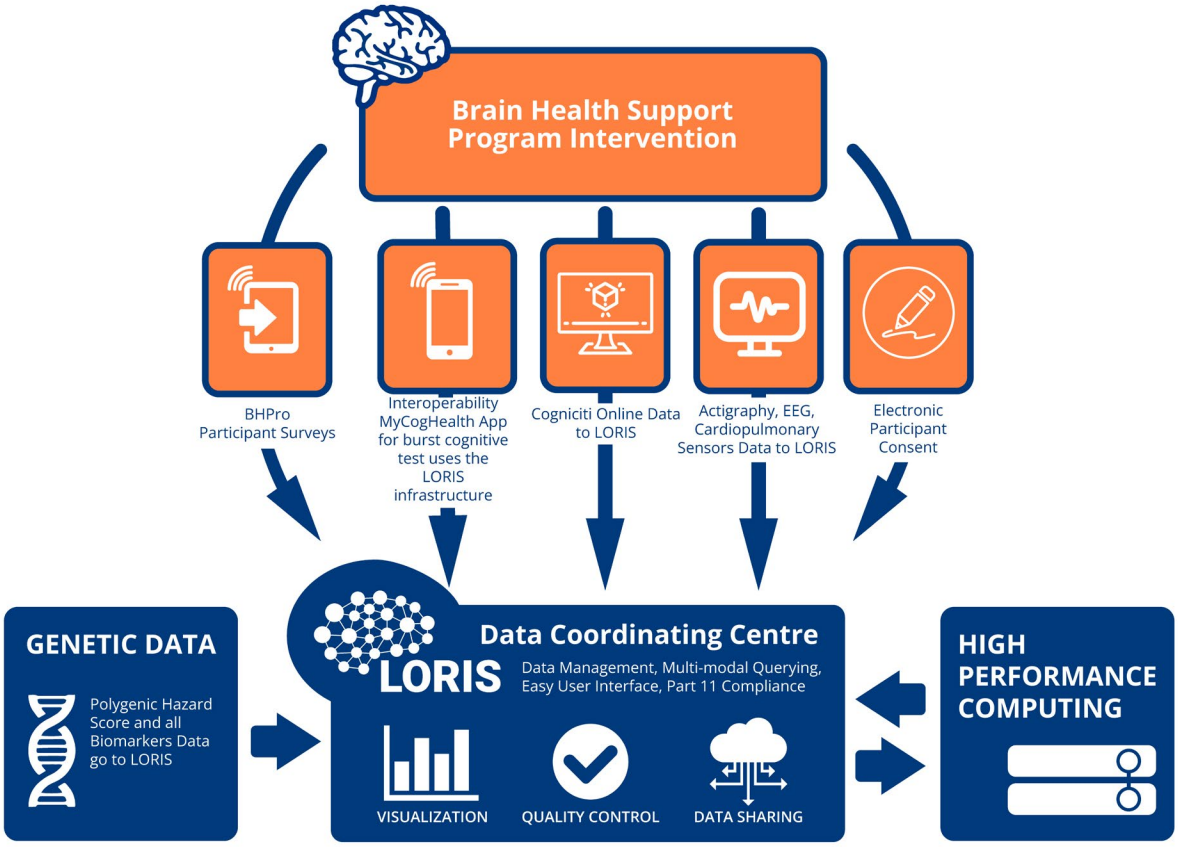


Figure 2. Brain Health PRO Data Flow

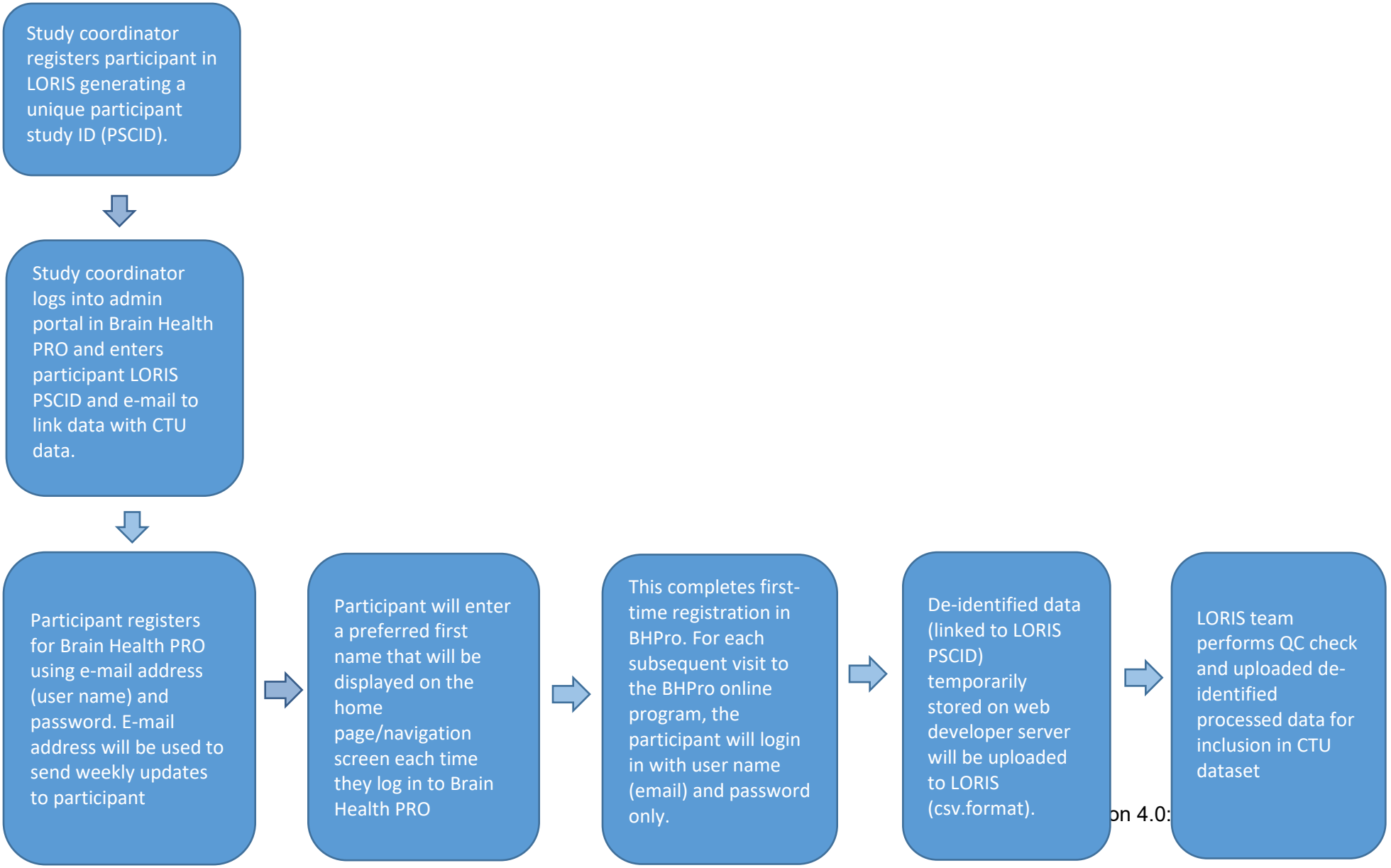


Figure 3. MyCogHealth Data Flow: Participant Using Phone Provided by CTU

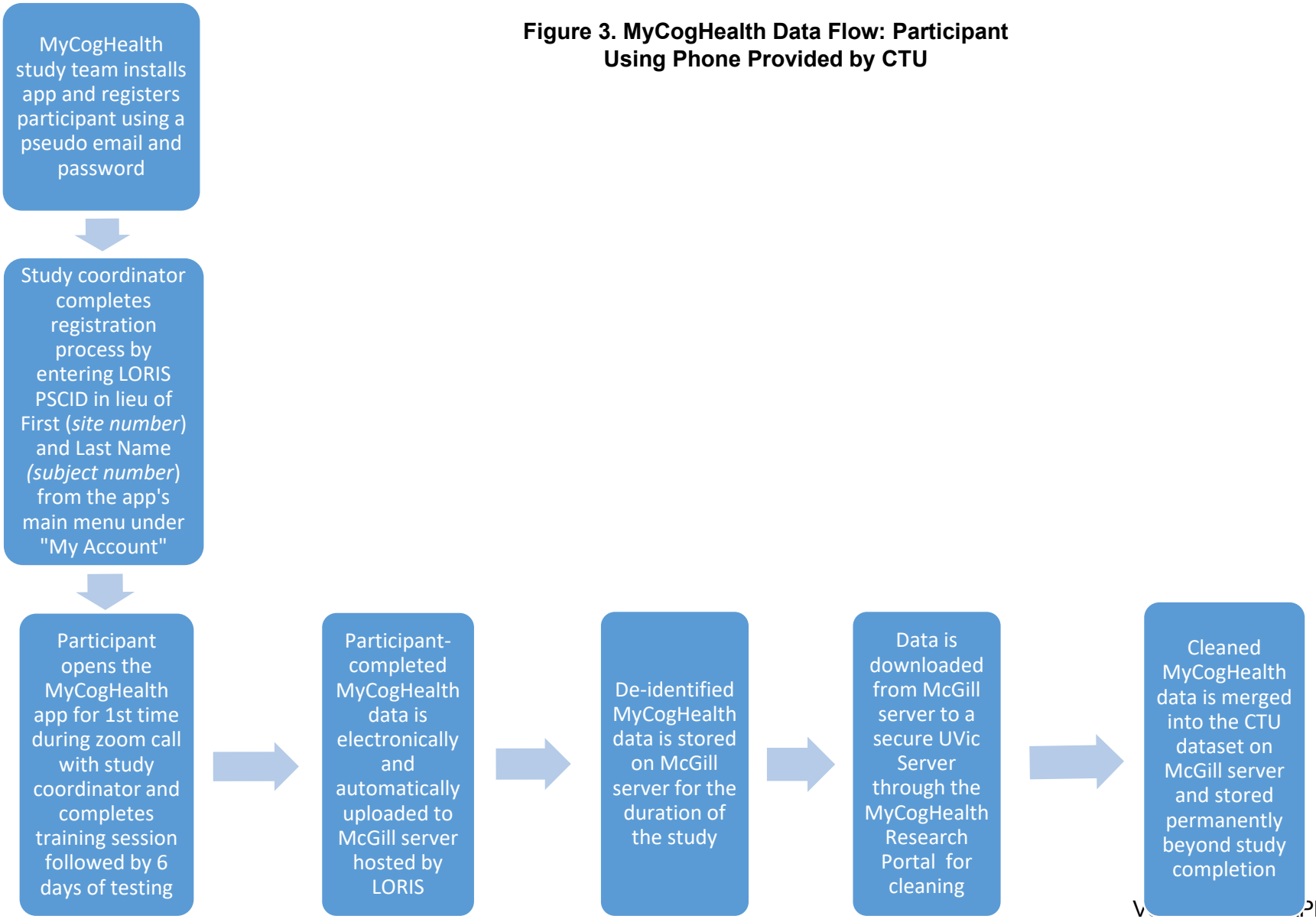


Figure 4. MyCogHealth Data Flow: Participant Using Phone Not Provided By CTU

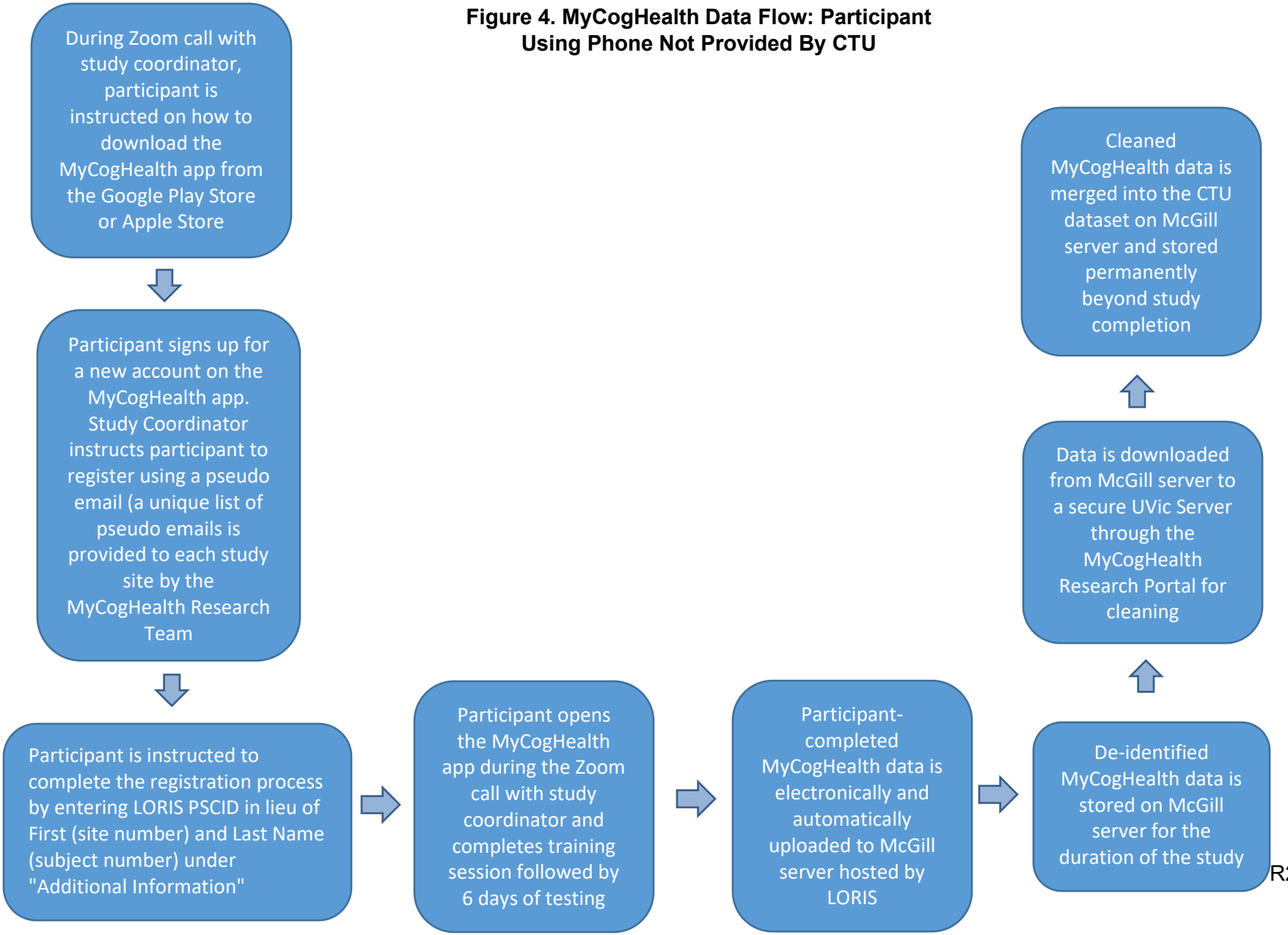


Figure 5. Actigraphy Data Flow

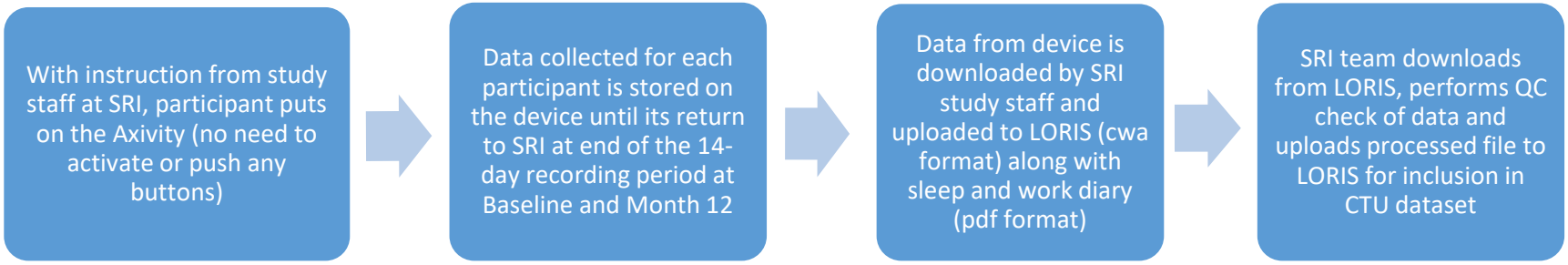
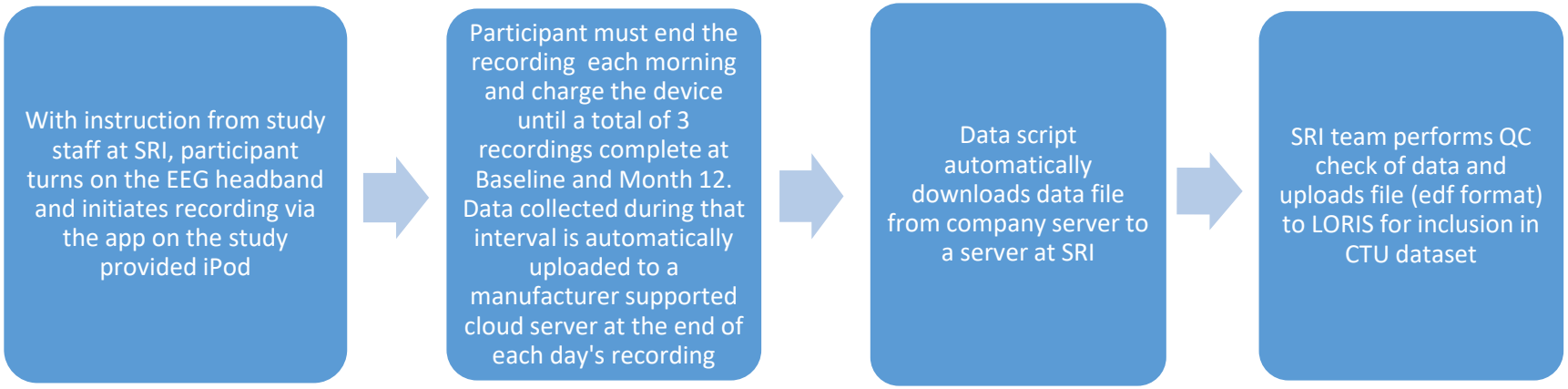


Figure 6. EEG Data Flow



17.6 APPENDIX 6: OPTIONAL CARDIOPULMONARY SENSOR SUB-STUDY

As part of an optional sub-study with a separate consent form, cardiopulmonary measurements (respirations, ECG, blood pressure) will be recorded for 24-hours at Baseline and Month 12 using a set of two water-resistant sensors attached to the sternum using ultrasound gel or adhesive and Tegaderm and to the index finger of the non-dominant hand using a Velcro band (ANNE sensor suite, Sibel Health, Chicago, USA). The chest sensor is a 4.4x2.4x0.5cm silicon-encased flexible waterproof adhesive that contains a triaxial accelerometer, 3-axis gyroscope, thermometer, and surface electrodes for bioimpedance from which ECG, respiratory movements, and temperature can be derived. The finger sensor is a 4.7x2.5x0.5cm silicone-encased flexible waterproof strip that wraps around the finger and allows for measurement of pulse oximetry and temperature.

After study equipment and materials are shipped to and received by the participant, study staff will instruct the participant on the proper application and use of the ANNE Vital Sign System over remote video-conference. Specifically, study staff will instruct the participant to affix the ANNE Vital Sign System chest sensor to the participant's chest using ANNE hydrogel adhesive and a clinical waterproof 3M Tegaderm dressing. Next, study staff will instruct the participant to affix the ANNE Vital Sign System finger sensor to the participant's dominant index finger using the ANNE strap (fabric wrap). Participants will wear the sensors for 24 hours before removing it themselves at home and shipping back to Sunnybrook Research Institute using a pre-paid, pre-addressed package. This procedure will be completed at the Baseline visit and repeated 12 months later.

Cardiopulmonary data – .shrd file type – from the ANNE Vital Sign System will be downloaded via Bluetooth locally to an iOS tablet, then converted to .edf file type, and manually annotated to extract information on sleep apnea. SRI will then upload de-identified processed data and summary measures to the Longitudinal Online Research and Imaging System120 (LORIS) using the media uploaded functionality. All uploads and downloads will be by Secure File Transfer Protocol (SFTP).