Protocol

Community-based *Brain Health Program* to Address Dementia Risk (C-BBHP)

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INVESTIGATOR

NAME:_____ Signature:_____

DATE:

By signing here, the investigator acknowledges that he or she has reviewed and understands the protocol referenced above and agrees to comply with it. Additionally, the Principal Investigator's signature indicates that his/her site has not been the recipient of prior FDA 483 reports or other detailed audit findings. Any and all prior FDA 483 reports or regulatory warnings have been submitted to Posit Science Corporation prior to the commencement of this clinical trial.

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Title

Community-based *Brain Health Program* to Address Dementia Risk (C-BBHP)

Principal Investigator and Key Staff

The trial is sponsored by Posit Science Corporation (PSC) and is funded exclusively by the National Institutes of Health (NIH). Posit Science will be the recruitment, enrollment, coordinating and data monitoring site for this clinical trial. Key staff and site information may be found below:

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Overview

This is a validation study to evaluate the acceptability, feasibility and preliminary efficacy of the *Brain Health Program,* a multimodal curriculum covering dementia risk factors and evidence-based change interventions. The goal of this study is to evaluate the *Brain Health Program* in individuals with identified risk factors for the onset of dementia and to prepare for a large-scale efficacy trial in this population.

Specific Aims

This study will employ an evidence-based *Brain Health Program* curriculum, which involves a twelve-week, group-administered, personalized program designed to improve brain health in individuals with identified risk factors for the onset of dementia. This is a single-arm open-label feasibility study, enrolling older adults with Alzheimer's disease risk factors in a public health, community-deployed, group-based and individualized multimodal *Brain Health Program* (targeting, among other domains, diet, exercise and cognitive exercise), with a set of baseline assessments intended to characterize the population, and outcome measure to evaluate the usability of the program, as well as preliminary efficacy to reduce dementia risk factors.

Background

Presently, in the U.S. more than 5.7 million Americans are diagnosed with Alzheimer's disease (AD), the most common form of dementia.[2] Prevalence of AD and the associated costs to individuals, as well as the health care industry, continue to grow, as our population ages without an effective therapeutic approach. Fortunately, there have been significant advances in our understanding of the modifiable risk factors for dementia and interventions that can reduce those risk factors. The primary goal of the current grant proposal is to design, develop and implement a small group-based and individualized *Brain Health Program* for older adults at higher risk for onset of AD (i.e., individuals with a family history of AD, genetic predictor, or current AD-related vulnerability) with the goal of promoting greater access to – and usage of – dementia-mitigating interventions intended to extend older adults' functional independence and delay the onset of dementia. We will design the program content in

collaboration with brain health experts at the University of California, San Francisco (UCSF) – Drs. Kristine Yaffe and Deborah Barnes – and work closely with the YMCA of San Francisco to build effective enrollment, administration and tracking strategies in a manner consistent with the successful behavioral change infrastructure, the *Diabetes Prevention Program*, which originated at the YMCA and is now supported by Medicare as a novel public health disease modifying program.

Our community-based *Brain Health Program* (BHP) to address dementia risk is based on the following three key ideas. First, dementia is, in part, a preventable disorder based on specific modifiable risk factors that, in aggregate, account for nearly one-third of new dementia cases every year. Second, risk factors can be addressed with specific behavioral interventions to lower dementia risk, as numerous randomized controlled trials have shown that these interventions can improve cognitive function and reduce dementia risk. Third, access to and usage of brain health interventions can be driven effectively through a *Brain Health Program* that leverages the behavioral change infrastructure of the successful *Diabetes Prevention Program (DPP)*. The DPP is a model curriculum for a series of group-based classes that drives behavioral change in diet/nutrition and physical exercise to lower the risk of type 2 diabetes; developed, validated, and maintained through a close collaboration between non-profits (YMCA), academic researchers and government agencies (CDC). The success of the DPP is grounded on the knowledge that behavioral change is difficult, but may be facilitated best with support from coaches and peers. The DPP has had enormous impact across the US – engaging 325,000+ participants through 3,000+ organizations, reducing new cases of type 2 diabetes by 58%, and reducing health care expenditures by $1.3 billion annually.

A multi-modal *Brain Health Program* delivered similarly to the DPP has the opportunity to significantly lessen the health and economic burdens that dementia places on individuals, families and society. Moreover, this unique program, unlike similar initiatives, will be administered in communities (i.e., not constrained to a healthcare system), supported by fellow members of a community (i.e., group-administered and supported by peers) and individualized (i.e., not *one size fits all*).We will accomplish the objectives of this proposal in accordance with the following specific aims.

In collaboration with subject-matter experts in brain health science (UCSF) and community program development experts (YMCA), we will develop a brain health curriculum in accordance with current guidelines set forth by NASEM, AHA, AAN and the WHO; combined with a delivery model fashioned in the likeness of the successful DPP via collaboration and guidance from veteran DPP administrators (YMCA). Far-reaching awareness of and usage of this curriculum by public (government agencies and community health centers) and private (corporations, healthcare providers) entities could alter the course of dementia – just as the DPP has altered the course of type 2 diabetes.

General Study Design

We will employ a single arm open label feasibility study to assess the *Brain Health Program* in individuals with identified risk factors for the onset of dementia and to evaluate the usability of the program, as well as preliminary efficacy to reduce dementia risk factors.

Approximately 100 participants will be recruited, assuming 20% attrition, to ensure the successful completion of 80 participants. A diagnostic interview will be performed to determine eligibility. Potential participants will be recruited by Posit Science and the YMCA, and will complete an informed consent. After consent, participants will complete screening assessments to determine full eligibility based on the inclusion/exclusion criteria (below). Those who are deemed eligible will complete a baseline assessment. Participants will then engage in the Brain Health Program, a multimodal educational and interactive diet, exercise and computerized cognitive exercise public health program that employs 1-hour weekly group-based training and education regarding modifiable AD dementia risk factors delivered over a 12-week period. Participants will be assigned into a group up to n=20, and participants will engage the Brain Health Program collaboratively, as administered by the program content leader (instructor), while also being monitored and supported by the tech leader (in accordance with the Diabetes Prevention Program model). The classes will be held at a local bay area YMCA location and/or remotely via video conferencing (e.g., Zoom). After completing the 12-week program, participants will then stop using the program materials and will complete post-program assessments to conclude their active enrollment in the study.

Volunteer selection will be equitable: all participants meeting Inclusion/Exclusion criteria will be offered the opportunity to participate in this study regardless of gender, race and/or ethnic origin. Basic demographic data will be collected from participants screened for participation but not meeting study eligibility requirements to ensure that the opportunity to participate in this research study has been extended to all potential participants in an equitable manner.

The protocol will be conducted in accordance with the protocol submitted to and approved by the reviewing Institutional Review Board and approval will be obtained prior to implementation.

Study Population

The study population is comprised of adults, aged 65 years or older, with identified risk factors for the onset of dementia. The study is open to all races, ethnicities, and genders.

Inclusion/Exclusion Criteria

Following informed consent, participants will be screened for the following inclusion/exclusion criteria.

Inclusion Criteria

1. Participants who are 65 years of age or older.
2. Participants who meet criteria for one or more ADRD dementia risk factors
    a. Family history of Alzheimer's dementia (1st degree relative)
    b. Genetic marker (APOE4++)
    c. Subjective or objective cognitive decline (neuropsychological testing; or self-reported "yes" to the following question: "In the past two years, have you experienced a decline in your memory or thinking?"
    d. Poorly controlled hypertension or diabetes
    e. Physical inactivity <150min/week per Surgeon General guidelines
    f. Social isolation, in which participant rarely or never gets social and emotional support when needed
3. Participants who are fluent English or Spanish speakers, per self-report, to ensure reasonable neuropsychological results on key assessments.
4. Participants have access to an internet accessible device (eg. laptop, desktop computer, tablet or smartphone)
5. Participants are able to attend all 12 classes (once a week for 12 weeks) and make up missed classes, as needed
6. Participants are able to travel to/from YMCA location, if they choose to be a part of the in-person group

Exclusion criteria:

1. Inability to provide informed consent
2. Cognitive Abilities Screening Instrument – Short (CASI-Short) scores ≤ 25 (suggestive of cognitive impairment)
3. Participants with untreated psychiatric conditions, including substance abuse/dependence disorders.
4. Participants enrolled in a concurrent clinical trial involving an investigational pharmaceutical, nutraceutical, medical device, or behavioral treatment that could affect the outcome of this study. However, participation in standard treatments (e.g., occupational therapy) or use of prescribed medications (e.g., anti-depressants) is allowable.
5. Participants presently attending classes or courses like this program that is focused on dementia risk and behavior management.

Recruitment

Study participants will be recruited via established and proven processes developed at Posit Science. All materials used for advertising or recruitment will have received IRB approval prior to implementation. Sponsor PI, Dr. Van Vleet will oversee recruitment efforts. *Recruitment/enrollment guidance will focus on operationalizing inclusion criteria in a public health setting*, including 1) promoting the availability of our Brain Health Program (BHP) to community members and referring physicians, 2) describing the benefits and requirements of the BHP to potential participants, 3) screening potential participants for dementia risk factors (requiring 2+ risk factors, one of which is age 65+, fully described in the Inclusion/Exclusion Criteria section). As adapted for use at the YMCA, the BHP will also engage the YMCA member network (e.g., marketing the program through member newsletters and flyers at our various branches), working with local news sources to increase visibility of the program to the broader Bay Area community, and most notably, involvement of local provider networks and related public health agencies. Our partnership with the YMCA will allow us to leverage existing recruiting and enrollment methods used widely across several related programs, including the YMCA led Diabetes Prevention Program.

The YMCA of San Francisco is comprised of 131 physical locations including more than 120 community-based public health centers (e.g., senior activity centers, family resource centers) and is fully adapted to remote video conference-facilitated program administration (due to constraints related to COVID19). Via a similar delivery model as the successful DPP, we will enroll 80 older adults with AD risk factors (up to 20 per course) in BHP courses led by veteran public health program leaders at the YMCA certified in BHP instruction (i.e., completed certification training described in the proposed model curriculum). We will collect feasibility measures, track behavior changes, administer validated proximal outcome measures and aim to demonstrate a reduction in risk factors for dementia via performance on a comprehensive dementia risk factor measure (ANU-ADRI) to establish preliminary efficacy.

Study participants will also be recruited both through the community and through the Internet. Following IRB approval, information about the study aims and procedures may be posted on Google, Facebook, Craigslist, Reddit, Nextdoor app, television, radio, the study website, as well as other web-based recruitment sites; in addition, efforts will be made to recruit participants through retirement and community centers. Participants may also contact the Posit Science team directly via the phone or the internet (email, website, social media, etc.). This approach is equivalent to a convenience sample approach, which is universal in controlled clinical trial recruitment.

To increase diversity, we will leverage advertising methods and social media campaigns proven effective in previous efforts. Social media recruiting methods include Google AdWords (recruitment based on internet searching), Facebook, Instagram, and Twitter ads (recruitment based on demographics, e.g., men and women aged 65 and older, and interests, e.g., health), and organic social media and blog posts. Posit Science has also created targeted Facebook ads amassing thousands of views and app downloads. Leveraging this experience, we shall construct a set of ads that target specific audiences based on geographical location, age, income, net worth, and device used. Facebook has a user database of 2 billion and while the average user tends to be younger and more educated than the general population,[1,2] underrepresented groups are still relatively large. For example, in 2016, 62% of adults over 65 years old had active Facebook accounts.[3] Consumer-friendly study progress updates and brain health content will be communicated to the public via *C-BBHP personalized* Facebook and Twitter accounts, as well as on *C-BBHP* primary website.

To increase yield of search engine and social media outreach, participants in *C-BBHP* will have an opportunity to invite friends and family to participate. Such "snowball" recruiting can be very efficient. For example, the myPersonality study was "seeded" with only 150 users on Facebook, and blossomed to 6 million users over 4 years.[4] Across these advertisements the overall project shall be described as an NIH study on Brain Health with key motivators being, one, an opportunity to learn more about your brain and, two, an opportunity to make a significant contribution to science. All ads will embed a direct link to the app or feature a scannable Quick Response (QR) Code.

Study recruitment materials will describe the opportunity to volunteer for a clinical trial to advance the science and reducing dementia risk. The emphasis of the benefit will be on advancing science to assist others with dementia. Compensation will be described in appropriate terms that are not overemphasized relative to the remainder of the text. No indication of "free medical treatment" will be communicated. All materials used for advertising or recruitment will have received IRB approval prior to implementation. If interested, they will be consented prior to completing any study tasks. The study personnel will manage these efforts and contact individuals that express interest.

Study personnel are required to follow Good Clinical Practices and institutional best practices in the identification and recruitment of research participants. This study will be managed in San Francisco, using standard and established methods.

Description of Informed Consent Process

Potential participants who express interest in the study will speak with a study personnel in-person or over the phone for the pre-screening process to assess for general eligibility and answer any questions. Those who are deemed eligible will be invited to complete the consent process, either in-person or over the phone. For those who are completing the consent process over the phone, two copies of the consent form will be mailed to the participants. During the consent process, participants will read through the consent form with the study personnel. The consent form will include the purpose of the study is to evaluate the effectiveness of the Brain Health Program in improving measures of dementia risk, along with the potential risks and benefits. It will also be emphasized that there is no established health-related benefit acquired through participation and that no medical benefits will be lost if they choose not to participate or drop out of the project at any time, for any reason.

To participate in this proposed study, an individual must be judged capable of understanding the nature of the research and the risks and potential benefits. Special care will be taken to ensure that participants understand each aspect of the informed consent clearly. The qualified study personnel authorized by the Principal Investigator (PI) will review the consent form with the participant and ask the potential participant to explain their understanding of the study and what their involvement in the study would entail. The designated study personnel will discuss the nature of the trial, the purpose of the research, the trial procedures, the possible risks and benefits of participation, confidentiality and the voluntary nature of participation in the trial (emphasizing the participant's right to withdraw from the study at any time). In addition to allowing time for participants to read the consent form, specific contents of the consent form will be discussed with each participant, and any questions will be answered.

Participants may invite a friend or family member to be present in-person or during the call to further discuss their decision to enroll in the study. In addition, participants will be provided the option to defer their decision to discuss their decision with friends or family members, and continue the consent process at a later time. At the participant's request, the study personnel may place them on 'hold' to provide privacy for such discussions. The consent form will include telephone and email contact information for the study personnel and the PI. At any point during or after completion of the study, the participant may contact the study personnel, PI or the reviewing Institutional Review Board to obtain additional information regarding his/her rights as a participant. No study activities will take place prior to completion of the consenting process. When the participant signs the consent form, a fully-executed copy of the informed consent will be provided directly to the participant (paper or electronic copy) and a second will be retained in a secure manner by the sponsor and be available for inspection upon

the request of representatives of the reviewing Institutional Review Board or other relevant regulatory agencies.

Individuals with altered mental capacity who are otherwise not capable of providing independent consent, or who require a Legally Authorized Representative (LAR) to consent, are not eligible for to enroll in the proposed study. We do not anticipate the need for obtaining ongoing consent or for re-assessing capacity. The informed consent form will be changed if increased risk or other adverse events, which will influence a person's willingness to participate or increase their risk of participation, are noted. In such cases, IRB review and approval will be obtained for the revised consent form and active participants will be re-consented.

The consenting study team member will inform participants about compensation for their participation in the study. Specifically, participants will be compensated $10 for completing the *Consent and Screening* assessment visit (V0), $20 for completing the *Baseline* (pre-intervention) assessment visit (V1), $50 for completing the *Immediate Post-program* (post-intervention) assessment visit (V2), and $9 for each weekly session completed during the intervention period (for a total of $108 for 12 weeks). Participants who complete the study in its entirety will earn $188. Compensation will be provided through CashPass, a reloadable debit card through a third-party vendor, CT Payer. All participants will be given their CashPass card (or mailed to a mailing address of their choice) following the completion of the Consent and Screening Visit (V0). Compensation for the V0 visit will be added to the card once the participant confirms receipt of the card. Compensation during the intervention period will occur on a weekly basis and after each assessment visit (V1 and V2). In the unlikely event that a participant must repeat an assessment visit due to administrative assessment or site study personnel errors, participants may be provided additional compensation for that session.

Participants that consent and complete the 12-week program/intervention (n=80)	
Visit	**Compensation**
Consent/Screening	$10
Baseline assessment	$20
Program participation ($9/session, 12 sessions)	$108
Immediate Post-program assessment	$50
Total Participant Compensation	$188

If, for any reason, e.g. technical or CT Payer vendor issues prevent the site study personnel from issuing the reloadable debit card, adding funds to the reloadable debit card, or making any other changes to the debit card, participants may be compensated through a gift card (e.g. Amazon eGift Card, Visa Gift Card, or similar vendor). In such cases, participants are expected to read the associated terms and conditions for the respective gift card. For Amazon eGift Cards, the participant must accept the eGift Card through their email; participants will be notified of this requirement prior to sending the payment, and will be asked to provide verbal consent to receiving payment in this method.

If the participant does not complete the study or withdraws early for any reason, the participant will only be compensated for the study visits and/or treatment sessions they have completed.

Screening Procedures

Following informed consent, potential participants will go through a set of structured interviews, short neuropsychological assessments, self-report questionnaires, and provide basic demographic information, medical and medication history to evaluate their suitability for the study given the inclusion/exclusion criteria. The following measures will be administered to participants at screening:

- Demographics, Medical History and Medications: A structured clinical interview will be used to collect key demographic (e.g. year of birth, age and education) and medical history information, including medical diagnoses or conditions that may be grounds for exclusion (including enrollment in other clinical trials that may be grounds for exclusion).
- Cognitive impairment will be assessed using the Cognitive Abilities Screening Instrument -Short (CASI-Short). Participants with scores ≤ 25 (suggestive of cognitive impairment) will not be eligible for enrollment.

Study Procedures/Research

Study Procedures: Participants will flow through the study in the following manner:

1. *Consent and Screening Visit* (V0)*:* Study staff will discuss study goals, activities, and requirements with the potential participant; complete the informed consent discussion, and if/when appropriate the potential participant will consent to join the study. Study staff will perform required inclusion/exclusion assessments. This visit will last approximately 1 hour.

2. *Baseline Visit (V1):* Participants will complete a set of cognitive and functional assessments, and questionnaires prior to establish baseline performance.

3. *Intervention Period:* Brain Health Program, a multimodal educational and interactive diet, exercise and computerized cognitive exercise public health program that employs 1-hour weekly group-based training and education regarding modifiable AD dementia risk factors delivered over a 12-week period.

4. *Post-Intervention Visit* (V2): Repeat all assessments performed at baseline to assess changes in performance following program use. In addition, participants will be asked to fill out an exit survey to rate enjoyment, usability, perceived benefits, and ease of fit into schedule. The participant will be informed that they will no longer have access to the intervention after this visit.

Retention

A potential problem in any clinical trial is attrition, so every effort will be made to retain participants. We will apply numerous retention strategies as outlined by Robinson et al (2015)[5] such as a clear study identity, consistent contact staff for scheduling, flexible appointment times and reminders, and financial incentives, and successfully applied in our prior studies. Our prior studies of cognitive training (one element of the multimodal brain health program curriculum) have limited attrition to 20%. We have accounted for this rate of attrition in our power analyses and trial simulations. The study requirements will be made clear up front by using easy-to-read study flow charts detailing all study visits with applicable dates. We will further promote retention using best practices such as consistent personnel making regular contact with participants when group sessions or assessments are missed. If we see rates of attrition higher than 20%, we will increase the sample size by expanding recruitment. However, compliance has not been a significant barrier in earlier studies. RCTs applying interventions that engage participants for 10-100 training hours have been conducted in about 5,000 older adults using site-administered programs following this model. 80-95% of enrollees in these studies completed computerized cognitive interventions.[6–9] Importantly, >90% of participants had access to suitable personal computers. Our compliance monitoring is based on established approaches from previous trials.

Intervention adherence, access to computers to complete the program at home, and/or technical difficulties are potential problems. In our prior studies of cognitive training, participants completed training at home with 87% adherence to complete all assigned hours of training. Our prior experience indicates that >90% of our older adult participants own a home computer and have internet access. However, to minimize barriers to participation, we will (1) provide a list of locations of local libraries and community centers that provide free computer and internet use, or (2) delivery of a device, provided availability. We have budgeted for

several Android tablet and will also utilize an existing set of 20 tablets from Posit Science that are available for research studies (contribute to the project at no cost). In previous studies, we found that <5% of older adults have technical difficulty accessing/using training as the programs were specifically designed for use by older adults. In the event difficulties arise, study team members will be available to assist the participant by telephone to access and complete the exercises at home and resolve any technical difficulties. In our experience, older adults are eager to participate and their ability to use a computer has not proven to be a significant challenge.

In the consent process, we will stress that enrolling in the study involves a commitment to complete the required online assessments and questionnaires, and 12 weeks of in-person and at-home study activities. Participants will each be provided with a flow chart of the study visits. The study staff will establish a positive rapport with participants by mailing greeting cards, newsletters, and or email appointment reminders. Telephone support and or reminders will be made at the participant's request. The team at the YMCA of San Francisco team provide the orientation, support and troubleshooting to participants regarding all modalities of participation in the program. When possible, every effort will be made to accommodate participants' schedules for assessment visits. We will indicate for each participant the best manner (e.g., email or phone) and times to contact them to facilitate communication. We will also ascertain information for a secondary contact person for each study participant to facilitate follow-up. If we lose contact for 7 days or more, we will reach out to the participant's secondary contact. All participants will be paid at the completion of each study visit.

All procedures will be overseen by Project PI, Dr. Thomas Van Vleet. Given our patient populations, prior experience, and resources, we are confident we can meet or exceed our recruitment and retention goals.

Assessments.
The complete cognitive assessment battery will be performed at the *Baseline Visit* (V1) and the *Post-Intervention Visit* (V2). For a full list of all assessments and administration times, please direct your attention to *Appendix I* and/or the *Description of Assessments*. All assessments will be administered to all participants, alternate forms of the assessments will be used when available to mitigate test-retest effects. Performance on all measures will be scored, submitted into the study database, and monitored for accuracy and integrity by the PSC Data Monitor(s). Any discrepancies in scoring will be resolved by referring to the raw data collected during the assessment visit(s).

Description of Assessments

Proximal Behavior Change Assessment

Metrics will employ weekly diaries (in the Participant Manual) completed by participants at home to measure how commonly participants engage with each intervention (i.e., physical activity, diet/nutrition, cognitive training, sleep hygiene, stress/mindfulness, social engagement).

Physical Exercise Assessment

The Rapid Assessment of Physical Activity for Older Adults (RAPA) will be used to assess an individual's levels of physical activity. This assessment is a 9-item, self-administered questionnaire regarding current levels of physical activity of adults older than 50 years. RAPA evaluates a wide range of physical activity level, from sedentary to vigorous activity, as well as strength and flexibility training.

Diet/Nutrition Assessment

The Mediterranean-DASH diet intervention for neurodegenerative delay **(MIND)** diet score measures participants' adherence to the MIND diet. The MIND diet is modeled after the Mediterranean and DASH (Dietary Approach to Stop Hypertension) diets with modifications based on findings in the diet-dementia field. Each diet component is scored from 0 to 1 based on frequency of consumption of each food item portion associated with that component. The total MIND diet score ranges from 0 to 15 and is the sum of the 15 component scores. Higher scores indicate greater diet concordance.

Sleep Assessment

The Insomnia Severity Index will be used to measure sleep problems. This assessment is a 7-item, self-rated questionnaire which assesses the nature and symptoms of their sleep problems using a Likert-type scale. Questions relate to subjective qualities of the respondent's sleep, including the severity of symptoms, the respondent's satisfaction with his or her sleep patterns, the degree to which insomnia interferes with daily functioning, how notice-able the respondent feels his or her insomnia is to others, and the overall level of distress created by the sleep problem.

Social Connections Assessment

The PROMIS Satisfaction with Participation in Discretionary Social Activities will be used to measure contentment with leisure interests and relationships with friends. This assessment is a 7-item questionnaire to measure satisfaction over the past seven days. The PROMIS Social Isolation tool will be used to assess perceptions of being avoided, excluded, detached, disconnected from, or unknown by, others.

Stress Assessment

The Perceived Stress Scale will be used to measure individual stress levels. This assessment is a 10-item questionnaire that includes items about the respondent's feelings and thoughts during the last month. In each case, the respondent is asked to indicate how often they felt or thought a certain way. This scale measures the degree to which situations in one's life are appraised as stressful.

Brain Health Assessment

The Cognitive Function Instrument (CFI) will be used to examine brain health. This assessment is a 14-item self-report inventory of cognitive and functional difficulties in every-day tasks (e.g., remembering appointments, managing finances, driving) that is a validated proxy measure of brain health, is sensitive to changes in cognition, and is correlated with the Clinical Dementia Rating global score (CDR).

Dementia Risk Assessment

The Australian National University AD Risk Index (ANU-ADRI) will be used to measure overall dementia risk. This assessment is a questionnaire-based measure that assesses fixed and modifiable risk factors for dementia. Behavioral change driven by progress in the brain health content modules will be captured in the ANU-ADRI measure and provide a straightforward way to assess dementia risk at baseline and post-intervention suitable for use in a community health center (similar to DPP, which uses a single measure - weight loss - as the primary effectiveness measure).

Cognitive Abilities Assessment

The Cognitive Abilities Screening Instrument-Short (CASI-Short) will be used to assess cognitive abilities and identify severity of dementia in individuals. This assessment is a 4-item measure which includes repeating three words, temporal orientation, generating animal names, and recalling three words that do not involve reading, writing, drawing, or arithmetic, which is particularly suitable for individuals with little or no formal education.

Program Usability Questionnaire

- Quantitative program-specific questionnaire with Likert scales (rating 1-5) on questions
    - Understanding of key program features
    - Usability of key program features
- Qualitative free response comments on each question

Description of Intervention Program

Brain Health Program

Participants will engage in the Brain Health Program, a multimodal educational and interactive diet, exercise and computerized cognitive exercise public health program that employs 1-hour weekly group-based training and education regarding modifiable AD dementia risk factors delivered over a 12-week period. Participants will be assigned into a group up to n=20, and participants will engage the Brain Health Program collaboratively, as administered by the program content leader (instructor), while also being monitored and supported by the tech leader (in accordance with the Diabetes Prevention Program model). The classes will be held at a local bay area YMCA location and/or remotely via video conferencing (e.g., Zoom). After completing the 12-week program, participants will then stop using the program materials and will complete post-program assessments to conclude their active enrollment in the study.

The Brain Health Program involves the development of *science content* (the foundation of the BHP), a *model curriculum* (a set of requirements for any program implementation), a set of *in-class activities* (which are designed to teach the essentials of each brain health module to all participants in a class), and a set of *at-home activities* (which are *individualized* activities unique to each brain health module assigned to participants depending on their assessed brain health needs). All BHP related materials will be constructed in a manner consistent with the successful DPP model, to ensure high levels of participant engagement/satisfaction based on learnings from years of experience with this program.

Brain health activity modules: The core in-class materials will establish a common knowledge of best practices in brain health by covering each risk factor and its relationship to dementia and teaching the use behavioral interventions targeting each risk factor. The in-class materials will comprise both instructor-facing materials (e.g., training materials on the science content, example scripts for in-class discussions) and participant-facing materials (e.g., activities, workbooks). The at-home materials will comprise participant-facing materials (e.g., activity logs, activity suggestions). This content will be developed in close collaboration with experienced facilitators. BHP coaches – trained and certified in the curriculum content and administration by experienced facilitators and the director of the YMCA DPP - will provide participants with several options for each targeted risk factor, and goals will be individualized to preferences, barriers, resources and motivators to optimize intervention adherence. The development of the curriculum will include the adaptation of existing DPP approaches to track activity adoption and adherence for each intervention. As adapted for use with the YMCA and Posit Science as collaborators, interventions will focus on YMCA resources (which provides access to fitness centers and senior activities) and involving Posit Science (which provides access to BrainHQ).

Coaching guidance: The curriculum will include instructor-facing training and materials to ensure that instructors can operate as successful brain health coaches. This material will focus

on motivational interviewing, coaching, and include guidance on how to talk with participants to understand their personal goals, their life circumstances, and the issues that can enable and prevent them from beginning and then adhering to engaging in brain healthy activities. After baseline assessments, the BHP administrators will use a standardized procedure to develop an individualized *dementia risk profile* for each participant that will include a graphic display of the targeted risk factors showing areas where the participant is doing well (green), areas where they can continue to improve (orange), and areas that are of particular risk for them (red). In the context of the first meeting, participants will review their risk profile and develop an initial personalized risk reduction action plan. In parallel, BHP administrators will elicit participants' values and motivators to reduce their risks and will use a decisional balance process informed by motivational interviewing and confidence ratings to help them choose 1–3 specific, achievable risk reduction steps that they are most ready to adopt. Participants will be provided with tools to track their progress. At each subsequent session, BHP administrators will review progress, problem-solve barriers, and set new goals as needed. Following detailed protocols, the BHP administrators will provide support or refer participants for professional help if participants experience distress related to their risk profile. BHP administrators will follow a standard protocol for delivering the interventions that allows for personalization of the specific risk reduction action plan; these plans will evolve over time according to participant progress, motivation and preferences or newly identified risk factors. Staff will use a tracking database to record information for each participant, including date and time of session, identified risk factors, motivational barriers and important values, and the outcome of discussions around developing goals.

Laboratory Specimens

There are no laboratory specimens collected for this study.

Sample Size Justification

Because this is a usability/feasibility pilot study, sample size is not determined from statistical tests of outcome measures. Sample size justification is based on a balance of having a sufficient number of participants to ensure diversity of participant experience against having a number that exceeds the ability of a user-experience designer to effectively debrief participants and synthesize their diverse experiences into actionable guidance for a next round of product improvements. In our experience, usability/feasibility trials are most effective with at least 6 and no more than 20 participants, for a total for n-size for the project at n=80.

Data Analysis

Primary outcome of this study is the Net Promoter Score, which is calculated based on responses to a single question: How likely is it that you would recommend Brain Health Program to a friend or colleague? The scoring for this answer is based on a 0 to 10 scale. Those who respond with a score of 9 to 10 are called Promoters, and are considered likely to exhibit value-creating behaviors, such as making more positive referrals to other potential program participants. Those who respond with a score of 0 to 6 are labeled Detractors, and they are believed to be less likely to exhibit the value-creating behaviors. Responses of 7 and 8 are labeled Passives, and their behavior falls between Promoters and Detractors. The Net Promoter Score is calculated by subtracting the percentage of customers who are Detractors from the percentage of customers who are Promoters. For purposes of calculating a Net Promoter Score, Passives count toward the total number of respondents, thus decreasing the percentage of detractors and promoters and pushing the net score toward 0. Net promoter score of >20 would lead us to conclude that the usability/feasibility study had been successful.

Secondary feasibility outcomes include, fidelity measures e.g., observing that 1) participants attend 80% of intended sessions, 2) 80% of participants state that they would like to continue the program activities/interventions.

Data Management

All study-related data will be recorded into a secure, web-based electronic case report form (eCRF) through REDCap Cloud. This system meets all relevant privacy and security standards for electronic clinical trial data entry and storage, as well as the Health Insurance Portability and Accountability Act (HIPAA) standards for confidentiality and privacy.

Following consent, each participant will be assigned a standardized Participant Identification Number (PIDN) composed of three digits to identify the site and 3 digits to identify the participant. The digits will begin with “xxx001” for the first consented participant and ascend thereafter. All eCRF data entry will use the PIDN only and not the participant name; Posit Science will be expected to maintain secure documentation that links the participant name and PIDN link.

Posit Science will be a single recruitment and enrollment site. Data collected by Posit Science will be transcribed into REDCap Cloud. Only authorized personnel will be granted access to REDCap Cloud and enter CRFs directly into the study database. Study personnel will upload de-identified data and de-identified source documentation into the study database for data monitoring. Periodic analysis of each data field (across all cases) will be performed by the PSC Clinical Data Monitor in order to examine the expected distributions of data, and to identify outliers for possible data mistakes. Particular attention will be paid to the following:

- *Data Cleaning:* All CRFs are automatically subjected to initial checks for omitted data and data inconsistencies. These deficiencies are required to be resolved at the point of data entry to prevent errors from entering the system.
- *Data Editing:* Each data record is evaluated on a regular interval. Any discovered error is then referred to the Investigator Designee by email, telephone, or secure communication through the Electronic Data Capture system via the Data Monitor. The Investigator Designee will review the queries and make the corrections through the eCRF system. All such changes are automatically logged to allow a complete audit trail and recovery to any point in the change log if required.
- *Data Update:* The cycle of data edit will be ongoing until all the data are clean. If further data entry or source documentation errors are discovered, corrections will be made at that time through the eCRF system.
- *Data Back-up*: The eCRF system employs an automatic continuous replication system to ensure that all data including change logs and access logs are replicated to two independent remote servers. At any point, the system can emit the entire store of eCRFs as paper CRFs for offsite storage or auditing if required.

We will take all standard and appropriate steps to protect the privacy and confidentiality of participants in this trial. At enrollment, participants will be assigned a PIDN as described above, and all study data collection derived from that participant will be coded by PIDN. All eCRF pages, including those with demographic as well as assessment data, will have the PIDN on them rather than the participant's name. The eCRF system runs on remote servers not physically accessible to any study staff; all electronic access to the eCRF system is logged and regularly reviewed for any inappropriate access. All study related paper materials will be stored in locked file cabinets inside of locked rooms when not in use. The study program will not collect or store any personally identifiable information on the laptop, mobile devices, or on PSC servers.

Confidentiality

Participation in research may involve a potential loss of privacy. All records and documents pertaining to participation in this study will be handled as confidentially as possible. However, absolute confidentiality cannot be guaranteed.

All information collected on paper will be kept in areas of limited access available to approved site study personnel only. Any physical records will be maintained in locked cabinets in locked offices, until the appropriate time at which documents may be shredded. Access to these cabinets will be limited to the study team.

Electronic data will be password protected and securely stored. The servers maintained by Posit Science are HIPAA compliant, secure servers that will require permissions from the study team to access.

Confidentiality will be maintained throughout the entire project period. Participant names will not appear on data records, or on any progress reports or publications, and a unique subject ID will be used to label each participant's data. Electronic data collected through RedCap Cloud are password-protected and stored on a secure network. Data collected through the web-based program does not include geographic location data. IP address data is stored only in memory and in request logs, and is used for technical support and troubleshooting, but not persisted with the participant's data. Data are uploaded using SSL over encrypted channels to secure servers every 30 seconds. Therefore, security of electronic data is ensured at the level of the server, the user, and the database.

Representatives of the Sponsor, the reviewing Institutional Review Board, and the National Institute of Health will be permitted to audit study-related data and related materials. Personally identifiable information will not be used in any study reports or publications; data contained in these will only be presented or published in aggregate form.

Disposition of Data

The following study records will be retained by the site for minimum of two years following the conclusion of the study:

1. signed participant informed consent forms,
2. patient medical records, including all significant diagnostic reports,
3. supporting documentation of all adverse events,
4. completed eCRFs, and;
5. study related correspondence and study reports.

The sources of the research material will be data collected strictly for research purposes. Participants will be carefully screened for contraindications prior to participation. All data are coded so as not to identify any given participant. Data will be recorded in REDCap Cloud, a secure, web-based software application designed to support data capture for research studies. REDCap Cloud is designed to comply with GCP and HIPAA-regulations, including Title 21 CFR Part 11. Data files will be retained for a minimum of two years after the study's completion. A list of names, email addresses and telephone numbers of all participants will be stored electronically on password protected computers with access limited to authorized study personnel for purposes of contacting the individual participants. The types of data collected will be: data concerning medical history, behavioral data from neuropsychological assessments, and self-reported questionnaires.

Paper records from this study must be stored in locked areas of limited access. During remote procedures, documents will be stored by the respective study personnel in a safe location with limited access until the documents can be shred or transferred to the Study Site. Electronic data must be securely held with restricted access available to personnel on a need-to-know basis only. Google Team Drive access will be restricted to authorized study personnel by invitation only.

Study staff will comply with the requirements (i.e., the enrolling institution) data storage and disposition policies at the conclusion of the record retention period.

Sharing Research Results

We will share the overall study results with all participants who enrolled in the study when such results are completed and accepted for publication. We will create a lay-person oriented summary of study results to be emailed to each participant at the end of the trial. Any participant screening positive for any of these medical issues will be referred to ensure they are receiving appropriate treatment. We do not intend to share individual assessment data with participants, as the assessment battery is not intended to be the type of comprehensive battery a rehabilitation psychologist would use to guide treatment. Any participant interested in such comprehensive assessment will be referred to an appropriate clinician.

Foreseeable Risks and Risk Management

This study will be performed with the approval of an IRB. All research studies conducted at Posit Science are submitted for review to the WCG IRB, an independent IRB that provides services for academic and non-academic institutions. WCG IRB is accredited by the Association for the Accreditation of Human Research Protection Programs (AAHRPP) and is capable of serving as the single reviewing IRB.

The following are our planned procedures for protecting against or minimizing potential risks, including risks to privacy of individuals and confidentiality of data, and an assessment of their likely effectiveness. This research does not involve vulnerable populations, as defined in the DHHS, Subparts B-D, i.e., pregnant women, human fetuses and neonates, prisoners, and children.

Participants may find the behavioral testing and/or Brain Health Program boring or frustrating, but there are no other foreseeable mental risks. Every effort will be made to reduce participants' anxiety about study procedures. Assessments will be discontinued if a participant reports becoming distressed. Study participants will be encouraged to report any adverse effects occurring during the duration of the study; if participants become uncomfortable

during any part of the study, they may decline to do any task or set of tasks, or withdraw from the study entirely at any time.

This study poses extremely low risks to participants. This study will use routine, standardized, non-invasive measures, psychological tests of cognition, and functional assessments. The risks involved in being assessed with noninvasive clinical and neuropsychological tests are minimal. It is possible that some patients may experience boredom or frustration with some of the testing or training materials. Some people may feel stressed, anxious, and/or fatigued but this generally resolves after testing or training.

Additionally, the following foreseeable risks are described in the consent form, as will the following measures be taken to minimize such risks:

- *Diagnostic interview and self-report measures*. Participants may feel uncomfortable or embarrassed due to sensitive questioning about their psychiatric condition and medical history during the diagnostic interview or on self-report measures. Participants will be reminded during each appointment that their participation in the study is voluntary and that as such, they are not required to complete any assessments and may skip individual questions or assessments entirely. However, if participants skip questions related to inclusion/exclusion criteria, they may not be able to participate as we are not able to confirm full eligibility for the study.
- *Discomfort During Assessments:* Assessments may be fatiguing for some individuals, particularly for those with persistent cognitive symptoms. To minimize this potential discomfort, breaks are encouraged and scheduled within the session. In the event that a participant appears to be under undue strain, test sessions are discontinued.
- *Lack of Assessment Feedback:* Participation in this study does not include feedback to participants on their individual assessment results. Though participants are informed of this policy during consent, some participants may find the lack of feedback to be frustrating.
- *Computer Use:* The following risks may be reasonably anticipated as the result of computer use: fatigue, mood complaint, headache, tremor, eye strain, neck/shoulder discomfort, leg/hip discomfort, arm/wrist discomfort, back discomfort, headache and sleep difficulty. To minimize the fatigue participants are encouraged to sit ergonomically correctly while completing study activities on their device. In addition, assessment and self-report sessions may be paused at any time and participants are encouraged to take breaks.
- *Loss of Privacy*: The most significant risk to the participants are those that would follow a breach of confidentiality and the disclosure of clinical information. Participation in any research study, including this one, may involve a loss of privacy, and absolute confidentiality cannot be guaranteed. Procedures designed to maintain data

confidentiality include (1) formal protocol training sessions for all study team members emphasizing the importance of confidentiality, (2) adherence to specific procedures developed to protect participants' confidentiality, and (3) formal mechanisms limiting access to information that can link data to individual participants. One reason for breaking confidentiality is that the study personnel are required by law to report cases of physical or sexual abuse to local law authorities; and another is that despite all procedures, an error may occur. To mitigate this risk, data forms that include identifying information, with the exception of dates assessments are completed, date of birth, and dates associated with other data collected, and personally identifying information volunteered by participants in the Zoom chat forum, will be kept in locked cabinets or secure servers at the site, and accessible only to authorized study personnel. Only the unique ID number, assigned by the study coordinator, will represent participants during participation in the study. In the Zoom platform, participants will have the choice to self-identify with their first name or an alias. To facilitate tracking, a password-protected computer file will be maintained containing the identity of participants, their ID numbers, and contact information. This file, however, will contain no clinical data. Electronic data will be password protected and stored on a secure network. All data keys will be stored separately and securely. Only study personnel will have access to the study data. No participant names will be used in study reports or publications.

- *Risks of Email Communication*: This study will rely on the use of email communication between study personnel and research participants as part of their participation in the intervention. Site study personnel may be expected to email participants about their upcoming appointments or communicate other important study information. Participants may also ask questions of site study personnel using email. There are risks associated with email communication, and these risks increase when emails are sent without an encryption service. Risks of sending or receiving unencrypted emails include, but are not limited to:
    - Others can intercept messages
    - If messages are sent or received on an employer-owned device, the employer may have the right to save and read the messages. The internet or cell-phone provider may also have the right to save and read email messages
    - A copy of the message may be saved on a device or computer system, even if it is deleted
    - If an email address is not typed correctly, it can be sent to the wrong person
    - Emails can spread computer viruses

- Others may be able to access messages on devices that were lost, stolen, or thrown away
- If a participant changes emails without notifying site study personnel, they may miss communications.

To address factors that contribute to non-compliance we have incorporated several elements of flexibility in the Brain Health Program to accommodate the challenges that older adults may encounter. These risks and associated accommodations will also be discussed with the participant.

- *Fatigue:* Participants may report symptoms of fatigue. To accommodate this issue, participants will be encouraged to take a short break and continue where they left off. The participant may discuss this with the study personnel, who will work out a program schedule that is feasible, given the participant's experience.
- *Location of Use*: For those who are participating remotely, participants partake in the program and complete the study activities remotely, at different locations, as convenient.
- *Variable Number of Total Number of Sessions*: We expect that some participants will not be able to complete all study activities. To accommodate this, we will be understanding of the participants' circumstances and explain to participants that the study will benefit from them doing as much of the program as their schedule permits. The study personnel will work with them to generate a feasible schedule, given the participants' life circumstances, as appropriate.
- *Cessation of Program While Continuing Participation in the Study*: In some cases, a participant may wish to stop or minimize use of the program going forward, while remaining in the study. Potential reasons for this decision might include a change in work circumstances, a change in residence health/psychiatric issues, family/personal issues, or a lack of interest in program activities. However, the participant may want to meet their personal commitment to the basic scientific research of the study. In such cases, after discussion with the study personnel, the participant will be permitted to cease using the program, and be scheduled for post-intervention assessments at the appropriate time relative to the baseline assessments, given that the participant has met the minimum number of sessions required to complete these assessments.

Several of these options in aggregate are likely to lead to variation with regard to the total number of sessions completed. Although this is not ideal, we believe that this is the correct approach given that such flexibility will allow more participants to join the study (compared to no program use flexibility) and may produce less drop-out. In addition, this approach has the

value of more closely mimicking real-world use of the program, increasing the prospective validity of the study.

Participants will be encouraged to report any adverse effects occurring during the duration of the study to the study point of contact.

PSC does not provide compensation for research-related injuries and will not reimburse or pay medical expenses for the treatment of research-related injuries.

Potential Benefits

One level of benefit will be described to participants:
Benefit to Science: This study will provide important scientific knowledge about the potential of a preventative public health program - the Brain Health Program proposed here – to help reduce dementia risk factors (per the ANU-ADRI).

Study Personnel

Key study personnel at PSC include:

- Principal Investigator (Dr. Van Vleet) is responsible for the overall design of the study protocol and data analysis plan as well as the eventual publication of the result (with input and authorship from all investigators. He will ensure coordination of the project to meet milestones and deliverables; working directly with the engineering team (Greg Sabatini), as well as designing Phase I trial implementation and evaluation outcomes. He will also have full responsibility for the direction and oversight of the program materials, as well as revisions to the supporting software and the final build of the program web-portal. He will supervise research personnel, administration of all project-related activities, project organization, ensure data integrity, and coordinate activities of the members of the research team. He will meet regularly with the entire project team to ensure trial success.
- Co-Investigator (Dr. Mahncke) will work closely with Dr. Van Vleet in designing and evaluating the results of the trial, as well as participating in decisions regarding the development of the product. As director of the company, he will oversee the proper implementation of the study, as well as the promotion of the product directly to consumers, licensing to third party companies or recruiting third-party partners.
- Clinical Trials Manager (Sarah-Jane Grant) will provide oversight and support the Research Coordinator with the implementation of this protocol. She will collaborate with and advise the site to organize activities related to deployment, recruitment, scheduling and testing. She will report directly to Dr. Van Vleet.
- Research Coordinator (Kathy Wannviroj) will carry out the administrative tasks required for this proposal, from IRB procedures to database monitoring, to advising

site staff on participant support. She will also collaborate with and advise the site to organize activities related to deployment, recruitment, scheduling and testing. She will report directly to Sarah-Jane Grant.

Dr. Van Vleet, Dr. Mahncke, Ms. Grant, and Ms. Wannaviroj disclose a conflict of interest: all are paid employees of PSC and shareholders, and could benefit if this intervention for dementia is shown to be an effective treatment in this trial.

This conflict will be mitigated by ensuring that the complete investigator team, including Dr. Van Vleet, Dr. Mahncke, Ms. Grant, and Ms. Wannaviroj and other study staff, have joint and overlapping responsibility for the design of the protocol, the execution of the protocol, the *a priori* design of the data analysis plan, the execution of the data analysis plan, the interpretation of the study results, and the authorship of publications emerging from the study. In addition, this conflict of interest will be disclosed to all study participants, and through standard mechanisms for all publications.

Withdrawal from the Protocol

Study participants may withdraw from the study at any time, for any reason, or for no stated reason. We anticipate that a common reason for study withdrawal will be the time required to complete the program. For participants seeking to withdraw for that reason, we will offer the alternative of discontinuing of the program and, if appropriate, scheduling and completing the post-assessments. The data analysis plan is structured so that their data will be valuable even if they do not complete the intended number of lessons. Participants who still wish to withdraw following that option will withdraw. Across all reasons for withdrawal, we will ensure an orderly end to the participant's involvement in the study by notifying the participant, identifying any issues with study conduct or adverse events that are relevant, and arranging study compensation for study activities that the participant completed.

In rare cases, a Principle Investigator may decide to prematurely discontinue a participant's involvement in the study for any of the following reasons:

a) Safety,
b) Participant non-compliance,
c) A change in circumstance that would prevent completion of protocol-required assessments,
d) Participant relocation to an area that, due to great distance, would prohibit a participant from receiving follow-up at the study site,
e) Participant displays inappropriate behavior toward study staff members or other participants,
f) Participant is hospitalized for psychiatric reasons;
g) Loss of funding, or;

h) A clinical determination, by the Principal Investigator, that continuation in the study is not in the participant's best interests.

Across all reasons for withdrawal, we will ensure an orderly end to the participant's involvement in the study by arranging for the site study coordinator to conduct an informational interview with the participant to understand the reasons for study withdrawal and identify any issues with study conduct or adverse events that are relevant, and arrange study compensation for sessions that the participant completed.

Modifications to the Protocol

Any significant changes to the protocol, including changes to inclusion/exclusion criteria, changes to assessments, changes to recommended levels of program use, changes that could potentially increase risk to study participants, and additions or removals of study site(s) will have to be approved by the grant recipients/PI (Thomas Van Vleet), any such changes will also be discussed with and approved by the Institutional Review Board in the form of a protocol amendment prior to implementation.

Protocol Deviations

Protocol deviations will be noted and recorded by study staff if they detect the deviation. All protocol deviations will be reviewed monthly and signed off by the PI (Thomas Van Vleet); any such deviations suggesting systematic problems with the protocol procedures as implemented by the study site will be reviewed and corrective action determined and implemented by the study site.

Reporting of Serious Adverse Effects & Unanticipated Device Effects

There is no significant risk to using the programs in this study, beyond the minor discomfort and tedium risks of using a computer or tablet. An event that is serious must be recorded on the case record and requires expeditious handling to comply with regulatory requirements. Any adverse events attributable to the study activities and/or the program will be reported to the reviewing IRB within 10 days of occurrence or detection. The NIA Project Officer (PO) will be informed of any actions taken by the IRB as a result of such adverse events. In the unlikely case of study-related serious adverse events (SAEs), they will be reported to the IRB and NIH PO within 48 hours of the study's knowledge of the event. In addition, an interim analysis will be performed in order to determine whether a change in the risk/benefit ratio has occurred. If so, this change will be brought to the attention of the reviewing IRB for review, current and future participants will be notified of this change, and stopping rules will be considered. The summary of SAEs will be reported to the NIA PO quarterly.

The study team will ask about any deterioration in symptoms during each contact with participants, and will be alert to any volunteered episodes of suicidality. All events of this nature will be documented on a standardized form and will be classified by the PI to their degree of seriousness and their relationship to the study protocol. Finally, we will also conservatively follow guidelines for medical devices (i.e., computerized cognitive training) in the reporting of adverse events in this trial, which defines unanticipated adverse device effects (UADEs) in The Code of Federal Regulations in 21 CFR 812.3(s) as any serious adverse effect on health or safety associated with, a device, if that effect, problem, or death, was not previously defined in nature, severity or degree of incidence in the investigational plan or application (or supplementary plan or application). Furthermore, an effect is classified as an UADE if it is judged by the PI to be a serious problem associated with a device that is related to the rights, safety, or welfare of participants. We will operationalize this definition of a serious problem as one that results in any of the following outcomes: death, life-threatening situation, inpatient hospitalization atypical of the participant's diseases condition, persistent or significant disability/incapacity; or any other adverse event that, based upon appropriate medical judgment, may jeopardize the participant's health or the health and well-being of all participants enrolled in the study. The study coordinators and clinicians will ask about any UADEs during each contact with participants, and will be alert to any volunteered UADEs. All UADEs will be documented and will be classified by the PI to their degree of seriousness and their relationship to the study software. All UADEs, whether or not we believe them to be related to the protocol, will be reported to the IRB and NIA PO within 48 hours of the study's knowledge of the event.

All deaths will be reported to the IRB and NIA PO within 24 hours of the study's knowledge of death.

Study participants may withdraw from the study at any time, for any reason, or for no stated reason. We anticipate that a common reason for study withdrawal will be the time required to complete the program. For participants seeking to withdraw for that reason, we will offer the alternative of discontinuing of the program and, if appropriate, scheduling and completing the post-assessments. The data analysis plan is structured so that their data will be valuable even if they do not complete the intended number of lessons. Participants who still wish to withdraw following that option will withdraw. Across all reasons for withdrawal, we will ensure an orderly end to the participant's involvement in the study by notifying the participant, identifying any issues with study conduct or adverse events that are relevant, and arranging study compensation for study activities that the participant completed.

Continuing Review and Final Report

In accordance with NIH SBIR guidelines, a continuing review report(s) as well as a Final report will be submitted via eRA Commons.

The knowledge of any pending compliance inspection/visit by the FDA, Department of Health and Human Services Office for Human Research Protection, or other Government agency concerning clinical investigation or research, the issuance of Inspection Reports, FDA Form 483, warning letters, or actions taken by any Regulatory Agencies, including legal or medical actions, and any instances of serious or continuing noncompliance with the regulations or requirements will also be reported.

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Appendix I. Table of Assessments

	Consent and Screening Visit (V0)	Baseline Visit (V1)	BHP Program Orientation and Intervention Period for 12 Weeks	Post-Intervention Visit (V2)
Informed Consent	X			
Inclusion and Exclusion Criteria	X			
Demographics	X			
Medical History	X			
Medications	X			
Cognitive Abilities Screening Instrument – Short (CASI-Short)	X			
Australian National University AD Risk Index (ANU-ADRI)		X		X
Rapid Assessment of Physical Activity for Older Adults (RAPA)		X		X
MIND diet score		X		X
Insomnia Severity Index (ISI)		X		X
PROMIS Satisfaction with Participation in Discretionary Social Activities; and Social Isolation tool		X		X
Perceived Stress Scale (PSS)		X		X
Cognitive Function Instrument (CFI)		X		X
Program Usability Questionnaire				X
Medications, Since Last Visit		X		X
Adverse Effects		X		X
Participant Manual			X	
UADE				X
Study Exit				X

Appendix II. Sample Debit Card Information

Attached separately.