**Title**: MSIM: Mobile Simultaneous Aerobic Exercise and Memory Training Intervention for Amnestic Mild Cognitive Impairment (mSIM)

**ClinicalTrials.gov ID**: NCT04185298

**Document Date:** 10/26/2021

**Study Title:**
**Mobile Technology-Based Simultaneous Aerobic Exercise and Memory Training Intervention for Older Adults with Mild Cognitive Impairment**

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## 1. BACKGROUND

According to the World Health Organization, 50 million people worldwide have dementia with an annual incidence of 10 million new cases every year[1]. Individuals diagnosed with mild cognitive impairment (MCI), specifically those with primary amnestic/memory loss (aMCI), are one of the highest risk groups for conversion to dementia, with approximately 34% developing dementia within one year[2]. Prevention strategies for cognitive decline are critical during this risk period[3]. The lack of medical treatments able to stop or slow down the development of dementia has shifted the research field focus towards the urgent need to develop preventative, non-pharmacological approaches and psychosocial therapies for people at-risk for the disease.

Both cognitive remediation and exercise training strategies have been developed for interventions in MCI patients and show small but not yet definitive improvements on cognition[4,5]. A large body of evidence suggests that regular physical exercise can improve cognition, specifically enhancing memory, attention, and executive functions in older adults[6,7] and is associated with a 35–38% reduction in the risk of cognitive decline and dementia[8]. However, a recent meta-analysis of exercise interventions in older adults concluded there is not yet enough evidence to support the definitive benefits of exercise alone on cognition[9]. Cognitive remediation interventions that target restoration of cognitive functioning through compensatory cognitive skills training in MCI patients show a clear advantage over the more generalized computer-based drill and practice neurocognitive training programs[10]. In contrast, studies that implement both targeted neurocognitive and exercise training interventions

(rather than each alone) are showing greater promise on improving cognitive function in older adults[11, 12] as well as having real-world functioning benefits in MCI and dementia[1314]. Study PI (McEwen) and Co-I (Merrill) recently published the first study that attempted to leverage the synergistic benefits of simultaneously performing compensatory memory skills training during aerobic exercise (stationary aerobic cycling; SIM training) in older adults with subjective memory impairments[15]. In our clinic-based, pilot RCT we validated the feasibility of the SIM training in older adults and found that it was more impactful on improving memory, attention and reasoning skills than in a group that performed the training separately.

Unfortunately, older adults experience extensive barriers to engaging in the aforementioned preventative practices due to mobility constraints, lack of access, and low motivation to engage in activities that are not tailored to their needs. Delivering low-cost, effective, prevention-focused interventions to cognitively impaired older adults could reduce these barriers by increasing ability, motivation, and adherence. Prior technology-enabled interventions to increase physical activity levels have included providing older adults with fitness trackers[16]. One study conducted in older adults found that the provision of a Fitbit monitor alone to objectively track one's own activity leads to increased physical activity levels beyond those of whom are concurrently receiving coaching prompts (via text message)[17]. T Consistent feedback through notifications, as well as integration wth social support and competition through "leaderboards" and "rewards," encourage participants to exercise, which led to overall increases in physical activity. [16]. Together, studies on this technology suggest that goal setting is effective for increasing physical activity. A comprehensive review of activity trackers used in research studies "that having a fitness tracker could actually be an intervention in and of itself[17]" and concluded that the use of fitness trackers, show a great deal of promise for measuring and encouraging physical activity. Therefore, for this pilot RCT, we will provide our "control" arm with continuous activity monitoring and provide instructions and training on device and feature usage. We anticipate an increase in their physical activity levels even without the rigorous schedule and program that our "mSIM" group is receiving.We are primarily trying to compare our intervention with "standard of care," which normally includes clinicians advising MCI patients to increase their physical activity habits.

Animal studies provide important mechanistic insights into the benefits of exercise in improving cognition. Specifically, aerobic exercise increases the density of blood capillaries (angiogenesis) and birth of new neurons (neurogenesis)[18,19]. Skilled-based exercises increase neuronal sprouting and synaptogenesis, important for re-establishing brain circuits impaired in disease states and required for normal cognition[20,21]. However, no study has been conducted in aMCI patients that explores the effects of memory skills training during aerobic exercise on cognition and functioning.

The underpinnings of exercise and cognitive training-induced memory improvements may lie in neurochemicals such as brain-derived neurotrophic factor (BDNF) and norepinephrine (NE). BDNF is the most widely distributed neurotrophin in the brain, with the highest density found in the hippocampus. BDNF can modulate neurogenesis, neuronal plasticity, and survival[22,23]. Furthermore, increased central BDNF expression has been causally linked to the learning and memory enhancement that is seen in both cognitive training and

physical exercise interventions with animals[24–26]. BDNF decreases with aging[27] and increases with physical activity and associated memory improvements in older adults[28] and those with MCI[29]. NE is released by the locus coeruleus (LC) during physical activity and may be facilitating these effects also. The LC is the main source of NE during physical activity. This activates the reticular system, thus increasing arousal levels, aiding to vigilance and attention during cognitive training[30]. LC neuronal loss is prominent in AD neuropathology and contributes to cognitive impairments[31]. Reduced concentrations of NE are believed to occur early in the course of the illness as seen in MCI patients[32]. Activation of the NE system during exercise may facilitate the long-term impact of memory training .

Electroencephalography (EEG) is a non-invasive method of measuring the electrical activity of the brain. Quantitative EEG (QEEG) is a method for recording and analyzing EEG data efficiently in a clinical setting. The brain has many brain rhythms, each associated with different mental states. As more populations of neurons act in greater synchrony, the amplitudes of these rhythms increase. The Alpha rhythm is 8-12 Hz and was originally identified as a resting state/idling brain rhythm. More advanced models show that Alpha is important for the inhibitory tone of the brain. Higher alpha power means more brain systems are being inhibited, whereas a low Alpha power means the brain is experiencing less inhibition, allowing for the engagement of more active states[33]. Alpha plays a critical role in the timing of neurological and cognitive processes[34] including working memory, attention, and anticipation. These and more decline with age and neuropathology[35]. Peak Alpha frequency slows with age and is correlated with cognitive decline. In older adults with poorer cognition, there is a greater degree of slowing in the Alpha band[36,37].

GABA is the neurotransmitter in the brain primarily responsible for inhibition. Animal studies show potential mechanisms by which exercise may improve cognition by restoring inhibitory tone. Mice that carry the APOE4 gene are, like humans, at risk for Alzheimer's. These mice have hyperexcitable brains when compared with normal mice[37]. They experience dysregulated and increased brain activity because they do not respond to their native GABAergic networks as well as normal mice. Another study, this time in aged rats, demonstrated that an aerobic fitness intervention was able to reduce the age-related hyperactivity in the rat brain and worked through improving the GABAergic system[38]. Increases in peak Alpha frequency may be a result of the mSIM intervention in humans and these findings could be mediated by the normalization of GABA-related signaling post intervention.

## 2. OBJECTIVES OF THE STUDY

One major study objective is to develop and conduct beta testing of a web-based application that will deliver a mobile-based simultaneous exercise and memory skills training program (mSIM) for aMCI patients. A second major objective of the study is to evaluate the efficacy of mSIM on memory performance and everyday functioning using two study arms: Group 1 or the activity monitoring control group (CON) and Group 2 or the activity monitoring plus

immediate treatment with the mSIM intervention group (mSIM). The CON will serve as the control group and be recommended to wear a Fitbit to track their physical activity habits, which has been shown to be an effective intervention to increase physical activity levels[16,17], throughout the duration of the intervention. They will also report one week's physical activity via phone calls with research staff at baseline, mid-intervention, and post-trial. Study objectives include measuring treatment related changes in quality of life and cognitive and functional abilities.

A third major objective of this study is to test mSIM treatment response on concentration levels of peripheral biomarkers [BDNF and NE] and neural markers (eg. peak alpha frequency) measured with QEEG. Study objectives include testing the relationship between increased peak alpha frequency, concentrations in BDNF and NE, and improvements in memory.

An exploratory objective of this study is to test treatment response to the mSIM intervention using magnetic resonance imaging (MRI). We will analyze functional resting state fMRI, structural MRI, arterial spin labelling (ASL) and diffusion tensor imaging (DTI) data for this study. We hypothesize that patients in the mSIM intervention, compared to the controls, will have increased default mode network (DMN) connectivity, increased frontal and temporal volumes, and increased temporal perfusion. We will seek to examine exploratory measures on structural connectivity using DTI. It is believed that the white matter deficits precede grey matter neuronal loss in preclinical AD since neuronal degradation begins in neuronal periphery, which consists of axons and dendrites. A meta-analysis of 41 DTI studies in MCI and AD[39] revealed almost all white matter tracts are implicated in the disease state. Limbic fibers, which have direct connections to the medial temporal lobe, had reduced integrity. Additionally, the cingulum bundle, mainly within the medial temporal lobe, the splenium of the corpus collosum, and the fornix were all reduced and were correlated with severity of reduced cognition as implicated on the MMSE and memory tests. The left cingulum bundle (within the hippocampus) showed decreased FA and increased MD, which were specifically associated with worse symptoms and ADAS-cog scores. Interventional exercise research in older adults has revealed that short-term exercise interventions have a positive benefit on white matter integrity in the corpus collosum.[40] Therefore, we hypothesize that the mSIM intervention will increase white matter integrity especially in the cingulum bundle, corpus collosum, and the fornix.

## 3. STUDY DESIGN

### Overview

Participants with primarily amnestic MCI (aMCI) will be enrolled in the trial. MCI will be defined according to either the Peterson or Jak/Bondi criteria[41,42] neuropsychological approach in which tests are organized by cognitive domain and criteria are set for defining impairment within any particular domain. Assessments of memory confirming diagnosis will

have occurred within 6 months prior to consent or will be conducted at screening to confirm eligibility.

**Subject Identification and Recruitment**

Study subjects will be recruited using a variety of techniques to identify participants that meet inclusion and exclusion criteria and who are able to participate in the trial. Recruitment techniques will include (1) identification of patients from a high-volume memory clinic (PBHC), (2) advertisement to participants in the Los Angeles area, and (3) establishment of a website landing page that permits interested individuals to contact the trial coordinator. A total of up to 30 aMCI participants (50-80 years old) will be enrolled in this prospective randomized study (15 for each arm). Because there are several inclusionary/exclusionary criteria that must be assessed after obtaining informed consent, up to 60 participants may consent to participate in this study.

**Procedures for Obtaining Informed Consent**

All subjects will receive and sign the Experimental Research Subject's Bill of Rights prior to signing the informed consent form (ICF). Subjects will also complete an authorization of use and disclosure of protected health information (PHI), and a second authorization of medical record release for the subject's treating physician, prior to enrolling in the study. A copy of all signed ICFs will be given to the subject, and the investigator will retain the originals.

**Screening and Enrollment**

Subjects interested in participating in the study will be screened based on the inclusion and exclusion criteria listed below.

<u>Inclusion Criteria</u>

- Subjects must be age 50 to 80 at time of informed consent.
- Subjects must confirm an aMCI diagnosis either by providing records from a clinical assessment within 6 months of enrollment in this study or through a brief memory assessment by study staff at screening.
- Subjects must be proficient in spoken and written English for consenting as well as for study participation since the intervention in this study is currently only available in English.
- Subjects with medical conditions must be stable for these conditions. Stable control on medication is acceptable.
- Subjects, with or without assistance, must be able to use a computer and web interface. If assistance is needed, it must be readily available to them.
- Subjects are required to have internet with Wi-Fi at the location of their mSIM training.
- Subject must have normal visual acuity (or corrected to normal) and normal color vision as indicated by self-report.
- Subject must have adequate hearing acuity as indicated by self-report.
- Subject must have adequate motor capacity to use a mobile phone/iPad/computer as indicated by self-report.

- Subjects must be able to provide medical clearance to participate in an unsupervised, moderate intensity exercise program from a physician.

Exclusion Criteria

- Subjects must not have an existing diagnosis of a neurodegenerative disorder (e.g., Alzheimer's Disease, Lewy Body Dementia, Frontal-Temporal Dementia).
- Subjects must not have a prior diagnosis that might impact cognition and movement abilities including: significant cardiovascular disease, significant respiratory disease, illness or injury, substance abuse, schizophrenia, bipolar disorder, or other neurological diseases.
- Subjects must not have a previous Mini Mental State Exam (MMSE) score below 19.
- Subjects must not have a previous Clinical Dementia Rating (CDR) global score of ≥2.
- Subjects must not have a Montreal Cognitive Assessment (MoCA)[43] score of below 18 previously or during their screening evaluation.
- Subjects must not demonstrate a progression of aMCI to dementia at screening based on the best judgement of a study Clinical Neuropsychologist.
- Subjects must not currently participate in a high level of physical activity prior to study start as assessed by the International Physical Activity Questionnaire (IPAQ) at screening.
- Subjects must not endorse that they are unable to participate in moderate intensity aerobic activities, such as fast walking or passing/kicking a ball to a partner at screening.

Participants may enroll in the RCT but not receive a brain MRI if they do not pass MRI screening. Participants will be excluded from MRI procedures (but not the RCT) if they have any of the following:

- Brain Aneurysm Clip
- Implanted neural stimulator
- Implanted cardiac pacemaker or defibrillator
- Cochlear implant
- Ocular foreign body (e.g. metal shavings)
- Other implanted medical devices (e.g. Swan Ganz catheter)
- Insulin pump
- Metal shrapnel or bullets in their bodies
- They are pregnant (participants who are uncertain as to whether they are pregnant will be required to have a screening urine or blood pregnancy test)
- They have had surgery of uncertain type where the presence of metal clips or wires cannot be excluded.
- They have unstable angina or New York Heart Association functional class IV heart failure

Participants with claustrophobia may participate in a truncated MRI protocol under sedation, if they elect to participate.

**Randomization**
A computerized randomized block design will be used for subjects who meet inclusion and exclusion criteria. Study staff will not see the assignments to arms provided by the computer in advance.

**Data Collection and Assessments**
We will monitor participants in the RCT for up to 26 weeks and perform evaluations to determine cognitive trajectory between the two arms. . Total participation will be approximately 6 months. We will specifically evaluate data consisting of biomarkers (BDNF, NE), QEEG metrics (for example, peak alpha frequency), brain MRI, lifestyle, physical activity, and objective and subjective neurocognition. We will use statistical and computational methods in an effort to explain the causal underpinning of any observed differences between the two arms.

At **pre-screening**, the following will occur:

- Phone screening
- Medical records release to confirm eligibility and determine if they will require additional assessments at screening

At **Screening**, the following will occur:

- Informed consent
- Intake questionnaires
- MRI Safety Screening Questionnaire
- May be required to participate in a brief memory assessment
- PARQ+ and Medical Clearance to Exercise
- Virtual neuropsychological, cognitive, and functional assessments. If clinical neuropsychologist determines that the participant has progressed to dementia or the participant scores below 18 on the MOCA, participant will not pass screening

At **Baseline**, the following will occur:

- Randomization into Group 1 or Group 2
- Biomarker draw (blood)
- Physical status assessment including: physical measurements and questions regarding current physical status
- QEEG Assessment
- Brain MRI (unless contraindicated based on MRI Safety Screening Questionnaire)
- Participant receives Fitbit device and information on usage
- On-going collection of lifestyle data from FitBit device

- Phone call with study staff for patient to report one week's cognitive activity
- Group 2 (mSIM): Participant receives binder with homework to be completed during the course of the mSIM intervention
- Group 2 (mSIM): Participant signs credit card authorization form for damages to study equipment. Form will be shredded at the end of study when participant returns all study equipment
- Group 2 (mSIM): Stationary bike is adjusted for the participant, and they receive instruction on the proper use of the bike
- Group 2 (mSIM): Participant receives instruction on the tablet and mobile application usage
- Group 2 (mSIM): Participant may be required to see a cardiologist for medical management as part of their standard of care if additional ischemic or hypertensive risk factors are uncovered during the physical status assessment. If participant's blood pressure continues to be above ACSM guidelines and the participant cardiologist will not clear them to participate in a moderately intense, unsupervised exercise program, the participant will be withdrawn from the study [44]

**Study equipment set-up**, the following will occur:

- On-going collection of lifestyle data from FitBit device
- Group 2 (mSIM): Delivery company will set up study equipment at participant's home
- Group 2 (mSIM): 2 (but up to 6*) weeks aerobic exercise ramp-up using the exercise equipment provided

**Study intervention period**:

- Group 2 (mSIM): Begin 24-session mSIM exercise and cognitive training intervention (24x/12 weeks at home)
- Group 2 (mSIM): May be asked to take blood pressure before each exercise session if deemed necessary
- Group 2 (mSIM): Weekly calls with a member from the research staff for troubleshooting and navigating the mSIM program, and for checking homework completion

**Mid-intervention testing:**

- Virtual neuropsychological, cognitive, and functional assessments
- Phone call with study staff for patient to report one week's cognitive activity
- Group 2 (mSIM): Participant satisfaction through a survey

**Study equipment break-down** (Group 2: mSIM):

- Delivery company will breakdown and remove equipment from participant's home

**Post-trial testing**, the following will occur:

- Virtual neuropsychological, cognitive, and functional assessments.
- Biomarker draw (blood)
- Physical status assessment including: physical measurements and questions regarding current physical status
- QEEG Assessment
- On-going collection of lifestyle data from FitBit device
- Phone call with study staff for patient to report one week's cognitive activity
- Brain MRI (unless contraindicated based on MRI Safety Screening Questionnaire)
- Group 2 (mSIM): Participant satisfaction with mSIM program through a survey

If participant wants to receive compensation for participation, participant must provide a W9 to study staff before the end of study.

*The optimal exercise ramp-up duration is 2 weeks based on our prior exercise study in this population[15,45]. However, participants may require up to 6 weeks depending on their baseline physical activity levels and ability to tolerate the aerobic exercise ramp-up phase. If, after 6 weeks of ramp-up, participants are unable to sustain 40-60%HRR during their exercise sessions, they may then be withdrawn from the trial by the principal investigator.

See **APPENDIX I** for a table view of the study timeline. Note all timepoints might be plus or minus one week.

**Mobile-Based Simultaneous Exercise and Memory Skills Training Program (mSIM)**: The mSIM intervention will be carried out in participants assigned to Group 2 (mSIM). Before the in-home training intervention can begin, a research staff member will set-up the participant's equipment while they are on site at PBHC, troubleshoot, plan exercise training days and times, and inform them of the exercise ramp-up procedures. The equipment required for the mSIM home training sessions is compact and low-cost and will include: a folding, stationary exercise bike, Fitbit heart rate and activity monitor synced to the participant's study account, and a tablet to access our mSIM web-based application (see **Figure 1**).


**Figure 1**. Home set-up of the mobile technology-based simultaneous exercise and memory skills training (mSIM) program.

The mSIM participants (Group 2 (mSIM)) will begin by undergoing a minimum of 2 weeks,[15,45,46] but up to 6 weeks if necessary, of aerobic exercise ramp-up. Participants will wear heart rate monitors (FitBit) to self-monitor and ensure that the exercise was completed within their prescribed aerobic target heart rate zone, which is 40-60% heart rate reserve (HRR)[46,47]. The target heart rate zone will be determined by the Karvonen formula[47], which determines the individual participant's HRR and training zone. The Karvonen Formula is:

220 - age = maximum heart rate
Maximum heart rate - resting heart rate = heart rate reserve
(Heart rate reserve X training%) + resting heart rate

The ramp-up for mSIM participants will start with 2 days per week for 2-6 weeks, where they will be asked to maintain an aerobic intensity of up to 40-60% HRR for 10-40 minutes, depending on their baseline physical activity level[45]. After the ramp-up phase the mSIM (Group 2) participants will begin the 12-week intervention, comprised of 2 times/week, 65-minute sessions. Each mSIM session will include up to 15 minutes of sedentary new memory skills introduction learning or review. They will then have a 5-minute warm-up on the bike (30% HRR), followed by 35 minutes of memory skills training and practice while aerobic cycling in their estimated 40-60% aerobic training zone. They will then have 5 min of interval training which is continuously monitored on the FitBit wrist-worn watch.The resistance level will be pre-set on their bike to meet their aerobic training zone. They will then finish with a 5-minute cool-down that may include a 5-minute summary of skills learned in the session. Participants will be instructed in the importance of staying within their target heart rate zone and not exceeding their heart rate zone. A research staff member will be available during the first 2 weeks of mSIM training sessions via phone to help with any technical issues the participant has during the training session. Participants will be asked to open the FitBit App during their training session to sync their FitBit and indicate the start and stop time of their training session on a session log, so data can be monitored in real-time with the Fitibit data aggregator by research staff and to aggregate study compliance data. All FitBit data will use a de-identified study email address so that no personal identifying data will be linked with either FitBit or the FitBit data aggregator. Participant will be trained on how to ensure they are within their individualized 40-60% HRR and of the safety reasons for not going above 60%HRR.

**Subject ID Assignment**
Upon enrollment, each participant will be assigned a study ID that will be used to link all data. Only the PI/Sub-PI, and designated members of the research team will have access to a method to link each participant with their subject ID. This database will be password protected and reside within the institution's HIPAA compliant system.

**Fees for Participation**
There are no costs associated with participating in this research. Routine medical care will be billed to the subject's insurance.

**Compensation**
Group 1 (activity monitoring group) will receive access to the web-based program after they complete their post-trial testing. All participants will be compensated per completed assessment ($25.00 x ≤ 3 for neuropsychology testing, $25.00 x ≤ 2 for QEEG assessment, $25.00 x ≤ 2 for MRI assessment, $25.00 x ≤ 2 for blood draw) not done during clinic visits to cover time, travel, and inconvenience. The mSIM participants will be compensated $10 x ≤ 12 weeks for completing study-related activities, which will be paid out at the end of their study

participation if they have reached at least 80% compliance (19/24 sessions). This includes for the mSIM group: completing mSIM training sessions and homework. The activity monitoring group participants will be compensated the same total amount over the course of the study ($10 x ≤ 12 weeks) for completing their study-related activities during the intervention, which will be paid out at the end of their study participation if they have reached at least 80% compliance (10/12 weeks). This includes daily wearing of the FitBit for an entire week and weekly syncing of the device, as well as completing cognitive activity monitoring. Parking validation will be provided for study-specific visits. If the participant is enrolled in the RCT and completes all study visits, intervention sessions, data collections, and completed their lab visits and QEEG not during clinic visits, the maximum amount they will receive is $345. All participants will be able to keep their FitBit after they complete the intervention period.

## 4. EVALUATIONS AND ASSESSMENTS

Physical Status Assessment

Each participant who is randomized into the RCT will undergo a physical status assessment.[48] During the physical status assessment participants will have their blood pressure, weight, and waist and hip circumferences measured. This assessment will occur at baseline and post-trial for Group 1 and Group 2 participants.

Biomarker Data

Each participant who is randomized into the RCT will be assessed for biomarker data. All biomarker data will be collected as fasting AM samples. Participants will have fasted overnight and will not participated in exercise or consumed alcohol or coffee in the past 24 hours.

Fasting blood will be collected for the BDNF and NE analysis at baseline and at post-trial at by nurses or licensed phlebotomists. A nurse or phlebotomist will draw up to 3 tablespoons of blood from the participant's forearm into one whole blood and one serum separator tube. By comparison, the amount of blood collected when people donate blood is 1 pint, or roughly 500 mL. The SJCI lab will conduct sample analysis post-trial via Bionesis and Cat Combi ELISA assay kits using the protocol described in Cat Combi[49].

**Cognitive and Functional Assessments**

Each participant who is randomized into the RCT will be assessed for cognitive and functional abilities using the following assessments:

- NIH Toolbox[50] is administered at screening, mid-intervention, and post-trial.
- The Rey Auditory Verbal Learning Test (RAVLT) is a measure of memory functioning. Administered at screening, mid-intervention, and post-trial.
- Wechsler Memory Scale–Fourth Edition (WMS-IV) Logical Memory I and II is a measure of memory functioning. Administered at screening, mid-intervention, and post-trial.

- Wechsler Memory Scale–Fourth Edition (WMS-IV) Visual Reproduction I and II is a measure of memory functioning. Administered at screening, mid-intervention, and post-trial.
- Oral Trails B is a measure of processing speed. Administered at screening, mid-intervention, and post-trial.
- Functional Activities Questionnaire (FAQ)[51] is a measure of functional impairment. Administered at screening, mid-intervention, and post-trial.
- Multifactorial Memory Questionnaire (MMQ)[52] is a measure of memory functioning. Administered at screening, mid-intervention, and post-trial.
- Montreal Cognitive Assessment (MoCA)[43] is a measure of global memory. Administered at screening, mid-intervention, and post-trial.

**Medical Record Collection**

A participant's medical record will be collected from their treating physician's office at screening/baseline for medication types, dosage, and frequencies as well as other existing medical conditions and their treatment. The data will be entered into an electronic data capture system by research staff at PBHC. In the event that a particular participant's data has extreme or outlier characteristics, their medical record will be reviewed to identify explanatory factors.

**Lifestyle Data**

Physical activity, heart rate, and sleep data will be collected automatically and on a nearly continuous basis by using a FitBit activity tracker, or similar commercially-available tracker, which will be provided to each participant in the study.

Participants will be asked to log their cognitive activities for 7 days around the time of their baseline, mid-study, and post-trial time points.We will also collect the IPAQ standardized measure of physical activity at baseline and post-trial time points to obtain a metric of METs of physical activity.

## 5. DATA AND SAMPLE STORAGE AND MONITORING

**Data Collection and Storage**

Biological samples may be stored for up to 50 years at a biostorage facility. A code number will be assigned to all samples. Participants' names, medical record numbers, or other identifying information will not be stored with the samples. Participants' names and contact information will be stored at SJCI and PBHC and not be shared with researchers outside of SJCI and PBHC. Researchers, other than those providing direct medical care, will not have access to personally identifying information.

All biological and questionnaire data described above, but not medical records, will be collected into a centralized secure database and protected by technological, physical, and

administrative safeguards as provided by HIPAA and other applicable privacy laws. Only clinical staff, research staff, and authorized operations personnel will have access to this data. Data may also be de-identified, then stored in a separate secure database for potential future use. SJCI and PBHC will also store archived biological specimens for future research. All samples will be stored as coded samples with no personal identifiers. Codes will be stored separately, password protected, and only accessible to authorized personnel. All cognitive assessment data and medical information collected from subject medical records (e.g., medication and existing medical conditions) will be entered in an electronic data capture system. Research data and de-identified medical information may be stored for up to 50 years at SJCI and PBHC.

**Data Analysis and Data Monitoring**

The process of analyzing participant study data may continue indefinitely. We will analyze the incoming participant data using multiple regression analysis for statistical changes in clinical health markers over time. Only individuals who have completed all applicable HIPAA training will be provided access to PHI.

**Data Storage and Confidentiality**

All data will be kept private and shared with the participant as outlined above. Participants' biological data is stored in one database with one set of security credentials and Personally Identifiable Information is stored on a different database with separate security credentials. All data will be stored in a password-protected secured server and only specifically identified study personnel will have access to the data. Discoveries derived from participant data that may be published and shared publicly will have all data de-identified.

## 6. ANALYTICAL METHODS

To determine feasibility of the protocol, we will analyze adherence and feasibility data from participants via a secure data-aggregation program from which will pull de-identified FitBit session data and also from the session dashboard profiles from the mSIM web-based application. During the intervention, we will collect data related to program adherence in the mSIM web-based application.

In order to determine whether the mSIM treatment protocol produces significant improvements in cognitive abilities, our primary analytic tool will be the linear regression model, which will be implemented as an ANCOVA in SPSS or similarly capable statistical software (e.g., R statistical software and SAS). Outcomes will be the post-trial assessment measurements, baseline measurements of the outcomes will be used as covariates, and treatment group (Group 2 (mSIM) or Group 1 (CON)) will be the key variable to assess the treatment effect.

We will also perform an analysis of peripheral biomarker data to help us understand the biological underpinnings of any cognitive changes produced by the mSIM treatment protocol. Outcomes will be the post-trial biomarker measurements of BDNF or NE corrected concentration levels, baseline measurements of BDNF or NE corrected concentration levels will be used as covariates, and treatment group (Group 2 (mSIM) or Group 1 (CON)) will be the

key variable to assess the treatment effect. We will also conduct an exploratory analysis where we will evaluate the extent to which changes in BDNF and NE separately relate to changes in memory performance (composite memory Z-score) through correlational analyses.

To quantify the effects of the mSIM intervention on cognitive inhibitory tone, we will perform an analysis of the QEEG data. Our primary indicator is a metric called peak Alpha frequency. Outcomes will be the post-trial peak alpha frequency, baseline measurements peak alpha frequency will be used as covariates, and treatment group (Group 2 (mSIM) or Group 1 (CON)) will be the key variable to assess the treatment effect. We will also conduct an exploratory analysis where we will evaluate the extent to which changes in peak alpha frequency separately relate to changes in memory performance (composite memory Z-score) or other biomarker data through correlational analyses. Additional metrics from the QEEG will be explored. EEG will be provided in-kind by Evox and not the NIA-funded study.

An exploratory objective of this study is to test the mSIM treatment response measured with brain MRI. We will analyze functional resting state fMRI, structural MRI, ASL, and DTI data for this study using standard neuroimaging tools to explore structural and functional brain changes related to the intervention.

## 7. PROCEDURES FOR STUDY DOCUMENTATION

### Informed Consent

If consent is conducted in person, a copy of all signed informed consent forms (ICFs) will be given to the subject, and the investigator will retain the originals. Section 3 provides further details regarding the specific requirements for informed consent.

If informed consent is conducted remotely, the study team will provide a copy of the informed consent document by email or mail to give the participant ample time to read the document. The study team will go over the details of the consent and answer questions by phone or HIPAA-compliant telehealth platform (e.g., Zoom). If the participant elects to participate, the participant and study team will provide electronic signatures using DocuSign. Digital copies of the signed ICF will be given to the subject and retained by the investigator.

### Investigator Study File

Documentation concerning the study including, but not limited to, study protocol and any amendments, the IRB documents, study logs, monitoring activities and correspondences, and case report forms (CRFs) will be kept on-site in a secure location.

### Monitoring and Quality Assurance

Quality assurance procedures will include training of all study personnel, monitoring of data and reviews to verify that all elements of Good Clinical Practice (GCP) guidelines and FDA regulations are met. Monitoring will be conducted to assure that data are accurate and in agreement with source documentation; verify that consent for study has been properly obtained and documented; confirm that participants enrolled in the study meet inclusion and

exclusion criteria; monitor for safety (e.g. adverse events) and assure that all essential documentation required by GCP guidelines are appropriately filed.

**Retention of Study Documents**

Study documents will be retained for a period of two years on-site following the completion of the study. Study documents will then be transferred to a storage facility and secured. If the investigator relocates, retires, or withdraws from the clinical study for any reason, all records required to be maintained for the study will be transferred to an agreed-upon designee, such as another investigator at the institution where the study was conducted. Medical records used for treatment purposes will be retained separately as required by state data retention laws, HIPAA and other applicable laws.

## 8. PROCEDURES FOR HANDLING ADVERSE EVENTS (AEs) AND SERIOUS ADVERSE EVENTS (SAEs)

Due to the nature of this study, we do not expect adverse events of the same nature as might be expected if an investigational pharmaceutical were being investigated. The exercise intervention in this study includes moderate intensity aerobic physical activity that is approved by a physician, which is likely to not include a physiological adverse event . However, adverse events could still occur to participants, including adverse events not related to the study. Suicide or attempted suicide would be an example of an adverse event. SAEs will be reported to the Institutional Review Board, Data and Safety Monitoring Board and NIA representatives within 48 hours of the PI learning of the events. A report of all AEs will be sent to the Chair of the DSMB on a monthly basis.

**Internal Data and Safety Monitoring Board (DSMB**)

This plan describes the monitoring activities of our internal DSMB. In addition to the activities of the DSMB, clinical monitoring is an ongoing process. These responsibilities are assumed by co-I and the Director of the Pacific Brain Health Center (Dr. Merrill) and the clinical infrastructure of the Pacific Brain Health Center.

The DSMB will be comprised of Chair, Dr. Kirk Erikson, and Dr. Prabha Siddarth and Dr. Sean Mullen. The DSMB will meet initially prior to patient enrollment in the first year of the trial and then twice in subsequent years (2020, 2021) via conference call to monitor/audit the following, for a total of up to 3 calls during the course of this study:

1. Review all adverse event reports since the study initiation or since the last review will be reviewed at the DSMB meetings;

2. Review the medical record of all patients who have had a protocol-related serious adverse event since the last review;

3. Perform random audits of informed consent documents to verify that the informed consent procedures have been carried out and that necessary informed consent documents have been signed by study participants and staff;

4. Review data quality, completeness, and timeliness;

5. Review adequacy of compliance with goals for recruitment and retention, including those related to the participation of women and minorities;

6. Review adherence to the protocol;

7. Discuss factors that might affect the study outcome or compromise the confidentiality of the trial data (such as protocol violations);

8. Discuss factors external to the study such as scientific or therapeutic developments that may impact participant safety or the ethics of the study;

9. Follow up on problems previously identified

At the end of the meeting, the Principal Investigator, will summarize the findings of the DSMB and will subsequently implement recommendations for improvement in a timely manner. Special meetings of the DSMB may be convened when necessary, for urgent concerns regarding patient safety or data integrity. We don't anticipate that there will be many urgent patient concerns given the low risks associated with this trial.

**Definition of an AE**

The following definition of an adverse event (AE) will be used for this study:

- Any untoward medical occurrence in an enrolled subject who underwent procedures required by the study.

An AE can be any unfavorable and unintended sign, symptom, or disease (new or exacerbated) occurring after starting the procedures required by the study, even if the event is considered not related to the study procedures.

As far as possible, each adverse event will also be described by its duration (start and end dates), the intensity, its expectedness related to the known risks associated with the study procedures, and the action(s) taken.

It is the responsibility of the investigator to perform periodic and special assessments for AEs. The investigator and clinical staff will note all AEs reported by the subjects. All clinical complaints volunteered by, or elicited from, the subject during the study will be recorded separately on the appropriate page of the CRF. If any AE occurs, the subject will receive appropriate treatment and medical supervision if warranted.

All AEs judged to be clinically significant will be followed until resolution.

**Definition of an SAE**

The definition of a serious adverse event (SAE) in this study is an AE that meets any of the following criteria:

- Results in death
- Is life-threatening

NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death if it were more severe.

- Requires hospitalization or a prolongation of an existing hospitalization

NOTE: In general, hospitalization signifies that the subject has been detained at the hospital or emergency ward for observation or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs but not necessarily SAEs. An occurrence or complication that prolongs hospitalization is an SAE. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered an SAE. Hospitalization for elective treatments of a pre-existing condition that did not worsen from its original baseline is not considered an SAE.

- A persistent or significant disability or incapacity

NOTE: The term disability means a substantial disruption of a person's ability to conduct his/her regular life functions. This definition is not intended to include AEs of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza and accidental trauma (e.g., sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

- Other important medical event

NOTE: Medical or scientific judgment should be exercised in deciding whether reporting is appropriate for other important medical events that may not result in death, be life-threatening, or require hospitalization but still may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed in this definition. These events should also be considered serious.

**Recording AEs and SAEs**

If an AE or SAE occurs, and it is deemed related and unanticipated to this study, it is the responsibility of the PI to review all documentation (e.g., hospital progress notes, laboratory,

and diagnostic reports) relative to the event(s). The PI is to record all relevant information regarding any AE (including SAEs) on the AE page of the CRF. The PI will also attempt to establish a diagnosis of the event based on the signs, symptoms, or other clinical information. In such cases, the diagnosis, not the individual signs and symptoms, should be documented on the appropriate CRF as the AE or SAE.

**Assessment of Intensity**

The PI will make an assessment of intensity for each AE and SAE reported during the study. The assessment will be based on the investigator's clinical judgment. The intensity of each AE recorded in the CRF should be assigned to one of the categories shown in Table 1.

**Table 1**: Classification of AEs by Intensity

| Intensity | Definition |
|---|---|
| Mild AE | An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities. |
| Moderate AE | An event that is sufficiently discomforting, causing interference with normal everyday activities. |
| Severe AE | An event that prevents the subject from performing their everyday normal activities. |

Any AE that changes in intensity or grade during its course will be recorded on the CRF at the highest-level experienced by the subject.

NOTE: An AE that is assessed as severe should not be confused with an SAE. Severity is a category utilized for rating the intensity of an event (such as mild, moderate, or severe myocardial infarction). However, the event itself may be of relatively minor medical significance (such as a severe headache), and both AE(s) and SAE(s) can be assessed as severe.

**Expectedness of AEs**

An expected AE is one that is consistent with the known risk information associated with the study procedures.

An unexpected AE is defined, as any AE, the specificity or severity of which is not consistent with the known risk information. "Unexpected," as used in this definition, refers to an AE that has not been previously observed rather than from the perspective of such an AE not being anticipated based on the known effects of procedures required by the study.

**Follow-Up of AEs and SAEs**

After the AE or SAE report, the PI will proactively follow each subject.
All AE(s) and SAE(s) will be followed until:

- Resolution

- The condition stabilizes
- The event is otherwise explained
- The subject is lost to follow-up

Once the event is resolved, the appropriate SAE report page will be updated. The PI will also ensure that the follow-up includes any supplemental information that may explain the causality of the event(s).

All SAEs will be reported to DSMB and NIH representatives within 48 hours of the PI learning about the SAE.

## 9. CONFIDENTIALITY

### Data

All information regarding the nature of the study provided by the sponsor or study monitor to the investigator (with the exception of information required by law or regulations to be disclosed to the IRB or the subject) must be kept in confidence by the investigator.

### Subject Anonymity

The anonymity of participating subjects must be maintained. Subjects will be identified by their initials and an assigned subject number on CRFs and other documents retrieved from the site or sent to the study monitor, sponsor, regulatory agencies or central laboratories/reviewers. Documents that identify the subject (e.g., the signed informed consent document) must be maintained in strict confidence by the investigator, except to the extent necessary to allow auditing by the appropriate authorities, the study monitor, or sponsor representatives.

**Table 1**: Classification of AEs by Intensity

| Intensity | Definition |
|---|---|
| Mild AE | An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities. |
| Moderate AE | An event that is sufficiently discomforting, causing interference with normal everyday activities. |
| Severe AE | An event that prevents the subject from performing their everyday normal activities. |

Any AE that changes in intensity or grade during its course will be recorded on the CRF at the highest-level experienced by the subject.

NOTE: An AE that is assessed as severe should not be confused with an SAE. Severity is a category utilized for rating the intensity of an event (such as mild, moderate, or severe

myocardial infarction. However, the event itself may be of relatively minor medical significance, such as a severe headache), and both AE(s) and SAE(s) can be assessed as severe.

Although subjects will be encouraged to complete the study, they may voluntarily withdraw at any time. The investigator will document the reasons for discontinuation.

**10. SUBJECT DISCONTINUATION AND TERMINATION OF STUDY**

Although subjects will be encouraged to complete the study, they may voluntarily withdraw at any time. The investigator will document the reasons for discontinuation.
Also the investigator may withdraw the subject from the study. The subject will be removed from the study without their consent for various health, safety or administrative reasons, including but not limited to the following:

- The investigator decides that continuing in the study would be harmful to subject.
- The sponsor cancels the study.
- Other administrative reasons.

The investigator will make the decision and let the subject know if it is not possible for him/her to participate.

**11. COVID-19 PRECAUTIONS**

If needed, depending on the status of the coronavirus pandemic, precautions may be taken to limit the risk of transmitting COVID-19 via study procedures per our institutional policies (Providence Health). Study visits including intake, neuropsychological evaluation at the discretion of the clinician, and physical status assessments may be done using remote procedures. In order to collect physical status assessments, study equipment such as a blood pressure cuff and a calibrated scale may be sent to the participant's home. The participant will be responsible for returning any additional study equipment. Although all COVID-19 related healthy and safety precautions will be addressed throughout this study, some participants may still not be willing to come on-site to PBHC to undergo the mSIM on-boarding session. In this instance then there will be an option for the study staff to perform this in-person visit at their home. Remote visits may continue after the COVID-19 crisis if deemed necessary by the PI or DSMB to preserve the integrity of the research study data. Some study participants may want to further minimize on-site activity. During COVID, participants may request to skip the MRI or QEEG assessments. The following precautions for any in-person study visits may be employed based on the discretion of the PI and institutional policies: screening of participants with questions regarding COVID-19 symptoms/exposure, temperature checks prior to in-person visits, physical distancing as much as possible during the visit, use of personal protective
equipment (e.g. masks) during in-person visits, or pre-visit COVID-19 testing.

If a study participant tests positive for COVID-19 and cannot exercise, they may pause participation in the study. They can re-initiate in the study where they left off and the timeline will be paused for up to four weeks and depending on the severity of the case. Participants

will be asked to provide medical clearance to re-initiate into the study. The participant may be asked to ramp up exercise for up to 2 weeks at the discretion of the PI and DSMB. If the participant requires more than 4 weeks to re-initiate into the protocol, they will be terminated from the study at that time.

## APPENDIX I. STUDY TIMELINE (IN MONTHS) THE MSIM TRIAL RCT

Each participant (N=30) will be enrolled for up to 26 weeks (6 months). Participants in the active arm (N=15, Group 2) arm will have the "mSIM Intervention" sessions outlined below, and patients in the control arm will only have activity monitoring via FitBit device. Group 1 will be granted access to the mSIM web-application after completing the intervention.

| | Screen | Randmz. | Baseline | 1 Mo | 2 Mo | 3 Mo | 4 Mo | 5 Mo | 6 Mo | Post-Trial |
|---|---|---|---|---|---|---|---|---|---|---|
| Visit Window | -30 to -1 days | +/- 7 days | +/- 7 days | +/- 7 days | +/- 7 days | +/- 7 days | +/- 7 days | +/- 7 days | +/- 7 days | |
| *Consent & screening | 1x | | | | | | | | | |
| *Intake questionnaires and assessments | 1x | | | | | | | | | |
| Medical Clearance to Exercise | 1x | | | | | | | | | |
| Randomization | | 1x | | | | | | | | |
| Credit card authorization | | | 1x | | | | | | | |
| Physical status assessment | | | 1x | | | | | 1x | | |
| Lifestyle and/or satisfaction data | | | 1x | | | 1x | | 1x | | |
| **mSIM Intervention (Group 2 (SIM))** | | | | | | | | | | |
| Equipment instruction | | | 1x | | | | | | | |
| Equipment drop-off | | | 1x | | | | | | | |
| Equipment pick-up | | | | | | | 1x | | | |
| Exercise ramp-up session | | | | 4-12x (2-6 weeks duration) | | | | | | |
| Gain access to mSIM web-app | | | | √ | | | | | | |
| Virtual Support Sessions | | | | √ | | | | | | |
| mSIM exercise session | | | | 24 x (12-14 weeks duration) | | | | | | |
| mSIM homework | | | | 24x (12-14 weeks duration) | | | | | | |
| **mSIM Intervention (Group 1 (CON))** | | | | | | | | | | |
| Access to mSIM web-app | | | | | | | | | | **1x** |
| **On-going Data Collection** | | | | | | | | | | |
| Fitbit | | | √ | | | | | | | |
| **Imaging Data Collection** | | | | | | | | | | |
| QEEG | | | 1x | | | | | 1x | | |
| MRI* | | | *1x | | | | | *1x | | |
| **Biological Sample Collection** | | | | | | | | | | |
| Blood sample | | | 1x | | | | | 1x | | |
| **Neuropsychological/Cognitive Assessments** | | | | | | | | | | |
| Virtual neuropsychological assessment | 1x | | | | | 1x | | 1x | | |

Notes: #x indicates the number of times a test or an intervention will occur in protocol window (e.g. 2x = two times). *In participants that are eligible for an MRI.

√ indicates ongoing data collection.

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