

GROUP 9

A randomized controlled, Phase II trial of moderate intensity physical activity in patients with Alzheimer's Disease aged over 65 years old

Team Members: Shao-Yun Chien, Zhining Sui, Arunrat Thepna, Joe Voth, and Thu Vu

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GROUP 9**A randomized controlled, Phase II trial of moderate intensity physical activity in patients with Alzheimer's Disease aged over 65 years old****LIST OF ABBREVIATIONS AND ACRONYMS**

AC	Activity control
AD	Alzheimer's Disease
ADR	Associate Dean for Research
AE	Adverse Event
AT	Aerobic training
ADAS-Cog 13	Alzheimer's Disease Assessment Scale—Cognitive Subscale 13 scores
CT	Cognitive training
CTSA	Clinical Translational Science Award
DSM	Data safety monitoring
ECs	Ethics Committees
EMR	Electronic medical record
FDA	The federal Food and Drug Administration
FTE	The calculation of full-time equivalent
GEE	Generalized estimating equations
HDRS17	Hamilton Depression Rating Scale 17
HSD	Human Subjects Division
IMA	University of Washington Intramural Activities Building
IRBs	Institutional Review Boards
ITHS	Institute of Translational Health Services
MCI	Mild Cognitive Impairment
RCT	Randomized controlled trial
REDCap	Research Electronic Data Capture
RID	Respondent identification number
SFT	Senior Fitness Test
SoN	School of Nursing

SRMCA	Self-Report Measurement of Cognitive Abilities
TRU	Translational Research Unit
UW	University of Washington
UW-IT	UW Information Technology
UW-OR	UW office for Research
WA	Washington

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PROTOCOL TEAM ROSTER

Name	Role	Department	Phone	Email
Voth, Joe	Project Investigator (PI)	Medicine/Neuroscience	507-822-0440	jpvoth@uw.edu
Chien, Shao-Yun	Co- Project Investigator (Co-PI)	Nursing	206-227-4997	schien2@uw.edu
Sui, Zhining	Co- Project Investigator (Co-PI)/ Statistician	Biostatistics	206-532-5597	zsui0603@uw.edu
Thepna, Arunrat	Co- Project Investigator (Co-PI)	Nursing	206-518-2102	arunrat@uw.edu
Vu, Thu	Co- Project Investigator (Co-PI)/ Statistician	Biostatistics	402-802-4171	tvu2@uw.edu

GROUP 9**A randomized controlled, Phase II trial of moderate intensity physical activity in patients
with Alzheimer's Disease aged over 65 years old
[FINAL version / Jun 1st, 2022]****Investigator signature page**

I, the Investigator of Record, agree to conduct this study in full accordance with the provisions of this protocol. I agree to maintain all study documentation for a minimum of three years after completion of the study, unless otherwise specified by UW IRB. Publication of the results of this study will be governed by the Principal Investigator. Any presentation, abstract, or manuscript will be made available by the investigators to the Principal Investigator for review prior to submission.

I have read and understand the information in this protocol and will ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about the obligations incurred by their contribution to the study.

Name of Site Investigator of Record

Signature of Site Investigator of Record

Date

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SCHEMA

Purpose: This study is to investigate the feasibility and efficacy of a 12-week aerobic training with cognitive training (exergame training) and equally long aerobic training, both compared to an active control group, on older adults with mild AD.

Design: This is a phase II, single-center, single-blind, randomized controlled trial to test the effectiveness of 12 weeks of aerobic training (AT) and AT with cognitive training (CT) on decreasing the rate of cognitive decline.

Study population: Older adults with mild AD and age and sex-matched controls

Study size: 627 participants

Treatment Regimen: We are using a parallel three-armed design in the current RCT: Aerobic training (AT), AT with cognitive training (CT), and Activity control (AC)

Study Duration: Overall study is designed for 3 years.

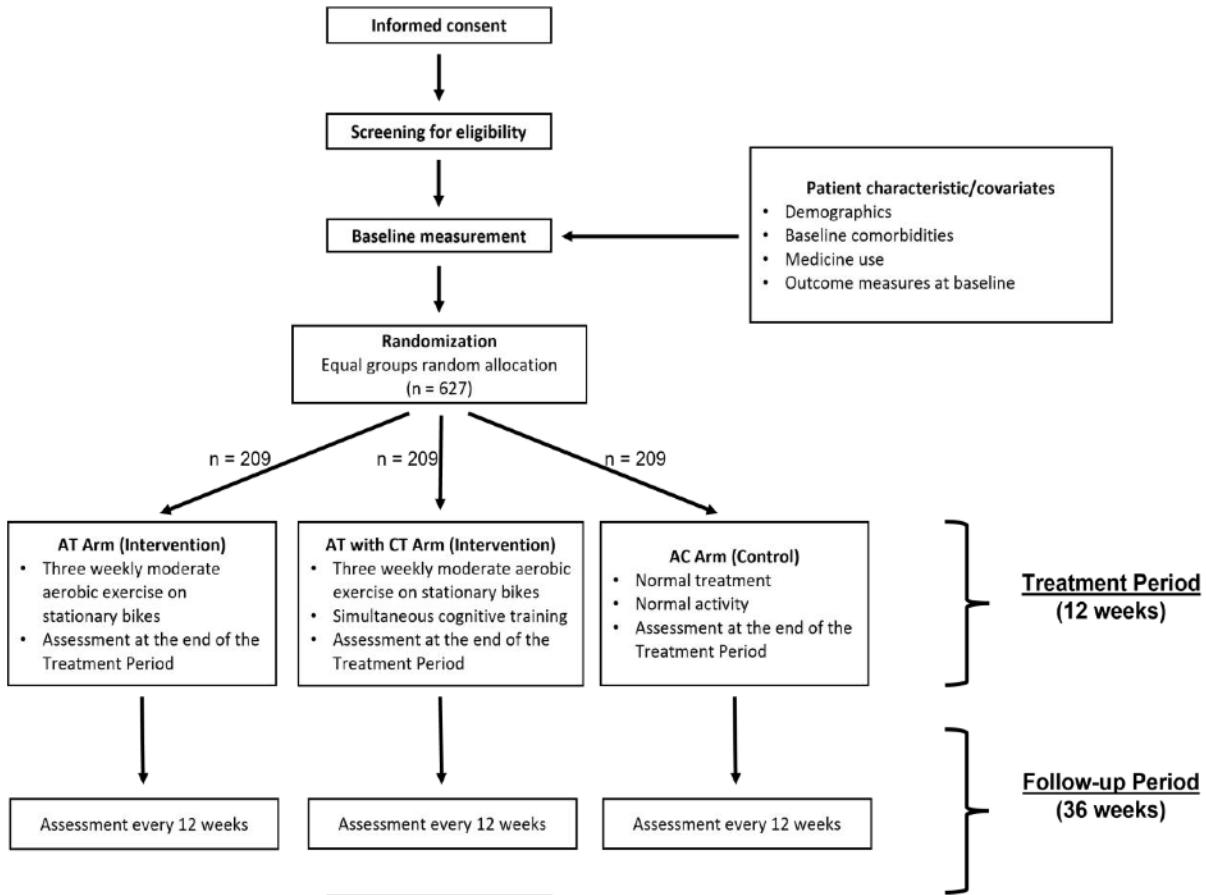
Primary Objectives: The primary objective of this study is to investigate the feasibility and efficacy of a 12-week exergame training and equally long aerobic training on cognitive decline in older adults aged over 65 years old with early mild AD compared with an active control group.

Secondary Objectives: The secondary objective of this study is to understand how exergame therapy benefits patients experiencing cognitive decline. To assess this, we will use the senior fitness test to assess physical fitness, a validated self-report cognitive measure survey, and a validated depression survey before and after treatment regimen completion. Together, these measures will provide insight into how exergame therapy compares with standard aerobic exercise, specifically in the 65+ year old group, in measures beyond cognitive acuity.

Study Sites: The University of Washington Medical Center, Seattle and its affiliated primary care, memory, and neurology clinics

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OVERVIEW OF STUDY DESIGN AND RANDOMIZATION SCHEME



1. INTRODUCTION

1.1 Background and Prior Research

Alzheimer's disease (AD) is a growing healthcare problem

Alzheimer's disease (AD) is a progressive neurologic disorder and the most common cause of dementia in older adults. It leads to progressive memory loss, a decline in the ability to think and live independently, disorientation, and many behavioral problems, ultimately culminating in death^{1,2}. AD is the most prevalent neurologic disorder in the United States, with over 6.5 million people affected, with over 12.7 million expected by 2050³. In addition to the decline in the individual's ability to perform activities of daily living, the demand for supportive care also increases, placing an enormous burden on the healthcare system, costing nearly \$300 billion annually³. Cognitive impairment and disruptive behavior in conjunction with AD significantly impact individuals, families, and society⁴. The demand for appropriate care and support for people with AD has been recognized as a priority, although effective therapies that alter disease course are not available at present. As the US population ages, the proportion that develop AD will increase as well, making the urgency of new and effective therapies paramount. Since aging is the greatest risk factor for AD⁵, care for older adults with AD is a global challenge as the population ages rapidly⁶.

Physical activity is a modifiable risk factor of AD

Currently, there are no effective treatments to cure nor slow AD progression⁷. At least one-third of AD cases can be attributed to risk factors, such as age, genetics/family history, comorbidities (cardiovascular disease, diabetes), smoking, physical inactivity, and vitamin and nutritional deficiencies^{8,9}. Among them, physical activity is a modifiable risk factor that may play a role in reducing or slowing down the progress of AD. Evidence suggests that exercise is essential for maintaining cognitive function and brain health in older adults, with physical activities improving cognitive resilience, while also improving mood and overall health¹⁰⁻¹³. Conversely, physical inactivity was associated with chronic disease and higher adverse health outcomes^{14,15}. In the last few years, evidence has been found that elderly patients who remain more physically active can decrease their risk of dementia by 30%, while decreasing the specific risk of AD development by 45%¹⁶. Together, this evidence suggests that altering physical activity may be an affordable and effective method of altering Alzheimer's disease course.

The evidence of whether exercise regimens directly alter AD disease course once AD has developed is inconsistent

Studies have shown that physical activity can improve cognitive function in cognitively healthy older adults¹⁷⁻¹⁹. In addition, regular physical activity has been shown to reduce AD patients' traditional cardiovascular risk factors, exert anti-inflammatory effects, stimulate the production of neurotrophic factors, and promote neurogenesis, which is likely beneficial in slowing the development of Alzheimer's disease²⁰. It is well-established that vascular injury and disease (i.e., carotid stenosis, stroke, ischemia, etc.) can be a key contributor to AD, partly through regional hypoperfusion and implied nutrient deprivation²¹. This may provide plausible hypotheses regarding how regular physical activity may prevent cognitive decline via increasing cardiovascular health and subsequent cerebral blood flow. However, current evidence of whether exercise regimens directly alter AD disease course once AD has developed are inconsistent^{20,22-24}. Evidence exists

documenting improved cerebral blood flow measures following consistent exercise in elderly patients, increased neurogenesis and prevented hippocampal atrophy associated with aging, and reductions in neuroinflammation, all suggesting regular physical activity may help prevent or slow AD progression²⁵. In contrast, other studies have found no significant reduction in AD incidence regardless of physical activity level, or that the activity-based benefits of physical activity may only be effective over a certain time frame, as evidenced by a study that found benefits in elderly patients over a four-year time span, but subsequent 14 year follow up showed no significant changes in AD incidence²⁵. In conclusion, how to effectively stimulate people with AD to participate in physical activity and overcome barriers to physical activity requires further research^{26,27}.

Exergames

Due to environmental enrichment and voluntary exercise increasing overall hippocampal neurogenesis, combining physical exercise and cognitive training may be more effective for cognitive enhancement than either physical exercise or cognitive training alone, resulting in a positive synergistic effect²⁸⁻³⁰. According to a review by Herold et al., synchronous training of exercise and cognitive stimulation significantly improves cognitive ability in different populations³¹. Therefore, combining exercise and cognitive training is expected to be a superior intervention than either component alone for AD patients to delay cognitive deterioration and even promote cognitive ability. Exergame uses video game technologies to instruct and guide users through exercise games, effectively combining cognitive training, a well-established strategy to slow or prevent cognitive decline as a result of old age, with exercise³². It allows AD patients to perform exercise training combined with cognitive stimulation in a safe and controlled environment. Therefore, this research proposal aims to explore whether exergame therapy would be beneficial to AD patients by combining physical activity and cognitive stimulants in a virtual environment to understand whether exergame can delay cognitive decline in AD patients.

1.2 Research Question

What type of exercise can slow the progression of cognitive impairment among older adults with early mild AD?

2. STUDY OBJECTIVES AND DESIGN

2.1 Primary Objectives

The primary objective of this study is to investigate the feasibility and efficacy of a 12-week exergame training and equally long aerobic training on cognitive decline in older adults aged over 65 years old with early mild AD compared with an active control group.

2.2 Secondary Objectives

The secondary objective of this study is to understand how exergame therapy benefits patients experiencing cognitive decline. To assess this, we will use the senior fitness test to assess physical fitness, a validated self-report cognitive measure survey, and a validated depression survey before and after treatment regimen completion. Together, these

measures will provide insight into how exergame therapy compares with standard aerobic exercise, specifically in the 65+ year old group, in measures beyond cognitive acuity.

2.3 Study Design

This is a phase II, single-center, single-blind, parallel randomized controlled trial to test the effectiveness of 12 weeks of aerobic training (AT) and AT with cognitive training (CT) on decreasing the rate of cognitive decline. We are using a parallel three-armed design in the current RCT: (1) aerobic training (AT), (2) AT with cognitive training (CT), and (3) activity control (AC). The interventions' acceptability, safety, and feasibility have been confirmed by an uncontrolled pilot study conducted in 2011³³. Participants will be recruited from the University of Washington Medical Center, Seattle and its affiliated primary care, memory, and neurology clinics, with recruitment groups beginning treatment every 12 weeks over the first 36 weeks. Assessors (who will be blinded to the group assignment throughout the study period) will complete the baseline evaluations after screening for eligibility and obtaining informed consent. Participants will then be randomly assigned to one of the three trial arms using a computerized block randomization algorithm at a 1:1:1 basis. Intervention groups will be preferred if the groups have an unequal number of participants. Participants in the two intervention groups will conduct three weekly moderate exercise sessions under supervision by experienced physiotherapists at UW Medicine's Physical Therapy Department. Participants assigned to the AC group will receive their usual treatments and maintain their routine activity levels with no specific regimen changes.

Outcome measures will be assessed at baseline, 12, 24, 36, and 48 weeks. Demographic data, such as age, sex, geographic location, country of birth, employment, education, and household income will be collected at enrollment appointment. All assessors performing the outcome measurements will be blinded to group assignment and properly trained to administer all survey and assessment measures. The primary outcome is the change in Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog) 13 scores. Follow up ADAS-Cog 13 assessments will be conducted every 12 weeks for one year. Secondary outcomes include Senior Fitness Test, Self-reported Cognitive Measures (assessed by Self-Report Measurement of Cognitive Abilities: SRMCA), all-cause hospital admissions, and Hamilton Depression Rating Scale (HDRS). Since intensity (and thus physical impact) of exercise regimens with or without video game enhancement may change, causing subsequent changes in ADAS-Cog13 scores, we will assess physical condition using the senior fitness test as a surrogate measure of overall physical fitness. This will aid in interpretation of our primary outcome measure as well as provide more information about our intervention's effects. The SRMCA is a peer-reviewed and validated measure of self-identified cognitive function, assessing how the person feels about their cognition. Since ADAS-Cog 13 focuses on objective measures and tasks to assess aspects of cognitive function, the SRMCA will supplement this information by interrogating how the person themselves identifies their cognitive status before and after treatment. Finally, the HDRS is a peer-reviewed and validated survey to identify depression severity in patients, and considering AD and depression have a 25% comorbidity or higher, it will be crucial to assess whether any cognitive benefits seen as a result of our exergame therapy are not simply the result of improved mood/reduced depressive symptoms³⁴. All participants and

caregivers will be advised not to disclose group assignments during the study period and test sessions.

2.4 Study Tools and Outcome Measures

Alzheimer's Disease Assessment Scale-Cognitive Subscale 13 (ADAS-Cog 13)

The ADAS-Cog 13 is an expanded and adapted version of the original ADAS-Cog, which itself was designed to assess the efficacy potential AD therapies^{35,36}. The ADAS was a 21-test battery to assess both cognitive and non-cognitive domains affected by AD, but the non-cognitive components are rarely used at present and will not be included in our assessments³⁵. The ADAS-Cog was designed to assess various key aspects of cognitive dysfunction seen in AD, including 11 tasks assessing memory (short and longer term), language, and praxis (mental planning of a movement)³⁵. Specifically, the 11 tasks composing the original ADAS-Cog 11 are: Word recall, naming objects and fingers, following commands, constructional praxis, ideational praxis, orientation, word recognition, and language. The ADAS-Cog 11 is well-established as a measure of cognitive decline in AD throughout the span of mild to severe AD. However, subsequent studies identified the 11-part battery was not as effective at identifying cognitive decline associated with earlier cognitive decline seen in mild cognitive impairment or earlier and milder AD, and thus the ADAS-Cog 11 was modified with two additional tasks assessing attention and concentration, planning and executive function and verbal and nonverbal memory³⁶. The ADAS-Cog 13 was superior to ADAS-Cog 11 at correctly discriminating between a mixed MCI and mild AD patient group, as well as being more sensitive to disease progression³⁶. In summary, the ADAS-Cog 13 seems to better detect early cognitive changes seen in MCI and mild AD patients, and thus will be our primary outcome measure for this study. This aligns with various other clinical trials that have relied on the ADAS-Cog 13 as their primary cognitive assessment tool.

The ADAS-Cog 13 is an untimed assessment graded on a scale of 0-85, with a higher score signifying increased cognitive impairment. A sample ADAS-Cog 13 with administration instructions is included in this proposal below. The assessment takes around an hour to complete, and no instruments are required beyond an administrator and the assessment materials. Since MCI and AD are progressive diseases, the cutoff scores for who constitutes a person with MCI versus a person with mild AD are not well-established. However, a 2016 study assessing sensitivity of ADAS-Cog 13 over 24 months with patients with MCI or mild AD will provide the cutoff values we will use for our study³⁷. In this study, they identified a score of 7 as representing early MCI, while a score of 11-12 will represent fully developed MCI. Mild-AD patients were identified with scores around 28 up to 38. Thus, we intend to recruit patients with scores between 15-35 to encompass the range of full MCI to mild AD, while excluding more severe AD phenotypes. Importantly, this study also identified ADAS-Cog 13 score changes of around 2 points over two years in MCI patients, and 2-3 points per 6-month interval over 24 months in mild AD patients³⁷. Together, the ADAS-Cog 13 will be sufficiently sensitive to detect cognitive change over the 12-month assessment in the target score range of 15-35.

Senior Fitness Test (SFT)

The senior fitness test uses seven tasks to assess fitness of an elderly individual³⁸. These tasks include chair stand/sit, arm curls, 6-minute walk, 2-minute stepping, chair sit with reaching, back scratching flexibility, and 8 foot up and go. These tasks are standardized by male and female sex, with expected ability ranges for each task and age group. Thus, this provides an objective and validated method to assess physical fitness specifically tailored to the elderly population and ability to complete normal everyday activities. This specific design for elderly patients is crucial for our study, as typical physical fitness measures are designed for more broad physical fitness assessment in younger populations, and thus will not be as sensitive to specific deficits seen in elderly patients. This assessment will identify whether our treatment groups improve in ability to complete these everyday living tasks like sitting, standing, walking, and flexibility. Since video components may alter efficacy of exercise regimens, this assessment will be a control measure to ensure the level of physical activity the aerobic and exergame groups exert are similar. This will aid in our analysis of the ADAS-Cog 13 data and will provide crucial context for our overall interpretation. The senior fitness test requires a trained professional to administer, a stopwatch, tape measure, and a chair to conduct, and takes around a half hour to complete.

Self-Report Measures of Cognitive Ability (SRMCA)

The SRMCA was designed in 2014 to be a reliable, valid and cheaper method of investigating cognitive ability using self-report methods³⁹. The SRMCA assesses three facets of cognition: comprehension and knowledge, fluid reasoning, and visual processing³⁹. These three components are assessed in 25 items in a seven-point scale from “1 = extremely difficult” to “7 = extremely easy”. At present, there is evidence that the SRMCA is reliable in elderly patients, and that it can assess self-estimated cognitive abilities⁴⁰. However, there is evidence that personality can strongly influence the results of this assessment, and thus this is not intended to be the primary outcome measure⁴⁰. That being said, a subjective insight into how a study participant rates their cognitive abilities will be valuable information to inform our conclusions for this study. The SRMCA takes between 15-20 minutes to complete.

Hamilton Depression Rating Scale 17 (HDRS17)

The HDRS17 is the most-widely used clinician-administered assessment for depression. The HDRS17 is a 17-question assessment filled out by a clinician following a structured interview, with questions being rated 0-4, with zero being “not present” and four being “fully present or most severe”⁴¹. This assessment will be conducted after the pre- and post-regimen appointments, where the ADAS-Cog 13 and SRMCA will be conducted. Higher scores on the HDRS17 signify more depression symptoms. Completion of the HDRS17 takes 15-20 minutes. The HDRS17 is included as a secondary outcome measure because depression is one of the most common comorbidities in AD, and thus is a large confounding variable in our study²⁵. By collecting HDRS17 data, we will be able to see whether our regimens reduce depressive symptoms, both in the context of AD and in general.

3. STUDY POPULATION

Older adults with mild AD will be included in this study. Participants will be selected for the study according to the criteria.

3.1 Inclusion Criteria

To be included in this study, a patient must be above the age of 65 and have an ADAS-Cog 13 score between 15 and 35 out of 85 prior to enrollment, as well as a clinically confirmed diagnosis of early mild AD. This range of ADAS-Cog 13 scores will selectively target individuals with clear cognitive deficits, thus signifying mild cognitive impairment and/or mild AD. However, scores of 36 and above on the ADAS-Cog 13 signify moderate to severe Alzheimer's Disease, at which point completion of the proposed therapies will be difficult for the participant to complete. Further, we predict the Exergame therapy will most dramatically benefit individuals who have not progressed to moderate/severe AD, justifying our inclusion criteria of ADAS-Cog 13 scores between 15-35 prior to beginning the trial. They must be physically capable of performing stationary bikes for 50 minutes in a controlled/supervised setting. They also must be able to read, speak and write English and access to online recourses and a telephone for study duration.

- Age: > 65
- Fluent in English (written and spoken)
- ADAS-Cog 13 score: 15 – 35
- Diagnosis of early mild AD
- Ability to participate in moderate physical activity
- Ability to send and receive SMS text messages
- Own a phone with a reliable internet connection and willing to use email
- Willing to be randomized

3.2 Exclusion Criteria

People to be excluded from our study include people with ADAS-Cog 13 scores outside the 15-35 range upon initial meeting. Individuals with a history of brain tumors, severe or recurrent traumatic brain injury, substance abuse disorders, co-morbidity that limited exercising, including severe cardiovascular, musculoskeletal, or neurological disease, severe psychiatric disease including diagnosis of bipolar disorder or psychotic disorder, and other major neurological illnesses that affect cognitive function will be excluded. Additionally, individuals with cardiopulmonary illnesses that prevent moderate exercise activity will be excluded.

- Physician diagnosis of the following:
 - Mental health conditions (e.g., eating disorder, alcohol and substance abuse, and schizophrenia)
 - Neurological conditions (e.g., epilepsy, stroke, multiple sclerosis, Parkinson disease, brain tumor, or severe traumatic brain injury)
 - Other significant health conditions limiting moderate physical activity (e.g., congestive heart failure, chronic obstructive pulmonary disease, coronary artery disease, renal failure, chronic kidney disease, and pulmonary hypertension)
- Recent cardiovascular event or recent treatment for cancer (within the last year), on dialysis, or on active organ transplant list
- Visual problems that prevent viewing screen at a normal distance
- Currently participating in a formal cognitive training coaching program or other lifestyle change program

- Not meeting all the inclusion criteria

3.3 Recruitment Process

Participants will be recruited from the University of Washington Medical Center, Seattle and its affiliated primary care, memory, and neurology clinics, with recruitment groups beginning treatment every 12 weeks over the first 36 weeks. UW Medicine Center is a hospital with an internationally recognized research center and a top-rated medical facility. Professional medical personnel provide care that emphasizes humanization and patient safety, focusing on healthcare quality and patient safety management, so as to provide high-quality medical services. Communication between the research team and study site will happen via phone, e-mail, online, and in-person meetings. The study procedures will be implemented using telephone, e-mail, online meetings, and in-person visits.

Recruitment will be commenced using the clients' database of UW Medicine Center. Research recruitment flyers will be posted in the center. The neurologists working at UW Medicine will be informed if there are prospective participants, the information of this study can be provided to them. The research team will contact those interested using telephone screening to recruit individuals who meet eligibility criteria. If an individual satisfies the study criteria and agrees to participate, the research team will schedule a meeting with the participant to explain the study in detail, sign the informed consent, and collect baseline attributes.

3.4 Participant Retention

Detailed description of the study visits and consultation schedule and procedural requirements will be provided during the informed consent process. At study enrollment visits, detailed locator information will be obtained, including addresses for home and work, contact information, and names and contact information for next of kin. Each subsequent visit will be accompanied by a review and an update of this information. The investigators will acquire permission in advance to locate participants who miss appointments using diverse locating methods.

The study technician at the study site will arrange 3-, 6- (if needed), 12-, and 36-week consultations for intervention participants. Participants will be reminded of these appointments 1 week in advance. The study technician will call control participants at least once to remind them of their 12-week consultation at the end of the treatment period. The participants will be updated weekly on the progress of the study and reminded of the trial's main components.

Potential issues will be identified by generating monthly statistics on the proportion of participants who complete follow-up visits. The investigators will convene to discuss solutions to these problems and assist the participants in returning to their usual schedule of follow-up visits.

3.5 Participant Withdrawal

Participants will be notified at the time of consent that their participation in this study is completely voluntary and that they can opt out at any time. All withdrawals from the study will be registered by the investigators in the participant's file.

Data gathered prior to participant withdrawal, including Protected Personally Identifiable Information (PPII), may continue to be stored and used accordance with the study objectives and procedures as described in this protocol, unless the participant tells the principal investigator that all participant information must be removed from the study.

Participant withdrawal due to participants' decision:

- A participant may withdraw from the study at any time by notifying the principal investigator and/or another member of the research team by calling the office or sending a withdrawal email to the principal investigator.
- When communicating with the participant, the investigators will ascertain whether the participant wants to withdraw from the whole trial or from just one component. If the latter is preferred, then measurements assessment in the follow-up period for which the participant previously consented may continue.

Participant withdrawal due to investigators' decision:

- If a participant's participation in a trial is terminated by the investigator, the investigator should explain to the participant the reasons for the withdrawal.
- The investigator may terminate a participant's participation in a study to safeguard the person from excessive risk or risk without demonstrable benefits.
- If a participant has a major adverse reaction to the aerobic training, the investigator will advise the participant to stop doing so.
- If a participant violates the data integrity by not following study procedures or providing inaccurate information on purpose, the investigator will terminate the participant's participation in the trial.

Participant withdrawal due to others decision

- If the study sponsor, government or regulatory authorities, or site IRBs/ECs terminate the study prior to the planned end date, the participants will be withdrawn.

4. STUDY TREATMENT/PRODUCT/INTERVENTION

4.1 Treatment/Product/Intervention Formulation/Content

- After participants have been recruited and screened as eligible for participation in the study, the study team member will provide them with the Information Sheet (printed copy or electronic version) and schedule their intervention sessions.
- At the beginning of the intervention, the study team member will review the Information Sheet with the participant.
- Participant will need to sign forms confirming understanding, as well as commitment to clinical trial.
- All data will be recorded and stored through REDCap software.
- The study team will explain the purpose and procedures for the intervention study in each (3 groups: AT, CT, and AC).

- Conducting 12 weeks intervention study in each group.
- After the intervention is done, the participants will require data collection visits for follow-up data of the study 12, 24, 36, and 48 weeks.

4.2 Treatment/Product/Intervention Regimen(s)

We are using a parallel three-armed design in the current RCT:

- Aerobic training (AT)
- AT with cognitive training (CT)
- Activity control (AC)

4.3 Treatment/Product/Intervention Administration

The educational measures include a discussion about participant safety during intervention, the consequences of intervention, and a presentation of the new expected treatment paradigm and the restrictions it places. (Identify the details in the risk IRB). To guarantee that all research staff administer the intervention in the same manner, the PI will provide training sessions that will be required by all personnel administering treatments before the start of the intervention and regularly throughout the treatment period to reduce possible protocol deviations. All members of the study team will be able to ask questions at the training sessions so that they are comfortable with all aspects of the study protocol. For instance, research assistants will perform recruitment and enrollment role-playing exercises to ensure they administer the enrollment procedures the same way and to ensure information being delivered to participants is accurate and complete. They will also be instructed on how to gain informed consent from the study participants. To achieve consistency and replication of the intervention, we will use standardized outcome measurements. Members of the study staff that will be using REDCap will be trained on how to use this database. In addition, we will create a document detailing the processes and flow of the research-related duties and responsibilities for the assistants' reference.

4.4 Adherence Assessment

Outcome measures will be assessed at baseline before implementing the interventions. The participation will last 12 weeks for intervention and require data collection visits for follow-up data of the study, 12, 24 ,36, and 48 weeks (a year). Since all exercise regimens will be conducted at the IMA, we will have a log filled out by the research team member supervising the session, and thus will know exactly how many sessions each participant has completed. If a participant does not attend two sequentially scheduled sessions, a phone call will be made to attempt to contact that participant. In this, attempts will be made to address concerns or limitations to participation. Additionally, if intractable issues arise, participant withdrawal will be discussed.

5. STUDY PROCEDURES

5.1 Stakeholder engagement

As participants were referred and introduced by UW Medicine Center, the research team maintains contact with the center. Communication between the research team and the centers will happen via phone, e-mail, online and in-person meetings. To keep them informed of the research purpose, process, and procedures.

5.2 Participants participate in twelve-week training sessions

Suppose the prospective participants agree to be part of this study. In that case, they will be assigned to one of three study groups: Group A, who will join the cognitive-aerobic bicycle training on a stationary bike connected to a video screen, the aerobic training component consisting of cycling for 50 minutes per session; Group B who will perform cycling training on a stationary bike for 50 minutes per session; Group C will maintain exercise intensity as usual. The random selection to one of the three groups is based on chance. The participation will last 48 weeks and require five data collection visits for baseline and follow-up data on the first day of the study, 12 weeks, 24 week, 36 weeks, and 48 weeks.

5.2.1 Group A -- AT with cognitive training (CT)

If the participants are randomized to group A, they will be invited to come to the University of Washington Intramural Activities Building (IMA) and receive access to the IMA. A research team member will help and assist them in riding on a stationary bike connected to a video screen. The screen will display the video of the scenery of different scenes from countryside, cities, and landmarks of various countries from a first-person's point of view, and the participants can experience an exploration of the tourist spots. Furthermore, the participants are able to choose the desired location they would like to explore. The bike will record the heart rate, the riding distance, and the place they have been to. The training session will be 50 minutes, and the participants are asked to come to the IMA on weekdays 3 times, so a total of 150 minutes per week. The research staff will schedule the days and times with the participants. A trained research staff member will be present for every trial to ensure the safety of the participant as well as ensure all information is properly recorded for each session. Technically, group sessions will be typical, although each participant will have their own bike plus video component and headphones provided.

5.2.2 Group B -- Aerobic training (AT)

If the participants are assigned to Group B, they will be invited to come to the University of Washington Intramural Activities Building (IMA) and receive access to the IMA. A research team member will help and assist them in riding on a stationary bike. It is aerobic training for 50 minutes, and the participants are asked to come to the IMA on weekdays 3 times, so a total of 150 minutes per week. The research staff will schedule the days and times with the participants.

5.2.3 Group C -- Activity control (AC)

If the participants are assigned to Group C, they will be asked to follow their usual exercise habits and treatment plan. The team members will call the participants weekly to check if they continue the treatment and usual physical activity. In addition, during these phone calls, participants will be asked to report their total exercise throughout the week if able. However, inability to record this information is not vital, as SFT will objectively assess physical fitness before and after experimental timeframe.

5.3 Data collection visits

All participants will meet in-person 5 times to collect data and follow up before and after the intervention. The first-time data collection point will be the first day of cycle training for participants in groups A and B; for participants in group C, one team member will contact them to schedule a meeting to collect data. During this first meeting, ADAS-Cog13, HDRS, SFT, and SMRCA assessments will be conducted, and thus a three-hour time slot will be needed. The second will be at 12 weeks, or right after the intervention, the third will be 24 weeks after the study initiation, fourth will be at 36 weeks, and the last will occur at 48 weeks post initiation of intervention. The purpose of each subsequent follow up visit after the initial meeting is to administer surveys and SFT and follow up on the progression of Alzheimer's disease. The process will take approximately two hours for each follow up.

A series of surveys, including a demographic and medical history questionnaire, and questionnaires about cognitive abilities and mood are required to fill by the participants. The surveys include a demographic and medical history questionnaire, Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog), Self-Report Measurement of Cognitive Abilities (SRMCA), All-cause hospital admissions, and Hamilton Depression Rating Scale (HDRS). The SFT will assess physical fitness of the elderly patients, as the tests in this assessment are tailored to daily life tasks for independent living, and thus are tasks the person would need to be able to complete to live independently. Demographic and medical history questionnaires will only be collected for the first time to have the participants' baseline attributes. The rest of the surveys and body measurements will be collected at every point (pre-intervention, 12 weeks, 24 weeks, 36 weeks, and 48 weeks). Note, all research team members who administer the ADAS-Cog13, HDRS, SFT, and SRMCA will be trained on how to properly administer each test, as well as how to properly score it. The training will be conducted by the PIs following the guidelines provided with each assessment, as each assessment comes with documentation regarding proper administration.

6. SAFETY MONITORING AND ADVERSE EVENT REPORTING

The trial data safety monitoring plan will be overseen by the Principal Investigators. The protocol, data collection tools, and consent forms will be reviewed and approved by the UW IRB. A data safety monitoring (DSM) Committee will review key study events including drop-out non-participation in planned study interventions, reports of mental health referrals, events related to activities of daily living, and calls by patients who report distress every 12 weeks. A data safety and monitoring committee (the researcher team) will review the collective of study-related adverse events every month. We do not anticipate the need for 'stopping rules' based on evidence of harm, changes in risks or benefits to participants, or overwhelming evidence of the benefit or lack of benefit of the intervention. However, since our interventions require elderly patients to exercise, a risk of cardiovascular events or other complications are possible. Thus, each session will have a trained research team member present to ensure rapid and appropriate emergency interventions are enacted if necessary. The team members will be trained how CPR, as well as provided with various resources and contacts in case of emergency. UW IRB approval

will be completed before data collection begins. The committee will have access to the study statistician as part of their evaluation. The Committee will prepare a report for the study investigator and study IRBs after each evaluation. The study Project Coordinator will be responsible for assisting DSM committee members in preparing the written reports.

Suggested DSM safety criteria:

- Hospitalization for injury from accidents causes
- Total cardiac-related hospitalizations
- Deaths
- Drop-out due to the study protocol, with increased emotional distress.

For adverse event reporting, in compliance with federal regulations and UW policy, the Principal Investigator will notify the UW Human Subjects Division (HSD) and or UW Institutional Review Board (IRB) of any unanticipated problems within 10 business days. In this study, adverse events and procedure-specific adverse events are expected to be rare. If any occurs, they will be reported to the UW IRB within 24 hours. Any breach or a possible breach of confidentiality of any participants in this study will be reported to UW HSD and/or IRB within the timeframe established by these ethics' committees.

7. STATISTICAL CONSIDERATIONS

7.1 Review of Study Design

This is a phase II, single-blind, cluster-randomized trial to evaluate the clinical efficacy of 12 weeks of AT with CT or 12 weeks of AT in older adults with early mild AD as assessed by ADAS-Cog 13 scores. Measurements of the patient's ADAS-Cog 13 scores will be collected at the start and end of the treatment regimen. Additionally, each patient will have cluster measurements every 12 weeks during the 36-week follow-up period. Thus, each patient will have their ADAS-Cog 13 scores recorded at weeks 0, 12, 24, 36, and 48. Our choice of collecting longitudinal data is to investigate the effect of the interventions on the process of AD over time.

7.2 Endpoints

7.2.1 Primary Endpoints

Consistent with the primary study objective to identify whether exercise with a video component is superior to exercise alone or baseline activity in the context of early AD, the following endpoint will be assessed: ADAS-Cog 13 scores pre- and post-12-week regimen, with calculation of change over duration. Follow up ADAS-Cog 13 assessments will be conducted every 12 weeks for one year.

7.2.2 Secondary Endpoints

Consistent with the secondary study objective to understand how exergame therapy benefits patients, the following endpoints will be assessed:

- Senior fitness test outcomes. Senior fitness test assesses physical fitness in an objective way, which will determine whether a patient is more or less fit doing AT vs CT, which could explain why we see improvements in cognition.

- Self-reported Cognitive Measures (assessed by Self-Report Measurement of Cognitive Abilities: SRMCA). SRMCA is a validated questionnaire that assesses self-reported cognitive function – it will assess how the person feels about their own cognitive status and quality of life.
- All-cause hospital admissions. Since MCI/AD patients are frequently hospitalized for reasons, such as falls or injuries, this is a measure of whether AT vs CT vs control decrease number of hospitalizations over time period we are assessing, as this would be a measure of improved quality of life.
- Hamilton Depression Rating Scale (HDRS). Depression is common among people with AD or other dementias. HDRS is a validated and reliable tool to measure depression symptoms.

7.3 Sample Size Calculation

The sample size was calculated based on the mean difference in ADAS-Cog 13 scores between the AT with CT group and AT group with the control after the treatment regimen at week 12. We will calculate the sample size with 90% power and a one-sided type I error rate of 0.1 with a 1:1:1 for treatment/control ratio. Also, we will account for a 15% expected drop-out rate in our sample size. The formula used for sample size calculation is:

$$n_i = 2 \left(\frac{(Z_{(1-\alpha)} + Z_{1-\beta})}{|\mu_1 - \mu_2|} \right)^2$$

where the appropriate Z values are substituted with α as the type I error rate, $1-\beta$ as the power, $\mu_1 - \mu_2$ represents the clinically meaningful reduction in mean ADAS-Cog 13 scores between the treatment and control groups, and σ is the standard deviation of ADAS-Cog 13 scores in the control group.

Based on results of a study measuring ADAS-Cog 13 scores in patients with mild AD over time, they found at baseline, the standard deviation of ADAS-Cog 13 scores is 7.35³⁷. Additionally, since the treatment regimen will be for 12 weeks, a mean difference of 2 points in the ADAS-Cog 13 scores is expected between the treatment and control groups. Therefore, to detect a 2-point (SD = 7.35) difference in mean ADAS-Cog 13 scores between the exercise groups and control group and to allow for attrition, 209 patients will be required for each group with a total of 627 patients in the RCT.

7.4 Random Assignment

A priori knowledge of group assignment introduces a potential selection bias that could contaminate the data. Therefore, allocation concealment will be implemented so that investigators, subjects, and others are unaware of which group a participant will be assigned to.

Simple randomization can create unbalanced designs, for instance by grouping all samples of the same condition in the same group. To prevent such severe imbalances in sample

allocation with respect to both known and unknown confounders, block randomization will be used. Participants will be randomly assigned to each of the three arms on a 1:1:1 basis using randomly mixed block sizes of 3, 6, and 9. Since the treatment allocation is predictable by the end of a block, the allocator will conceal the block sizes from the executors who will conduct the randomization to prevent them from anticipating the next assignment.

A piece of paper labeled "Intervention (AT)", "Intervention (AT + CT)", or "Control (AC)" will be sealed in a separate, sequentially numbered, non-resealable, opaque envelope for randomization. After a participant has been registered and consented, the next sequentially numbered envelope on the stack will be opened to decide which arm the participant will enter. Research assistants will record the participant's unique respondent identification number (RID) and the arm to which he/she is assigned once the participant has been assigned. A follow-up email will be sent to the assigned participant containing elements of the arm he/she is in.

7.5 Blinding

This study is single blinded. Blinding participants to the group they are assigned to is not possible due to the nature of the intervention arms and the organization of the study. This might influence test performances. To reduce the effect of the observer bias, the outcome assessor assessing the ADAS-cog 13 score and the secondary outcomes will be blinded. The procedure of unblinding is not planned as the intervention is considered safe.

7.6 Interim Analysis

We do not plan an interim analysis since the primary and secondary outcomes do not measure life-threatening survival endpoints, and detectable changes in our target population, using the assessments we intend, do not have that high of sensitivity. Thus, it would be inefficient and burdensome to have interim assessments beyond the every-12-week design.

7.7 Data Analysis

7.7.1 Primary Analyses

The mean and standard deviation of the ADAS-Cog 13 scores in the three groups: AT with CT, AT, and AC, at each time measurement (week 0, 12, 24, 36, 48) will be reported to describe the primary endpoint. Cross-sectional, between group differences in the baseline ADAS-Cog 13 scores will be assessed using analysis of variance (ANOVA). We expect no difference in the baseline measurements between the intervention and control groups.

To assess how ADAS-Cog 13 scores change over time on a population level based on the type of exercise regimen the patients complete, ANOVA will be used for the group comparisons at each measurement beginning at week 12. These comparisons will be implemented using generalized estimating equations (GEE) with an exchangeable working correlation. Using the GEE approach allows us to obtain robust standard errors that account for correlation within clusters of each patient's

respective measures and examine the population average effect. The response will be ADAS-Cog 13 scores ranging from 8 to 85. The fixed covariates will be:

- Time (week 0, 12, 24, 36, 48)
- Group (2=AT with CT, 1=AT, 0=Active Control)
- Time by Group interaction

When calculating treatment effects, activity control will be used as the reference group. When comparing the two treatment groups, AT will be the reference group and the baseline for time will be week 0. To investigate the mean difference in ADAS-Cog 13 scores between the three groups, AT with CT, AT, and AC, point estimates along with 95% confidence intervals for the time by group interaction will be examined and reported. Additionally, statistical significance will be determined at a level of $\alpha = 0.1$.

Groups	Time (week)		Mean \pm SD	Estimate (95% CI)
Aerobic Training (AT) with Cognitive Training (CT)	Treatment	0		(Baseline)
		12		
	Follow-Up	24		
		36		
		48		
	Treatment	0		(Baseline)
		12		
Aerobic Training (AT)	Follow-Up	24		
		36		
		48		
		0		(Reference group)
	Treatment	12		
		24		
		36		
		48		

Table 1: Dummy Table to illustrate mean \pm standard deviation of the ADAS-Cog 13 scores and the point estimates (95% confidence intervals) of time by group interaction.

7.7.2 Secondary Analyses

Secondary endpoints will be recorded and analyzed in a similar format to the primary analysis (see Table 1). Mean, standard deviation, and 95% confidence interval will be reported for continuous data. Percentages/proportions will be reported for categorical data.

The Senior Fitness Test (SFT)

The SFT information will be collected at two time points, before beginning the exercise regimen and at 12 weeks, following completion of the regimen. The SFT does not have a composite score, and thus each individual test result will be recorded

and compared amongst groups. Participants will be separated by sex for analysis, as normal range values are provided by sex. After separating by sex and condition, mean and standard deviation will be calculated for each test, both before and after regimen completion. A one-way ANOVA will be used to determine significance, comparing exercise condition groups.

Self-Report Measures of Cognitive Ability (SRMCA)

The SRMCA will be administered at 0, 12, 24, 36, and 48 weeks, along with the ADAS-Cog 13. The SRMCA does not have true composite scores, but each individual question is on a scale of 1-7, so mean and standard deviation for each question can be calculated between each regimen group. These values can be compared using ANOVA amongst the three conditions to see whether self-reported cognitive measures changed as a result of the regimen they completed.

Hamilton Depression Rating Scale 17 (HDRS17)

The HDRS17 is a clinician-completed assessment of depression symptoms in a person following a structured interview. The HDRS17 will be completed at 0, 12, 24, 36, and 48 weeks, along with SRMCA and ADAS-Cog 13. Since depression is a large confounding variable in AD, we need to assess depression status at each ADAS-Cog 13 measurement. The HDRS17 has 17 questions, rated on a scale of 0-4. A non-depressed person will score between 0-7, while clinical depression typically scores 20 or higher. In between 7-20 can indicate depressive symptoms that do not quite reach threshold of clinical depression. Composite scores will be separated by treatment group, mean and SD calculated, and ANOVA conducted to assess whether statistically significant differences between treatment groups exist. Additionally, statistical analysis of longitudinal score changes within a group will be assessed to determine whether any one of the treatment groups affected depressive symptom presentation throughout duration of the trial.

All Cause Hospital Admissions

We will collect all information regarding hospitalizations during the 48 weeks of the participants' inclusion in the trial. This will be useful information to contextualize our results, as well as ensure no unintended consequences of our therapy occur outside our controlled treatment sessions. This information will be pulled from EMR and REDcap, as well as supplemented with questions regarding this during the follow ups. Each hospital admission will be assigned to a broad category based on chief complaint, and descriptive statistics will be conducted. ANOVA will be used to assess whether statistically significant changes in hospitalization number occur between our groups.

7.8 Missing Data

The main goal will be to collect all data per protocol and minimize the amount of missing data through effective communication with study participants and training of staff. However, participants may drop out of the study due to lack of efficacy, failure to complete exercise regimen, or data may be missing for other reasons unrelated to participant behavior. Therefore, reasons for missing data will also be collected to minimize impact on

statistical analyses and help make the correct assumptions about missing data patterns. To mitigate missing data identified as:

- Missing Completely at Random – All available data for participants who were able to complete the treatment regimen will be used in the primary and secondary analyses
- Missing not at Random (nonignorable missing data) – Appropriate imputation methods will be implemented or if it is determined that specific subgroups are under-represented in the observed data, weighted GEE estimates will be used to compensate for this issue. Besides, Heckman's selection model and pattern-mixture models may also be used.
- Missing at Random (missing at random conditionals on values of observed variables) – Depending on the specifics of the missing data, different methods will be used to handle it. The full information maximum likelihood method handles missing values by finding model parameters that maximize the likelihood if each case's observed data. Inverse probability weighting and multiple imputation may also be implemented for secondary outcomes.

Sensitivity analyses will be conducted to validate assumptions about the type of missing data.

8. HUMAN SUBJECTS CONSIDERATIONS

8.1 Ethical Review

The template informed consent form(s) contained in Appendix — and any subsequent modifications will be reviewed and approved by the UW Institutional Review Board (IRB) with respect to scientific content and compliance with applicable research and human subject's regulations. The protocol, site-specific informed consent form, participant education and recruitment materials, and other requested documents and any subsequent modifications also will be reviewed and approved by the ethical review bodies responsible for oversight of research conducted at the study site. After initial review and approval, the responsible IRBs will review the protocol at least annually. The Investigator will make safety and progress reports to the IRBs at least annually, and within three months of study termination or completion. These reports will include the total number of participants enrolled in the study, the number of participants who completed the study, all changes in the research activity, and all unanticipated problems involving risks to human subjects or others.

8.2 Informed Consent

Prior to the study, the researchers will ask patients who meet the basic inclusion criteria if they are interested in participating in the study, then have the research nurse assess those patients for additional eligibility criteria. If participants have eligibility criteria in the study, the researchers will send participants an electronic copy of the Information Sheet, which will explain the study process and purpose, explain how we will handle privacy and confidentiality, risks and benefits, plans to record the sessions, and what consent to participate in the study means. The Information Sheet will be sent via email. At the beginning of intervention, the study team member will go over the Information Sheet and

answer questions. To ensure that participants understand the consent process the study team members ask participants repeat back the study purpose and procedures. The study team will engage in interactions with the subjects and will make sure to address any questions that they have. The researchers will explain the main parts of the Information Sheet in clear, easy-to-understand language. The researchers will obtain written informed consent with the assurance of the voluntary nature of participation and the ability to withdraw from the study at any time without penalty.

8.3 Risks

The interventions that AT with cognitive training (CT) and aerobic training (AT) are being compared to activity control (AC), who are given no regimen to follow but will instruct to continue with their usual level of activity, both physically and mentally. The study interventions are low risk for causing morbidity or mortality in research participants. The intervention programs are designed to decrease the rate of cognitive decline and improve physical performance with exergame training (aerobic training with cognitive training: CT), yielding more significant benefits than aerobic training and activity control group. However, it is possible that patients might experience injury from accidents during the study. We do not anticipate due to evidence of harm, changes in risks or benefits to subjects, or overwhelming evidence of the intervention's benefit or lack of benefit. The main risk to subjects in research participation is that focusing on the injury from accident intervention may individuals to reflect on the topic more than they would have otherwise. This may lead to emotional distress. Questionnaire items may assess sensitive topics. Minimizing the cognitive load associated with completing questionnaires was a major factor in selecting the questionnaires, and every effort was made to reduce questionnaire completion time to less than 1 hour. Beyond the risk of incurring emotional distress, invasion of privacy, confidentiality, and inconvenience of screening, there are few risks to subjects associated with study data collection and treatment procedures. Participants will be asked to notify the study personnel if and when any difficulties arise. All patients, whether or not they agree to participate in the study, will continue to receive usual care by their designated AD providers throughout the study period. All patients will be fully informed of the purposes of the study. Patient information will be collected through electronic medical record (EMR) review, paper-and-pencil questionnaires, and telephone conversations. Certain specific medical information will be requested from participants' medical records to verify that inclusion criteria are met and to obtain demographic and hospitalization referral information.

Every attempt will be made to honor each participant's right to privacy by using a secure, and locked and password-protected online data storage. Patients will be informed of their rights to withdraw from the study at any point without penalty or effect on their health care, that some memory questions will be asked during telephone screening, and that some questionnaires will ask them to think about emotional topics. The study will use written informed consent approved by the UW IRB. All research study personnel will have completed the required HIPAA and research training.

8.4 Benefits

It is anticipated that this research will lead to more appropriate care of patients with mild AD. The potential risk to patients is reasonable compared to the potential benefits that could derive from the study. Patients who participate may benefit from knowing that they have contributed to knowledge development that will help other patients in the future. It is possible that patients who do not receive the intervention could benefit from the study, if they feel that their experience is noteworthy of study.

8.5 Incentives

The patient incentive for participation is set at US\$390, an amount determined to be attractive without generating economic coercion.

8.6 Confidentiality

Several safeguards will be in place to protect confidentiality. Firstly, all participant data will be coded with a study-specific identification number. Secondly, participants' contact information will be stored separately from the study data along with the identifying numbers. For statistical analysis, information will be in an anonymized format so that no individual can be identified. The original data will be stored on program software and protected by a secure password. Coded data will also be stored on a password-protected computer. Thirdly, all electronic data will be stored on password-protected servers. All information collected for this project will remain anonymous and not used for any other objective, apart from the project and its publication. Only the researcher will have access to participant data during the study. Participant's study information will not be released without the written permission of the participant.

8.7 Study Discontinuation

This study may be discontinued at any time by study sponsor, government or regulatory authorities, or UW IRB/EC.

9. ADMINISTRATIVE PROCEDURES

9.1 Ethical Approval

IRB review is required since this study involves humans and individual-level data about living humans. UW IRB will classify and approve the study based on its possible impact on the health and well-being of study participants. The study protocol and intervention have been described so that UW IRB can perform a thorough review. UW IRB will assess any materials relevant to data collection (e.g., questionnaires) and participant recruiting (e.g., advertising flyers). Most IRBs require at least one month to complete their review, and many advise allowing for a longer review period.

After approval, protocols that have not been exempt are subject to ongoing review, including reporting of any new staff, changes to study procedures, changes to questionnaires used, and reporting of adverse events.

All investigators and study staff who will have direct contact with study participants or access to personally identifiable information will complete the CITI program training course.

9.2 HIPAA Individual Authorization

The study includes data containing personally identifiable information that are considered Protected Health Information (PHI) under HIPAA. A signed record of an individual's authorization will be required.

However, certain requirements of authorization may be waived or altered at the discretion of UW IRB with adequate justification from the investigators. Therefore, the authorization and the informed consent process may be combined.

9.3 Protocol Registration

Before implementing this protocol and any subsequent full-version amendments, the site must have the protocol and protocol consent form approved, as appropriate, by UW IRB/EC and any other applicable regulatory body (RE). Upon receiving final approval, to ensure transparency of the study, the study must be registered on clinicaltrials.gov as well as with UW IRB. This is accomplished by submitting all required protocol registration documents. The UW IRB will examine the submitted protocol registration packet to confirm that all necessary documents have been received.

UW IRB will evaluate and approve site-specific informed consent forms (ICFs) and the site will receive an Initial Registration Notification from UW IRB confirming successful registration. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

9.4 Study Activation

Pending successful protocol registration and submission of all required documents, study staff will "activate" the site to begin study operations. Study implementation may not be initiated until a study activation notice is provided to the site.

9.5 Study Coordination

Study implementation will be directed by this protocol which outline procedures for conducting study visits; data and forms processing; ensuring data safety and storage; AE assessment, management, and reporting; and other study operations.

Study case report forms and other study instruments will be developed by the protocol team. Data will be transferred to the protocol team for data entry, cleaning, reporting and analysis. Quality control reports and queries will be generated and distributed to the study site on a routine schedule for verification and resolution.

Close coordination between protocol team members will be necessary to track study progress, respond to queries about proper study implementation, and address other issues in a timely manner. Rates of accrual, adherence, follow-up, and AE incidence will be monitored closely by the team. The PI and the UW IRB will address issues related to study

eligibility and AE management and reporting as needed to assure consistent case management, documentation, and information-sharing.

9.6 Study Monitoring

On-site study monitoring will be performed to ensure participant safety and trial integrity such that the study is implemented in accordance with the protocol.

Study monitors will visit the site to:

- verify compliance with human subjects and other research regulations and guidelines;
- assess adherence to the study protocol, study-specific procedures manual, and local counseling practices;
- monitor safe and effective delivery of study treatments to study participants;
- assure that the study protocol and the actions of study staff minimize the risks to participants;
- confirm the quality, timeliness, and accuracy of information collected at the study site and entered into the study database; and
- if necessary, recommend early conclusion of a trial when significant benefits or risk have been demonstrated OR when the trial is unlikely to achieve sufficient precision or sample size

Site investigators will allow study monitors to inspect study facilities and documentation (e.g., informed consent forms, clinic and laboratory records, other source documents, case report forms) and watch study operations. In addition, researchers shall permit scrutiny of all study-related documents by authorized representatives and all U.S. and in-country government and regulatory agencies. A log of all site visits will be maintained at the study site to document all visits.

9.7 Protocol Compliance

The study will be conducted in full compliance with the protocol. The protocol will not be amended without prior written approval by the PI and UW IRB. All protocol amendments must be submitted to and approved by UW IRB/EC prior to implementing the amendment.

9.8 Data Security

Informed consent will be obtained in a private counseling room. Every effort will be made to ensure data confidentiality. Only members of the study team will have access to both the paper and electronic data records. The participant-specific respondent identification number (RID) will be used on all case report forms and database reporting. REDCap, a database that is HIPPA-compliant, encrypted, and password protected, will be employed. Any hard copies will be stored in a locked cabinet in a locked office. We will use SMS service that does not collect PHI for text messaging.

Since the study contains PHI, descriptions of data security procedures to safeguard the PHI will be provided to the IRB, the participants, and some funders. This document will include a description of user access controls, data sharing policies, encryption or password policies,

and potential for re-identification. There will be strict adherence to protocols for data management and security.

In order to prevent loss of essential data, such as raw data, treatment assignment lists, and crosswalks between de-identified RIDs and PPII, they will be backed up regularly. (More details in data storage and management in Section 10 - TECHNOLOGY RESOURCES)

9.9 Investigator's Records

Throughout the duration of the study, the study site investigator shall preserve and store in a secure manner, complete, accurate, and up-to-date study records.

The investigators will maintain all study records for a minimum of three years after the completion of the study. Data will be stored in REDCap which is HIPPA compliant, encrypted, and password protected. Work will only be done on password protected computers. Only members of the study team will have study information access.

Study records include

- administrative documentation — including protocol registration documents and all reports and correspondence relating to the study; and
- documentation related to each participant screened for and/or enrolled in the study — including informed consent forms, locator forms, case report forms, notations of all contacts with the participant, and all other source documents.

9.10 Use of Information and Publications

We intend to use the data from this study to compose a manuscript for publication in a reputable peer-reviewed journal. The choice of journal will depend on the study findings, but will likely relate to neuroimaging, Alzheimer's Disease, and cognitive decline.

Some academic journals require data and replication code sharing as a condition of publication. Therefore, it is necessary to obtain permission from the study participants to publish de-identified data. Publication of the results of this study will be governed by the PI. Any presentation, abstract, or manuscript will be made available by the investigators to the PI for review prior to submission.

10. FACILITIES, RESOURCES AND EQUIPMENT

The University of Washington (UW)

The UW, founded in 1861 is one of the nation's premier educational and research institutions. UW faculty and staff are the backbone of the school's continued top-ranking position committed to the pursuit of excellence in education, research, and community service. Ranked No. 16 in the world on the 2020 Academic Ranking of World Universities, the UW educates more than 54,000 students annually. All faculty at the UW

are required to attend training on the ethical conduct of research. All trainees have instruction in the nine elements of responsible conduct of research (I.e., data acquisition, management, sharing, ownership, mentor/trainee responsibilities, publication practices and responsible authorship, peer review, collaborative science, protection of human subjects, research involving animals, research misconduct, and conflict of interest and

commitment). Bioethics & Humanities at the UW provides academic education & professional training in medical humanities through various continuing education activities for practicing health care professionals. The department focuses on issues of justice, health disparities, improving end-of-life care, genetics, & research ethics. The research community at the UW hosts a variety of accessible presentations, supported by schools and departments within the individual Schools of Health Sciences and the Institute of Translational Health Services (ITHS), that highlight state of the art research done by UW and visiting faculty. This gives the faculty a chance to view examples of completed research projects, which may be relevant in their field or using similar methodology.

UW office for Research (UW-OR)

The UW-OR provides numerous resources focused on supporting investigators during applications and throughout the grant lifecycle. This includes helping investigators to adhere to all state and federal compliance standards through our Office of Sponsored Projects. UW-OR offers support for faculty and graduate students who are seeking research funding, including a database that catalogues thousands of funding opportunities tailored to each School's programs of research. The Office of Research Information Systems is constantly developing new electronic tools to facilitate grant application, compliance, and management. The office provides frequent and up-to-date training on scientific writing, grants management, compliance, and other topics via their webpage, through seminars and training sessions.

University of Washington Intramural Activities Building (IMA)

UWIMA has the latest sports facilities such as basketball courts, Crags Climbing Center, badminton courts, gymnasiums, rhythm centers, indoor running track, standard swimming pools, etc. Provide users with a variety of sports and comfortable leisure spaces and updated sports equipment, to help them promote and maintain physical fitness, and relieve tension and pressure. Memberships to the IMA are available on a quarter or annual basis for University of Washington students, UW employees, UW retirees, Plus Ones, and University of Washington Alumni Association (UWAA) Members. The fee is \$70/per quarter for a person.

Office of Nursing Research (ONR)

The ONR provides rich infrastructure which supports the UW School of Nursing (SoN)'s research mission to advance nursing science. UW is among the top ranked SoN in research funding from the National Institutes of Health (NIH), with five centers of research excellence and more than 200 active and pending research projects. ONR offers Statistical & Research Design Consulting to faculty, postdoctoral fellows and PhD students in the SoN. Under the ONR, the Associate Dean for Research (ADR) is responsible for overseeing the infrastructure for all aspects of research within the SoN. The ADR is available to support researchers at every stage of the research project development and implementation; assist individual investigators with identifying which of the UW core facilities can house and support projects; help facilitate networking within the SoN, the University of Washington, and the greater research community as well as assist in the development of the researchers' long-term program of research and

career goals. Through the ONR, the ADR also facilitates faculty access to resources that address issues in grant preparation including, methodology, analysis, statistical methods, grant form preparation, and scientific writing. The ADR leads the Group Consultations (aka Modeling Parties) designed to help faculty, postdoctoral fellows and PhD students develop and critique grant applications. Reviewers are made up of faculty from the SoN or other units on campus who have relevant experience with research design, analysis, the subject matter, and/or have served on internal and external grant review committees. ONR assists the researcher by identifying potential reviewers to provide feedback and coordinating the meeting time, place and any conferencing technology needed.

Statistical & Research Design Consulting

Services are available for faculty, postdoctoral fellows and PhD students in the School of Nursing through the Office for Nursing Research (ONR).

Biostatisticians: Study design and interpretation; advanced statistical analysis methods including logistic regression, random and mixed effects models, survival time analysis, and generalized estimating equations for analysis of clustered data.

Statistician: Multivariate models, variable and selection, graphical models and social networks.

Social & Behavioral Research Consultant: Social and Behavioral Research in naturalistic and community-based settings, qualitative study design from conceptual phase through implementation: research problem definition, appropriate methodology selection, data collection (interview, focus group, participant observation), data analysis/interpretation, mixed method study design.

Survey Design & Research Consultant: Catalyst and REDCap survey design, statistical programming in Stata, panel and pooled time series designs, structural equation models, multi-level modeling longitudinal analysis including latent growth models, random and mixed effects models

Other Research Resources at the University of Washington

The University of Washington Office for Research

The UW Office for Research provides resources that are focused on supporting investigators during applications and throughout the grant lifecycle. The UW Office for Research offers support for faculty who are seeking research funding, including a database that catalogues thousands of funding opportunities. Their Office of Research Information Systems is constantly developing new electronic tools to facilitate grant application, compliance, and management. The office provides training on scientific writing, grants management, compliance, and other topics via their webpage, through seminars, and training sessions (www.washington.edu/research/or/).

Institute of Translational Health Sciences

The UW's Institute of Translational Health Sciences (ITHS) is funded by a Clinical Translational Science Award (CTSA). ITHS is dedicated to speeding science to the clinic

for the benefit of patients and communities throughout Washington, Wyoming, Alaska, Montana, and Idaho. ITHS promotes this translation of scientific discovery to practice by fostering innovative research, cultivating multi-disciplinary research partnerships, and ensuring a pipeline of next generation researchers through robust educational and career development programs. ITHS can support researchers by offering a number of resources, tools, and services. Among its programs are expert consultations in biostatistics, biomedical informatics, and bioethics. The ITHS Education Program supports investigators, scholars and research support staff through the development and maintenance of curriculum and career development education.

The ITHS Research Coordination Center is a multidisciplinary team of research coordinators, regulatory specialists, research nurses, and study monitors who provide creative research staffing solutions for projects involving human subjects. ITHS also offers mentoring in preclinical development of novel therapeutic products, and in clinical trials design and implementation. Their Research Navigator is available for personalized guidance on resources, services and strategies to most effectively translate research from the lab to the clinic.

For investigators that require clinical research space to conduct clinical research, the ITHS maintains the Translational Research Unit (TRU), which is located in the UW Medical Center. The University of Washington Translational Research Unit is a core resource within the Institute of Translational Health Sciences (ITHS) that provides clinical research space and support for investigators conducting research with human subjects. The mission of the TRU is to enable investigators to conduct research protocols in the clinical setting. The TRU offers access to dedicated inpatient and outpatient facilities, ten private and semi-private beds, office and computer space for research teams, a CLIA-certified laboratory, meal services, and two consultation rooms.

The ITHS provides access and administers the UW's Research Electronic Data Capture (REDCap) tool, a rapidly evolving web tool that features a high degree of customizability for forms and advanced user controls. REDCap is a secure web application that can be used to build, collect, and manage online surveys, questionnaires, and databases. REDCap supports HIPAA compliance and has a sophisticated export module with support for all the popular statistical programs. We will use REDCap for collecting and managing the data from this study.

ITHS provides UW investigators with a user friendly, self-service interface (Leaf) for querying the UW Medicine electronic medical records (EMR) system. In de-identified mode, Leaf can be used to plan and design a research study, particularly in relation to recruitment feasibility. With Institutional Review Board approval for human subject research, investigators can interact directly with live, identified data from the EMR system and generate reports in real time to aid in identifying potential research participants. Leaf is supported and administered by the ITHS and UW Medicine analytics team.

University of Washington Libraries

The UW, one of the nation's great public universities, is committed to educating future global citizens and leaders, creating a vibrant intellectual community, and linking academic excellence to cutting edge research through scholarly exploration and intellectual rigor. The Libraries are deeply woven into this fabric of learning and discovery. The UW Libraries ranks among the top North American academic research libraries. The Libraries' collections and services, physical and virtual, provide outstanding support for internationally recognized research in more than 80 doctoral programs while also addressing the learning needs of more than 30,000 undergraduate students across three campuses. Students and faculty rank the Libraries as the most important source of information for their work, and graduating seniors consistently give the Libraries the highest satisfaction rating of any academic service or program. The Libraries were commended in the University's 2003 accreditation review for its rich collections, well-qualified staff, and "exceptional service to students, staff development, and a commitment to planning and assessment of service." In 2004, the Libraries were awarded the prestigious Excellence in Libraries Award from the Association of College and Research Libraries.

Over the past five years, the Libraries have developed a diversified approach to resource use and discovery, which can meet the needs of both new and experienced researchers. The libraries have created digital content from the Libraries' own collections and make widely available what had once been primarily "hidden treasures." Library facilities are being reframed as more flexible learning spaces—collaborative, individual study, instruction, and café environments—to meet a variety of user needs. The libraries have made significant progress toward the goal of becoming a more user-centered, "any time and any place" library. UW faculty, students, and staff enjoy access to a robust and growing digital library, which directly supports their work (www.lib.washington.edu).

We will continue to utilize resources available through the libraries, including librarian support services for literature searches that will be conducted for dissemination of the proposed research.

TECHNOLOGY RESOURCES - University of Washington

Data Management

The University of Washington maintains robust data management resources to facilitate all aspects of safe, rigorous, and reproducible data management. Our University Libraries provide one-on-one consultations to help investigators design a secure data management plan that encompasses the lifespan of the data. Starting with designing the data management plan that is consistent with all local and national standards through to the helping investigators store, preserve and archive data to maximize its value. New UW investigators are encouraged to attend its recurring Research Data Management Workshop, which provides information on basic data stewardship concepts as well as pointers to a host of UW resources.

Data Security

The University of Washington's (UW) computing facilities are managed by UW Information Technology (UW-IT), the central UW computing services organization.

These data centers are secured facilities administered with identity-controlled physical access. The data centers are used for the UW Medical Center (UWMC) clinical systems, as well as for School of Nursing and University administrative systems, and are equipped with fire suppression equipment, redundant power, redundant connectivity, and are located in seismically secure physical facilities. Both clusters are directly connected to the Pacific Northwest GigaPop (the regional Internet-2 high performance network node), for enhanced reliability and high-speed network performance, and located in secure facilities that also house both identified and de-identified patient data used in a variety of clinical and public health research projects, including the University hospitals' operational clinical systems, and access is limited to the security administrators and system programmers. The security infrastructure is driven by concerns about participant privacy and therefore all data systems, whether research or operational, are treated as if they contain identified data.

Database management in the UW School of Nursing is built with multiple layers of security and follows best practices for securing sensitive data. The main levels of security are fourfold and include secure cloud-based security of the primary data sources in the office of principal investigator, data directory access controls, physical server security as described above, and firewall level security. Project computers and drives are all password protected, are protected by the UW SoN firewall, and are in locked offices within a building having limited, electronic passkey access.

Secure Data Transfer

To facilitate the secure transfer of data collected or developed during research (e.g., raw data, data sets, student info, personal health info) the UW has developed a streamlined process for establishing data transfer agreements amongst institutions through CoMotion (<https://comotion.uw.edu/>). Sponsored research involving human subjects, PHI, or restricted data will complete the appropriate DTA, preferably based on the templates developed in the Federal Demonstration Project. The UW Office of Sponsored Projects will review the DTA, and if necessary, negotiate terms on behalf of the PI, and approve the final DTA.

Computer Resources

UW has abundant computer and information and technology (IT) resources, which are sufficient to provide the needs of this project. As with the UWIT division, which is accountable for Communications Solutions & Relationship Management, they deliver support and assistance for the researchers, such as facilitating the delivery of networking and communication services, cooperating with clients to discover strategic solutions to satisfy their necessities, and identifying unique initiatives for inclusion in assistance offerings. If the participants encounter technical issues that the study team is not able to solve, we will refer IT members for assistance.

11. ORGANIZATION AND ADMINISTRATION

This trial is organized in a hierarchical format, with the principal investigators at the top, providing oversight, design and data interpretation, and all aspects regarding approval and management and reporting of the trial. The research assistants will be conducting the day-

to-day aspects of the trial, including survey and assessment administration and scoring, exercise regimen proctoring, and data management. These research assistants will be trained by the PIs and research coordinators to effectively conduct all aspects of the trial. Statisticians will work with both RAs and PIs to analyze data. Finally, the research coordinator will be in control of budget/pay, blinding data analysis, and being the first point of contact for concerns from participants in the trial. Together, this group of individuals will work as a team to efficiently and diligently conduct this trial.

12. BUDGET

Categories	Year 1	Year 2	Year3	Total
01 Salaries Faculty, Staff & Student, % FTE or Hourly	\$298,110	\$298,110	\$298,110	\$894,110
02 Contract Personal Services Reimbursement for Research Subjects, Outside Consultants, Individuals Outside Services	\$598,947	\$598,947	\$598,947	\$3,688,599
03 Other Contractual Services Telephone, Postage/Freight, Membership Dues, Conference Registration, Campus Services (ex: copying, printing), Outside Services	\$33,460	\$4,200	\$4,200	\$37,660
04 Travel Per Diem Lodging/meals/expenses, Air Fare, Mileage, Car Rental	\$0	\$25,120	\$0	\$25,120
05 Supplies and Materials Books, Tapes, Assays, Office Supplies, Equipment, Software	\$ 1,000	\$ 1,000	\$ 1,000	\$ 3,000
06 Equipment Equipment Over \$2,000 (note: equipment/computers purchased with university funds remains the property of the University after completion of study)	\$0	\$0	\$0	\$0
Total Budget	\$1,011,807	\$738,017	\$712,897	\$2,462,722

01 Salaries

Principal investigator

The principal investigator will lead the study, overseeing recruitment, data analysis, obtaining IRB approval, manuscript preparation, and presenting results. Requested effort: 25% (3 calendar months). $\$87,000 * 0.25 * 3 \text{ years} = \$65,250$

Co-principal investigators

Two co-principal investigators will share equal responsibility with the PI for project oversight, budget management, and reporting as part of a multi-investigator team. Requested effort: 20% (3 calendar months). $\$87,000 * 0.25 * 3 \text{ years} = \$65,250$

Statisticians

Two co-principals who work as statisticians will provide service and guidance in collecting, organizing, analyzing, and interpreting data. They interpreted the findings using appropriate statistical methods such as parametric and nonparametric statistical analysis, multiple regression, logistic regression, and analysis of covariance. Requested effort: 20% (3 calendar months). $\$87,000 * 0.25 * 3 \text{ years} = \$65,250$

Research assistants

Ten research assistants will be hired to do the recruitment, data collection, help with data analysis, and present the results. The job description includes assisting in contacting participants, creating and posting invitation flyers, and companying the participants while they are cycling, as well as preliminary data compilation, key in, and coding. The average salary for a research assistant is \$18 per hour in Seattle, WA. $3 \text{ years} * 12 \text{ months} * 4 \text{ weeks} * \$18 * 40 \text{ hr/week} = \$103,680$

Research coordinator

A research coordinator will be hired to manage multiple trial sites, assisting the development of research data from clinical trials, and other administrative matters. The average salary for a research assistant is \$23 per hour in Seattle, WA. $720 \text{ weeks} * \$23 * 3 \text{ hr/week} = \$33,120$

Research technicians

Five research technicians will be hired to facilitate managing the time schedules of participants, providing information and reminders of the study to the participants, identifying potential issues by generating monthly statistics, managing inventories and stock supplies, recording observations, and developing reports for further examination. The average study technician's salary in the USA is \$18 per hour. $3 \text{ years} * 12 \text{ months} * 4 \text{ weeks} * \$18 * 40 \text{ hr/week} = \$103,680$

Physiotherapists

Four physiotherapists will be hired to involve participants in interventions affected by injury, illness, or disability through movement and exercise, manual therapy, education, and advice. They maintain health for participants, helping patients to manage pain and prevent disease. The physiotherapists will meet with the participants three times (1 time: an hour per month) in groups A and B to ensure their postures and movement are correctly and safely.

The average physiotherapist's salary in the USA is \$38.27 per hour. $[209 \text{ (participants group A)} + 209 \text{ (participants group B)}] * 3 \text{ hr} * 38.27 = \$47,991$

02 Contract Personal Services

Research Subjects

A reimbursement fee for data collection: \$30 for completing baseline assessments on the first time point. Participants will be paid an additional \$300 for completing the intervention. Participants will be paid \$30 for each follow-up time point (at 24 weeks, and 36 weeks). $\$390 *$

627 participants will be compiled to thank participants for their time and for sharing information.
 $\$390^* 627 = \$244,530$

03 Other Contractual Services

Telephone costs

It is required to effectively contact the participants. In the investigator's experience, some participants are difficult to reach, while others cannot be contacted again after a voicemail message has been left. To prevent attrition, ten phone service contracts will be purchased for the project period at an estimated cost of $\$35/\text{month}^*12 \text{ month}^*3 \text{ years}^*10 \text{ phone plans} = \$12,600$.

Membership of the Gym

For the participants to ride on the bicycles, $\$70/\text{quarter}^*209^*2 \text{ participants (CT and AT groups)}$.
 $70^*418 \text{ participants} = \$29,260/\text{quarter}$

04 Travel

In case the participants are not able to come to the lab, the research assistant can go visit them at their homes. We estimate that 25% of participants in each group are not able to come to the site. There are 627 study participants, we assume 157 participants might need home visits, and each of whom is assumed to live 20 miles (approximately 30 minutes' drive away) from the researcher's location; the average cost of Uber/Lyft would be \$40/trip. After the intervention is over, data collection will be required at 24 weeks and 36 weeks. Therefore, two home visiting are needed, $157 \text{ participants}^*4(\text{round trips})^* \$40/\text{trip} = \$25,120$

05 Supplies and Materials

Printer and supplies

The project will purchase a printer, ink cartridges, A4 printer paper, and office supplies to be housed within project offices, for exclusive use by this project only. The requisite funds for project-specific supplies are estimated to be \$3,000.

	TOTAL BUDGET	Salary	FTE	YR1 BUDGET	Salary	FTE	YR2 BUDGET	Salary	FTE	YR3 BUDGET
01 - Salaries and Wages										
Joe Voth (PI)	\$ 65,250	\$ 87,000	25.00%	\$ 21,750	\$ 87,000	25.00%	\$ 21,750	\$ 87,000	25.00%	\$ 21,750
Shao-Yun Chien (Co-D)	\$ 65,250	\$ 87,000	25.00%	\$ 21,750	\$ 87,000	25.00%	\$ 21,750	\$ 87,000	25.00%	\$ 21,750
Arunrat Thepna (Co-D)	\$ 65,250	\$ 87,000	25.00%	\$ 21,750	\$ 87,000	25.00%	\$ 21,750	\$ 87,000	25.00%	\$ 21,750
Zhining Sui (Co-I & Statistician)	\$ 65,250	\$ 87,000	25.00%	\$ 21,750	\$ 87,000	25.00%	\$ 21,750	\$ 87,000	25.00%	\$ 21,750
Thu Vu (Co-I & Statistician)	\$ 65,250	\$ 87,000	25.00%	\$ 21,750	\$ 87,000	25.00%	\$ 21,750	\$ 87,000	25.00%	\$ 21,750
TOTAL SALARIES AND WAGES	\$ 326,250			\$ 108,750			\$ 108,750			\$ 108,750
02 - Contract Pers. Services		hrly rate	hours							
Research assistant 1	\$103,680	\$ 18	1,920	\$34,560	\$ 18	1,920	\$ 34,560	\$ 18	1,920	\$ 34,560
Research assistant 2	\$103,680	\$ 18	1,920	\$34,560	\$ 18	1,920	\$ 34,560	\$ 18	1,920	\$ 34,560
Research assistant 3	\$103,680	\$ 18	1,920	\$34,560	\$ 18	1,920	\$ 34,560	\$ 18	1,920	\$ 34,560
Research assistant 4	\$103,680	\$ 18	1,920	\$34,560	\$ 18	1,920	\$ 34,560	\$ 18	1,920	\$ 34,560
Research assistant 5	\$103,680	\$ 18	1,920	\$34,560	\$ 18	1,920	\$ 34,560	\$ 18	1,920	\$ 34,560
Research assistant 6	\$103,680	\$ 18	1,920	\$34,560	\$ 18	1,920	\$ 34,560	\$ 18	1,920	\$ 34,560
Research assistant 7	\$103,680	\$ 18	1,920	\$34,560	\$ 18	1,920	\$ 34,560	\$ 18	1,920	\$ 34,560
Research assistant 8	\$103,680	\$ 18	1,920	\$34,560	\$ 18	1,920	\$ 34,560	\$ 18	1,920	\$ 34,560
Research assistant 9	\$103,680	\$ 18	1,920	\$34,560	\$ 18	1,920	\$ 34,560	\$ 18	1,920	\$ 34,560
Research assistant 10	\$103,680	\$ 18	1,920	\$34,560	\$ 18	1,920	\$ 34,560	\$ 18	1,920	\$ 34,560
Research Coordinator	\$49,680	\$ 23	720	\$16,560	\$ 23	720	\$ 16,560	\$ 23	720	\$ 16,560
Study technician 1	\$103,680	\$ 18	1,920	\$34,560	\$ 18	1,920	\$ 34,560	\$ 18	1,920	\$ 34,560
Study technician 2	\$103,680	\$ 18	1,920	\$34,560	\$ 18	1,920	\$ 34,560	\$ 18	1,920	\$ 34,560
Study technician 3	\$103,680	\$ 18	1,920	\$34,560	\$ 18	1,920	\$ 34,560	\$ 18	1,920	\$ 34,560
Study technician 4	\$103,680	\$ 18	1,920	\$34,560	\$ 18	1,920	\$ 34,560	\$ 18	1,920	\$ 34,560
Study technician 5	\$103,680	\$ 18	1,920	\$34,560	\$ 18	1,920	\$ 34,560	\$ 18	1,920	\$ 34,560
Physiotherapist 1	\$47,991	\$ 38.27	418	\$15,997	\$ 38.27	418	\$ 15,997	\$ 38.27	418	\$ 15,997
Physiotherapist 2	\$47,991	\$ 38.27	418	\$15,997	\$ 38.27	418	\$ 15,997	\$ 38.27	418	\$ 15,997
Physiotherapist 3	\$47,991	\$ 38.27	418	\$15,997	\$ 38.27	418	\$ 15,997	\$ 38.27	418	\$ 15,997
Physiotherapist 4	\$47,991	\$ 38.27	418	\$15,997	\$ 38.27	418	\$ 15,997	\$ 38.27	418	\$ 15,997
TOTAL CONTRACT PERS. SERVICES	\$3,688,599			\$598,947			\$598,947			\$ 598,947
03 - Other Contractual Services	\$ 4,014,849			\$ 707,697			\$ 707,697			\$ 707,697
Telephone calls (10 people)	\$ 8,400	\$ 350	12	\$ 4,200	\$ 350	12	\$ 4,200	\$ 350	12	\$ 4,200
Memberships of the gym for Group A	\$ 14,630	\$ 70	209	\$ 14,630			\$ -			\$ -
Memberships of the gym for Group B	\$ 14,630	\$ 70	209	\$ 14,630			\$ -			\$ -
TOTAL OTHER CONTRACTUAL SERVICES	\$ 37,660			\$ 33,460			\$ 4,200			\$ 4,200
04 - Travel					cost	#				
Cost of Uber/Lyft in SEA	\$ 25,120				\$ 40	628	\$ 25,120			
TOTAL TRAVEL	\$ 25,120			0			\$ 25,120			0
05- Supplies and Materials		cost	#		cost	#		cost	#	
Printers and office supplies	\$ 1,000			\$ 1,000	\$ 1,000		\$ 1,000	\$ 1,000		\$ 1,000
TOTAL SUPPLIES AND MATERIALS	\$ 3,000			\$ 1,000			\$ 1,000			\$ 1,000
06 - Equipment & Library Materials		cost	#		cost	#				
TOTAL EQUIPMENT & LIBRARY MATERIALS										
07 - Retirement & Benefits		cost	#							
Reimbursement for participants	\$292,500	\$ 390	627	\$ 244,530						
TOTAL RETIREMENT & BENEFITS	\$ 244,530			\$ 244,530			0			0
TOTAL EXPENDITURES	\$ 2,462,722.3			\$ 1,011,807			\$ 738,017			\$ 712,897

Budget 3yr spreadsheet

REFERENCE

1. Vlček, Kamil, and Jan Laczó. "Neural correlates of spatial navigation changes in mild cognitive impairment and Alzheimer's disease." *Frontiers in behavioral neuroscience* 8 (2014): 89.
2. Sperling RA, Dickerson BC, Pihlajamaki M, et al. Functional alterations in memory networks in early Alzheimer's disease. *Neuromolecular medicine*. 2010;12(1):27–43.
3. Alzheimer's Association. 2021 Alzheimer's disease facts and figures. *Alzheimer's Dement. 17*, 327–406 (2021).
4. Holthe T, Halvorsrud L, Karterud D, Hoel K, Lund A. Usability and acceptability of technology for community-dwelling older adults with mild cognitive impairment and dementia: a systematic literature review. *Clin Interv Aging*. 2018; Volume 13:863-886. doi:10.2147/cia.s154717
5. Currais A, Huang L, Goldberg J et al. Elevating acetyl-CoA levels reduces aspects of brain aging. *Elife*. 2019;8. doi:10.7554/elife.47866
6. Dementia: a public health priority. Who.int. <https://www.who.int/publications-detail-redirect/dementia-a-public-health-priority>. Published 2022. Accessed May 8, 2022.
7. Dementia. World Health Organization. <https://www.who.int/news-room/fact-sheets/detail/dementia>. Accessed May 8, 2022.
8. Livingston G, Sommerlad A, Orgeta V, et al. Dementia prevention, intervention, and care. *Lancet*. 2017;390(10113):2673-2734.
9. Chen J, Lin K, Chen Y. Risk Factors for Dementia. *Journal of the Formosan Medical Association*. 2009;108(10):754-764. doi:10.1016/s0929-6646(09)60402-2
10. Angevaren M, Aufdemkampe G, Verhaar HJ, Aleman A, Vanhees L. Physical activity and enhanced fitness to improve cognitive function in older people without known cognitive impairment. *Cochrane Database Syst Rev*. 2008;3(3):1-73.
11. Voss MW, Nagamatsu LS, Liu-Ambrose T, Kramer AF. Exercise, brain, and cognition across the life span. *J Appl Physiol*. 2011;111(5):1505-1513.
12. Jackson D, Bowers C, Phillips N, Rampersad N, Leibowitz S. Denying the grim reaper. *Journal of the American Academy of Physician Assistants*. 2017;30(12):1-1. doi: 10.1097/jaa.0000526985.26267.d4
13. Petersen AM, Pedersen BK. The anti-inflammatory effect of exercise. *Journal of Applied Physiology*. 2005;98(4):1154-1162. doi:10.1152/japplphysiol.00164.2004
14. Ekelund U, Steene-Johannessen J, Brown WJ, et al. Does physical activity attenuate, or even eliminate, the detrimental association of sitting time with mortality? A harmonised meta-analysis of data from more than 1 million men and women. *Lancet*. 2016;388(10051):1302-1310.
15. Andersen LB, Schnohr P, Schroll M, Hein HO. All-cause mortality associated with physical activity during leisure time, work, sports, and cycling to work. *Arch Intern Med*. 2000;160(11):1621-1628.
16. Physical Exercise and dementia. Alzheimer's Society (UK). <https://www.alzheimers.org.uk/about-dementia/risk-factors-and-prevention/physical-exercise>. Accessed May 8, 2022.
17. Angevaren M, Aufdemkampe G, Verhaar HJ, Aleman A, Vanhees L. Physical activity and enhanced fitness to improve cognitive function in older people without known cognitive impairment. *Cochrane Database Syst Rev*. 2008;3(3):1-73.

18. Colcombe S, Kramer AF. Fitness effects on the cognitive function of older adults a meta-analytic study. *Psychol Sci*. 2003;14(2):125-130.
19. Smith PJ, Blumenthal JA, Hoffman BM, et al. Aerobic exercise, and neurocognitive performance: a meta-analytic review of randomized controlled trials. *Psychosom Med*. 2010;72(3):239-252.
20. Valenzuela PL, Castillo-García A, Morales JS, et al. Exercise benefits on alzheimer's disease: State-of-the-science. *Ageing Research Reviews*. 2020; 62:101108. doi: 10.1016/j.arr.2020.101108
21. Govindpani, K. et al. Vascular dysfunction in Alzheimer's disease: A prelude to the pathological process or a consequence of it? *J. Clin. Med.* 8, 1–57 (2019).
22. Eggermont L, Swaab D, Luiten P, Scherder E. Exercise, cognition and alzheimer's disease: More is not necessarily better. *Neuroscience & Biobehavioral Reviews*.
23. Song D, Yu DSF, Li PWC, Lei Y. The effectiveness of physical exercise on cognitive and psychological outcomes in individuals with mild cognitive impairment: A systematic review and meta-analysis. *Int JNurs Stud*. 2018; 79:155-164.
24. Heyn P, Abreu BC, Ottenbacher KJ. The effects of exercise training on elderly persons with cognitive impairment and dementia: a meta-analysis. *Arch Phys Med Rehabil*. 2004;85(10):1694-1704.
25. Valenzuela, P. L. et al. Exercise benefits on Alzheimer's disease: State-of-the-science. *Ageing Res. Rev.* 62, 101108 (2020).
26. van der Wardt V, Hancox J, Gondek D, et al. Adherence support strategies for exercise interventions in people with mild cognitive impairment and dementia: A systematic review. *Prev Med Rep*. 2017; 7:38-45
27. van Alphen HJ, Hortobagyi T, van Heuvelen MJ. Barriers, motivators, and facilitators of physical activity in dementia patients: A systematic review. *Arch Gerontol Geriatr*. 2016.
28. Bamidis PD, Fissler P, Papageorgiou SG, et al. Gains in cognition through combined cognitive and physical training: the role of training dosage and severity of neurocognitive disorder. *Front Aging Neurosci*. 2015; 7:152.
29. Fabel K, Kempermann G. Physical activity, and the regulation of neurogenesis in the adult and aging brain. *Neuromolecular Med*. 2008;10(2):59-66.
30. Olson AK, Eadie BD, Ernst C, Christie BR. Environmental enrichment and voluntary exercise massively increase neurogenesis in the adult hippocampus via dissociable pathways. *Hippocampus*. 2006;16(3):250-260.
31. Herold F, Hamacher D, Schega L, Muller NG. Thinking While Moving or Moving While Thinking - Concepts of Motor-Cognitive Training for Cognitive Performance Enhancement. *Front Aging Neurosci*.2018;10:228.
32. Gavelin, H. M. et al. Combined physical and cognitive training for older adults with and without cognitive impairment: A systematic review and network meta-analysis of randomized controlled trials. *Ageing Res. Rev.* 66, 101232 (2021).
33. Frederiksen, Kristian S. et al. Moderate-to-High Intensity Aerobic Exercise in Patients with Mild to Moderate Alzheimer's Disease: A Pilot Study. *International Journal of Geriatric Psychiatry* 29, no. 12 (December 2014): 1242–48
34. Mulyala, K. P. & Varghese, M. The complex relationship between depression and dementia. *Ann. Indian Acad. Neurol.* 13, (2010).

35. Raghavan, N. et al. The ADAS-Cog revisited: Novel composite scales based on ADAS-Cog to improve efficiency in MCI and early AD trials. *Alzheimer's Dement.* 9, 131–146 (2013).
36. Kueper, J. K., Speechley, M. & Montero-Odasso, M. The Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog): Modifications and Responsiveness in Pre-Dementia Populations. A Narrative Review. *J. Alzheimer's Dis.* 63, 423–444 (2018).
37. Podhorna, J., Krahnke, T., Shear, M. & E Harrison, J. Alzheimer's Disease Assessment Scale-Cognitive subscale variants in mild cognitive impairment and mild Alzheimer's disease: Change over time and the effect of enrichment strategies. *Alzheimer's Res. Ther.* 8, (2016).
38. Jones, C.J. and Rikli, R.E. (2002) Measuring Functional Fitness in Older Adults. *The Journal of Active Ageing*, 25-30.
39. Jacobs, K. E. & Roodenburg, J. The development and validation of the Self-Report Measure of Cognitive Abilities: A multitrait-multimethod study. *Intelligence* 42, 5–21 (2014).
40. Herreen, D. & Zajac, I. T. The reliability and validity of a self-report measure of cognitive abilities in older adults: More personality than cognitive function. *J. Intell.* 6, 1–15 (2018).
41. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960; 23:56–62.

APPENDIX I

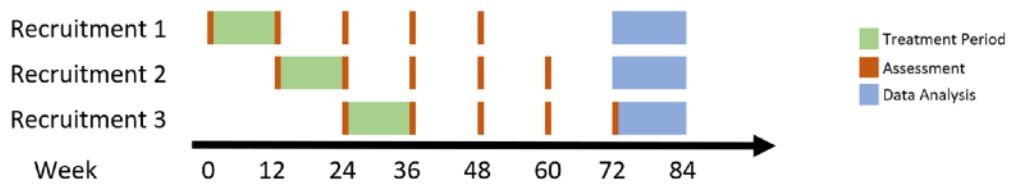
SUMMARY OF MEASURES COLLECTED AT EACH DATA COLLECTION VISIT

Category and measurement	Baseline	Week 12	Week 24	Week 36	Week 48
Informed consent	Yes	No	No	No	No
Age (years)	Yes	No	No	No	No
Race	Yes	No	No	No	No
Education level	Yes	No	No	No	No
Marital status	Yes	No	No	No	No
Employment	Yes	No	No	No	No
Household income	Yes	No	No	No	No
Locator information	Yes	Yes	Yes	Yes	Yes
Resting blood pressure (heart rate)	Yes	Yes	Yes	Yes	Yes
Supplement and medication list	Yes	Yes	Yes	Yes	Yes
Height and weight; BMI	Yes	Yes	Yes	Yes	Yes
SFT	Yes	Yes	No	No	No
ADAS-Cog 13	Yes	Yes	Yes	Yes	Yes
SRMCA	Yes	Yes	Yes	Yes	Yes
HDRS17	Yes	Yes	Yes	Yes	Yes
All-cause hospitalization	Yes	Yes	Yes	Yes	Yes

APPENDIX II

SCHEDULE OF STUDY VISITS

Study Visit	Time	Purpose and Activities
1	Day 0 (Baseline data)	Pre-intervention: Giving information in project and Consent form with participants Baseline assessment and data collection
2	Week 1- 12 (Treatment period)	All Intervention: Group A - AT with cognitive training (CT) Group B - Aerobic training (AT) Group C - Activity control (AC) Consultation in Week 3 and 6 (if needed) for participants in the treatment groups
3	Week 12	Post-intervention: Participant assessment and data collection (Follow up time 1st) Consultation for participants in both treatment and control groups
4	Week 24	Participant assessment and data collection (Follow up time 2nd)
5	Week 36	Participant assessment and data collection (Follow up time 3rd) Consultation for participants in treatment groups
6	Week 48	Participant assessment and data collection (Follow up time 4th)



APPENDIX III

SAMPLE INFORMED CONSENT FORM(S): A preliminary informed consent

Study Information

We are inviting you to participate in a study. This information will help you decide whether or not to participate. If you don't understand, please ask questions. You can choose to be in the study, not be in the study, or take more time to decide.

What is the name of the study?

Exergame-Based Exercise to stave off Cognitive Decline in Mild Alzheimer's disease: A Randomized Control Trials

Who is in charge of the study?

The Research Team:

Name	Department	E-mail
Shao-Yun Chien	Nursing	schien2@uw.edu
Zhining Sui	Biostatistics	zsui0603@uw.edu
Arunrat Thepna	Nursing	arunrat@uw.edu
Joe Voth	Medicine	jpvoth@uw.edu
Thu Vu	Biostatistics	tvu2@uw.edu

Organization: University of Washington, Seattle, WA

Why am I being invited to take part in a research study?

We invite you to take part in our research as a person living with Mild Alzheimer's disease.

Why is this research being done?

The purpose of this research is to learn if cognitive-aerobic bicycle training on a stationary bike is helpful for people with mild Alzheimer's disease age 65 and older to slow down the progression of cognitive decline. We are curious to find out whether cognitive-aerobic bicycle training will be helpful compared to regular bicycle training and usual exercise intensity. If you choose to be part of this study, you will be randomly assigned (like with a flip of a coin) to one of three study groups: Group A, who will join the cognitive-aerobic bicycle training on a stationary bike connected to a video screen, the aerobic training component consisted of cycling for 50 minutes per session; Group B who will perform cycling training on a stationary bike for 50 minutes per session; Group C will maintain exercise intensity as usual.

Study procedure: what will happen to me in the study?

If you choose to be part of this study, you will be assigned to one of the groups randomly, cognitive-aerobic bicycle training, normal cycling training, or the control group. This random selection to one of the three groups is based on chance. Your participation will last 48 weeks and

will require five data collection visits for having baseline and follow-up data on the first day of the study, 12 weeks, 24 weeks, 36 weeks, and 48 weeks.

Group A

If you are randomized to the group, you will be invited to come to the University of Washington Intramural Activities Building (IMA) and receive access to the IMA. A member of the research team will help you and assist you to ride on a stationary bike connected to a video screen. On the screen, it will display the video of the scenery of different countries from a first-person's point of view, which is like you are actually exploring the tourist spots. Furthermore, you are able to choose the desired location you would like to explore. The bike will record your heart rate, the distance you ride, and the place you have been to. The training session will be 50 minutes, and please come to the IMA on weekdays 3 times, so a total of 150 minutes per week. The research staff will schedule the days and times you are coming.

Group B

If you are assigned to Group B, you will be invited to come to the University of Washington Intramural Activities Building (IMA) and receive access to the IMA. A member of the research team will help you and assist you to ride on a stationary bike. It is aerobic training for 50 minutes, and please come to the IMA on weekdays 3 times, so a total of 150 minutes per week. The research staff will schedule the days and times you are coming.

Group C

If you are assigned to Group C, please follow your usual exercise habits and treatment plan. The team members will call you weekly to check if you continue the treatment and usual physical activity.

Data collection visits

All participants will meet in-person 5 times for collecting data and follow-up before and after the intervention, please come to the University of Washington facility, and a member of the research staff will help you to collect the surveys and body measurements. The first visit will be the first day of the intervention, the second will be in week 12, right after the intervention, the third will be 24 weeks after the study initiation, the fourth will be in week 36 and the last will take place in week 48. The purpose of the visit is to collect surveys from you and follow up on the progression of Alzheimer's disease. The process will last approximately an hour.

Study Visit

The following will occur at the study visit:

1. Surveys: You will complete a series of surveys including a demographic and medical history questionnaire, and questionnaires about your cognitive abilities and mood.
2. Body measurements: We will conduct a senior fitness test that measures your heart's ability to respond to exercise in a controlled clinical environment. Your heart rate and blood pressure will be measured, and we will help you connect to an electrocardiogram (ECG) to collect related data.

How long would I be in the study?

If you choose to take part in all the study visits, you would be in the study for 48 weeks. The intervention will be 12 weeks, we will follow up on your condition at 12, 24, 36, and 48 weeks

after the study is initiated. You may refuse to participate, and you are free to withdraw from this study at any time without penalty or loss of benefits to which you are otherwise entitled. If you wish to withdraw, please contact the researcher listed on page 1 of this consent form.

Alternatives to taking part in this study

If you are interested in seeking information about cognitive cycling training and do not want to participate in this study, please check with Shao-Yun Chien: (206)227-4997.

What are the potential benefits if I join this study?

You may benefit from engaging in the research process to help improve cognitive resilience, while also improving mood and overall health. We hope that the results of this study will help develop knowledge and measures for older adults with Alzheimer's disease in the future; guide the development of new interventions combining cognitive training and physical activities for the older population.

What are the potential harms or risks if I join this study?

In general, there are small risks if you take part in this study.

Cycling training: Stationary bikes are safer than riding a bike outside on the road, but there are still potential harms or risks. Over-stress your muscles, tendons, and joints might happen from repetitive motion or from using incorrect posture and cause muscle fatigue or pain. There is the possibility of falling off the bike or injuring yourself if you balance yourself inaccurately.

Please adjust the training of the day according to your own physical fitness and tolerance. If you feel any discomfort such as difficulty breathing or shortness of breath, pain or pressure in the chest or abdomen, please suspend the training and rest for a while; if the situation does not improve, please seek medical attention as soon as possible and contact the researcher.

Answering questions: When filling out questionnaires, you may feel that answering questions about yourself is uncomfortable, an inconvenience, or an invasion of privacy. If you feel uncomfortable about any of the questionnaire information, you do not need to complete the questionnaire. You are able to choose whether or not to answer the question and the level of disclosure.

Confidentiality: You may feel that participating in the study involves a loss of privacy. Confidentiality and privacy of your data are the researchers will strive to maintain. All of the information you provide will be confidential. Confidentiality and privacy of participant data will be strictly maintained by the researchers. Any identifiable records and personal privacy data will be kept confidential and will not be disclosed. You will be assigned a study identification (ID) number when you joined the study. This ID number is used to encode the data during analysis. In order to protect your identity and information of you, all data will be stored on computers with passwords, and only the researchers of this study can access and use it. The researchers will ensure the confidentiality and privacy of the data.

The identities of the participants will remain confidential when the study results are published in the future. Government or university staff sometimes review studies such as this one to make sure they are being done safely and legally. If a review of this study takes place, your records

may be examined. The reviewers will protect your privacy. The study records will not be used to put you at legal risk of harm.

A description of this clinical trial will be available on <http://www.clinicaltrials.gov>, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

We have a Certificate of Confidentiality from the federal National Institutes of Health. This helps us protect your privacy. The Certificate means that we do not have to give out information, documents, or samples that could identify you even if we are asked to by a court of law. We will use the Certificate to resist any demands for identifying information.

We can't use the Certificate to withhold your research information if you give your written consent to give it to an insurer, employer, or other people. Also, you or a member of your family can share information about yourself or your part in this research if you wish.

There are some limits to this protection. We will voluntarily provide the information to:

- a member of the federal government who needs it in order to audit or evaluate the research;
- individuals at the institution(s) conducting the research, the funding agency, and other groups involved in the research, if they need the information to make sure the research is being done correctly;
- the federal Food and Drug Administration (FDA), if required by the FDA;
- individuals who want to conduct secondary research if allowed by federal regulations and according to your consent for future research use as described in this form;
- State and local authorities, if we learn of child abuse, elder abuse, or the intent to harm yourself or others.

Government or university staff sometimes review studies such as this one to make sure they are being done safely and legally. If a review of this study takes place, your records may be examined. The reviewers will protect your privacy. The study records will not be used to put you at legal risk of harm.

A description of this clinical trial will be available on <http://www.clinicaltrials.gov>, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Using Your Data in Future Research

The information that we obtain from you for this study might be used for future studies. We may remove anything that might identify you from the information. If we do so, that information may then be used for future research studies or given to another investigator without getting additional permission from you. It is also possible that in the future we may want to use or share study information that might identify you. If we do, a review board will decide whether or not we need to get additional permission from you.

Other information

In return for your time, effort, and sharing, you will be paid a total of \$390 for taking part in this study: \$300 for complete the training, \$90 for the completion of the surveys and senior fitness test in the follow-up period.

You may refuse to participate, and you are free to withdraw from this study at any time without penalty or loss of benefits to which you are otherwise entitled. If you wish to withdraw, please contact the researcher listed on page 1 of this consent form.

Research-related injury

If you think you have an injury or illness related to this study, contact Shao-Yun Chien at (206)227-4997, and you will be referred for treatment.

Consent Presenter Statement

I have provided this participant and/or their legally authorized representative (LAR) with information about this study. The participant/LAR has been given sufficient time to consider participation and I have answered any questions they had. The participant and/or their LAR indicated that they understand the nature of the study, including risks and benefits of participating.

Printed name of study staff obtaining consent

Date

Subject's statement

This study has been explained to me. I volunteer to take part in this research. I have had a chance to ask questions. If I have questions later about the research, or if I have been harmed by participating in this study, I can contact one of the researchers listed on the first page of this consent form. If I have questions about my rights as a research subject, I can call the Human Subjects Division at (206) 543-0098 or call collect at (206) 221-5940. I will receive a copy of this consent form.

Printed name of subject

Signature of subject

Date

Copies to: Researcher Subject

APPENDIX IV

SAMPLE INFORMED

ADAS-Cog 13 – Note: this is form the person ADMINISTERING the ADAS-Cog 13 fills out, not the form the patient sees. The patient does not have any form, they are just asked questions following a format provided in the ADAS-Cog 13 manual.

Alzheimer's Disease Cooperative Study ADAS – Cognitive Behavior SAMPLE FORM – Page 1 of 4				
Center Name	Patient Number	Patient Initials	Examiner Initials	Examination Date
P R - - 				Month Day Year
1. WORD RECALL TASK: Indicate the total number of <i>correct</i> responses for each trial			7. WORD RECOGNITION TASK: Scoring will be done by the A.D.C.S. Data Coordinating Center.	
<input type="checkbox"/> Trial 1 <input type="checkbox"/>	<input type="checkbox"/> Trial 2 <input type="checkbox"/>	<input type="checkbox"/> Trial 3 <input type="checkbox"/>	<input type="checkbox"/> Trial 1 <input type="checkbox"/>	<input type="checkbox"/> Trial 2 <input type="checkbox"/>
2. NAMING OBJECTS AND FINGERS: Check each object/finger named <i>correctly</i> or check "NONE."			8. LANGUAGE: Check level of impairment.	
<input type="checkbox"/> Flower <input type="checkbox"/> Rattle <input type="checkbox"/> Wallet <input type="checkbox"/> Bed <input type="checkbox"/> Mask <input type="checkbox"/> Harmonica <input type="checkbox"/> Whistle <input type="checkbox"/> Scissors <input type="checkbox"/> Stethoscope <input type="checkbox"/> Pencil <input type="checkbox"/> Comb <input type="checkbox"/> Tongs <input type="checkbox"/> Thumb <input type="checkbox"/> Index <input type="checkbox"/> Ring <input type="checkbox"/> Pinky <input type="checkbox"/> Middle			<input type="checkbox"/> None: patient speaks clearly and/or is understandable. <input type="checkbox"/> Very Mild: one instance of lack of understandability. <input type="checkbox"/> Mild: patient has difficulty < 25% of the time. <input type="checkbox"/> Moderate: patient has difficulty 25–50% of the time. <input type="checkbox"/> Moderately Severe: patient has difficulty more than 50% of the time. <input type="checkbox"/> Severe: one- or two-word utterances; fluent, but empty speech; mute.	
3. COMMANDS: Check each command performed <i>correctly</i> or check "NONE."			9. COMPREHENSION OF SPOKEN LANGUAGE: Check level of impairment	
<input type="checkbox"/> Make a fist. <input type="checkbox"/> Point to the <u>ceiling</u> , then to the <u>floor</u> . <input type="checkbox"/> Put the <u>pencil</u> on top of the <u>card</u> , then <u>put it back</u> . <input type="checkbox"/> Put the <u>watch</u> on the <u>other side of the pencil</u> and <u>turn over</u> the <u>card</u> . <input type="checkbox"/> Tap each shoulder twice with <u>two fingers</u> keeping your <u>eyes shut</u> .			<input type="checkbox"/> None: patient understands. <input type="checkbox"/> Very Mild: one instance of misunderstanding. <input type="checkbox"/> Mild: 3–5 instances of misunderstanding. <input type="checkbox"/> Moderate: requires several repetitions and rephrasing. <input type="checkbox"/> Moderately Severe: patient only occasionally responds correctly; i.e., yes – no questions. <input type="checkbox"/> Severe: patient rarely responds to questions appropriately; not due to poverty of speech.	
4. CONSTRUCTIONAL PRAXIS: Check each figure drawn <i>correctly</i> .			10. WORD FINDING DIFFICULTY: Check one response.	
<input type="checkbox"/> None: attempted but drew no forms correctly. <input type="checkbox"/> Patient drew no forms; scribbled; wrote words. <input type="checkbox"/> Circle <input type="checkbox"/> Two overlapping rectangles <input type="checkbox"/> Rhombus <input type="checkbox"/> Cube			<input type="checkbox"/> None. <input type="checkbox"/> Very Mild: 1 or 2 instances, not clinically significant. <input type="checkbox"/> Mild: noticeable circumlocution or synonym substitution. <input type="checkbox"/> Moderate: loss of words without compensation on occasion. <input type="checkbox"/> Moderately Severe: frequent loss of words without compensation. <input type="checkbox"/> Severe: nearly total loss of content words; speech sounds empty; 1- to 2-word utterances.	
5. IDEATIONAL PRAXIS: Check each step completed <i>correctly</i> or check "NONE."			11. REMEMBERING TEST INSTRUCTIONS: Check level of impairment.	
<input type="checkbox"/> Fold a letter. <input type="checkbox"/> Put letter in envelope. <input type="checkbox"/> Seal envelope. <input type="checkbox"/> Address envelope. <input type="checkbox"/> Indicate where stamp goes.			<input type="checkbox"/> None. <input type="checkbox"/> Very Mild: forgets once. <input type="checkbox"/> Mild: must be reminded 2 times. <input type="checkbox"/> Moderate: must be reminded 3–4 times. <input type="checkbox"/> Moderately Severe: must be reminded 5–6 times <input type="checkbox"/> Severe: must be reminded 7 or more times.	
6. ORIENTATION: Check each item answered <i>correctly</i> or check "NONE."				
<input type="checkbox"/> Full name <input type="checkbox"/> Day <input type="checkbox"/> Month <input type="checkbox"/> Season <input type="checkbox"/> Date <input type="checkbox"/> Place <input type="checkbox"/> Year <input type="checkbox"/> Time of day				

WHITE- ADCS COPY

YELLOW- INVESTIGATOR'S COPY

PINK- CLINICAL MONITOR'S COPY

Alzheimer's Disease Cooperative Study ADAS – Word Recall SAMPLE FORM – Page 2 of 4								
Center Name	Patient Number P R - <table border="1" style="display: inline-table; vertical-align: middle;"><tr><td style="width: 15px; height: 15px;"></td><td style="width: 15px; height: 15px;"></td></tr></table> <table border="1" style="display: inline-table; vertical-align: middle;"><tr><td style="width: 15px; height: 15px;"></td><td style="width: 15px; height: 15px;"></td></tr></table>					Patient Initials <table border="1" style="display: inline-table; width: 15px; height: 15px;"></table> <table border="1" style="display: inline-table; width: 15px; height: 15px;"></table> <table border="1" style="display: inline-table; width: 15px; height: 15px;"></table>	Examiner Initials <table border="1" style="display: inline-table; width: 15px; height: 15px;"></table> <table border="1" style="display: inline-table; width: 15px; height: 15px;"></table>	Examination Date <table border="1" style="display: inline-table; width: 15px; height: 15px;"></table> <table border="1" style="display: inline-table; width: 15px; height: 15px;"></table> Month Day Year
Present Word List #2.								
Check EACH word correctly recalled.								
TRIAL 1		TRIAL 2		TRIAL 3				
BOTTLE		FOREST		GIRL				
POTATO		TEMPLE		TEMPLE				
GIRL		BOTTLE		POTATO				
TEMPLE		STAR		ANIMAL				
STAR		POTATO		FOREST				
ANIMAL		GIRL		LAKE				
FOREST		CLOCK		OFFICE				
LAKE		ANIMAL		CLOCK				
CLOCK		LAKE		BOTTLE				
OFFICE		OFFICE		STAR				
TOTAL	<table border="1" style="width: 15px; height: 15px;"></table>	TOTAL	<table border="1" style="width: 15px; height: 15px;"></table>	TOTAL	<table border="1" style="width: 15px; height: 15px;"></table>			
Indicate total number of words correctly recalled for EACH trial on the ADAS Cognitive Behavior Form.								
12. Executive Function (Maze): a. <table border="1" style="display: inline-table; width: 15px; height: 15px;"></table> number of errors b. <table border="1" style="display: inline-table; width: 15px; height: 15px;"></table> time at completion or second error (total seconds)			If any item(s) 1-13 are incomplete or not done, please specify reason: <input type="checkbox"/> Subject too cognitively impaired to complete <input type="checkbox"/> Subject was unable to complete for physical reasons <input type="checkbox"/> Subject refused <input type="checkbox"/> Not Done, for reason other than above explain: _____ <hr/> <hr/> <hr/>					
13. Number Cancellation: a. <table border="1" style="display: inline-table; width: 15px; height: 15px;"></table> number of targets hit (Range: 0 - 40) b. <table border="1" style="display: inline-table; width: 15px; height: 15px;"></table> number of errors c. <table border="1" style="display: inline-table; width: 15px; height: 15px;"></table> number of times to remind of task								

WHITE- ADCS COPY

YELLOW- INVESTIGATOR'S COPY

PINK- CLINICAL MONITOR'S COPY

Alzheimer's Disease Cooperative Study

ADAS – Delayed Recall
SAMPLE FORM – Page 3 of 4

Center Name	Patient Number P R - <input type="text"/> <input type="text"/> <input type="text"/>	Patient Initials <input type="text"/> <input type="text"/> <input type="text"/>	Examiner Initials <input type="text"/> <input type="text"/> <input type="text"/>	Examination Date <input type="text"/> <input type="text"/> <input type="text"/> Month Day Year
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Instructions: Say to the patient, "NOW I WANT YOU TO TRY TO REMEMBER THE WORDS THAT I SHOWED YOU EARLIER ON PRINTED CARDS. CAN YOU TELL ME ANY OF THOSE WORDS?"

Allow a maximum of two minutes for recall.

check EACH word correctly recalled.

BOTTLE	<input type="checkbox"/>
POTATO	<input type="checkbox"/>
GIRL	<input type="checkbox"/>
TEMPLE	<input type="checkbox"/>
STAR	<input type="checkbox"/>
ANIMAL	<input type="checkbox"/>
FOREST	<input type="checkbox"/>
LAKE	<input type="checkbox"/>
CLOCK	<input type="checkbox"/>
OFFICE	<input type="checkbox"/>
TOTAL	<input type="checkbox"/>

WHITE- ADCS COPY

YELLOW- INVESTIGATOR'S COPY

PINK- CLINICAL MONITOR'S COPY

Alzheimer's Disease Cooperative Study ADAS – Word Recognition SAMPLE FORM – Page 4 of 4																																																																																																																																																																																																																															
Center Name	Patient Number P R - <input type="text"/> - <input type="text"/>	Patient Initials	Examiner Initials	Examination Date <input type="text"/> / <input type="text"/> / <input type="text"/> Month Day Year																																																																																																																																																																																																																											
Present Word List #2.																																																																																																																																																																																																																															
<p>Check subject's response for each word. Subject should respond "yes" to original words which are bolded. INCORRECT responses are shaded. Three trials of reading and recognition are given.</p> <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 33%; vertical-align: top;"> <table style="width: 100%; border-collapse: collapse;"> <tr><td>COST</td><td style="text-align: center;">Yes</td><td style="text-align: center;">No</td></tr> <tr><td>NATION</td><td style="background-color: #cccccc;"></td><td></td></tr> <tr><td>CHIMNEY</td><td style="background-color: #cccccc;"></td><td></td></tr> <tr><td>SPARROW</td><td style="background-color: #cccccc;"></td><td></td></tr> <tr><td>DAMAGES</td><td style="background-color: #cccccc;"></td><td></td></tr> <tr><td>TRAFFIC</td><td style="background-color: #cccccc;"></td><td></td></tr> <tr><td>SANDWICH</td><td style="background-color: #cccccc;"></td><td></td></tr> <tr><td>SERVICE</td><td style="background-color: #cccccc;"></td><td></td></tr> <tr><td>SHELL</td><td style="background-color: #cccccc;"></td><td></td></tr> <tr><td>SOLUTION</td><td style="background-color: #cccccc;"></td><td></td></tr> <tr><td>YARD</td><td style="background-color: #cccccc;"></td><td></td></tr> <tr><td>TUBE</td><td style="background-color: #cccccc;"></td><td></td></tr> <tr><td>BODY</td><td style="background-color: #cccccc;"></td><td></td></tr> <tr><td>GROUND</td><td style="background-color: #cccccc;"></td><td></td></tr> <tr><td>STICK</td><td style="background-color: #cccccc;"></td><td></td></tr> <tr><td>ENGINE</td><td style="background-color: #cccccc;"></td><td></td></tr> <tr><td>RICHES</td><td style="background-color: #cccccc;"></td><td></td></tr> <tr><td>GRAVITY</td><td style="background-color: #cccccc;"></td><td></td></tr> <tr><td>SUMMER</td><td style="background-color: #cccccc;"></td><td></td></tr> <tr><td>WISDOM</td><td style="background-color: #cccccc;"></td><td></td></tr> <tr><td>MAN</td><td style="background-color: #cccccc;"></td><td></td></tr> <tr><td>MEAL</td><td style="background-color: #cccccc;"></td><td></td></tr> <tr><td>PASSENGER</td><td style="background-color: #cccccc;"></td><td></td></tr> <tr><td>ACID</td><td style="background-color: #cccccc;"></td><td></td></tr> </table> </td> <td style="width: 33%; 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WHITE- ADCS COPY

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PINK- CLINICAL MONITOR'S COPY

HDRS: Note – this form is also filled out by a trained research member, not the participant.

Hamilton Depression Rating Scale (HDRS)	
PLEASE COMPLETE THE SCALE BASED ON A STRUCTURED INTERVIEW	
<p>Instructions: for each item select the one "cue" which best characterizes the patient. Be sure to record the answers in the appropriate spaces (positions 0 through 4).</p>	
1 DEPRESSED MOOD (sadness, hopeless, helpless, worthless)	2 FEELINGS OF GUILT
0 <input type="checkbox"/> Absent. 1 <input type="checkbox"/> These feeling states indicated only on questioning. 2 <input type="checkbox"/> These feeling states spontaneously reported verbally. 3 <input type="checkbox"/> Communicates feeling states non-verbally, i.e. through facial expression, posture, voice and tendency to weep. 4 <input type="checkbox"/> Patient reports virtually only these feeling states in his/her spontaneous verbal and non-verbal communication.	0 <input type="checkbox"/> Absent. 1 <input type="checkbox"/> Self reproach, feels he/she has let people down. 2 <input type="checkbox"/> Ideas of guilt or rumination over past errors or sinful deeds. 3 <input type="checkbox"/> Present illness is a punishment. Delusions of guilt. 4 <input type="checkbox"/> Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations.
28	
3 SUICIDE 0 <input type="checkbox"/> Absent. 1 <input type="checkbox"/> Feels life is not worth living. 2 <input type="checkbox"/> Wishes he/she were dead or any thoughts of possible death to self. 3 <input type="checkbox"/> Ideas or gestures of suicide. 4 <input type="checkbox"/> Attempts at suicide (any serious attempt rate 4).	11 ANXIETY SOMATIC (physiological concomitants of anxiety) such as: gastro-intestinal – dry mouth, wind, indigestion, diarrhea, cramps, belching cardio-vascular – palpitations, headaches respiratory – hyperventilation, sighing urinary frequency sweating 0 <input type="checkbox"/> Absent. 1 <input type="checkbox"/> Mild. 2 <input type="checkbox"/> Moderate. 3 <input type="checkbox"/> Severe. 4 <input type="checkbox"/> Incapacitating.
4 INSOMNIA: EARLY IN THE NIGHT 0 <input type="checkbox"/> No difficulty falling asleep. 1 <input type="checkbox"/> Complains of occasional difficulty falling asleep, i.e. more than $\frac{1}{2}$ hour. 2 <input type="checkbox"/> Complains of nightly difficulty falling asleep.	12 SOMATIC SYMPTOMS GASTRO-INTESTINAL 0 <input type="checkbox"/> None. 1 <input type="checkbox"/> Loss of appetite but eating without staff encouragement. Heavy feelings in abdomen. 2 <input type="checkbox"/> Difficulty eating without staff urging. Requests or requires laxatives or medication for bowels or medication for gastro-intestinal symptoms.
5 INSOMNIA: MIDDLE OF THE NIGHT 0 <input type="checkbox"/> No difficulty. 1 <input type="checkbox"/> Patient complains of being restless and disturbed during the night. 2 <input type="checkbox"/> Waking during the night – any getting out of bed rates 2 (except for purposes of voiding).	13 GENERAL SOMATIC SYMPTOMS 0 <input type="checkbox"/> None. 1 <input type="checkbox"/> Headaches in limbs, back or head. Backaches, headaches, muscle aches. Loss of energy and fatigability. 2 <input type="checkbox"/> Any clear-cut symptom rates 2.
6 INSOMNIA: EARLY HOURS OF THE MORNING 0 <input type="checkbox"/> No difficulty. 1 <input type="checkbox"/> Waking in early hours of the morning but goes back to sleep. 2 <input type="checkbox"/> Unable to fall asleep again if he/she gets out of bed.	14 GENITAL SYMPTOMS (symptoms such as loss of libido, menstrual disturbances) 0 <input type="checkbox"/> Absent. 1 <input type="checkbox"/> Mild. 2 <input type="checkbox"/> Severe.
7 WORK AND ACTIVITIES 0 <input type="checkbox"/> No difficulty. 1 <input type="checkbox"/> Thoughts and feelings of incapacity, fatigue or weakness related to activities, work or hobbies. 2 <input type="checkbox"/> Loss of interest in activity, hobbies or work – either directly reported by the patient or indirect in listlessness, indecision and vacillation (feels he/she has to push self to work or activities). 3 <input type="checkbox"/> Decrease in actual time spent in activities or decrease in productivity. Rate 3 if the patient does not spend at least three hours a day in activities (job or hobbies) excluding routine chores. 4 <input type="checkbox"/> Stopped working because of present illness. Rate 4 if patient engages in no activities except routine chores, or if patient fails to perform routine chores unassisted.	15 HYPOCHONDRIASIS 0 <input type="checkbox"/> Not present. 1 <input type="checkbox"/> Self-absorption (body). 2 <input type="checkbox"/> Preoccupation with health. 3 <input type="checkbox"/> Frequent complaints, requests for help, etc. 4 <input type="checkbox"/> Hypochondriacal delusions.
8 RETARDATION (slowness of thought and speech, impaired ability to concentrate, decreased motor activity)	16 LOSS OF WEIGHT (RATE EITHER a OR b) a) According to the patient: b) According to weekly measurements: 0 <input type="checkbox"/> No weight loss. 0 <input type="checkbox"/> Less than 1 lb weight loss in week. 1 <input type="checkbox"/> Slight retardation during the interview. 2 <input type="checkbox"/> Obvious retardation during the interview. 3 <input type="checkbox"/> Interview difficult. 4 <input type="checkbox"/> Complete stupor.
9 AGITATION 0 <input type="checkbox"/> None. 1 <input type="checkbox"/> Fidgetiness. 2 <input type="checkbox"/> Playing with hands, hair, etc. 3 <input type="checkbox"/> Moving about, can't sit still. 4 <input type="checkbox"/> Hand wringing, nail biting, hair-pulling, biting of lips.	17 INSIGHT 0 <input type="checkbox"/> Acknowledges being depressed and ill. 1 <input type="checkbox"/> Acknowledges illness but attributes cause to bad food, climate, overwork, virus, need for rest, etc. 2 <input type="checkbox"/> Denies being ill at all.
10 ANXIETY PSYCHIC 0 <input type="checkbox"/> No difficulty. 1 <input type="checkbox"/> Subjective tension and irritability. 2 <input type="checkbox"/> Worrying about minor matters. 3 <input type="checkbox"/> Apprehensive attitude apparent in face or speech. 4 <input type="checkbox"/> Fears expressed without questioning.	Total score: <input type="checkbox"/>
<small>This scale is in the public domain.</small>	