Lifestyle Interventions for the Treatment of EOAD Study (LITES)

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Abbreviations

AA	Alzheimer's Association
ACTIVE	Advanced Cognitive Training for Independent and Vital Elderly
AD	Alzheimer's Disease
ADCS-ADL	Alzheimer's Disease Cooperative Study – Activities of Daily Living
ANCOVA	Analysis of Covariance
ATRI	Alzheimer's Therapeutic Research Institute
BDI-2	Beck Depression Inventory - 2
CANTAB	Cambridge Neuropsychological Test Automated Battery
CSRQ	Cognitive Self-Report Questionnaire
DSMC	Data Safety Monitoring Committee
EOAD	Early-Onset Alzheimer's Disease
GUID	Global Unique Identifier
IU	Indiana University
LAR	Legally Authorized Representative
LEADS	Longitudinal Early-Onset AD Study
MCI	Mild Cognitive Impairment
MOCA	Montreal Cognitive Assessment
MSPSS-6	Multidimensional Scale of Perceived Social Support 6
PCQ	Perception of Change Questionnaire
PSS-4	Perceived Stress Scale 4
QOL-AD	Quality of Life in Alzheimer's Disease
RCT	Randomized Clinical Trial
SAE	Significant Adverse Event

1.0 Background & Rationale

EOAD is an Overlooked Condition

Despite the rapid expansion of research on interventions for Alzheimer's disease (AD), treatment for patients diagnosed at a younger stage of life (aged 40 to 64 years old) has been overlooked. This is likely due to the rareness of the condition – less than 5% of patients with AD have onset before 65 years old [1] – and also to challenges identifying disease modifying treatments in traditional-onset AD. These "early onset-AD" (EOAD) patients experience a unique set of complications related to their functioning, including cognitive declines while raising families and performing at the height of their careers. As a result of relatively preserved insight and this early decline, elevated rates of depression are common in EOAD [2]. Identification of successful treatments for this condition would lead to significant improvements for patients and families across multiple aspects of life.

EOAD and Traditional-Onset AD Present Differently

EOAD does not appear to be traditional-onset AD at an earlier age. EOAD tends to possess a more aggressive disease course [3] and greater cognitive severity [4] than traditional AD. Additionally, EOAD is proposed to manifest with greater relative involvement of non-memory cognitive domains, [5] and phenotypes associated with logopenic progressive aphasia, posterior cortical atrophy, progressive ideomotor apraxia, frontal variant AD, and corticobasilar syndrome are common [4]. Subgroups of EOAD tend to have higher rates of neurological symptoms than traditional AD and decreased comorbidities such as diabetes, obesity, and circulatory disorders [6]. On magnetic resonance imaging, greater parietal and overall cortical atrophy is seen in

EOAD, with less atrophy in the medial temporal lobe and hippocampus [7]. Relatedly, fluorodeoxyglucose positron emission tomography studies show greater parietal lobe hypometabolism in EOAD, [8] and diffuse tensor imaging studies indicate that white-matter degradation in EOAD patients is greater posteriorly (posterior cingulate and parietal), with less medial temporal involvement [9]. While recent studies have suggested some promise of monoclonal antibodies (i.e., Lecanemab) for the treatment of traditional AD, at present no attempts at pharmacological interventions in EOAD have been undertaken.

Lifestyle Interventions Offer Promising Results

Extensive research on the benefit of lifestyle interventions for older adults' functioning exists across a variety of cognitively intact and impaired samples. Computerized cognitive training, for example, has repeatedly shown benefit in a host of conditions impacting cognition, including brain injury [10] and healthy aging [11]. The largest study of its kind – a randomized controlled trial (RCT) of 2800 older adults in the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) study [12, 13] – showed that cognitive training improved cognitive performance in non-demented older adults upon completion of training, [12] and at 2-years, [12] 5-years, [14] and 10-years post-training [15]. *BrainHQ* (Posit Science) is a brain plasticity-based adaptive cognitive training program involving a suite of 29 online exercises that target several cognitive domains. Since 2019, >50 studies have been published on the use of *BrainHQ*, including those showing treatment benefits in cognitively intact participants, [16, 17] and those with schizophrenia, [18] Mild Cognitive Impairment (MCI), [19, 20] and mood disorders [21]. Training dosage effects have been observed in older adults with or without a cognitive disorder, with higher rates of training suggesting greater benefit from treatment [22]. Additionally, stronger cognitive training improvements have been suggested in participants with stronger baseline cognition, [22] and preliminary evidence in MCI suggests that women show greater treatment effects compared to men [23].

Physical exercise paradigms have additionally been shown to benefit cognition [24, 25]. A recent meta-analysis of 13 RCTs (n = 673) showed that physical exercise interventions improved performance in patients with AD on the Mini-Mental State Exam (*SMD*=1.12, *CI*: 0.66-1.59) compared to control groups [26]. A separate meta-analysis of 20 studies (n=2,553) of *Tai Chi* intervention in adults aged 60 and over found support for cognitive enhancement [27]. Specifically, effect sizes were large (*Hedge's g* =0.51; p=0.003) for executive functioning outcomes in cognitively healthy adults relative to controls, and moderate (*Hedge's g* =0.35; p=0.004) for global cognition outcomes in cognitively impaired adults [27]. A more recent systematic review (9 studies, n=456) suggested *Tai Chi* improved short-term cognitive function in the elderly, including for global cognitive functioning, visuospatial skills, semantic memory, verbal learning/memory, and self-perception of memory [28].

The unique benefits of cognitive training and physical exercise have led some researchers to combine these treatments into a single intervention. Meta-analytic findings of 10 RCTs (n=742) involving combined cognitive training and physical exercise suggest a small-to-medium positive effect of interventions on global cognitive function (*SMD*=0.32, *CI*: 0.17-0.47) in older adults with MCI and dementia, and a moderate-to-large positive effect for activities of daily living (*SMD* = 0.65, *CI*: 0.09-1.21) [29]. Additional research is underway to examine the efficacy of a cognitively-enhanced *Tai Chi* intervention on cognitive health delivered remotely to older adults with MCI ("*Tai Ji Quan: Moving to Maintain Brain Health*"; NIH 5R01AG059546), with preliminary data (n=69) suggesting feasibility, acceptability, and safety of the intervention [30]. The **synergistic effects** of using both interventions have been associated with "guided plasticity facilitation" [31-33]. Specifically, it is proposed that physical exercise facilitates synaptic plasticity and neurogenesis due to the release of neurotrophic factors like brain-derived neurotrophic factor (BDNF) and

cytokine/hormonal factors, [34] and stimulation of synapses and neurons during cognitive training guides synapse formation and integration of new neuronal structures in brain circuitry, resulting in enhanced gray matter/dorsolateral prefrontal lobe density [35, 36] and cognitive processing [32].

An Opportunity Exists for Lifestyle Interventions in EOAD

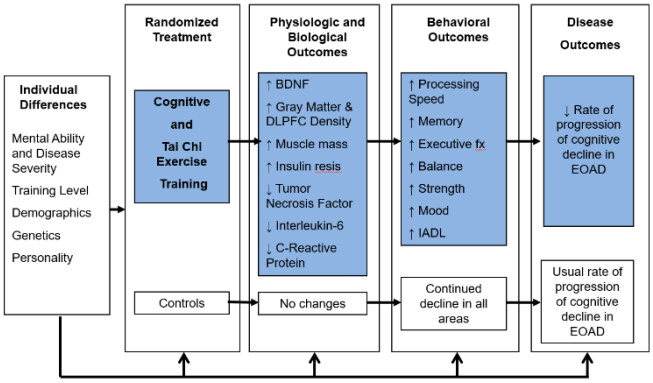


Figure 1. Proposed Conceptual Model of Intervention Effects in EOAD

As a result of this support for lifestyle interventions, we offer a conceptual model (**Figure 1**) of cognitive and *Tai Chi* exercise training for improved cognition in EOAD individuals, moderated by individual differences in training and participant variables. To date, these interventions have had limited consideration in EOAD populations, due to its rareness and the severity/aggressive course commonly observed in EOAD [4]. Given the increased focus on EOAD by the Alzheimer's Association and leading AD scientists, this reflects a gap in knowledge in AD literature. This also overlooks a potential treatment option for patients with EOAD and their families. Consequently, we are undertaking an *NIH-defined Stage IB (NIH Stage Model)* study to collect preliminary data to investigate the feasibility and pilot testing of this combined lifestyle intervention on short-term and long-term cognition, functioning, and mood in participants with EOAD from the Longitudinal Early-Onset Alzheimer's Disease Study (LEADS), relative to an Active Control group. Because LEADS is a multi-site study across the U.S., all aspects of this proposed study will be **conducted remotely**. Current LEADS participants classified as *amyloid-positive* EOAD (n = 60) will be recruited for our study. Our research team is uniquely positioned to examine this model, given our extensive experience with lifestyle interventions, access to the most well-characterized cohort of EOAD participants in the U.S., and the inclusion of several pre-eminent scholars in neurodegeneration, AD clinical trials, and EOAD. We are currently unaware of any other research attempting to identify the efficacy of lifestyle interventions in this population.

Preliminary Data: As the goal of this application is to generate preliminary data on the benefit of cognitive and *Tai Chi* training in participants with EOAD – which has previously been unexamined in the literature – little to no previous findings exist to directly support our proposal. As such, a brief review of related literature will be provided to support our Aims.

Aim 1. Evaluate feasibility of a lifestyle intervention and outcomes in participants with EOAD

In a recent pilot study applying *BrainHQ* cognitive training to patients with mild to moderate traditional-onset dementia, 8 of 10 participants studied were able to complete the 36 hours of cognitive training, with participant eagerness, rate of non-refusal, and attentiveness being strong (refusal rate for the 384 training sessions was only 3%) [37]. Cognitive screening scores on the Montreal Cognitive Assessment (MOCA) were notably low (M = 13.1 ± 1.6), suggesting that *BrainHQ* can be tolerated by severely-cognitively impaired populations. These results are relevant to our proposal as the mean MOCA score for our current EOAD cohort is 16.9 (± 5.6). Relatedly, both *BrainHQ* and *Tai Chi* have been found to be efficacious when administered remotely-to-home, [16, 38] consistent with the procedure planned for the current study. Together, these findings suggest that use of this lifestyle intervention remotely in our cognitively compromised EOAD cohort is **feasible**.

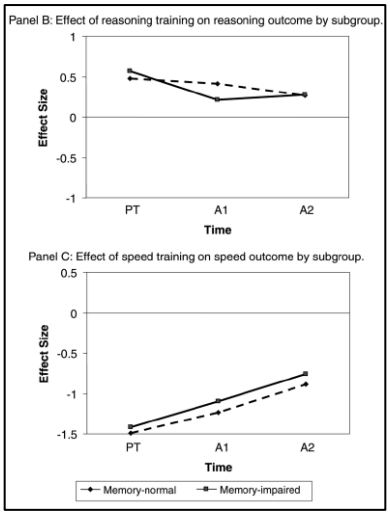


Figure 2. Improvements in cognition on reasoning/speeded training post-treatment (PT) and at follow-up years 1 (A1) and 2 (A2)

Aims 2 & 3. Efficacy and Moderation of a lifestyle intervention in EOAD

Dr. Unverzagt (Co-Mentor) has been centrally involved with lifestyle interventions – and cognitive training in particular – over the past 20 years. He has shown that memory impaired participants failed to benefit from memory training in the ACTIVE program, but did show expected training gains on domains of reasoning and processing speed [13] (**Figure 2**). Additionally, his work helped show the aforementioned benefit of cognitive training in ACTIVE immediately and after a delay [12, 14, 15]. Overall, his research into cognitive training **established empirical support for the paradigm** – paving the way for its application in EOAD – and suggests that severity of memory impairment may play a moderating role in treatment outcomes in our sample.

2.0 Objective(s)

2.1 Primary Objective

The Primary Objective is to **evaluate the feasibility of the combined lifestyle intervention and outcome assessments for use in future trials in participants with EOAD.** Hypothesis 1.a: We will monitor adherence to interventions and outcome assessments. Adherence to treatments and completion of outcome assessments will be ≥75% and ≥90%, respectively. Hypothesis 1.b: We will monitor acceptability and attrition of the lifestyle intervention. At least 70% of participants will rate each aspect of the intervention as enjoyable, and attrition will be <15%.

2.2 Secondary Objective

The Secondary Objective is to **investigate if the lifestyle intervention combining cognitive training and *Tai Chi* improves (2a) short-and long-term cognition and (2b) functioning and mood in participants with EOAD compared to an active control condition.** Hypotheses 2.a and 2.b: The EOAD participants in the experimental training condition will perform better on outcomes related to (2.a) cognition and (2.b) functioning and mood at Week 15 and Week 40 follow-up compared to the EOAD participants assigned to the active control condition.

2.3 Tertiary/Exploratory/Correlative Objectives

The Tertiary Objective is to **explore potential moderators on the degree of benefit from a combined cognitive training and *Tai Chi* lifestyle intervention in EOAD.** Because of sample size limitations in this preliminary study, focus will be on determining effect sizes and sample-size magnitude needed for future work. Exploratory hypotheses include: Hypothesis 3.a: A

greater treatment response will be seen in women with EOAD relative to men. Hypothesis 3.b: Better response will be related to increased hours of training and decreased disease severity.

3.0 Outcome Measures/Endpoints

3.1 Primary Outcome Measures

To not interfere with the NACC-UDS 3.0 battery being administered at annual LEADS visits, the current study will administer a novel and streamlined battery at Baseline, immediately after completion of treatment (at Week 15 Post-Intervention Follow-Up), and approximately 6-months after treatment (at Week 40 Post-Intervention Follow-Up).

Primary outcome measures will be Week 15 and Week 40 Post-Intervention Follow-Up performance on **CANTAB Connect computerized Cognitive Composites of Memory and Executive skills**, after controlling for the respective baseline Composite performance. The Memory Composite will be calculated from CANTAB Connect measures of Paired Associates Learning, Pattern Recognition Memory, and Verbal Paired Associates subtests, with higher scores reflected better performance. The Executive Composite will be calculated from CANTAB Connect measures of Stockings of Cambridge, Spatial Working Memory, Rapid Visual Processing, and Match To Sample subtests, with higher scores reflected better performance.

CANTAB measures were selected for their assessment of memory, executive functioning, and visuospatial working memory, with validation in AD samples [39]. Based on meta-analytic findings [40], cognitive domains of episodic memory and executive/working memory were expected to result in the highest benefit from behavioral interventions, which provides rationale for our selection of Memory and Executive Cognitive Composites. CANTAB Connect research has suggested that at-home testing is feasible [41] and practice effects are generally low with repeat testing,[42] making it appropriate for use in this remote repeated assessment protocol.

3.2 Secondary Outcome Measures

Secondary outcomes include performance on the following measures at Week 15 Post-Intervention Follow-Up and Week 40 Post-Intervention Follow-Up, after controlling for baseline performance:

a. Cognitive Self-Report Questionnaire **(CSRQ)**, which is a 25-item self-report questionnaire of subjective cognitive difficulties [43]. Scores range from 0-125, with higher scores denoting greater symptoms of cognitive impairment. This measure has been used in a variety of studies examining benefit from cognitive training [44, 45].
b. Alzheimer's Disease Cooperative Study – Activities of Daily Living Inventory [46] **(ADCS-ADL)** scale. This informant-based rating scale assesses the participant's ability to perform a variety of activities of daily living over the past four weeks, and has been shown to discriminate between healthy elderly controls and those with mild AD [46]. Scores range from 0-78, with higher scores denoting better functional ability.
c. 21-item Beck Depression Inventory-2 **(BDI-2)** [47] was used as a measure of self-reported depression. Scores range from 0-63, with higher scores denoting greater self-reported depression symptoms.
d. Perceived Stress Scale 4 **(PSS-4)**[53] was used as an index of self-reported psychological stress. Scores range from 0-16, with higher scores denoting greater self-reported stress[54].
e. Quality of Life in Alzheimer's Disease **(QOL-AD)**[55] is a 13-item self-report and informant-report questionnaire rating various aspects of physical health, energy, family, money, etc., using a scale of poor (1 point), fair (2 points), good (3 points), and excellent (4 points).

f. 6-Item Multidimensional Scale of Perceived Social Support (MSPSS-6) [56] was used as a measure of self-reported support from family, friends, and a significant other. Scores range from 1-7, with higher scores denoting greater perceived social support [57].

3.3 Tertiary/Exploratory/Correlative Outcome Measures

A brief self-reported Perception of Change Questionnaire (**PCQ**) will also be administered to gauge blinding procedures. Further, exploration of participant satisfaction will be undertaken with the use of two separate satisfaction surveys (**Cognitive Training Satisfaction Survey** and **Exercise Satisfaction Survey**) for each aspect of the combined intervention. Each survey will assess safety/ability to navigate, challenge and enjoyment, appropriateness of intensity, helpfulness in improving brain health, and overall intervention satisfaction. Each survey has been modified from a previously documented Tai Chi satisfaction survey [30].

4.0 Eligibility Criteria

4.1 Inclusion Criteria

- Enrolled in the Longitudinal Early-Onset AD Study (LEADS), [48] and being classified via LEADS consensus criteria as having amyloid-positive EOAD
- Aged 40-64 years at the time of enrollment into LEADS
- Fluent in English
- In good general health and absent another neurological disorder
- Have a knowledgeable informant.
- Have had a Clinical Dementia Rating scale of 0.5 to 1.0 at the time of enrollment into LEADS.
- Have sufficient vision, hearing, comprehension, and manual dexterity to participate in the testing and training program

4.2 Exclusion Criteria

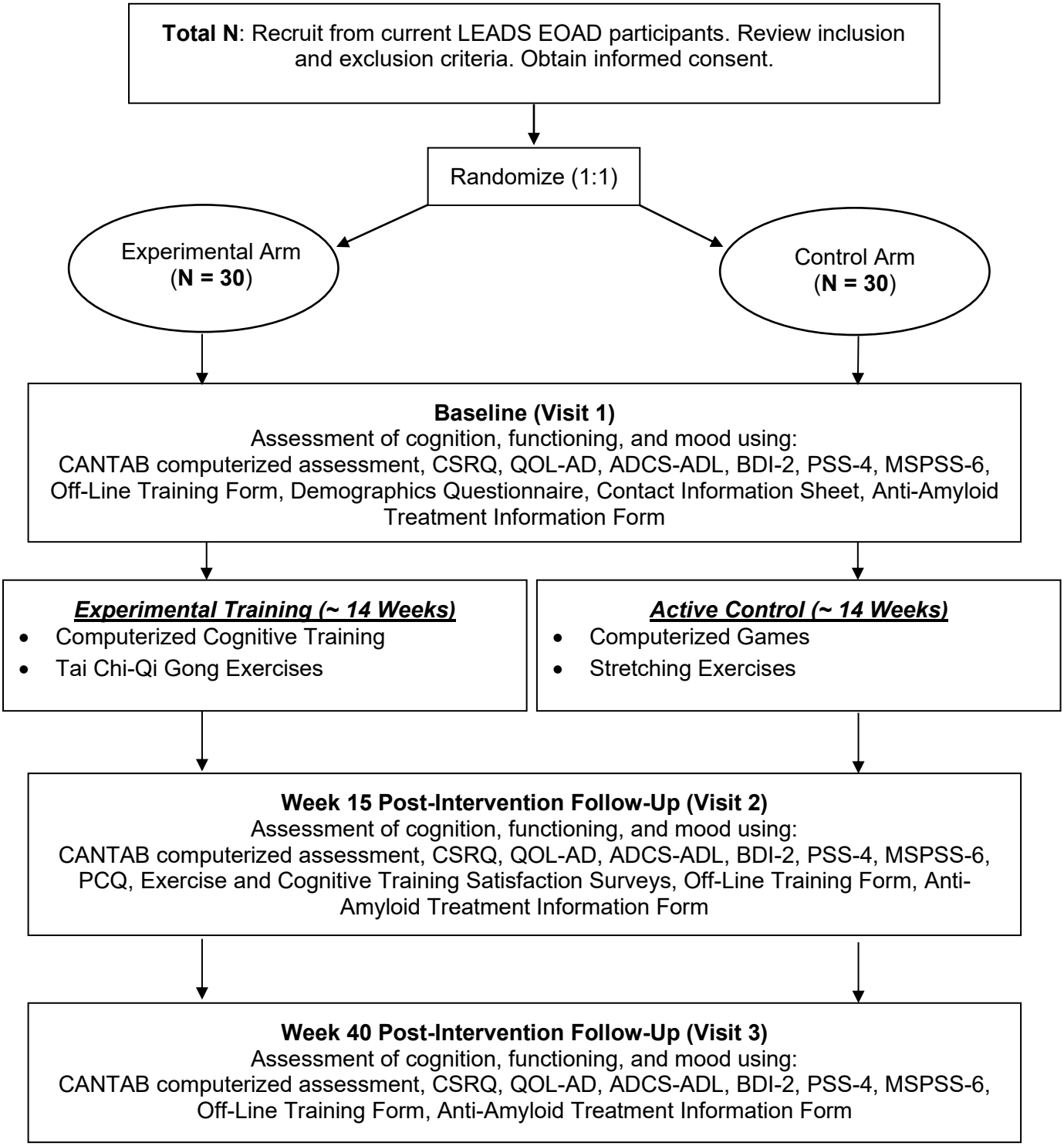
- Have access to the internet (e.g., home, family, , etc.) for **less than 4 hours per week**.

5.0 Study Design

This research study aims to generate preliminary data regarding the efficacy of a combined cognitive-training and *Tai Chi* exercise lifestyle intervention in participants diagnosed with EOAD. Participants will complete a series of cognitive, functional, and mood assessments at a remotely-assessed baseline visit, and then be randomized into one of two conditions: (1) **Computerized Cognitive Training + *Tai Chi* Exercise** or (2) **Active Control**. Outcome measures will be repeated immediately after treatment (15 Week Post-Intervention Follow-up visit) and at the 40 Week Post-Intervention Follow-Up visit . Specific Aim 1 will examine the feasibility of this lifestyle intervention and outcome assessments when applied to participants with EOAD. Specific Aim 2 will investigate if this lifestyle intervention improves short- and long-term cognition, functioning, and mood. Specific Aim 3 will be exploratory to assess whether individual differences in training or clinical/demographic characteristics moderate the degree of benefit from this intervention; owing to sample size limitations in this feasibility study, focus of

this latter aim will be on determining effect sizes and sample-size magnitude needed for future work.

The following schematic provides an overview of the study procedures:



6.0 Enrollment/Randomization

Recruitment

The proposed study will recruit 60 participants with amyloid-positive Early Onset Alzheimer's Disease through the ongoing NIH-funded multi-center Longitudinal Early-Onset Alzheimer's Disease Study (LEADS). To date, LEADS has enrolled 370 EOAD participants, along with 115 early-onset non-AD and 99 control participants. New participants will be added to LEADS on a rolling basis until final enrollment numbers reach 400 EOAD participants, 200 early-onset non-AD participants, and 100 control participants.

The LEADS sites for recruitment include Indiana University (IU) and a subset of other sites throughout the multi-site study, potentially including Banner Health Research Institute, Butler Hospital/Brown University, Columbia/Presbyterian Medical Center, Georgetown University, Houston Methodist Hospital, Massachusetts General Hospital, Mayo Clinic - Jacksonville, Mayo Clinic – Rochester, John Hopkins Medicine, Stanford University, University of California – Los Angeles, University of California – San Francisco, Emory University, Northwestern University, University of Pennsylvania, Washington University in St. Louis, Wien Center – Mount Sinai Medical Center.

Individuals will be recruited by LEADS study members during ongoing LEADS appointments. When participants arrive to these already-scheduled LEADS appointments, a LEADS research member will let them know that they may be eligible for a research study that examines the benefit of a combined lifestyle intervention for EOAD. Site researchers will provide potential participants with limited study information and Dr. Hammers/Study Coordinators contact information. The LITES research team will also obtain diagnosis, demographics, and contact information of LEADS participants at a point after their LEADS baseline visit to 1) confirm eligibility and 2) additionally identify those who are eligible to enroll in LITES and directly contact them. Following the completion of a telephone screen, those interested in participating will be scheduled for the informed consent process at a convenient time, and informed consent will be obtained through the IU IRB-approved *e-consent process* (given the remote nature of this study). Study procedures may either immediately follow written consent, or be scheduled for another visit, depending on interest and availability. Despite the low risk of this study, there is the possibility that some participants with EOAD will have limited capacity to provide informed consent. In those instances, consent will be obtained from the participant's legally authorized representative (LAR) and assent will be obtained from the participant with EOAD. First name, telephone number, and email addresses will be obtained to confirm the scheduled visit,but will be destroyed upon completion of the study.

Participants will be able to access study procedures using either their personal computer or tablet, or using a tablet provided by the study team.

Randomization and Blinding

Participants will be randomly assigned to the experimental or active control group via a computer-generated schedule. Randomization will occur after the Baseline visit in permuted blocks of six with random variation of blocking number. Given the increasing likelihood for participants to be prescribed an Anti-amyloid medication (e.g., Lecanemab) after the first year of enrollment, an adaptive randomization design will be implemented upon the first instance of a recruited participant taking such a medication pre-enrollment. Group membership will be coded and blinded until analyses are complete. Participants will be informed that the intervention

involves “cognitive and physical exercises” to enhance face validity of all groups and blind participants to group assignment. They will be told that two different types of training programs are being studied to see which one works best. The effectiveness of participant blinding will be evaluated by administering a questionnaire at post-treatment to compare the groups on self-reported perception of change in cognitive function (PCQ). We will also compare the proportions of voluntarily withdrawals from each group.

7.0 Study Procedures

The Appendix includes materials that participants will receive regarding BrainHQ, CANTAB, Demographics Questionnaire, Anti-Amyloid Treatment Information Form, CSRQ, QOL-AD, ADCS-ADL, BDI-2, PSS-4, MSPSS-6, PCQ, Exercise and Cognitive Training Satisfaction Surveys, and Self-Reported Off-Line Training Forms.

Procedures:

1. **Informed Consent**. Informed consent will be sought from all individuals that will participate in the proposed projects, including participants (and their informants). When a potential participant has been identified s/he will be presented with a brief overview of the study, as well as a brochure that further describes the study and its procedures. Additional questions will be answered by the LITES principal investigator or research assistant(s). If interested, a virtual visit will be scheduled to review the informed consent document with the potential participant (and informant), answer additional questions, and obtain written consent (through the *e-consent process*). For participants at Indiana University, the study team will additionally offer the participant the opportunity to proceed through the consent process in person in conjunction with their in-person LEADS visit. Since many of our potential participants will be cognitively impaired, we will also make a determination about capacity to provide informed consent. Following presentation of the informed consent document, participants will be asked questions about the study (e.g., purpose, procedures, risk and benefits). If these questions are adequately answered, then the participant will be judged to have capacity to provide informed consent. However, if these questions are not adequately answered, the participants will be judged to not have this capacity. In these latter cases, assent will be obtained from the participant and informed consent will be obtained from the participant’s LAR (e.g., spouse, adult child).

   At the conclusion of informed consent, participants will receive a participant manual that will serve as a step-by-step guide for accessing the lifestyle training program to which they have been assigned.

2. **Baseline (Visit 1)**. During this visit, participants will complete measures of baseline functioning pertaining to cognition (CANTAB and CSRQ), daily functioning (ADCS-ADL), and mood (BDI-2, PSS-4, MSPSS-6, QOL-AD). Demographics Questionnaire, Anti-Amyloid Treatment Information Form, and Off-Line Training Form will additionally be administered. This visit should take approximately 13-4 hours.

3. **Lifestyle Intervention**

a. **Experimental Training Program**:

i. Remote Computerized Cognitive Training from Posit Science's BrainHQ Program.
This web-based application [49] was designed to improve the speed and accuracy of memory, executive functioning, and visual processing skills. Exercises will continually adjust difficulty levels to maintain an 85% correct rate. A set of computerized cognitive training exercises have been selected based on their validation in lifestyle intervention programs for older adults. Users will be expected to play 18 levels per session, 4 sessions per week for 14 weeks. Below is an example of a cognitive exercise that will appear in their schedule: 1) A divided attention and visual tracking task that requires the monitoring of a select number of moving objects upon a backdrop filled with identical moving objects. As the task continues the number of objects the participant must track increases ("Target Tracker").

To use the experimental treatment program, a participant opens an Internet-browser and navigates to a general log-in screen via the LITES website or clicks on the BrainHQ app downloaded onto their laptop or tablet from the App Store or Google Play store. The participant then logs into the experimental treatment program server using an anonymized email address and password created on their behalf by a staff member. This will allow us to track their progress through the program and provide personalized reminders for training. A game-like experience begins, where the participant is encouraged to earn stars and in-game rewards to advance. To do so, the participant completes the cognitive exercises scheduled for the day, and must achieve at least 6 stars to advance to the next exercise in their queue (stars are derived from normalized z-score performance). Notification of session completion is achieved when the user finishes at least 18 levels. The exercise itself contains the core therapeutic exercise task built into a game-like experience. Participants perform numerous trials over the course of a session, with auditory and visual feedback and rewards to indicate if the trial was performed correctly or incorrectly. Within each session, target frequency is titrated according to performance to maintain ~80% target accuracy across training session. Also, after each session, the difficulty of the next session is updated (e.g., less inter-stimulus-interval jitter) to ensure that each participant is appropriately challenged. Summary screens including game metrics (stars, scores) and exercise metrics (usage, progress) are shown to the participant at the end of each session. All usage and progress data are encrypted then transmitted to a central server. In a research study such as this one, no personally identifiable information is stored on the server (including internet protocol addresses). On the server, the data are available for review by an un-blinded research coordinator through a secure web portal. The research coordinator will use the secure web portal to regularly check on usage and progress of each active participant to customize their biweekly telephone calls to provide helpful guidance and coaching, if needed, outside of the telephone reminders.

The scheduling mechanism ensures that a participant progresses through the exercises in an optimally defined order, generally moving from simple (e.g., easy to discriminate stimulus types, moderate pacing) exercises to complex (e.g.,

greater self-pacing required, greater rule complexity) exercises over the course of the 14-week experience.

Participants will be asked to complete 18 levels per session (approximately 45 minutes), 4 sessions per week for 14 weeks (corresponding to approximately 40 hours of training total).

At the start and completion of the 14-week BrainHQ training, participants will receive a 5-10-minute Train-to-Task measure through the BrainHQ portal that will gauge the amount of learning that occurred over the course of the training (independent of the cognitive outcomes).

ii. Tai Chi- Qi Gong Exercises.
This remote training of *Tai Chi* exercises will be modeled after the virtually-administered *Tai Ji Quan: Moving for Better Balance* program [50]. Specifically, it will involve practice of a core of 8 therapeutically-modified exercise forms aimed at stimulating and integrating musculoskeletal, sensory, and cognitive systems [51]. These self-initiated *Tai Chi* exercises will additionally incorporate synchronized breathing, center of gravity displacement, and unilateral weight-bearing and weight-shifting movements (of the trunk, pelvis, ankle, head, and hands). Participants will be asked to complete 14 hours of training total (in 30-minute sessions, 2 days per week for 14 weeks). Initial sessions will focus on learning and engaging in *Tai Chi* movements across multiple positions (e.g., seating, standing only, stepping) as necessary, with later sessions honing skills. Because participants will live in multiple time zones, pre-recorded videos created by the Tai Chi Foundation specifically for the current study – using Tai Chi Foundation certified instructors - will be available to watch online individually through an online portal.

b. **Active Control Training Program**:

i. Computerized Games Through the BrainHQ Web Portal.
A set of computerized games have been selected that are engaging, but have not been empirically validated to improve cognition. In each training session, participants will be presented with at least 5 pre-determined exercises, each lasting for 9 minutes, for a total of 45 minutes. Participants will be asked to complete 40 hours of training total (in 45-minute sessions, 4 days per week for 14 weeks).

ii. Stretching Exercises.
Active Control participants will also be provided video-instructional materials through a series of stretching routines. The central aspect of the exercise will involve stretching of the upper and lower body, and trunk. Participants will be asked to engage in these stretching exercises twice per week, for approximately 10-15 minutes per session. This will total 7 hours over the course of 14 weeks. Because participants will live in multiple time zones, pre-recorded videos created by a certified physical therapist through Yes2Next.com will be available to watch online individually through an online portal.

Of note, all participants will receive an anonymized email address and password for Posit Science/*BrainHQ*, which will determine the specific cognitive training content that they can access. For example, participants randomized into the Active Control arm will only have access to the active control training through the *BrainHQ* web portal. A separate set of instructions will be created for access to the respective online video-instruction for physical exercise. The amount of time spent on BrainHQ will be tracked based on the number of levels completed per session (which corresponds to a particular amount of time). This will be paired with a paper-and-pencil "training log" for each participant to record the date and start/stop times of each of their cognitive and exercise sessions. These variables may be used in the proposed moderation analyses in Specific Aim 3.

Remote coaching and technical support. Both computer programs through the *BrainHQ* portal will be accompanied by a coaching and technical support service by IU staff familiar with *BrainHQ*, to provide ongoing participant support and ensure that any technical issues are resolved promptly and successfully. This familiarity will be enhanced with coaching documents provided by BrainHQ. Staff will conduct remote 15-minute check-ins with participants every two weeks to discuss progress and answer questions. This remote support system is consistent with existing lifestyle interventional trials, such as EXERT, US POINTER, PACT, among others.

4. Week 15 Post-Intervention Follow-Up **(Visit 2)**. Upon completion of the intervention schedule (approximately 14 weeks after baseline), the outcome measures (CANTAB, CSRQ, QOL-AD, ADCS-ADL, BDI-2, PSS-4, MSPSS-6) will be repeated for all participants. The **PCQ** will also be administered to gauge blinding procedures. Exercise and Cognitive Training Satisfaction Surveys and Off-Line Training Form will also be administered. This visit should take approximately 3-4 hours.

5. Week 40 Post-Intervention Follow-Up **(Visit 3**). Approximately 6 months after the completion of training, outcome measures (CANTAB, CSRQ, QOL-AD, ADCS-ADL, BDI-2, PSS-4, MSPSS-6, and Off-Line Training Form) will again be repeated for all participants. This visit should take approximately 3-4 hours.

8.0 Study Calendar

	Baseline (Visit 1)	Lifestyle Training Intervention	Week 15 Post-Intervention Follow-Up (Visit 2)	Week 40 Post-Intervention Follow-Up (Visit 3)
	Week 1	Week 1 – Week 14	Week 15	Week 40
STUDY PROCEDURES				
CANTAB	X		X	X
CSRQ	X		X	X
ADCS-ADL	X		X	X
BDI-2	X		X	X
PSS-4	X		X	X
MSPSS-6	X		X	X
QOL-AD	X		X	X

	Baseline (Visit 1)	Lifestyle Training Intervention	Week 15 Post-Intervention Follow-Up (Visit 2)	Week 40 Post-Intervention Follow-Up (Visit 3)
	Week 1	Week 1 – Week 14	Week 15	Week 40
Demographics Questionnaire	X			
Contact Information Sheet	X			
Anti-Amyloid Treatment Information Form	X		X	X
Cognitive Training		X		
Train-to-Task Measurement		X (twice; at start and end of training)		
Exercise Satisfaction Survey			X	
Cognitive Training Satisfaction Survey			X	
Self-Reported Off-Line Training Form	X		X	X
Exercise Training		X		
Perception of Change Questionnaire			X	
*Variations of +/- 3 weeks from the scheduled visit are permitted				

9.0 Reportable Events

There are no expected adverse events. As described in the Protection of Humans subjects, it is possible that participants will experience distress related to cognitive training, or could lose their balance as a result of following along with the Tai Chi or Stretching videos. As such, keeping a chair nearby while engaging in exercise is being encouraged. Otherwise, there are no other known side effects anticipated. All promptly reportable events will be reported to the IU IRB within 5 business days of discovery. All non-promptly reportable events will be reported to the IU IRB at the time of the next study renewal or at the time of study closure if no renewal is required. Any serious adverse event will be reported within 24 hours of learning of the event, in accordance with the standard IU IRB reporting guidelines.

Participants will be informed in the consent document for Specific Aims 1-3 of circumstances under which licensed psychologists might be required to break confidentiality due to mandated reporting laws. These cases include: concerns for participants' risk to self (suicidality) or others (homicidality), or information that suggests a child, older adult, or dependent adult are being abused. If a participant described an intent or inability/unwillingness to develop and follow a safety plan, Dr. Hammers will be immediately located for additional assessment and intervention, and will work in conjunction with the respective LEADS site-PI given the remote nature of the data collection.

10.0 Data Safety Monitoring

This data safety monitoring plan was developed based on prior studies using similar types of cognitive training (including *BrainHQ)* and *Tai Chi* exercises, where no adverse events have

been reported (i.e., relatively low risk to participants). This plan will monitor the collected data for accuracy and completeness. The Principal Investigator, Research Assistant, and data manager will review the study data and files for accuracy and completeness after the first six participants' data are collected. If procedures are not accurately or completely capturing study data, then procedures will be modified to allow for more accurate and complete data capture. If any changes in the procedures will be necessary, then the IRB be informed in an amendment. If these changes are approved by the IRB, then the Alzheimer's Association and the National Institute of Aging will be informed of these changes in our annual progress report. All research data will be stored on encrypted Indiana University (IU) servers as well as encrypted external hard drives that will be kept in a locked cabinet in the PI's office. Additionally, participant identifiers will be stored separately from the coded test data.

A Safety Officer/ Medical Monitor has been obtained to review on an ongoing basis the safety of all subjects enrolled in this clinical trial. Meetings will be held approximately quarterly – as necessary – after the first subject is enrolled and will be held via virtual conference. The frequency of meetings may change at the discretion of the Safety Officer. The Safety Officer will be regularly informed of the occurrence of any serious adverse event (SAE) and immediately notified of any fatal or life-threatening event. After reviewing the safety data, the Safety Officer will make recommendations regarding the conduct of the study. These recommendations include amending the safety monitoring procedures, modifying the protocol or consent, performing additional analyses, terminating the study, or continuing the study as designed. Given the co-enrollment of the proposed study's participants with the LEADS study, the Safety Officer is also affiliated with the Data and Safety Monitoring Committee (DSMC) utilized by LEADS. Specifically, the Alzheimer's Therapeutic Research Institute (ATRI) at the Keck School of Medicine of the University of Southern California serves as the DSMC for LEADS, and Dr. Michael Rafii (ATRI Medical Director) has agreed to serve as Safety Officer for the current study. Any subsequent reports will be filed in the regulatory binder at IU, with a copy also being sent to the LEADS Executive Committee and the IRBs at all participating sites.

The following will be monitored as part of the Data Safety Monitoring Plan: data quality, subject recruitment, accrual, retention, outcome and adverse event data, assessment of scientific reports or therapeutic development, results of related studies that may impact subject safety, and procedures designed to protect the privacy of subjects. No pre-planned stoppage analyses will be conducted given the preliminary nature of the data collection.

11.0 Study Withdrawal/Discontinuation

Withdrawal from the study will occur by the participant (or study partner) contacting the PI or study team to report a desire for study discontinuation. Withdrawal prior to the completion of the lifestyle interventions will result in a discontinuation of access to *BrainHQ* and the *Tai Chi/*Stretching exercise programs.

12.0 Statistical Considerations

All statistical hypothesis tests will be performed on a comparison-wise basis, using a 2-sided $\alpha=0.05$ without adjustment for multiple comparisons. The risk of inflated Type 1 error due to multiple comparisons will be limited in the current aims by designating a small number of primary analyses for each Specific Aim. A total sample size of n = 60 (n = 30 per arm) is being used in this study.

Specific Aim 1: Evaluate feasibility of a lifestyle intervention in participants with EOAD.

Analysis: Hypothesis 1.a: "Adherence to treatments and completion of outcome assessments will be ≥75% and ≥90%, respectively." Successful adherence will be defined as participants completing 75% of training sessions/visits across the 14-week intervention. Successful completion of 15-Week and 40-Week Post-Intervention Follow-Up outcome assessments will be defined as obtaining valid outcome data in 90% of assessments. *One-sample proportion tests* will be used to determine differences from expectation (e.g., difference between observed adherence and 75%).
Hypothesis 1.b: "At least 70% of participants will rate each aspect of the intervention as enjoyable, and attrition will be <15%." An intervention attrition rate of <15% for both cognitive and *Tai Chi* exercises will define successful study retention. Dropping out of the intervention will mean notifying project staff of discontinuation, or not responding to participation reminders after falling behind training goals. Exploration of participant satisfaction will additionally be undertaken with the use of two modified five-item surveys, with "satisfaction" defined as endorsing "Extremely Satisfied" or "Somewhat Satisfied"; we specified an a priori overall satisfaction level of ≥70% for both cognitive training and *Tai Chi*. *One-sample proportion tests* will be used in this hypothesis as well to determine differences from expectation.

Power: Our hypothesized adherence rate of 75% was based on similar studies in the literature. Previous research observed 79% adherence with a virtual Tai Chi- Qi Gong intervention, and 77% adherence to BrainHQ in MCI participants.[52] Our sample size of 60 would permit an estimated power of 0.80 to detect a proportion difference of 10% at a significance level of 0.05.

Specific Aim 2: Investigate if a lifestyle intervention improves (2a) cognition and (2b) functioning and mood in participants with EOAD compared to an active control condition.

Analysis: Primary outcome measures will be 15-Week and 40-Week Post-Intervention Follow-Up performances on Memory and Executive Composites from CANTAB Connect. Secondary outcomes include CSRQ, QOL-AD, ADCS-ADL, PSS-4, MSPSS-6, and BDI-2 scores.
Hypothesis 2.a: Treatment effect will be analyzed using Analysis of Covariance (ANCOVA) comparing CANTAB Connect Composites at both 15-Week and 40-Week Post-Intervention Follow-Up visits for the experimental treatment arm versus active controls, while controlling for the baseline performance. Hypothesis 2.b: ANCOVA analyses will be used to compare treatment effects at 15-Week and 40-Week Post-Intervention Follow-Up for functioning and mood-related outcomes.

Power: We expect to complete the 15-Week and 40-Week Post-Intervention Follow-Up visits for 92.5% and 85% of the 60 randomized subjects, respectively (which accounts for attrition). Power estimates were based on a study of an 8-week RCT of cognitive training, physical exercise, and dietary education in patients with MCI (n = 57) and normal cognition (n = 62). The authors calculated a cognitive composite from the ADAS-Cog, Trail-Making Test B, Symbol Digit Modalities Test, and Category Fluency test, with z score differences between experimental and control groups being z = 0.25 at both 3- and 6-months post treatment. Based on this data, with our sample size we will have 90% power with a 2-sided α = 0.05 to detect effect size differences of 0.23 at 15-Week and 40-Week Post-Intervention Follow-Up visits.

Specific Aim 3: Explore potential moderators (training, clinical) on lifestyle intervention benefit.

Analysis: Although this preliminary study's sample size is limited, the impact of moderators on training benefit will be examined as follows: linear mixed effect regression will be used to model longitudinal data including random effects for participants to examine the impact of training dose, sex, and disease severity on CANTAB performance between groups, with separate interaction models being applied (treatment assignment x training hours/sex/severity).

Power: As indicated previously, the focus of Aim 3 will be on determining effect sizes and the magnitude of sample sizes needed for future work. We will not estimate the sizes of these effects as feasibility trials are underpowered for reliable estimates.

All statistical analysis will be conducted with the Biostatistics Core Leader of LEADS, Ani Eloyan, PhD.

13.0 Privacy/Confidentiality Issues

Data will be obtained from individually identifiable living human subjects in the form of demographic information, medical and psychiatric history, presence of memory and other cognitive complaints, report of activities of daily living, ratings of quality of life, performance on neuropsychological tests, and responses on a depression assessment and a brief stress measure. Most of this information will be collected during one-on-one virtual research visits with the participants. Information will also be collected from interviews with knowledgeable informants. LEADS records will be accessed to confirm diagnosis and incorporate demographic and clinical data into the LITES study. To facilitate access to LEADS records, Global Unique Identifiers (GUIDs) for all LITES participants will be acquired. Each GUID unambiguously identifies a research study participant across different research studies without exposing PHI. When investigators pool data together from multiple studies, GUIDs provide the means to detect participants who participate in more than one study.

Data will be obtained specifically for research purposes and it will not be used for clinical or other purposes. Research data will only be accessible to members of the research team. To maintain privacy/confidentiality, study identification numbers will be created with a name-to-identification number key stored in a separate document to reduce the likelihood of loss of confidentiality. Some research team members will have access to greater levels of individually identifiable information. For example, the research assistants who schedule visits, obtain consent, and collect cognitive test data will have access to the most identifiable information. Conversely, the biostatisticians will only have access to data that has already been largely de-identified (e.g., identification numbers instead of names of participants).

14.0 Data Management

Primary data will be collected via direct data capture from measurement instrument and stored electronically in REDCap. The storage location will be backed up automatically. Other data sources include data from the LEADS study that will be stored in separate electronic files and merged with the primary data as needed. Quality assurance steps will include: 1) built in range checks; and 2) testing of database by study team prior to moving to production mode. The following quality control method will be used: extraction and cleaning of data that will be used for analysis every 3 months.

15.0 Follow-up and Record Retention

For each participant, treatment will last approximately 14 weeks, followed by post-treatment follow-up at 15 Week and 40 Week Post-Intervention Follow-up visits. This will result in the length of involvement for a particular participant being approximately 11 months. The duration of the entire study will be six years. Records will be retained for seven years following the completion of the study, with paper records being shredded and electronic records being deleted at that time.

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17.0 Appendix

The Appendix includes materials that participants will receive regarding BrainHQ, CANTAB, Demographics Questionnaire, Anti-Amyloid Treatment Information Form, Cognitive Self-Report Questionnaire, ADCS-ADL, BDI-2, PSS-4, MSPSS-6, PCQ, Cognitive Training Satisfaction Survey, Exercise Satisfaction Survey, Self-Reported Off-Line Training Forms.

BrainHQ Training

The core battery of BrainHQ tasks are taken from the “Focus on Visual Process” schedule. This focus is designed to improve the speed and accuracy of visual processing, attention, and memory. The overall program is composed of five interrelated training exercises that in aggregate span the organization of visual perception and cognition from spatial frequency processing to visuo-spatial memory. The tasks include speed of processing time-order judgments, discrimination between pairs of like items, and sustained tracking of multiple objects that increase their complexity by progressively moving to more and more rapidly presented stimuli and greater memory loads.

This Focus presents five exercises (Double Decision, Eye for Detail, Target Tracker, Hawk Eye, Visual Sweeps) that are delivered over 40 sessions. .

The tables below describe more detailed aspects of the exercises (Table 1) as well as which exercises and stages are presented for each of the 40 sessions (Table 2).

Table 1

Commercial name	~ levels per stage	# of stages	~ minutes per stage
Eye for Detail	6	4	18
Double Decision	6	7	18
Target Tracker	9	7	27
Hawk Eye	6	10	18

Visual Sweeps	8	7	24

Table 2

session	exercise name & stage number	~ mins per session
1	Target Tracker 1, Double Decision 1	24
2	Visual Sweeps 1, Eye for Detail 1	30
3	Hawk Eye 1, Visual Sweeps 2	30
4	Target Tracker 2, Eye for Detail 2	45
5	Visual Sweeps 3, Double Decision 3	42
6	Target Tracker 3, Hawk Eye 2	45
7	Visual Sweeps 4, Eye for Detail 3	42
8	Target Tracker 4, Double Decision 4	45
9	Visual Sweeps 5, Hawk Eye 3	42
10	Target Tracker 5, Eye for Detail 4	45
11	Visual Sweeps 6, Double Decision 6	42
12	Target Tracker 6, Hawk Eye 4	45
13	Visual Sweeps 7, Eye for Detail 2	42
14	Target Tracker 7, Double Decision 7	45
15	Visual Sweeps 2, Hawk Eye 5	42
16	Target Tracker 2, Eye for Detail 3	45
17	Visual Sweeps 3, Double Decision 10	42
18	Target Tracker 3, Hawk Eye 6	45
19	Visual Sweeps 4, Eye for Detail 4	42
20	Target Tracker 4, Double Decision 3	45
21	Visual Sweeps 5, Hawk Eye 7	42
22	Target Tracker 5, Eye for Detail 2	45
23	Visual Sweeps 6, Double Decision 4	42
24	Target Tracker 6, Hawk Eye 8	45
25	Visual Sweeps 7, Eye for Detail 3	42
26	Target Tracker 7, Double Decision 6	45
27	Visual Sweeps 2, Hawk Eye 9	42
28	Target Tracker 2, Eye for Detail 4	45
29	Visual Sweeps 3, Double Decision 7	42
30	Target Tracker 3, Hawk Eye 10	45
31	Visual Sweeps 4, Eye for Detail 2	42
32	Target Tracker 4, Double Decision 10	45
33	Visual Sweeps 5, Hawk Eye 2	42
34	Target Tracker 5, Eye for Detail 3	45
35	Visual Sweeps 6, Double Decision 3	42
36	Target Tracker 6, Hawk Eye 3	45
37	Visual Sweeps 7, Eye for Detail 4	42
38	Target Tracker 7, Double Decision 4	45
39	Visual Sweeps 2, Hawk Eye 4	42
40	Target Tracker 2, Eye for Detail 2	45

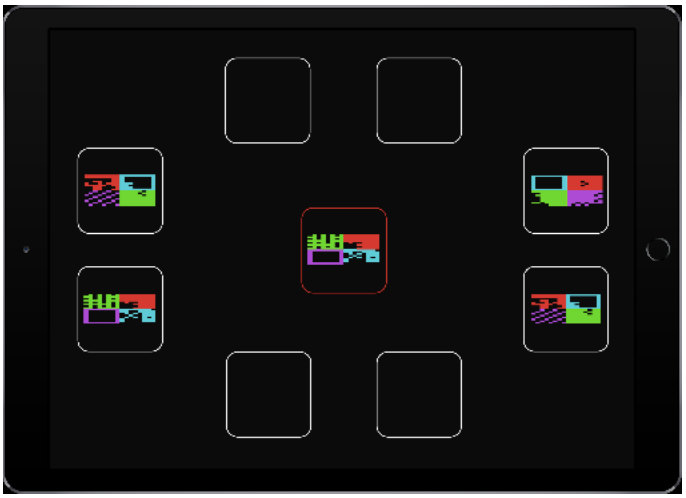
CANTAB Connect Assessment Subtests

Rapid Visual Information Processing (RVP)

RVP is a sensitive tool for assessment of sustained attention. Single digits appear one at a time at a rate of 100 digits per minute. Subjects must detect a series of target sequences (e.g. 3-5-7) and touch a button when they see the last digit of a target sequence. Nine target sequences appear every 100 numbers. Performance on the RVP test has been shown to be associated with activation in a network of brain structures including the frontal and parietal lobes (Coull et al., 1995).

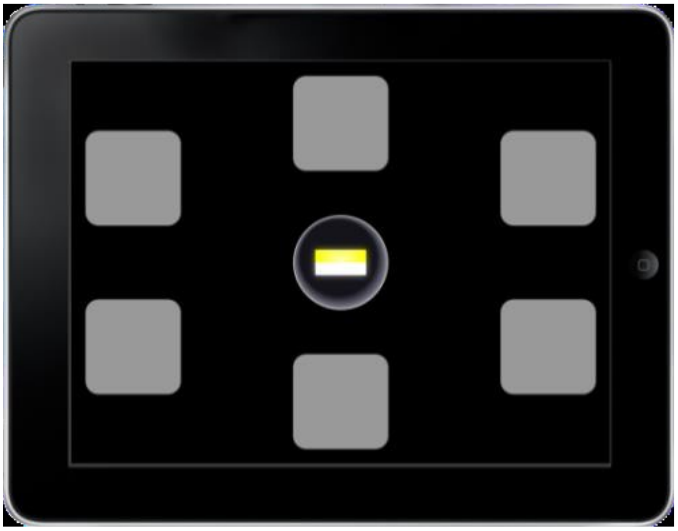
Key outcome measures include RVP A prime, a signal detection measure of target sensitivity and RVP median response latency.

Match to Sample Visual Search (MTS)



MTS assesses attention and visual searching, with a speed-accuracy trade-off. A complex visual pattern is shown in a box in the middle of the screen. After a brief delay, a number of similar patterns are shown in a circle of boxes around the edge of the screen. The subject must touch the one that matches the sample in the middle. The number of patterns to choose from varies across trials, but there is always only one which matches the center pattern.

Paired Associates Learning (PAL)

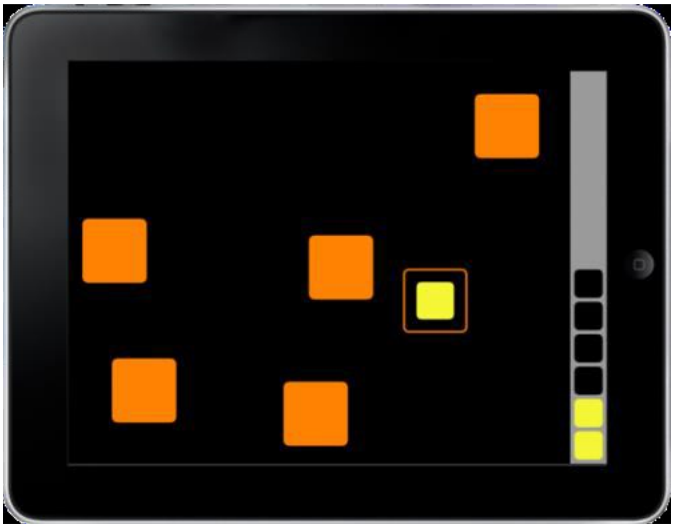


PAL assesses visual memory and new learning, and is a sensitive tool for accurate assessment of episodic memory. Boxes are displayed on the screen and open one by one in a randomized order to reveal patterns hidden inside. The patterns are then displayed in the middle of the screen, one at a time, and the subject must touch the box where the pattern was originally located. If the subject makes an error, the patterns are re-presented to remind the subject of their locations. Practice trials with fewer patterns are available to familiarize subjects with the test.

Pattern Recognition Memory (PRM)

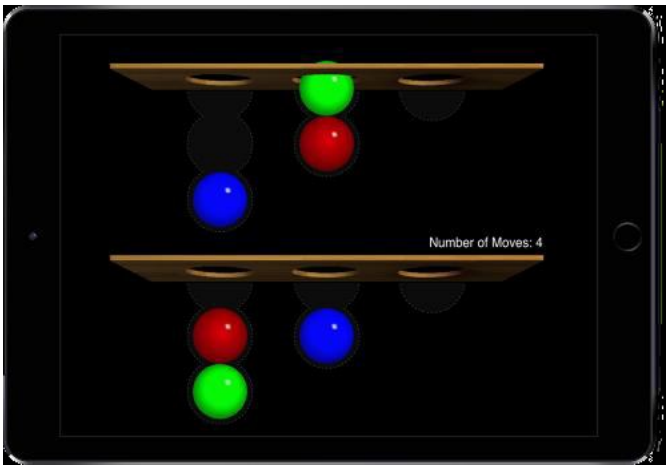
PRM is a measure of visual recognition memory. The subjects watch a series of 12 patterns appear, one at a time, on the screen. These patterns are designed so that they cannot be given verbal labels. In the recognition phase, the subject chooses which two patterns they have already seen before.

Spatial Working Memory (SWM)



SWM requires retention and manipulation of visuospatial information. This test has notable executive function demands, and measures strategy use as well as errors. The test begins with colored boxes being shown on the screen. The aim of this test is that, by touching the boxes and using a process of elimination, the subject should find one 'token' in each of the boxes and use them to fill up an empty column on the right-hand side of the screen. The key test instruction is that the computer will never hide a token in the same colored box, so once a token is found in a box the subject should not return to that box to look for another token. The color and position of the boxes used are changed from trial to trial to discourage the use of stereotyped search strategies. The key outcome measures for SWM include errors (touching boxes that have been found to be empty and revisiting boxes which have already been found to contain a token) and strategy, a measurement of executive function.

Stockings of Cambridge (SOC)



SOC assesses spatial planning and requires individuals to use problem-solving strategies to match two sets of stimuli. The subject is shown two displays. In each of these displays, three stockings - containing three colored balls - are suspended from a beam. The two displays appear at the top and bottom of the screen. The balls are arranged in different patterns in each display. The subject must move the balls in the bottom display to copy the pattern shown in the top display. The balls are moved one at a time by selecting the required ball, then selecting the position to which it should be moved. The subject is instructed to make as few moves as possible to match the two patterns. In a distinct phase of the test, subjects are instructed to copy the moves the computer makes. These moves mimic the moves the subject made, and allow movement time to be discounted from thinking time measures.

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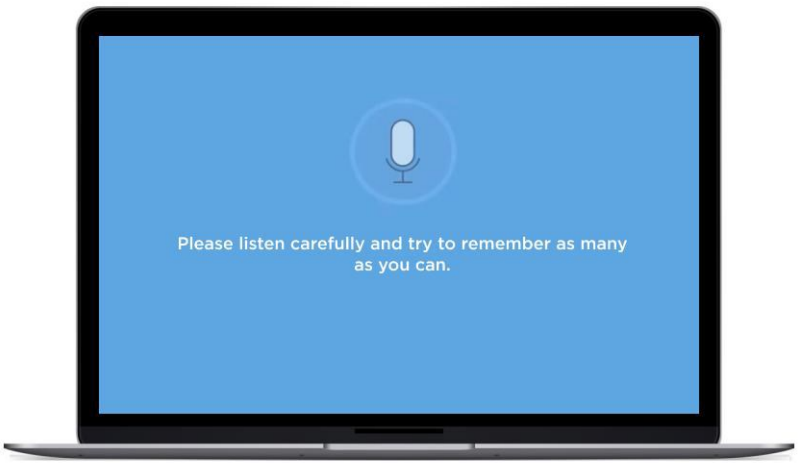
Verbal Paired Associates (VPA)



Verbal Paired Associates (VPA) is an assessment of associative and episodic memory in which the task is to learn a set of word-pairs. This is a verbal task, with stimuli presented auditorily, and responses spoken by the participant and scored automatically by the software. The difficulty of the task (i.e., the memorability of the word-pair items) has been carefully calibrated so that parallel forms of the test can be used in repeated testing.

FOR STUDY STAFF USE ONLY:
Study Staff Initials: _____ Date of Visit: _____/_____/_____
Study ID #: _____
Has the patient signed informed consent? ☐YES ☐NO ⇨ STOP: DO NOT CONTINUE WITHOUT SIGNED INFORMED CONSENT

Lifestyle Interventions in Early-Onset Alzheimer's Disease

Demographics Questionnaire

1. First, Middle, and Last Name: _____
2. Full Name at Birth: _____
3. City, State, and Country of Birth: _____
4. Date of Birth: _____ /_____ /_____
5. Age: _____ years
6. Sex: ☐Male ☐Female
7. Handedness: ☐Left ☐Right
8. Have you previously participated in a research study on brain health outside of LEADS? ☐Yes ☐No
   If yes, please specify which study:
   _____
9. How many YEARS of education have you COMPLETED?
   _____years
   (For example, if you graduated high school in the USA, it would be 12 years)
10. Approximately how many hours per week do you engage in cognitively stimulating activities? (e.g., card or board games, puzzles, Sudoku, meaningful conversation, crafts, etc.) _____hours per week
11. Approximately how many hours per week do you use a computer?
    _____hours per week
12. Do you consider yourself to be Hispanic or Latino? ☐Yes ☐No ☐Decline
13. Do you consider yourself to be: (Check all that apply)

a. White/Caucasian ☐
b. Black/African American ☐
c. Asian ☐
d. Native Hawaiian/Pacific Islander ☐
e. American Indian/Alaskan Native ☐
f. Other: (specify)_____ ☐
g. Decline ☐

14. **If** you put more than one response for **question 13**, which do you consider to be your **PRIMARY** racial background?
a. White/Caucasian ☐
b. Black/African American ☐
c. Asian ☐
d. Native Hawaiian/Pacific Islander ☐
e. American Indian/Alaskan Native ☐
f. Other: (specify)_____ ☐

15. Is English your primary language? ☐Yes ☐No

If no, please specify your primary language:
_____

16. What is your marital status? ☐Single ☐Married ☐Divorced ☐Widowed

17. What is your current living situation?
a. My Own Home ☐
b. Independent Living Facility ☐
c. Assisted Living Facility ☐
d. Other: (specify)_____ ☐

18. During your adult life, what has been the highest total gross ANNUAL income for your household from all sources (before taxes and deductions)? Please check one:
a. Under $25,000 ☐
b. $25,001 to $49,999 ☐
c. $50,000 to $74,999 ☐
d. $75,000-$99,999 ☐
e. $100,000 to $149,999 ☐
f. $150,000 and over ☐

19. What is your employment status?

☐Retired ☐Semi-Retired ☐Not Yet Retired ☐Disabled

20. During your adult life, what has been your primary occupation?

_____

Study Staff Initials: _____	Date of Visit: ____ /____/_____
Study ID #: _____	Participant Initials: _____

Lifestyle Interventions for the Treatment of Early-Onset Alzheimer's Disease Study

Anti-Amyloid Treatment Information Form

Did this participant receive an Anti-Amyloid treatment?	**No** ☐	**Yes** ☐
If No, initial, date and line through the rest of this form.		
If Yes, did they receive Aducanumab? ☐ Yes ☐ No If yes, provide treatment **start date,** if known: _____ (YYYY – MM – DD) Provide treatment **end date,** if known: _____ (YYYY – MM – DD) ☐ Check if missing or not applicable		
Dose of treatment: _____ Unit of dose: ☐ milligram (mg)/ milliliter (mL) ☐ other If other, specify: _____		
Frequency of treatment: ☐ every 4 weeks ☐ other If other, specify: _____		

Route of treatment:
☐ Intravenous (IV)
☐ other

If other, specify:

_____

If Yes, did they receive Lecanemab?

☐ Yes
☐ No

If yes, provide treatment **start date,** if known:
_____ (YYYY – MM – DD)

Provide treatment **end date,** if known:
_____ (YYYY – MM – DD)
☐ Check if missing or not applicable

Dose of treatment:
_____

Unit of dose:
☐ milligram (mg)/ milliliter (mL)
☐ other

If other, specify:

_____

Frequency of treatment:
☐ every 4 weeks
☐ other

If other, specify:

_____

Route of treatment:
☐ Intravenous (IV)
☐ other

If other, specify:

_____

If Yes, did they receive Donanemab?

☐ Yes
☐ No

If yes, provide treatment **start date,** if known:
_____ (YYYY – MM – DD)

Provide treatment **end date,** if known:
_____ (YYYY – MM – DD)
☐ Check if missing or not applicable

Dose of treatment:
_____

Unit of dose:
☐ milligram (mg)/ milliliter (mL)
☐ other

If other, specify:

_____

Frequency of treatment:
☐ every 4 weeks
☐ other

If other, specify:

_____

Route of treatment:

☐ Intravenous (IV)

☐ other

If other, specify:

_____

Please provide any additional comments:

_____
_____
_____
_____
_____
_____
_____
_____
_____

Study Staff Initials: _____ Date of Visit: _____/_____/_____
Study ID #: _____ Participant Initials:_____

LITES - COGNITIVE SELF-REPORT QUESTIONNAIRE (CSRQ)
INSTRUCTIONS:

"Below is a list of statements about how you see your everyday thinking skills and feelings. Please read each one carefully and circle the response that would best describe you <u>over the last two weeks, including today.</u>"

1. I have felt I have a good memory. CG1	Almost Always 1	Often/Usually 2	Sometimes 3	Seldom 4	Hardly Ever 5	Does not apply to me 0
2. I have had difficulty hearing conversations in noisy places (e.g. in a restaurant or crowded room). HR2	Almost Always 5	Often/Usually 4	Sometimes 3	Seldom 2	Hardly Ever 1	Does not apply to me 0
3. I have been happy to me overall. SL1	Almost Always 1	Often/Usually 2	Sometimes 3	Seldom 4	Hardly Ever 5	Does not apply 0
4. I have had difficulty me remembering things that people told me. CG3	Almost Always 5	Often/Usually 4	Sometimes 3	Seldom 2	Hardly Ever 1	Does not apply to 0
5. I have felt me self-confident.	Almost Always 5	Often/Usually 4	Sometimes 3	Seldom 2	Hardly Ever 1	Does not apply to 0SL10
6. When I met someone new, I remembered their name later. CG5	Almost Always 1	Often/Usually 2	Sometimes 3	Seldom 4	Hardly Ever 5	Does not apply to me 0
7. I have been in a bad mood. SL6	Almost Always 5	Often/Usually 4	Sometimes 3	Seldom 2	Hardly Ever 1	Does not apply to me 0
8. I have been able to think quickly. SL2	Almost Always 1	Often/Usually 2	Sometimes 3	Seldom 4	Hardly Ever 5	Does not apply to me 0
9. I have not been able to remember grocery shopping items unless I looked at the shopping list. CG4	Almost Always 5	Often/Usually 4	Sometimes 3	Seldom 2	Hardly Ever 1	Does not apply to me 0
10. I couldn't find the right word in a conversation. CG2	Almost Always 5	Often/Usually 4	Sometimes 3	Seldom 2	Hardly Ever 1	Does not apply to me 0
11. I could hear what people said when they spoke softly or mumbled. HR3	Almost Always 1	Often/Usually 2	Sometimes 3	Seldom 4	Hardly Ever 5	Does not apply to me 0

12. I have felt unproductive. SL3	Almost Always 5	Often/Usually 4	Sometimes 3	Seldom 2	Hardly Ever 1	Does not apply to me 0
13. I have lost my train of thought. CG8	Almost Always 5	Often/Usually 4	Sometimes 3	Seldom 2	Hardly Ever 1	Does not apply to me 0
14. It has been easy for me to organize activities. SL8:	Almost Always 1	Often/Usually 2	Sometimes 3	Seldom 4	Hardly Ever 5	Does not apply to me 0
15. I could remember where I left things. CG10	Almost Always 1	Often/Usually 2	Sometimes 3	Seldom 4	Hardly Ever 5	Does not apply to me 0
16. I have said or done things without considering the consequences. CG7	Almost Always 5	Often/Usually 4	Sometimes 3	Seldom 2	Hardly Ever 1	Does not apply to me 0
17. I have had difficulty hearing what people say when they spoke quickly. HR4	Almost Always 5	Often/Usually 4	Sometimes 3	Seldom 2	Hardly Ever 1	Does not apply to me 0
18. Given the opportunity, I engaged in activities with other people. SL4	Almost Always 1	Often/Usually 2	Sometimes 3	Seldom 4	Hardly Ever 5	Does not apply to me 0
19. I have not been able to remember numbers. CG6	Almost Always 5	Often/Usually 4	Sometimes 3	Seldom 2	Hardly Ever 1	Does not apply to me 0
20. I have been interested in trying new things. SL5	Almost Always 1	Often/Usually 2	Sometimes 3	Seldom 4	Hardly Ever 5	Does not apply to me 0
21. I have been able to take-in/process information quickly. SL7	Almost Always 1	Often/Usually 2	Sometimes 3	Seldom 4	Hardly Ever 5	Does not apply to me 0
22. I have walked into a room and then forgotten why I needed to go there. CG9	Almost Always 5	Often/Usually 4	Sometimes 3	Seldom 2	Hardly Ever 1	Does not apply to me 0
23. I have felt pessimistic. SL9	Almost Always 5	Often/Usually 4	Sometimes 3	Seldom 2	Hardly Ever 1	Does not apply to me 0
24. I have had trouble hearing conversations on the telephone. HR1	Almost Always 5	Often/Usually 4	Sometimes 3	Seldom 2	Hardly Ever 1	Does not apply to me 0
25. I slept well at night.	Almost Always 1	Often/Usually 2	Sometimes 3	Seldom 4	Hardly Ever 5	Does not apply to me 0

ADCS – Activities of Daily Living Inventory

Galasko, D., Bennett, D., Sano, M., Ernesto, E., Thomas, R., Grundman, M., and Ferris, S. *Alzheimer's Disease and Associated Disorders* 1997; 11:S33--S39.

Information source: ☐ Participant Visit ☐ Telephone Call

INSTRUCTIONS: For each question, use the participant's name where "{P}" appears. Before beginning, read the guidelines to the study partner. For instructions on completing the ADL please refer to the Administration Guidelines.

1. Regarding **eating**, which best describes {P} **usual performance** during the past 4 weeks:

3 ☐ ate without physical help, and used a knife
2 ☐ used a fork or spoon, but not a knife, to eat
1 ☐ used fingers to eat
0 ☐ {P} usually or always was fed by someone else

2. Regarding **walking** (or getting around in a wheelchair), in the past 4 weeks, which best describes his/her **optimal performance**:

3 ☐ mobile outside of home without physical help
2 ☐ mobile across a room without physical help
1 ☐ transferred from bed to chair without help
0 ☐ required physical help to walk or transfer

3. Regarding **bowel and bladder function at the toilet**, which best describes his/her **usual performance** in the past 4 weeks: 3 ☐ did everything necessary without supervision or physical help
2 ☐ needed supervision, but no physical help
1 ☐ needed physical help, and was usually continent
0 ☐ needed physical help, and was usually incontinent

4. Regarding **bathing**, in the past 4 weeks, which best describes his/her **usual performance**: 3 ☐ bathed without reminding or physical help
2 ☐ no physical help, but needed supervision/reminders to bathe completely 1 ☐ needed minor physical help (e.g., with washing

hair) to bath completely 0 ☐ needed to be bathed completely

5. Regarding **grooming**, in the past 4 weeks, which best describes his/her **optimal performance**: 3 ☐ cleaned and cut fingernails without physical help
2 ☐ brushed or combed hair without physical help
1 ☐ kept face and hands clean without physical help
0 ☐ needed help for grooming of hair, face, hands, and fingernails

6a. Regarding dressing, in the past 4 weeks, which best describes his/her **usual performance** when **selecting his/her first set of clothes** for the day:

3 ☐ without supervision or physical help 2 ☐ with supervision
1 ☐ with physical help
0 ☐ {P} did not select his/her clothes for the day 0 ☐ don't know

6b. Regarding **physically getting dressed**, which best describes his/her **usual performance** in the past 4 weeks: 4 ☐ dressed completely without supervision or physical help
3 ☐ dressed completely with supervision, but without help
2 ☐ needed physical help only for buttons, clasps, or shoelaces
1 ☐ dressed without help if clothes needed
no fastening or buttoning 0 ☐ always needed help, regardless of type of clothing
0 ☐ don't know

7. Regarding **telephone usage** in the past 4 weeks, which best describes his/her **highest level of performance**:

5 ☐ made calls after looking up numbers in white or yellow pages, or by dialing directory assistance 4 ☐ made calls only to well-known numbers, without referring to a directory or list
3 ☐ made calls only to well-known numbers by using a directory, list, or pre-programmed numbers 2 ☐ answered the phone; did not make calls
1 ☐ did not answer the phone, but spoke when put on the line 0 ☐ did not use telephone
0 ☐ don't know

8. During the past 4 weeks, did {P} watch **television**?

☐ yes
☐ no
☐ don't know

If yes, ask all questions:

8a. Did {P} usually select or ask for different programs or his/her favorite show?

1 ☐ yes
0 ☐ no
0 ☐ don't know

8b. Did {P} usually talk about the content of a program while watching it?

1 ☐ yes
0 ☐ no
0 ☐ don't know

8c. Did {P} usually talk about the content of a program within a day (24 hours) after watching it?

1 ☐ yes
0 ☐ no
0 ☐ don't know

9. During the past 4 weeks, when {P} appeared to be paying attention to **conversation or small talk** for at least 5 minutes, which best describes his/her **usual degree of participation**:

NOTE: *{P} did not need to initiate the conversation.*

3 ☐ usually said things that were related to the topic
2 ☐ usually said things that were not related to the topic 1
☐ rarely or never spoke
0 ☐ did not participate in conversations or small talk 0
☐ don't know

10. During the past 4 weeks, which best describes how {P} **usually cleared dishes from the table** after a meal or snack: 3 ☐ without supervision or help
2 ☐ with supervision 1 ☐ with physical help
0 ☐ {P} did not clear dishes
0 ☐ don't know

11. During the past 4 weeks, which best describes how {P} **usually managed to find his/her**

personal belongings at home: 3 ☐ without supervision or help
2 ☐ with supervision 1 ☐ with physical help
0 ☐ {P} did not find personal belongings 0 ☐ don't know

12. During the past 4 weeks, which best describes {P}'s **highest level of performance** when **obtaining a hot or cold beverage** for him/herself:

3 ☐ made a hot beverage, usually without physical help
2 ☐ made a hot beverage, usually if someone else heated the water 1 ☐ obtained a cold beverage, usually without physical help
0 ☐ {P} did not obtain a beverage for him/herself 0 ☐ don't know

13. During the past 4 weeks, which best describes {P}'s **highest level of performance** when **making him/herself a meal or snack** at home:

4 ☐ cooked or microwaved food, with little or no help 3 ☐ cooked or microwaved food, with extensive help
2 ☐ mixed or combined food items for a meal or snack, without cooking or microwaving (e.g. made a sandwich) 1 ☐ obtained food on his/her own, without mixing or cooking it
0 ☐ {P} did not make him/herself a meal or snack at home 0 ☐ don't know

14. During the past 4 weeks, which best describes how {P} **usually disposed of garbage or litter** in the appropriate place or container at home:

3 ☐ without supervision or help 2 ☐ with supervision
1 ☐ with physical help
0 ☐ {P} did not dispose of garbage or litter in an appropriate place or container 0 ☐ don't know

15. During the past 4 weeks, which best describes {P}'s **optimal performance** when **getting around (or traveling) outside of his/her home:**

4 ☐ alone, went at least 1 mile away from home 3 ☐ alone, but remained within 1 mile of home
2 ☐ only when accompanied and supervised regardless of the trip 1 ☐ only with physical help regardless of the trip
0 ☐ {P} did not get around (or travel) outside of his/her home 0 ☐ don't know

16a. On **shopping trips** during the past 4 weeks, which best describes how {P}

usually selected items: 3 ☐ without supervision or physical help
2 ☐ with some supervision or physical help
1 ☐ not at all, or selected mainly
random or inappropriate items 0 ☐ {P}
did not go shopping
0 ☐ don't know

16b. On **shopping trips** during the past 4 weeks, did {P} **usually pay for items without supervision or physical help**?

1 ☐ yes
0 ☐ no
0 ☐ {P} did not go shopping 0 ☐ don't know

17. During the past 4 weeks, when keeping appointments or meetings with other people such as relatives, a doctor, the hairdresser, etc., which best describes {P}'s **awareness of the appointment or meeting ahead of time:**

3 ☐ usually remembered, may have needed written reminders,
e.g., notes, a diary, or calendar 2 ☐ only remembered the
appointment after verbal reminders on the day
1 ☐ usually did not remember, in spite of
verbal reminders on the day 0 ☐ {P} did not
keep any appointments or meetings
0 ☐ don't know

18. During the past 4 weeks, was {P} **ever left on his/her own**?

NOTE: *Being taken to day care or having a sitter at home does not constitute being left alone.*

☐ yes
☐ no
☐ don't know
☐ not applicable --- {P} is institutionalized

If yes, ask all questions:

18a. Was {P} left away from home, for 15 minutes or longer, during the day?

1 ☐ yes
0 ☐ no
0 ☐ don't know

18b. Was {P} left at home, for an hour or longer, during the day?

1 ☐ yes
0 ☐ no
0 ☐ don't know

18c. Was {P} left at home, for less than 1 hour, during the day?

1 ☐ yes
0 ☐ no
0 ☐ don't know

19. During the past 4 weeks, did {P} **talk about current events**?

NOTE: *This means events or incidents that occurred during the past month.*

☐ yes
☐ no
☐ don't know

If yes, ask all questions:

19a. Did {P} talk about events that he/she heard or read about or saw on TV but did not take part in?

1 ☐ yes
0 ☐ no
0 ☐ don't know

19b. Did {P} talk about events that he/she took part in outside home involving family, friends, or neighbors?

1 ☐ yes
0 ☐ no
0 ☐ don't know

19c. Did {P} talk about events that occurred at home that he/she took part in or watched?

1 ☐ yes
0 ☐ no
0 ☐ don't know

20a. Did {P} usually talk about details of what he/she read while or shortly (less than 1 hour) after reading?

1 ☐ yes
0 ☐ no
0 ☐ don't know

20b. Did {P} usually talk about what he/she read 1 hour or longer after reading?

1 ☐ yes
0 ☐ no
0 ☐ don't know

21. During the past 4 weeks, which best describes the **most complicated things**

that {P} wrote down: 3 ☐ letters or long notes that other people understood
2 ☐ short notes or messages that other people understood 1 ☐ his/her signature or name
0 ☐ {P} did not write things down 0 ☐ don't know

22. During the past 4 weeks, which best describes how {P} **usually performed** his/her **most common pastime, hobby, or game:**

NOTE: *Walking does not count as a pastime/hobby for this scale.*
Examples include card or board games (including bridge, chess, checkers), bingo, crosswords, art, musical instrument, knitting, sewing, reading, gardening, golf, tennis, workshop, fishing.

3 ☐ without supervision
or help 2 ☐ with
supervision
1 ☐ with physical help
0 ☐ {P} did not perform any
pastimes, hobbies, or games 0 ☐
don't know

If {P} performed hobbies/pastimes, were they performed only at day care?

☐ yes
☐ no

23. Regarding the use of a **household appliance to do chores** during the past 4 weeks, which best describes how {P} **usually used the most common appliances**:

NOTE: *This does not include a TV. Examples include washer, dryer, vacuum, dishwasher, toaster, toaster oven, range, microwave, food processor.*

4 ☐ without help, operating more than on-off controls if needed 3 ☐ without help, but operated only on-off controls
2 ☐ with supervision, but no physical help 1 ☐ with physical help
0 ☐ {P} did not use a household appliance to do chores 0 ☐ don't know

Galasko, D., Bennett, D., Sano, M., Ernesto, E., Thomas, R., Grundman, M., and Ferris, S. *Alzheimer Disease and Associated Disorders* 1997; 11:S33-S39.

Beck's Depression Inventory- 2

1.
0 I do not feel sad.
1 I feel sad
2 I am sad all the time and I can't snap out of it.
3 I am so sad and unhappy that I can't stand it.

2.
0 I am not particularly discouraged about the future.
1 I feel discouraged about the future.
2 I feel I have nothing to look forward to.
3 I feel the future is hopeless and that things cannot improve.

3.
0 I do not feel like a failure.
1 I feel I have failed more than the average person.
2 As I look back on my life, all I can see is a lot of failures.
3 I feel I am a complete failure as a person.

4.
0 I get as much satisfaction out of things as I used to.
1 I don't enjoy things the way I used to.
2 I don't get real satisfaction out of anything anymore.
3 I am dissatisfied or bored with everything.

5.
0 I don't feel particularly guilty
1 I feel guilty a good part of the time.
2 I feel quite guilty most of the time.
3 I feel guilty all of the time.

6.
0 I don't feel I am being punished.
1 I feel I may be punished.
2 I expect to be punished.
3 I feel I am being punished.

7.
0 I don't feel disappointed in myself.
1 I am disappointed in myself.
2 I am disgusted with myself.
3 I hate myself.

8.
0 I don't feel I am any worse than anybody else.
1 I am critical of myself for my weaknesses or mistakes.
2 I blame myself all the time for my faults.
3 I blame myself for everything bad that happens.

9.
0 I don't have any thoughts of killing myself.
1 I have thoughts of killing myself, but I would not carry them out.
2 I would like to kill myself.
3 I would kill myself if I had the chance.

10.
0 I don't cry any more than usual.
1 I cry more now than I used to.
2 I cry all the time now.
3 I used to be able to cry, but now I can't cry even **though I want to.**

11.
0 I am no more irritated by things than I ever was.
1 I am slightly more irritated now than usual.
2 I am quite annoyed or irritated a good deal of the time.
3 I feel irritated all the time.

12.
0 I have not lost interest in other people.
1 I am less interested in other people than I used to be.
2 I have lost most of my interest in other people.
3 I have lost all of my interest in other people.

13.
0 I make decisions about as well as I ever could.
1 I put off making decisions more than I used to.
2 I have greater difficulty in making decisions more than I used to.
3 I can't make decisions at all anymore.

14.
0 I don't feel that I look any worse than I used to.
1 I am worried that I am looking old or unattractive.
2 I feel there are permanent changes in my appearance that make me look unattractive
3 I believe that I look ugly.

15.
0 I can work about as well as before.
1 It takes an extra effort to get started at doing something.
2 I have to push myself very hard to do anything.
3 I can't do any work at all.

16.
0 I can sleep as well as usual.
1 I don't sleep as well as I used to.
2 I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.
3 I wake up several hours earlier than I used to and cannot get back to sleep.

17.
0 I don't get more tired than usual.

1 I get tired more easily than I used to.
2 I get tired from doing almost anything.
3 I am too tired to do anything.

18.
0 My appetite is no worse than usual.
1 My appetite is not as good as it used to be.
2 My appetite is much worse now.
3 I have no appetite at all anymore.

19.
0 I haven't lost much weight, if any, lately.
1 I have lost more than five pounds.
2 I have lost more than ten pounds.
3 I have lost more than fifteen pounds.

20.
0 I am no more worried about my health than usual.
1 I am worried about physical problems like aches, pains, upset stomach, or constipation.
2 I am very worried about physical problems and it's hard to think of much else.
3 I am so worried about my physical problems that I cannot think of anything else.

21.
0 I have not noticed any recent change in my interest in sex.
1 I am less interested in sex than I used to be.
2 I have almost no interest in sex.
3 I have lost interest in sex completely.

FOR STUDY STAFF USE ONLY:

Study Staff Initials: _____ Date of Visit:_____/_____/_____

Study ID #: _____

Perceived Stress Scale 4 (PSS-4)

Instructions: The questions in this scale ask you about your feelings & thoughts during **the last month**. In each case, please indicate your response by selecting the option representing **how often** you felt or thought a certain way.

	Never 0	Almost Never 1	Sometimes 2	Fairly Often 3	Very Often 4
1. In the last month, how often have you felt that you were unable to control the important things in your life?	☐	☐	☐	☐	☐
2. In the last month, how often have you felt confident about your ability to handle your personal problems?	☐	☐	☐	☐	☐
3. In the last month, how often have you felt that things were going your way?	☐	☐	☐	☐	☐
4. In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?	☐	☐	☐	☐	☐

Scoring for the Perceived Stress Scale 4:

Instructions: Total score is determined by adding together the scores of each of the 4 items. Questions 2 and 3 are reverse coded.

Questions 1 and 4:
0 = Never
1 = Almost Never
2 = Sometimes
3 = Fairly Often
4 = Very Often

Questions 2 and 3:
4 = Never
3 = Almost Never
2 = Sometimes
1 = Fairly Often
0 = Very Often

Lowest score: 0
Highest score: 16

Higher scores are correlated to more stress.

FOR STUDY STAFF USE ONLY:

Study Staff Initials: _____ Date of Visit:_____/_____/_____

Study ID #: _____ 15 Week Follow Up

Lifestyle Interventions for the Treatment of Early-Onset Alzheimer's Disease Study

Perceptions of Change Questionnaire

Please circle the response that best matches how you feel about the following statements:

1. The training program helped improve my memory.

Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree

2. The training program helped improve my overall thinking abilities.

Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree

3. I enjoyed the training program overall.

Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree

4. Do you think you were assigned to the experimental or control group?(Circle one)

Experimental	Don't Know	Control

FOR STUDY STAFF USE ONLY:	
Study Staff Initials: _____	Date of Visit:
_____/_____/_____	
Study ID #: _____	Week 15 Follow-Up

Lifestyle Interventions for the Treatment of Early-Onset AD Study (LITES)
Cognitive Training Satisfaction Survey and Questionnaire

Survey:

INSTRUCTIONS:

"Below is a list of statements or questions about your experience with the Cognitive Training Intervention. Please read each one carefully and circle the response that would best describe your feeling during the training period."

1. I found the online program easy to navigate	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
2. I found the exercises challenging but enjoyable	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
3. I found the intensity of the cognitive training program appropriate and manageable	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
4. How helpful did you find the cognitive training program to improve your brain health overall?	Extremely Helpful	Very Helpful	Moderately Helpful	Little Helpful	Not at All Helpful
5. Overall, how satisfied were you with the cognitive training program?	Extremely Satisfied	Somewhat Satisfied	Neither Satisfied nor Dissatisfied	Somewhat Dissatisfied	Extremely Dissatisfied

Additional User Questions:

1. <u>Which of the following prevented you from using the cognitive training program (check all that apply):</u>

- ☐ I did not have easy access to a computer with internet
- ☐ I did not understand how to use a computer well
- ☐ I did not understand how to use the training program
- ☐ I found the training program too frustrating

- ☐ I did not have enough time to complete the training program
- ☐ I did not want to do the training program
- ☐ I did not believe the training program was helping me
- ☐ I found the training program boring
- ☐ I found the training program annoying
- ☐ Nothing prevented me from using the training program
- ☐ Other (Specify):_____

2. <u>What do you think could improve the cognitive training program (check all that apply)?</u>

- ☐ More thorough instructions in the program
- ☐ More thorough paper instructions to take home
- ☐ Take away the sounds and animations not necessary to the exercises
- ☐ Add more sounds and animations to provide feedback
- ☐ I like the training program the way it is
- ☐ Other _____

3. <u>Which browser did you normally use to access the cognitive training program?</u>

- ☐ Internet Explorer (IE) 
- ☐ Mozilla Firefox 
- ☐ Safari 
- ☐ Google Chrome 
- ☐ Other:_____

4. When using the cognitive training program, did you normally use a:

- ☐ Mouse
- ☐ Track pad
- ☐ Touchscreen
- ☐ Other:_____

Modified from:
Li, F., Harmer, P., Fitzgerald, K. et al. A cognitively enhanced online Tai Ji Quan training intervention for community-dwelling older adults with mild cognitive impairment: A feasibility trial. *BMC Geriatr* 22, 76 (2022). https://doi.org/10.1186/s12877-021-02747-0

FOR STUDY STAFF USE ONLY:
Study Staff Initials: _____ Date of Visit:
_____/_____/_____
Study ID #: _____ Week 15 Follow-Up
Questionnaire

Lifestyle Interventions for the Treatment of Early-Onset AD Study (LITES)
Exercise Satisfaction Survey

INSTRUCTIONS:

"Below is a list of statements or questions about your experience with the Exercise Intervention. Please read each one carefully and circle the response that would best describe your feeling during the training period."

1. I found the exercise program safe to practice	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
2. I found the exercises challenging but enjoyable	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
3. I found the intensity of the exercise program appropriate and manageable	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
4. How helpful did you find the exercise program to improve your brain health overall?	Extremely Helpful	Very Helpful	Moderately Helpful	Little Helpful	Not at All Helpful
5. Overall, how satisfied were you with the exercise program?	Extremely Satisfied	Somewhat Satisfied	Neither Satisfied nor Dissatisfied	Somewhat Dissatisfied	Extremely Dissatisfied

Modified from:
Li, F., Harmer, P., Fitzgerald, K. et al. A cognitively enhanced online Tai Ji Quan training intervention for community-dwelling older adults with mild cognitive impairment: A feasibility trial. *BMC Geriatr* 22, 76 (2022). https://doi.org/10.1186/s12877-021-02747-0

FOR STUDY STAFF USE ONLY:
Study Staff Initials: _____ Date of Visit: _____/_____/_____
Study ID #: _____ Baseline

Self-Reported Off-Line Training
BASELINE

Now I have some questions about your activities in the last 3 months (i.e., prior to the start of training). In the last 3 months….

1. Did you visit a YMCA, health club, gym, or wellness center?

   YES……..1 NO……..0 [SKIP TO #2]

   1A. Name of club/center: _____

   1B. Frequency of attendance (on average): < 1 day per week or discontinued after trivial exposure 1
   1-2 days per week 2
   3-4 days per week 3
   5-7 days per week 4

2. Did you take a class for exercise, swimming, yoga, or Tai Chi (i.e., structured group led by an instructor)?
   [Note: Do NOT include prescribed physical therapy]

   YES……..1 NO……..0 [SKIP TO #3]

   2A. Type of class: _____

   2B. Frequency of attendance (on average): < 1 day per week or discontinued after trivial exposure 1
   1-2 days per week 2
   3-4 days per week 3
   5-7 days per week 4

3. Did you take an adult education course, such as a continuing education course at a local university or community college?

   YES……..1 NO……..0 [SKIP TO #4]

   3A. Course matter/subject: _____

3B. Frequency of attendance (on average): < 1 day per week or discontinued after trivial exposure 1
1-2 days per week 2
3-4 days per week 3
5-7 days per week 4

3C. Length/Duration of course: __ __ months

4. Did you participate in any brain exercise program or training (i.e, web-based, in-person, DVD)?

YES……..1 NO……..0 [SKIP TO #5]

4A. Name of program: _____

4B. Frequency of participation: < 1 day per week or discontinued after trivial exposure 1
1-2 days per week 2
3-4 days per week 3
5-7 days per week 4

5. Did you participate in any cognitively stimulating activities (e.g., card or board games, puzzles, Sudoku, crafts, etc.)?

YES……..1 NO……..0 [SKIP TO #6]

5A. Name of activity: _____

5B. Frequency of participation: < 1 day per week or discontinued after brief engagement.. 1
1-2 days per week 2
3-4 days per week 3
5-7 days per week 4

6. Approximately how many hours per week on average do you use a computer?
≤ 1 hour per week.. 1

2-5 hours per week
2
6-13 hours per week
3
14+ hours per week
4

FOR STUDY STAFF USE ONLY:
Study Staff Initials: _____ Date of Visit:
_____/_____/_____
Study ID #: _____ 15 Week Follow Up

Self-Reported Off-Line Training
15 WEEK POST INTERVENTION FOLLOW UP

Now I have some questions about your activities in the last 14-15 weeks (i.e., since training began). In the last 15 weeks….

1. Did you visit a YMCA, health club, gym, or wellness center?

   YES……..1 NO……..0 [SKIP TO #2]

   1A. Name of club/center: _____

   1B. Frequency of attendance (on average):
   < 1 day per week or discontinued after trivial exposure 1
   1-2 days per week 2
   3-4 days per week 3
   5-7 days per week 4

2. Did you take a class for exercise, swimming, yoga, or Tai Chi *outside of this research project* (i.e., structured group led by an instructor)?
   [Note: Do NOT include prescribed physical therapy]

   YES……..1 NO……..0 [SKIP TO #3]

   2A. Type of class: _____

   2B. Frequency of attendance (on average):
   < 1 day per week or discontinued after trivial exposure 1
   1-2 days per week 2
   3-4 days per week 3
   5-7 days per week 4

3. Did you take an adult education course, such as a continuing education course at a local university or community college?

   YES……..1 NO……..0 [SKIP TO #4]

   3A. Course matter/subject: _____

3B. Frequency of attendance (on average): < 1 day per week or discontinued after trivial exposure
1
1-2 days per week
2
3-4 days per week
3
5-7 days per week
4

3C. Length/Duration of course: __ __ months

4. Did you participate in any brain exercise program or training *outside of this research project* (i.e, web-based, in-person, DVD)?

YES……..1 NO……..0 [SKIP TO #5]

4A. Name of program: _____

4B. Frequency of participation: < 1 day per week or discontinued after trivial exposure
1
1-2 days per week
2
3-4 days per week
3
5-7 days per week
4

5. Did you participate in any cognitively stimulating activities *outside of this research project* (e.g., card or board games, puzzles, Sudoku, crafts, etc.)?

YES……..1 NO……..0 [SKIP TO #6]

5A. Name of activity: _____

5B. Frequency of participation: < 1 day per week or discontinued after brief engagement..
1
1-2 days per week
2
3-4 days per week
3
5-7 days per week
.....
4

6. At any time during your participation in this study, did you participate in any other research?
YES……..1 NO……..0 [SKIP TO #7]

What was the project?

_____

If yes, when did you participate in the project?

_____

7. *Outside of this research project*, approximately how many hours per week on average do you use a computer?

≤ 1 hour per week..
1
2-5 hours per week
2
6-13 hours per week
3
14+ hours per week
4

FOR STUDY STAFF USE ONLY:
Study Staff Initials: _____ Date of Visit:
_____/_____/_____
Study ID #: _____ 40 Week Follow Up

Self-Reported Off-Line Training
40 WEEK FOLLOW-UP

Now I have some questions about your activities in the last 6 months (i.e., since the end of training). In the last 6 months….

1. Did you visit a YMCA, health club, gym, or wellness center?

   YES……..1 NO……..0 [SKIP TO #2]

   1A. Name of club/center: _____

   1B. Frequency of attendance (on average):
   < 1 day per week or discontinued after trivial exposure 1
   1-2 days per week 2
   3-4 days per week 3
   5-7 days per week 4

2. Did you take a class for exercise, swimming, yoga, or Tai Chi *outside of this program* (i.e., structured group led by an instructor)?
   [Note: Do NOT include prescribed physical therapy]

   YES……..1 NO……..0 [SKIP TO #3]

   2A. Type of class: _____

   2B. Frequency of attendance (on average):
   < 1 day per week or discontinued after trivial exposure 1
   1-2 days per week 2
   3-4 days per week 3
   5-7 days per week 4

3. Did you take an adult education course, such as a continuing education course at a local university or community college?

   YES……..1 NO……..0 [SKIP TO #4]

   3A. Course matter/subject: _____

3B. Frequency of attendance (on average): < 1 day per week or discontinued after trivial exposure
1
1-2 days per week
2
3-4 days per week
3
5-7 days per week
4

3C. Length/Duration of course: __ __ months

4. Did you participate in any brain exercise program or training *outside of this program* (i.e, web-based, in-person, DVD)?

YES……..1 NO……..0 [SKIP TO #5]

4A. Name of program: _____

4B. Frequency of participation: < 1 day per week or discontinued after trivial exposure
1
1-2 days per week
2
3-4 days per week
3
5-7 days per week
4

5. Did you participate in any cognitively stimulating activities *outside of this research project* (e.g., card or board games, puzzles, Sudoku, crafts, etc.)?

YES……..1 NO……..0 [SKIP TO #6]

5A. Name of activity: _____

5B. Frequency of participation: < 1 day per week or discontinued after brief engagement..
1
1-2 days per week
2
3-4 days per week
3
5-7 days per week
.....
4

6. At any time during your participation in this study, did you participate in any other research?
YES……..1 NO……..0 [SKIP TO #7]

What was the project?

_____

If yes, when did you participate in the project?

_____

7. *Outside of this research project*, approximately how many hours per week on average do you use a computer?

≤ 1 hour per week..
1
2-5 hours per week
2
6-13 hours per week
3
14+ hours per week
4

Quality of Life in Alzheimer's Disease cont'd

QOL-AD

UWMC/ADPR/QOL
Aging and Dementia: Quality of Life in AD
Quality of Life: AD
(Family Version)

ID Number	Assessment Number	Interview Date	Score (for clinician's use only)
☐☐☐☐☐☐	☐☐	☐☐ ☐☐ ☐☐ Month Day Year	

Instructions: Please rate your relative's current situation, as you see it. Circle your responses.

1. Physical health	Poor	Fair	Good	Excellent	
2 Energy	Poor	Fair	Good	Excellent	
3. Mood	Poor	Fair	Good	Excellent	
4. Living situation	Poor	Fair	Good	Excellent	
5. Memory	Poor	Fair	Good	Excellent	
6. Family	Poor	Fair	Good	Excellent	
7. Marriage	Poor	Fair	Good	Excellent	
8. Friends	Poor	Fair	Good	Excellent	
9. Self as a whole	Poor	Fair	Good	Excellent	
10. Ability to do chores around the house	Poor	Fair	Good	Excellent	
11. Ability to do things for fun	Poor	Fair	Good	Excellent	
12. Money	Poor	Fair	Good	Excellent	
13. Life as a whole	Poor	Fair	Good	Excellent	

Comments:

_____

_____

Total

Study Staff Initials: _____	Date of Visit: ____ /____/_____
Study ID #: _____	Participant Initials: _____

Multidimensional Scale of Perceived Social Support 6 (MSPSS-6)

Instructions: We are interested in how you feel about the following statements. Read each statement carefully. Indicate how you feel about each statement.

Circle the "1" if you **Very Strongly Disagree**
Circle the "2" if you **Strongly Disagree**
Circle the "3" if you **Mildly Disagree**
Circle the "4" if you are **Neutral**
Circle the "5" if you **Mildly Agree**
Circle the "6" if you **Strongly Agree**
Circle the "7" if you **Very Strongly Agree**

.

	Very Strongly Disagree	Strongly Disagree	Mildly Disagree	Neutral	Mildly Agree	Strongly Agree	Very Strongly Agree
1. There is a special person with whom I can share joys and sorrows.	1	2	3	4	5	6	7
2. There is a special person who is around when I am in need.	1	2	3	4	5	6	7
3. I can count on my friends when things go wrong.	1	2	3	4	5	6	7
4. I can talk about my problems with my friends.	1	2	3	4	5	6	7
5. I get the emotional help and support I need from my family.	1	2	3	4	5	6	7
6. My family really tries to help me.	1	2	3	4	5	6	7

FOR STUDY STAFF USE ONLY:
Study Staff Initials: _____ Date of Visit: _____/_____/_____

Lifestyle Interventions in Early-Onset Alzheimer's Disease Study

Contact Information

1. Participant's Name: _____
2. Preferred Name:_____
3. Preferred Phone Number:_____ ☐Home ☐Cell ☐Other

   Alternate Phone Number: :_____ ☐Home ☐Cell ☐Other
4. Best Time to Call: _____
5. Mailing Address: _____

   _____
6. E-Mail Address:

   _____
7. Preferred Method of Contact: ☐E-Mail ☐Phone ☐Mail ☐Other:_____
8. Name of Study Partner:

   _____
9. Study Partner's Relationship to You:

   _____
10. Email Address of Study Partner:

    _____
11. Phone Number of Study Partner:_____ ☐Home ☐Cell ☐Other

12. Best Time to Call Study Partner:_____

I authorize the research team to contact my study partner and inquire about me, as outlined in the Consent and Authorization Document.
_____ (Initial Here)

13. After the conclusion of this study, would you be interested in hearing about other research opportunities at our center? ☐Yes ☐No