RH Studio 2 OpCo 22, Inc, doing business as Together Senior Health

Small Business Innovation Research (SBIR) Phase II Trial

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PRÉCIS

Study Title

Extending Independence and Quality of Life for People with Alzheimer's Disease or Dementia through Telehealth Program Delivery

Objectives

The primary goals of this Phase II Small Business Innovation Research (SBIR) grant are to: 1) determine whether livestreaming virtual group delivery of the Moving Together program improves quality of life in people living with mild Alzheimer's disease and related disorders (ADRD) and caregivers, including exploration of potential mechanisms of action; 2) refine the platform for people with mild cognitive impairment (MCI) to expand the target audience; and 3) develop an instructor training program to meet the needs of a larger client base. **This study protocol focuses on Aim 1 only.**

Design and Outcomes

We will perform a randomized, controlled trial (RCT) with a 12-week delayed start control group in 224 dyads of people with memory loss (PWML) and caregivers (CGs). Our primary outcome in PWML will be self-rated quality of life (Quality of Life in Alzheimer's Disease, QOL-AD). Secondary outcomes will include: a) self-reported emotional well-being; b) self-reported social isolation; c) self-reported mobility; and d) directly assess cognitive performance. In CGs, the primary outcome will be self-rated quality of life (SF-12). Secondary outcomes in CGs will include: a) healthy days; b) self-efficacy; c) burden; d) social isolation; e) ability to self-regulate; f) positive affect; and g) sleep quality. In addition, we will ask CGs to report sleep quality, mobility, and cognitive function for PWML. Additional exploratory outcomes will include health services utilization (hospitalizations, emergency department visits) and falls.

Interventions and Duration

Eligible dyads will be enrolled in cohorts of 16. After being screened for eligibility, consented (V0), and completing baseline assessments (V1), dyads will be randomly assigned to immediate start intervention (n=8 dyads/cohort) or delayed start control (n=8 dyads/cohort). A total of 14 cohorts will be enrolled to achieve our target sample size of 224 dyads. Immediate start groups will participate in the livestreaming Moving Together program from their homes for 1 hour, 2 days/week, for 12 weeks, while delayed start groups will engage in usual activities. Twelve-week follow-up assessments will be performed in both groups (V2). The immediate start group will then be invited to participate in maintenance classes on a paid basis, while the delayed start group

participates in the Moving Together program for 1 hour, 2 days /week for 12 weeks. Twenty-four-week follow-up assessments will then be performed in both groups (V3), and the delayed start group will be invited to join the maintenance classes on a paid basis.

Sample Size and Population

224 dyads of persons with memory loss and their caregivers (448 persons total).

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1 STUDY OBJECTIVES

1.1 Primary Objective

To determine whether Moving Together improves quality of life in people with memory loss, including exploration of potential mechanisms of action, by performing an RCT with a delayed start control group in 224 dyads.

1.2 Milestones

Milestone 1a: Test the hypothesis that Moving Together significantly improves self-rated quality of life compared to delayed start controls on validated measures.

Milestone 1b: Perform exploratory analyses to determine whether improvements in quality of life are correlated with 'dose' based on number of classes attended and to examine potential mechanisms (such as changes in mobility, well-being or social isolation).

2 BACKGROUND AND RATIONALE

2.1 Background

In 2020, it is estimated that there are nearly 6 million people living with ADRD in the U.S. and more than 16 million unpaid caregivers, and prevalence is expected to nearly triple by 2050.[1] Current dementia medications help with some symptoms but do not change the disease course and are often discontinued due to side effects.[2,3]

Meta-analyses and systematic reviews of RCTs have found that behavioral interventions have a variety of benefits in people with ADRD and caregivers: exercise can improve physical function;[4] cognitive/social activities can improve cognitive function and quality of life;[5] music can improve mood and quality of life;[6] and caregiver education can improve caregiver knowledge and well-being.[7] Multi-domain programs that combine physical, cognitive and social elements with music and caregiver education have the greatest potential to improve multiple outcomes simultaneously.[7] Yet few multi-domain programs are widely available to people living in the community with ADRD or their caregivers.

The Preventing Loss of Independence through Exercise (PLIÉ) program is a multi-domain, in person, program that was developed specifically for people with mild to moderate ADRD.[8,9] PLIÉ capitalizes on recent discoveries in neuroscience, integrative health, and behavioral psychology by targeting abilities and neural mechanisms that are relatively well-preserved in people with ADRD. This includes: 1) training procedural or 'muscle' memory for movement sequences to support daily function (such as transitioning safely between sitting and standing, balancing while standing, and range of motion);[10,11] 2) using non-judgmental, mindful body awareness to promote awareness and acceptance of the present moment;[12,13] and 3) supporting social connection and emotional well-being through sharing of group movements, appreciations, and personally meaningful music.[6,14] Paired PLIÉ is an adapted version that is designed for groups of people with ADRD and caregivers to do together.[15]

Our research suggests that these programs are associated with participant- and caregiver-reported improvements in quality of life including psychological well-being (happiness, enjoyment, relaxation); physical function (mobility, posture); social connection (engagement); and cognitive function (memory, awareness).[8,9,15] However, some caregivers have reported increased burden associated with the logistics of having to bring persons with dementia to the in-person classes.[15]

During our Phase I SBIR grant, we applied human-centered design principles[16-18] to

develop and pilot an online version of Paired PLIÉ called Moving Together. We successfully delivered the 12-week Moving Together program using a livestreaming virtual group class format to 21 people (11 persons with ADRD/MCI and 10 caregivers/study partners) in their homes. Of the 21 participants, 15 (70%) successfully completed the program, all of whom reported being highly satisfied with livestreaming virtual class delivery. When asked what they enjoyed most about the program, participants described physical, social and emotional benefits and also highlighted the benefits of being able to participate from home.

After completing the Phase I pilot, we have continued offering online Moving Together classes to 'graduates' of our online program as well as 'naïve' participants, including several new classes that were offered in response to COVID-19. As of June 2020, we have offered 164 classes that have included 52 unique individuals (30 people living with memory loss or MCI, 22 caregivers).

2.2 Study Rationale

Despite mounting evidence that non-pharmacological and behavioral interventions—including our in-person PLIÉ and Paired PLIÉ programs—have psychological, physical, cognitive, and social benefits in people living with memory loss and caregivers, few programs are available online or have been rigorously tested in RCTs. The primary goal of this RCT is to determine whether the online Moving Together program improves self-rated quality of life in people living with memory loss or caregivers and to explore potential mechanisms of action.

3 STUDY DESIGN

We will perform a randomized, controlled trial (RCT) with a 12-week delayed start control group in 224 dyads (Figure 1). Dyads will be enrolled in cohorts of 16. After being screened for eligibility, consented (V0), and completing baseline assessments (V1), dyads will be randomly assigned to immediate start intervention (n=8 dyads/cohort) or delayed start control (n=8 dyads/cohort) groups. A total of 14 cohorts will be enrolled to achieve our target sample size of 224 dyads. Immediate start groups will participate in the livestreaming Moving Together program from their homes for 1 hour, 2 days/week, for 12 weeks, while delayed start groups engage in usual activities. Twelve-week follow-up assessments will be performed in both groups (V2). The immediate start group will then be invited to participate in maintenance classes on a paid basis, while the delayed start group participates in the Moving Together program for 1 hour, 2 days/week for 12 weeks. Twenty-four week follow-up assessments will then be performed in both groups (V3), and the delayed start group will be invited to join the maintenance classes on a paid basis. Those who participate in the maintenance classes will be invited to provide ongoing feedback.

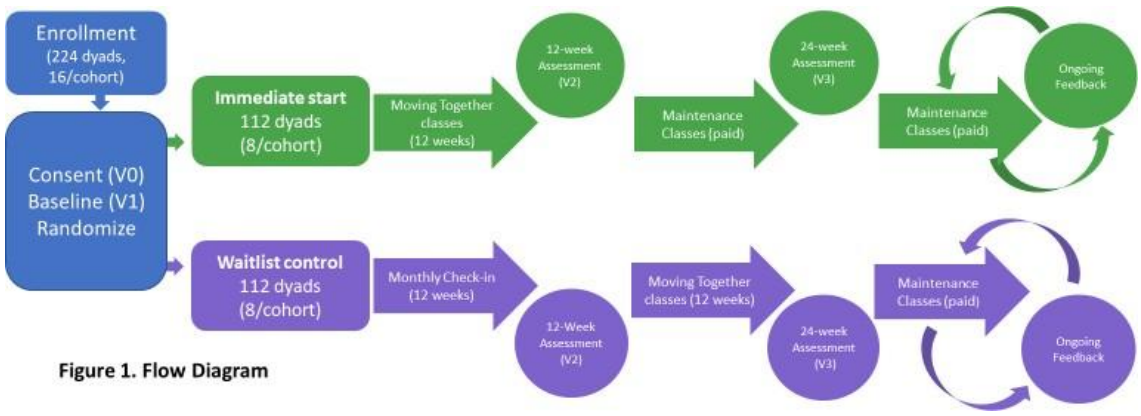

Figure 1. Flow Diagram

3.1 Setting

The primary setting for this study will be online. Together Senior Health, Inc.'s offices are physically located in San Francisco, CA. Co-investigators may have offices at UCSF or the San Francisco VA (SFVA); however, SFVA is not listed as a study site because the study is not VA-funded and data will not be collected or stored at SFVA. Research participants will participate from their homes, and research staff will participate from their homes or from research offices. The UCSF team will oversee participant enrollment and collection of outcome data using REDCap and/or Qualtrics. Together Senior Health will oversee delivery of the intervention through their secure web-based platform. Some data may be transferred securely and stored in a project-specific, restricted-access UCSF MyResearch folder. SFVA investigators will work on their UCSF time and be paid through JPA. All identifiable data will be collected and stored off-site by the prime grant holder -- Together Senior Health -- or using UCSF systems (e.g., MyResearch, REDCap, Qualtrics).

3.2 Regulatory Review and Approval

All study procedures have been reviewed and approved by the Institutional Review Board (IRB) at UCSF, and the study will be registered on ClinicalTrials.gov (Number: NCT04621448). All study participants will provide written, informed consent before participating in research activities; study participants who lack capacity to consent for themselves will be asked to provide assent, and their legally authorized representative (LAR) will sign the consent form on their behalf. We received a consent and Health Insurance Portability and Accountability Act (HIPAA) waiver to use electronic health records (EHR) to identify and recruit potential participants.

4 SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Inclusion Criteria

Participants must meet all the inclusion criteria to participate in this study.

Persons With Memory Loss (PWML):

- English language fluency;
- Reside in U.S.
- Diagnosis of mild cognitive impairment (MCI), Alzheimer's disease or other dementia
- Mild severity, assessed using the Quick Dementia Rating System (scores of 2.5 to 12.5)

Caregivers (CGs):

- English language fluency;
- Reside in U.S.
- caregiver for PWML;
- own one or more devices that can be used to participate in two-way livestreaming video classes (e.g., smart phone/tablet + TV, laptop or desktop with webcam, smart TV);
- willing and able to participate in two-way livestreaming group movement classes with PWML.

4.2 Exclusion Criteria

Any candidates meeting any of the exclusion criteria during the telephone screening will be excluded from study participation.

- Age < 18 years;
- primarily use wheel-chair inside home;
- limited life expectancy (e.g., enrolled in hospice, meta-static cancer);
- physical limitations that could affect ability to participate (e.g., difficulty sitting for 1 hour, chronic pain, vertigo);
- severe visual impairment (e.g., unable to observe instructor's movements on screen);
- severe hearing impairment (e.g., unable to hear instructor's requests);
- behavioral or psychiatric issues that could be disruptive in group setting (e.g., history of physical or verbal abuse, schizophrenia, bipolar disorder, substance abuse);
- unable to provide consent/assent;
- planning to travel for >1 week during initial 12-week study period
- current participation in another research study
- started dementia medication in past 3 months
- planning dementia medication change during next 6 months
- a fracture of back or spine including a compression fracture or hairline fracture

4.3 Recruitment

We will use a variety of strategies to recruit study participants.

- We plan to collaborate with the CTSI Consultation Service to provide cohort identification and direct mail for recruitment. The Dear Patient letter will be sent to individuals identified from the APeX record systems via a data extraction by Academic Research Systems (ARS) of patients with

diagnoses of cognitive impairment, Alzheimer's disease or dementia. These patients are not known to or under the care of the researchers.

- We will contact individuals from our previous studies who have indicated that they are willing to be contacted for future research.
- We will ask graduates of our previous studies to distribute recruitment fliers
- We will post recruitment materials in public settings such as community bulletin boards and senior centers; post electronically to social media platforms; present at community events such as senior fairs and caregiver support groups
- We may use CTSI recruitment services or an online recruiting service or platform (such as Research Match)
- We will post on websites such as Together Senior Health, clinicaltrials.gov, TrialMatch, and UCSF Clinical Trials, Researchmatch.org
- We will ask clinical colleagues to share our recruitment materials with their patients who have dementia or are caregivers of someone with dementia
- ARS generated a list of UCSF patients with diagnoses of MCI or dementia that we used for recruitment for a previous study. We will send recruitment materials to those who were not previously contacted.
- We will ask key stakeholders (e.g., Alzheimer's Association, caregiver support group leaders, adult day centers) to share our recruitment materials with their networks
- We may pay for advertisements on social media platforms (e.g., LinkedIn, Facebook), websites (e.g., Family Caregiver Alliance), or other electronic or printed locations (e.g., Google search engine, newspapers, magazines)
- We may purchase email or mail distribution lists and send recruitment materials to those on the lists.

5 STUDY PROCEDURES

5.1 Schedule of Evaluations

Assessment	Recruitment/ Screening	Consent/ Assent (V0)	Baseline (V1)	Monthly Check-Ins (C1,2,3)	12 Week Assessment (V2)	Monthly Check-Ins (C4,5,6)	24 Week Assessment (V3)
Person With Memory Loss (PWML)							
Inclusion/Exclusion Criteria	**X**						
Informed Consent/Assent		**X**					
Quality of Life in Alzheimer's Disease (QOL-AD)			**X**		**X**		**X**
NeuroQOL Well-being			**X**		**X**		**X**
PROMIS Social Isolation			**X**		**X**		**X**
NeuroQOL Mobility			**X**		**X**		**X**
t-MOCA			**X**		**X**		**X**
Caregiver (CG)							
Inclusion/Exclusion Criteria	**X**						
Informed Consent		**X**					
SF-12/Healthy Days			**X**		**X**		**X**
GAIN in Alzheimer Care			**X**		**X**		**X**
Zarit Burden Interview			**X**		**X**		**X**
PROMIS Social Isolation			**X**		**X**		**X**
MAIA-2 Self-Regulation			**X**		**X**		**X**
Positive States of Mind			**X**		**X**		**X**
SCL Sleep (CG & PWML)			**X**		**X**		**X**
Neuro-QOL Mobility (PWML)			**X**		**X**		**X**
Cognitive Function Instrument – Modified (PWML)			**X**		**X**		**X**
Adverse Events (CG & PWML)				**X**		**X**	
Co-Interventions (CG & PWML)				**X**		**X**	
MOVING Together Experience				**Wks 2,6,12 (Group 1)**		**Wks 14,18,24 (Group 2)**	
Final Evaluation					**X (Group 1)**		**X (Group 2)**

5.2 Description of Evaluations

5.2.1 Screening

Individuals who are interested in participating in the study will contact us directly through the study website or by email or telephone. Study participants will be screened for eligibility using an online questionnaire or by telephone/video conference. Screening will include a technology test to ensure that they can participate in two-way, livestreaming group video classes. If necessary, we may provide study participants with equipment to help them access the study website. Those who meet eligibility criteria will be scheduled for a consent and baseline assessment.

5.2.2 Consent/Assent (V0)

During the telephone screening, we will obtain verbal consent from the caregiver to assess eligibility. For those who are eligible and interested, we will conduct the consent process using a video-conferencing platform such as zoom or using Together Senior Health's platform with both the PWML and the CG together. The consent form will be reviewed, and the PWML will be asked a series of questions about the study to assess their capacity to consent using the Consent Comprehension form (e.g., understanding of study procedures, risks, benefits, and the voluntary nature of research). Questions will be worded in a yes/no format to minimize the potential impact of word-finding difficulty; however, correct responses will be varied so that a participant cannot get all of the answers correct by simply answering 'yes' or 'no' to all of the questions. The consent form may be signed electronically using DocuSign, or REDCap may be used to obtain online consent with signature lines configured to allow this. Participants who demonstrate capacity to consent will be asked to sign for themselves; those who do not demonstrate capacity to consent will be asked to assent to participating in the study and to having their caregiver sign on their behalf; they also may designate another person to sign on their behalf if they wish. The caregiver/designated individual will be asked to fill out the Surrogate Self Certification form, which is valid for research performed in the state of California. Participants who do not assent to study procedures will not be eligible to participate. Shaking their head 'no' or appearing agitated or worried about the study will be considered signs of lack of assent. Caregiver participants also will sign the consent form related to their participation. The Capacity to Consent form will be completed to document the capacity assessment process. A blank consent form may sent in advance by mail, email or fax. If participants prefer, they may sign and return a paper copy of the consent form rather than using DocuSign or REDCap.

A Waiver of Consent/Waiver of Authorization is only being requested for recruitment purposes.

5.2.3 Baseline and Follow-Up Assessments (V1, V2, V3)

All participants will complete the assessments listed below at baseline (V1), 12 weeks (V2) and 24 weeks (V3). Detailed descriptions of each measure are provided below, in section 5.3.

Persons with Memory Loss (PWML) outcome measures:

- Primary:
  - Quality of life (Quality of Life in Alzheimer's Disease Scale, QOL-AD)[19]
- Secondary:
  - Well-being (Neuro-QOL v1.0 Positive Affect and Well-Being Short Form)[20]
  - Social isolation (PROMIS v2.0 social isolation scale)[21]
  - Mobility (Neuro-QOL Short Form V1.0 - Lower Extremity Function - Mobility)[20]
  - Cognitive function (telephone Montreal Cognitive Assessment, t-MoCA)[22]

Caregivers outcome measures:

- Primary:
  - SF-12[23]
- Secondary:
  - Healthy Days (CDC)[24]
  - Caregiver self-efficacy (GAIN in Alzheimer Care Instrument)[25]
  - Caregiver burden (Zarit Burden Interview, 6-item version)[26]
  - Caregiver social isolation (PROMIS v2.0 social isolation scale)[21]
  - Caregiver self-regulation (Abbreviated MAIA-2 self-regulation subscale)[27]
  - Caregiver positive affect (Positive States of Mind)[28]
  - Caregiver sleep (Symptom Checklist, 3 items)
  - PWML sleep (Symptom Checklist, 3 items)
  - PWML mobility (Neuro-QOL Short Form V1.0 - Lower Extremity Function - Mobility)[20]
  - PWML cognitive function (Cognitive Function Instrument – Modified)

5.2.4 Monthly Check-Ins (C1, C2, C3, C4, C5, C6)

Monthly check-ins will be performed with caregivers in both groups throughout the 24-week study period. The goals of the check-ins are to: a) assess for adverse events, including hospitalizations, emergency department visits, and falls; b) assess for co-interventions that could impact our study outcomes; and c) maintain contact and interest in the waitlist control group. Check-ins may be performed by email, telephone, text, or online survey.

5.2.5 MOVING Together Experience Scale

We have created the MOVING Together Experience Scale to capture feelings of stigma as well as elements of the program that participants have self-reported change. The six items ask participants how they feel in the classes (belonging, acceptance, problems are not unique, energy, relaxation, enjoying being with similar people) on a 4-point Likert scale from 1 (never/rarely) to 4 (mostly/always). This questionnaire will be administered immediately following the classes (weeks 2, 6 and 12 for the immediate start group and weeks 14, 18, and 24 for the delayed start group). Persons with dementia and caregivers will be asked to answer the questions separately.

5.2.6 Final Evaluation Survey

After participants complete their final class (week 12 in the immediate start group, week 24 in the delayed start group), they will receive a final evaluation survey. They will be asked to provide an overall rating the program (poor, fair, good, or excellent) and to indicate whether they would recommend it to others on a 11-point Likert scale (0, not at all likely to 10, highly likely). In addition, open-ended questions will ask about qualitative changes observed in themselves, their study partners, and others in the class; what they liked most; and suggestions for improvement. Persons with dementia and caregivers will be asked to respond separately.

5.3 Outcome Measures

5.3.1 Primary Outcome: Persons with Memory Loss (PWML)

The **Quality of Life in Alzheimer's Disease (QOL-AD) scale**.[19] The QOL-AD is a standard quality of life measure that has been validated for people with cognitive impairment. Participants living with memory loss are asked to rate their current quality of life as poor (1 point), fair (2 points), good (3 points) or excellent (4 points) in 13 areas: physical health, energy, mood, living situation, memory, family, marriage/most significant relationship, friends, self as a whole, ability to do chores, ability to do things for fun, money, and life as a whole. Scores may range from 13 to 52 with higher scores reflecting better quality of life. Prior studies have found that the QOL-AD is a valid and reliable measure, with Cronbach's alpha of 0.82 and interrater reliability based on Cohen's kappa values >0.70. In addition, QOL-AD has been recommended as a measure of choice for evaluating psychosocial interventions research in dementia care[29,30] and it has been sensitive to change in our prior studies.[8]

5.3.2 Primary Outcome: Caregivers (CGs)

The SF-12 Health Survey (**SF-12**)[23] is a 12-item questionnaire that was developed as a shorter alternative to the SF-36.[31] It consists of a subset of 12 items from the SF-36 Health Survey (SF-36) covering the same eight domains of health outcomes, including physical functioning (PF), role-physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role-emotional (RE), and mental health (MH). Physical and Mental Health Composite Scores (PCS & MCS) are computed using the scores of the twelve

questions and range from 0 to 100, where a zero score indicates the lowest level of health measured by the scales and 100 indicates the highest level of health. The SF-12 components have been demonstrated to be a reliable and valid measure, with multiple *R* squares of 0.911 and 0.918 in predictions of the SF-36 PCS and SF-36 MCS score.[23,32] Additionally, The SF-12 is one of the most widely used instruments for assessing self-reported HRQOL.[33]

5.3.3 Secondary Outcomes: Persons with Memory Loss (PWML)

Secondary outcomes are designed to enable us to examine potential mechanisms of action based on our quality of life conceptual framework (Figure 2). Based on our pilot work and conceptual models of quality of life in person with memory loss and caregivers,[14,34] we hypothesize that participation in Moving Together may result in improved quality of life for persons with memory loss through the domains of emotional well-being, social relationships (reduced social isolation), physical function (improved mobility), and/or improved cognitive function. In caregivers, we hypothesize that improved quality of life may be due to the changes observed in their loved ones (well-being, isolation, mobility, cognitive function) as well as changes in themselves (improved self-efficacy, reduced burden, reduced social isolation, improved ability to self-regulate, positive affect).

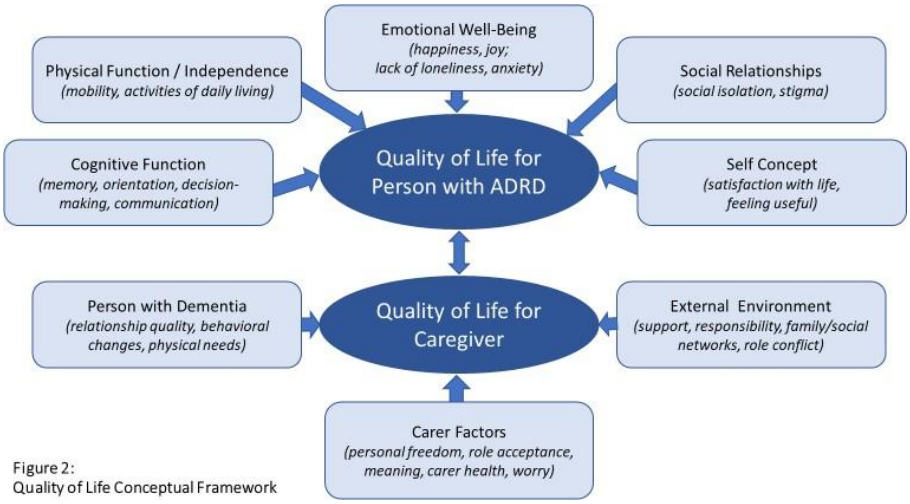

Figure 2:
Quality of Life Conceptual Framework

- Well-being: We will measure well-being using the Neuro-QOL v1.0 Positive Affect and Well-Being Short Form.[20] It includes 9 items (e.g. sense of well-being, feeling hopeful, life was satisfying, etc.) with 5-point responses from never (1), to always (5). Scores may range from 9 to 45, with higher scores reflecting greater feelings of well-being. Persons Living with Memory Loss will answer for themselves. All Neuro-QOL measures, including Neuro-QOL Short Form v1.0 – Lower Extremity Function – Mobility listed below, have been shown to have internal consistency (Cronbach α) ranging from 0.85 to .97.[20]
- Social isolation: We will measure social isolation using the PROMIS v2.0 Social Isolation Scale, which consists of 4 items (feeling left out, people barely know me, feeling isolated, people are around but not with me) that are rated as 1 (never), 2 (rarely), 3 (sometimes), 4 (usually), or 5 (always). Scores may range from 4 to 20, with higher

scores reflecting greater social isolation. Persons living with memory loss will answer for themselves. The PROMIS Social Isolation scale demonstrated high reliability coefficients (>0.98), and item-total correlations were moderate.[21] Based on qualitative results from previous PLIÉ studies,[15] we anticipate that social isolation will decline in Moving Together participants.

- Mobility: We will measure mobility using the Neuro-QOL Short Form v1.0 – Lower Extremity Function – Mobility.[20] It includes 8 items for functional mobility (e.g. getting on and off the toilet, getting in and out of a car, getting out of bed into a chair etc.) Responses on a 5-point Likert scale from 'without any difficulty' (5) to 'unable to do' (1) yield a score range from 8 to 40, with higher scores indicating better mobility. As part of the Neuro-QOL measures, the Neuro-QOL Short Form v1.0 – Lower Extremity Function – Mobility has been shown to have internal consistency (Cronbach α) ranging from 0.85 to .97. To confirm the responses of persons living with memory loss, we plan to ask caregivers to answer these questions regarding their loved ones.
- Cognitive function: We will measure cognitive function in PWML using the telephone version of the Montreal Cognitive Assessment (t-MoCA). The t-MoCA is extracted from the original face-to-face MoCA and uses items not requiring the use of a pencil and paper or visual stimulus.[22] Scores range from 0 to 22 with lower scores indicating more severe impairment.

5.3.4 Secondary Outcomes: Caregivers (CGs)

Consistent with our conceptual framework (Figure 2), we hypothesize that caregiver quality of life will be associated with factors related to the person with dementia as well as factors related to the caregiver.

Factors related to PWML: Several factors in the person with memory loss contribute to quality of life in the caregiver, including the quality of the relationship, changes in the person with dementia especially related to cognition and personality, and the physical demands of caregiving.[34] As noted in the preceding section, we will ask caregivers to rate their loved ones' level of difficulty with **mobility** to determine whether changes in this scale are associated with changes in caregiver quality of life. We also will use the measures in PWML described above to determine whether self-perceptions of their own **well-being** and **social isolation** or objectively measured **cognitive function** are associated with caregiver quality of life.

Factors related to the caregiver: In addition to our primary outcome of caregiver QOL assessed using the SF-12,[23] we will administer several other questionnaires.

- Caregiver Healthy Days: We will use the Center for Disease Control and Prevention 4-item Healthy Days Core Module as a secondary measure of CG self-rated health.[24] This includes a question about overall health status (same as first item on SF-12) and 3 questions about the number of days during the past 30 days that physical or mental health was not good or poor physical or mental health kept from doing usual activities. The full "Healthy Days Measures" consists of 14 items spanning physical and mental health and demonstrated an internal consistency of .81. Higher scores indicate worse health status.
- Caregiver self-efficacy**:** We will use the GAIN in Alzheimer Care Instrument to assess

caregiver-self efficacy.[25] Internal consistency of GAIN by Cronbach's was 0.89 and test-retest reliability (2 weeks) by Intraclass Correlation Coefficient was 0.70. The instrument consists of 10-items (e.g., increased my self-awareness, increased my knowledge and skills in dementia care) using a Likert scale from 0 (disagree a lot) to 4 (agree a lot), with scores ranging from 0 to 40. Higher scores signify higher gains in self-efficacy.

- Caregiver burden: We will use the Zarit Burden Interview (6-item version) to measure caregiver burden.[26] The Zarit Burden Interview is one of the most widely used assessments for caregiver burden covering areas including (e.g., caregiver's health, psychological well-being, finances, social life, and the relationship between the caregiver and the person with dementia.[35] The 6-item version has emerged as the most optimal short version and has demonstrated high correlation with Center for Epidemiological Studies Depression Scale (CES-D) scores and does not significantly differ from the original ZBI (all Bonferroni adjusted *ps*>0.05).[26] The responses to every item are in 5-point Likert scale from 0 (never) to 4 (nearly always). The overall burden is assessed by the total score of all items, with scores ranging from 0 to 20, and a higher score indicating a greater caregiver burden.[36]
- Caregiver social isolation: We will measure social isolation using the PROMIS v2.0 social isolation scale,[21] which consists of 4 items (feeling left out, people barely know me, feeling isolated, people are around but not with me) that are rated as 1 (never), 2 (rarely), 3 (sometimes), 4 (usually), or 5 (always). The PROMIS Social Isolation scale has demonstrated high reliability coefficients (>0.98), and moderate item-total correlations.[21] Scores may range from 4 to 20, with higher scores reflecting greater social isolation.
- Caregiver self-regulation: We will use the Abbreviated MAIA-2 – Self-regulation subscale to measure self-regulation.[27,37] The MAIA-2 – Self-regulation subscale is designed to assess ability to regulate distress by attention to body sensations (e.g., when I feel overwhelmed, I can find a calm place inside). It includes 4 items rated on a 6-point Likert scale from 0 (Never) to 5 (Always). Scores range from 0-20. Higher scores indicate greater self-regulation.
- Caregiver positive affect: We will use the Positive States of Mind scale to measure positive affect.[28] The Positive States of Mind scale is designed to assess types of positive mood (e.g., focused attention, productivity, responsible caregiving, etc.). This scale consists of 6-items using a 4-point Likert scale from 0 (Unable to have it) to 3 (Have it Easily). Each subject receives six specific state scores and scores can be added up for a total positive state score. Total scores may range from 0 to 18, with higher scores reflecting more positive affect.
- Caregiver sleep: We will use 3 items from the Symptom Checklist to measure caregiver sleep.[38] The Symptom Checklist-90-Revised is a 90-item self-report questionnaire often used to assess global psychological distress.[39] The 3 sleep items (trouble falling asleep, awakening in the early morning, and sleep that is restless or disturbed) were shown to be predictive of overall poor sleep, as measured by an elevated Pittsburgh Sleep Quality Index score and probable insomnia disorder according to DSM-5 diagnostic criteria.[38] Responses use a 5-point Likert scale ranging from 0 (Never) to 4 (Extremely) with scores ranging from 0 to 12. Higher scores indicate more severe sleep problems.
- PWML sleep: We will use the same assessment measure listed above to assess PWML sleep.[38] Caregivers will answer these questions regarding their loved ones

- PWML mobility: We will use the Neuro-QOL Short Form v1.0 – Lower Extremity Function – Mobility[20] to measure mobility in PLML based on caregiver report. As described above, it includes 8 items for functional mobility (e.g. getting on and off the toilet, getting in and out of a car, getting out of bed into a chair, etc.). The instrument has been determined to have good reliability Responses on a 5-point Likert scale from 'without any difficulty' (5) to 'unable to do' (1) yield a score range from 8 to 40, with higher scores indicating better mobility.
- PWML cognitive function: We will use a modified version of the Cognitive Function Instrument (CFI) to measure cognitive function in PWML based on caregiver report. The CFI was developed to detect early changes in cognitive and functional changes.[40] The original scale included 14 items that asked about decline in cognitive function (e.g., memory, tendency to repeat questions, misplacing things, etc.) compared to 1 year ago with responses of yes (1), no (0) or maybe (0.5). Results demonstrated reasonable test-retest reliability at three months for both subject and study partner responses.[41] The modified version excludes 3 items (driving, managing money, work); asks about change in the past 3 months (to match the duration of our study); and uses a 5-point Likert scale from 1 (a lot worse) to 5 (a lot better). Total scores may range from 5 to 55, with higher scores indicating improved cognitive abilities and function.

6 RANDOMIZATION AND BLINDING

6.1 Randomization

Study participants will be enrolled in cohorts (blocks) of 16 dyads and randomly allocated to the immediate start intervention group (n=8/cohort) or the delayed start control group (n=8/cohort). The randomization sequence will be generated in advance by the data manager using a random number generator on a computer and will be stored separately and securely. Research staff will be unaware of the randomization sequence.

6.2 Blinding

Because we are using a delayed start control group, it will not be possible to blind participants living with memory loss or their caregivers to their group assignment. However, research staff who collect outcome data and the study statistician will be blinded to group assignment. Every effort will be made to ensure that blinding is maintained including:

- Maintaining the group assignment list separately from other study documentation.
- Having outcomes assessors remind study participants not to discuss any aspect of the study or ask any questions related to the study prior to scheduling or performing assessments.
- Randomly labeling intervention arms as Group A and Group B for the study statistician.
- Excluding assessors from staff meetings that discuss details of the intervention.
- Restricting access to the intervention section of the database to authorized personnel.

If unblinding occurs, the following will be recorded:

- The ID(s) of the unblinded participant
- The reason for unblinding

- The study staff person responsible for unblinding
- A list of person(s) who have been unblinded

Future assessments will be performed by team members who remain blinded.

7 STUDY INTERVENTIONS

7.1 Schedule of Intervention Procedures

The Moving Together Intervention includes an Initial Contact call; Home Set-up and Goals Assessment videoconference; two-way livestreaming online group classes offered for 1 hour, 2 days/week for 12 weeks; Monthly Check-Ins; PLIÉ Experience surveys (administered monthly when participants are taking classes); and a Final Evaluation survey. Each step is described in more detail below. The Schedule of Intervention Procedures in the immediate and delayed start groups is shown in the Table below.

The Intervention Team consists of trained Moving Together Instructors/Coaches and a Community Support Coordinator who will work together to accomplish the intervention tasks. In general, the instructor will perform the goals assessment and teach the Moving Together classes, which will consist of verbal instructions, demonstrations, discussions of program themes, and brief explanations for the movements and goals of the program; the community manager will provide technology support and will administer the check-ins and class surveys.

Intervention	Week 0	Weeks 1-11	Week 12	Weeks 13-23	Week 24
Initial Contact	**Both groups**				
Home Set-Up and Goals Assessment	**Immediate start group**		**Delayed start group**		
Moving Together Classes		**Immediate start group**		**Delayed start group**	
Monthly Check-Ins		**Both groups (weeks 4, 8, 12, 16, 20, 24)**			
MOVING Together Class Experience Surveys		**Immediate start group (weeks 2, 6, 12)**		**Delayed start group (weeks 14, 18, 24)**	
Final Evaluation Survey			**Immediate start group**		**Delayed start group**

7.2 Description of Intervention Procedures

7.2.1 Initial Contact

After study participants complete their consent (V0) and baseline (V1) visits and are randomized to the immediate or delayed start groups, they will be contacted by a member of the Intervention Team to let them know when their classes will begin and next steps. For participants randomly allocated to the immediate start group, the next step is to prepare for the first class by completing the Home Set-up and Goals Assessment. For

participants randomly allocated to the delayed start group, the next step is the first Monthly Check-In.

7.2.2 Home Set-Up and Goals Assessment

Before the first class, the Community Support Coordinator will determine the dyad's technology requirements to access the class videoconference portal, based on the technology information collected during telephone screening and the initial contact. Materials to enable the dyad's technology to access the class video portal including adapters or cords will be mailed if necessary, in addition to a Setup Guide and Participant Handbook in preparation for the first class.

The Instructor will then help the dyad through the Home Set-Up process to create a safe environment for the classes and will conduct the Goals Assessment to learn about each participants' personal goals, motivations and challenges. The Goals Assessment interview questions will ask about their background, interests and hobbies, including musical preferences; physical challenges; and what they hope to gain from participating in the program, potential barriers and strategies to overcome them. This information will be used to tailor the program to optimally meet the needs of each dyad. The Instructor will remind the dyad of the class days and times, and the Community Support Coordinator will email class details, online class access instructions, and contact information.

7.2.3 Moving Together Classes

The Moving Together class principles are based on those from the in-person PLIÉ and Paired PLIÉ program. The program will focus on the following Moving Together guiding principles, themes and goals:

7 Guiding Principles	12 Themes	Goal
Repetition with variation	Repetition builds muscle memory	Promote procedural learning
Progressive functional movement	Principles of functional movement	Improve daily function
Slow pace and step-by-step instruction	Go slow; Patience, respect & dignity	Minimize cognitive demands
Participant-centered goal orientation	Know your goals The power of touch	Enhance personal meaningfulness of movements
Body awareness, mindfulness and breathing	Sense and breathe Creating a learning environment	Encourage present-centeredness
Social interaction	Social engagement & emotional connection; Community	Promote meaningful connection
Positive emotions	Enjoy and explore; Music	Promote feelings of well-being

The Instructor will conduct the online livestreaming Moving Together class with the Community Support Coordinator assisting the participants through the class video platform and by phone if necessary before, during and after the class to ensure the participant's successful access to the class video platform and their class participation.

Each Moving Together class will begin with greetings and a brief check-in, to ensure that everyone feels welcomed and acknowledged. Next participants will engage in seated, mindful body awareness movements that involve massaging or tapping all major body parts (including hands, arms, thighs, calves, ankles/feet, belly, back, neck and head) and deep breathing movements (raising arms overhead while inhaling and vocalizing while exhaling). The goal of these movement sequences is to bring participants into awareness of their bodies and breathing in the present moment, and to create a calming ritual that is repeated at the beginning and end of each class. These movements are designed to be relaxing and engaging at the same time. Next participants will engage in a series of seated, standing and/or paired movements (i.e., performed with their partner) that focus on increasing capacity to perform movements that are most needed for daily function, such as increasing range of motion, reaching, turning, transitioning smoothly between sitting and standing, and balancing while standing and walking. These movement sequences will build slowly in complexity over the course of the program, depending on the functional ability levels of each class. Whenever possible, we will strive to group dyads with similar levels of physical or cognitive abilities. Finally, each class will end with repetition of the mindful body awareness and breathing movements and an invitation for participants to share what makes them feel grateful, appreciative, joyful or happy. The goal in this section of the program is to facilitate positive emotions and feelings of social connection.

Over the Intervention period of 12 weeks/24 classes, the Moving Together program will gradually and methodically progress participants through safe, functional movement sequences from simple to more complex while deepening self-awareness and mindfulness skills and building social engagement and connection through the Moving Together online video class portal.

The Instructor will adapt the program based on feedback and observations during class, Monthly Check-In data, and Moving Together Class Experience survey responses.

The final day of class will include a graduation. Participants will receive a graduation certificate in the mail prior to that day.

The Instructor and Community Support Coordinator will document class attendance and class content. Class reports during team meetings, class documentation and class video recordings will be reviewed regularly by senior team members for program fidelity.

7.2.4 Monthly Check-Ins

Monthly check-ins surveys will be sent to caregivers in both groups by email to assess for adverse events and co-interventions in both groups. Surveys may also be completed by phone, text, or paper if preferred.

We will identify adverse events by asking about hospitalizations, emergency department visits, falls, and other unexpected major medical events or changes in health status for both the CG and the PWML. If any adverse events are reported, the Community Support Coordinator will follow-up to gather more

information and will enter the information into the Adverse Event log. The procedures for reporting Serious Adverse Events and Unexpected Problems are described in detail in section 8.

In addition, we will assess for co-interventions (other life events that could potentially impact study outcomes) by asking CGs if they or PWML have started any new programs to improve their health or well-being, or whether there have been any changes to their home environment.

7.2.5 Moving Together Class Experience Surveys

The Community Support Coordinator will ask participants to complete the Moving Together Class Experience surveys immediately after class during weeks 2, 6, and 12 (immediate start group) and weeks 14, 18, and 24 in the delayed start group. PWML and CGs will be asked to answer separately. The goal of these surveys is to gather information in 'real time' to assess participant experience.

7.2.6 Final Evaluation Survey

After the final class, the Community Support Coordinator will ask participants to complete the Final Evaluation survey. PWML and CGs will be asked to answer separately. The goal of these surveys is to gather information about participant satisfaction and qualitative observations.

7.2.7 Delayed Start Control

The delayed start control group will be encouraged to continue with their usual daily activities while they wait for their classes to begin.

8 SAFETY ASSESSMENTS

8.1 Potential Risks and Benefits

Potential Risks:

- Movements may cause muscle strain, soreness, dizziness, or other injuries.
- Movements that involve standing may increase the risk of falling, although instructors work closely with participants to minimize this risk (for example, by having those with balance issues hold on to chairs for stability).
- Some participants may be frustrated by using new technology.
- Some participants may be concerned about loss of privacy associated with video-conferencing and video-recording.

Potential Benefits:

- Study participants may benefit directly by experiencing improved quality of live, better mobility, lower stress, or less social isolation.
- Study participants may increase their knowledge about ways to improve quality of life for people living with memory loss.

- Study participants may feel that they are helping others by contributing to knowledge about memory loss and caregiving.

8.2 Adverse Events (AEs) and Serious Adverse Events (SAEs)

Study participants will be monitored for adverse events (AEs) during livestreaming classes by Moving Together coaches. Prior to the first class, instructors will create a list of class participants that is easily accessible and includes their names, phone numbers, addresses, emergency contact information, and local 10-digit emergency center number in case of potential AEs during class. If there is an emergency, the instructor will stop class, contact the Community Support Coordinator/PI, and call the local emergency center.

In addition, we will elicit information about AEs including falls and healthcare utilization in all study participants during monthly check-ins. All AEs will be tracked in a research study database that will include:

- Dyad PIDN
- Person affected (PWML or CG)
- Date of occurrence
- Date of first awareness
- Brief description of AE
- Initial determination of whether the event was study-related (definitely, possibly, unrelated)
- Initial determination of whether the event was serious or unexpected (yes/no)
- Whether the event is reportable (yes/no)
- If yes:
  - Date reported to SO
  - Date reported to NIA PO
  - Date reported to UCSF IRB
- Comments

Definitions are provided below.
Adverse event (AE):
Any negative medical occurrence in a research study participant that is temporally associated with their participation in the research, whether or not considered related to participation in the research.

Serious adverse events (SAEs):
Any AE that:

- Results in death
- Is life-threatening, or places the participant at immediate risk of death from the event as it occurred
- Requires or prolongs hospitalization
- Causes persistent or significant disability or incapacity
- Requires medical or surgical intervention to prevent an outcome listed above
- Changes the risk/benefit ratio

Unanticipated Problems (UPs):

- Unexpected, in terms of nature, severity, or frequency given (a) the research procedures described in the study protocol and informed consent documents and (b) the characteristics of the study population
- Definitely or possibly related to participation in the research
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized

Definitely Related: An AE is definitely related to study participation if it is clear that the event was caused by study participation. A definitely related event has a strong temporal relationship, and an alternative cause is unlikely.

Possibly Related: An AE is possibly related when there is a reasonable possibility that the event might have been caused by study participation or there is uncertainty about the relationship. For example, the AE may have a strong temporal relationship, but a potential alternative cause may be present. In other circumstances, there may be significant uncertainty about the cause of the event, or a possible relationship to study participation cannot reasonably be ruled out.

Unrelated: The cause of the AE is known, and the event is in no way related to any aspect of study participation. If there is any uncertainty regarding AE causality, then the event should be assessed as possibly related to research participation. Often, the cause of an unrelated AE is disease progression.

8.3 Reporting Procedures

All AEs that are both serious (SAE) and unexpected (regardless of whether they are related or not) will be reported to the NIA Program Officer (PO), the Safety Officer (SO), and the Institutional Review Board (IRB) at the University of California, San Francisco (UCSF) within 48 hours of awareness.

A summary of all other SAEs will be reported to the NIA PO and SO every six months based on the recommendations of the SO, given the relatively low risk of this study.

Because the study population includes older adults (many in their 80s or 90s) with dementia and other underlying health conditions, expected SAEs include:

- Death due to underlying health condition
- Life-threatening event due to underlying health condition
- Hospitalization for underlying health condition or illnesses unrelated to the study (such as infectious diseases)
- Decline in physical or cognitive function consistent with disease progression

8.4 Follow-up for Adverse Events

Unresolved AEs will be followed until resolved or considered stable. The Moving Together intervention team will follow up during subsequent contact until the AE is resolved for participants in the intervention.

8.5 Safety Monitoring

Dr. Barnes (UCSF PI) and Ms. Benjamin (Together Senior Health PI) will be responsible for overseeing participant safety on a daily basis. Dr. Barnes will be responsible for tracking AEs, SAEs and UPs and for preparing reports for the UCSF IRB, NIA PO and SO. The SO will act in an advisory capacity to the NIA PO to monitor participant safety and evaluate the progress of the study.

8.6 Protocol Violations and Research-Related Incidents

The University of California, San Francisco (UCSF) Institutional Review Board (IRB) is serving as the IRB of record for this study. Consistent with current UCSF guidelines, we will track all protocol violations and research-related incidents.

Protocol Violations: Any unapproved changes, departures or deviations from the study design or procedures of the research project that are under the investigator's control and have not been reviewed and approved by the IRB.

Major (Reportable) Protocol Violations: Any protocol violations that affect the participant's rights, safety, or well-being, or the completeness, accuracy and reliability of the study data. Criteria for defining major violations including any of the following:

- The violation has harmed, or posed a significant or substantive risk of harm, to the research participant.
- The violation resulted in a change to the participant's clinical or emotional condition or status.
- The violation has damaged the completeness or soundness of the data collected for the study.
- The violation is evidence of willful or knowing misconduct on the part of the investigator(s).
- The violation involves serious or continuing non-compliance with federal, state or local guidelines.

Minor (Non-Reportable) Protocol Deviations: Any protocol violations that do not have a major impact on participant's rights, safety, or well-being or the completeness, accuracy, and reliability of the study data. For example:

- A study participant skips a question on a survey, and the research team fails to check the survey for completeness.

Major (Reportable) Incidents: Any problematic or unanticipated events involving the conduct of the study or study participants that affect the rights, safety, or well-being of participants or others, or the completeness, accuracy and reliability of the study data. Examples include:

- Significant complaint or concern received from a potential or enrolled study participant.
- Inappropriate behavior of study participants and/or research personnel.
- Problems during study recruitment or the informed consent process.
- Problems with the study design in which a majority of participants have difficulty adhering to the study schedule of procedures.
- Potential breach of study participant's privacy or confidentiality (must be reported within 48 hours of PI awareness).
- Withdrawal or significant reduction in resources necessary to safely and adequately conduct study activities.

- Changes to the protocol to eliminate or reduce an apparent immediate hazard to the safety research participants or others.

Minor (Non-Reportable) Incidents: Any events involving the conduct of the study or study participants that are not problematic and do not involve significant potential to harm participants or others. Example:
- Receipt of a minor complaint from a study participant that is resolved by the research team.

Reporting of Protocol Violations and Research-Related Incidents
- All major protocol violations and major incidents will be reported to the UCSF IRB within 10 working days, and a copy of the report will be sent immediately to the NIA PO, and SO.
- Any breach of study participant's privacy or confidentiality will be reported to the UCSF IRB within 48 hours, and a copy of the report will be sent immediately to the NIA PO, and SO.
- All minor protocol violations and minor incidents will be tracked in the research database and available for review by the NIA PO, and SO if requested.

9 INTERVENTION DISCONTINUATION

Study participants may withdraw voluntarily from participation in the study at any time and for any reason. Participants will continue to be followed, with their permission, even if the study intervention is discontinued. Follow-up assessment visits will continue to be scheduled if the participant is agreeable. If not, we will follow-up via phone calls, letters, emails, text messages and/or medical record review, as allowed by the participants.

10 STATISTICAL CONSIDERATIONS

10.1 General Design Issues

The primary outcomes in people living with memory loss and caregivers will be self-rated quality of life using validated measures. Secondary outcomes in PWML will include change in mobility, well-being, social isolation and cognitive function. In CGs, secondary outcomes will include CG-rated self-efficacy, burden, social isolation, self-regulation, positive affect, and sleep as well as sleep, mobility, and cognitive function in PWML. Our hypotheses include the following:

1. We hypothesize that participation in Moving Together results in improved quality of life for PWML primarily through the domains of physical function (mobility), emotional well-being, social relationships (reduced social isolation) and cognitive function.
2. In CGs, we hypothesize that improved quality of life will be due to the changes observed in their loved ones (improved mobility, well-being, isolation, cognitive function, sleep) as well as changes in themselves (improved self-efficacy, reduced burden, reduced social isolation, improved self-regulation, increased positive affect, and improved sleep).

10.2 Sample Size and Power

To be conservative, power estimates were based on an unpaired t-test analysis with two-sided alpha=0.05. A sample size of 224 (112/group) will provide us with 80% power to detect a clinically meaningful standardized effect size of 0.375 to test Hypothesis 1a. Assuming 20% attrition, we would have 80% power to detect a standardized effect size

of 0.395. For hypothesis 1b, we will be able to conduct exploratory analyses using the full sample of 224, since both groups will receive the intervention and will be offered the opportunity to participate in maintenance classes. Again assuming 20% attrition, a final sample of 179 will provide 80% power to detect correlation coefficients as small as 0.20.

10.3 Data Analyses

We will examine distributions of all variables to assess for missingness, outlier values or skewed distributions using standard techniques (e.g., means, medians, standard deviations, ranges, tables, graphical techniques). We will assess balance between the immediate and delayed start groups by comparing baseline characteristics (e.g., means ± SD, N [%]). If meaningful differences occur by chance, we will perform sensitivity analyses adjusting for these differences.

Our primary analytic approach will be linear mixed models (LMMs) with terms included for group, time, and group*time interaction with random intercepts and slopes. This approach will enable efficient estimation of change in primary outcomes over time while including all participants randomized (intent-to-treat) and accounting for baseline values and correlations between repeated measures over time. Milestone 1a will determine if there is a significant group*time interaction for our primary outcome of quality of life, with separate analyses performed for PWML and CGs. Milestone 1b will involve exploratory analyses to examine potential mechanisms of action. These will include using PROCESS to assess for indirect effects (mediation) and contingent effects (moderation) based on baseline characteristics of our study participants (e.g., age, sex, caregiving relationship) and changes in secondary outcomes (e.g., mobility, well-being, isolation). Exploratory analyses also will examine the impact of 'dose' (based on class attendance), and sensitivity analyses will be restricted to those with high compliance (≥75% class attendance). For covariates that have more than 10% missing data, we will consider using multiple imputation.

10.4 Interim Analyses and Stopping Rules

No interim data analyses are planned. The SO or NIA PO may request that an interim analysis be performed at their discretion. If interim analyses are requested, criteria for stopping the study will be clearly defined in advance by SO and NIA PO.

11 DATA COLLECTION AND QUALITY ASSURANCE

11.1 Data Collection Forms

Our primary approach to data collection will be online surveys administered through REDCap or Qualtrics, with data stored on the UCSF network (e.g., in REDCap or project-specific MyResearch folders). If participants prefer, questionnaires may also be completed by telephone or email, or paper forms may be sent through the mail. For PWML, assessors may assist participants with online questionnaire completion (for example, by sharing a screen with the questions shown, and entering responses for them).

11.2 Data Management

UCSF is responsible for collection and secure storage of all research data. A REDCap database will be created to enable research staff to track enrollment of study participants, collection of outcome data, and delivery of the intervention. Access to the database will be restricted to the research team. In addition, the enrollment and assessment team will not be able to see or access the intervention section of the database, and the intervention team will have read access only to the enrollment and assessment section of the database. The outcomes section of the database will not include any protected health information (PHI) and will identify participants by unique personal identification numbers (PIDNs) only.

Sharing permissions will be configured to ensure files containing PHI can only be accessed by authorized individuals. Two-step verification will be used as an additional safeguard against unauthorized access. Permissions will be updated when personnel roles change and they no longer need access to PHI or when they leave the research team.

Digital signatures on will be obtained using DocuSign or REDCap. Paper copies of consent forms, signatures, or other research-related documents will be stored in locked file cabinets. Electronic data may be collected using REDCap or Qualtrics or stored in UCSF's MyResearch environment in a folder that is accessible only to approved research team members.

11.3 Quality Assurance

11.3.1 Training

New research team members will be trained by having them first review current versions of the Study Protocol and Manual of Operations (MOP). They will observe senior team members engaging with study participants and will then practice with senior team members through role play. Senior team members will then observe them interacting with study participants and provide feedback until they achieve competency. Competency will be reassessed annually or more frequently if needed.

Any documents containing personally identifying information (e.g., names and contact information for potential study participants) will be sent by encrypted email.

All study staff will be trained by the same lead person in the same manner. Dr. Barnes will train staff in administering assessments. Jennifer Lee will train the interventionists. Each lead will also monitor performance and provide feedback to ensure consistency.

11.3.2 Monitoring

The database manager, supervised by the PIs, will enact and monitor data quality control checks. Data quality control checks will be included to identify potential data anomalies such as:

- Missing data or forms
- Out-of-range or erroneous data
- Inconsistent and illogical dates over time
- Data inconsistency across forms and visits
- Not completing all fields of a "completed form" or no reason for missing data is provided

The data entry forms will include logic and range checks to minimize the possibility of missing or invalid entries. Electronic data entry forms will mirror paper case report forms. Calculations will be automated whenever possible.

At the end of each outcome assessment, research staff will review all questionnaires to check for incomplete data and logical inconsistencies. Whenever possible, errors will be identified and corrected in the moment. If incomplete data or logical inconsistencies are discovered later, research staff may follow up with study participants to clarify if possible. Otherwise, those items will be entered as missing.

12 PARTICIPANT RIGHTS AND CONFIDENTIALITY

12.1 Institutional Review Board (IRB) Review

The UCSF IRB will serve as the IRB of record for this study. They will review and approve the initial Study Application, on which this Study Protocol is based. In addition, they will review and approve all patient-facing materials and scripts such as recruitment materials, telephone screeners, informed consent documents, and intervention-related scripts. All modifications of these documents will be reviewed and approved by the IRB before being used with study participants.

12.2 Informed Consent Forms

All study participants will sign informed consent documents or will assent to having a legally authorized representative sign on their behalf. Signatures may be on paper forms or may use DocuSign or REDCap. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. Some participants may be concerned about loss of privacy associated with other participants and the group-based format of the intervention. Each dyad will receive a copy of the consent form in paper or electronic form.

12.3 Participant Confidentiality

All research team members will complete mandatory trainings in human subjects research and confidentiality required by the UCSF IRB, including training to ensure Health

Insurance Portability and Accountability Act (HIPAA) compliance. All forms and study procedures are reviewed by UCSF's IRB for compliance with HIPAA and human subjects protections. Any data that will be accessed or disclosed outside the research team will meet HIPAA requirements, through the use of business associate agreements, data use agreements, de-identification, and/or accounting of disclosures, as applicable.

Research team members will be required to use computers that require passwords and DUO authentication to access the research database and participant PHI.

12.4 Study Discontinuation

The study may be discontinued at any time by the IRB, the NIA, the SO, or other government agencies as part of their duties to ensure that research participants are protected.

13 INTELLECTUAL PROPERTY AND DATA SHARING

13.1 Cooperative Research and Development Agreement (CRADA)

Together Senior Health, Inc., previously entered into a Cooperative Research and Development Agreement (CRADA) with the U.S. Department of Veterans Affairs (VA) and the Northern California Institute for Research and Education (NCIRE) related to their Phase I SBIR grant. This agreement includes sections on financial and equipment contributions, inventions and intellectual property, licensing, ownership and rights of access to data and publication, confidentiality, warranties, expiration and termination, disputes, indemnification and liability, and other pertinent agreements related to this research. This CRADA will be amended to reflect the Scope of Work (SOW) for the Phase II SBIR grant.

13.2 Material Transfer Agreement (MTA)

Together Senior Health, Inc., will enter into a Material Transfer Agreement (MTA) with UCSF that will govern sharing of research data between these organizations.

14 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by the policies and procedures of UCSF and NIA.

15 REFERENCES

1. 2020 Alzheimer's disease facts and figures. *Alzheimers Dement.* 2020.
2. Birks JS, Harvey RJ. Donepezil for dementia due to Alzheimer's disease. *Cochrane Database Syst Rev.* 2018;6:CD001190.
3. McShane R, Westby MJ, Roberts E, et al. Memantine for dementia. *Cochrane Database Syst Rev.* 2019;3:CD003154.
4. Forbes D, Forbes SC, Blake CM, Thiessen EJ, Forbes S. Exercise programs for people with dementia. *Cochrane Database Syst Rev.* 2015(4):CD006489.

5. Bahar-Fuchs A, Martyr A, Goh AM, Sabates J, Clare L. Cognitive training for people with mild to moderate dementia. *Cochrane Database Syst Rev.* 2019;3:CD013069.
6. van der Steen JT, Smaling HJ, van der Wouden JC, Bruinsma MS, Scholten RJ, Vink AC. Music-based therapeutic interventions for people with dementia. *Cochrane Database Syst Rev.* 2018;7:CD003477.
7. Olazaran J, Reisberg B, Clare L, et al. Nonpharmacological therapies in Alzheimer's disease: a systematic review of efficacy. *Dement Geriatr Cogn Disord.* 2010;30(2):161-178.
8. Barnes DE, Mehling W, Wu E, et al. Preventing loss of independence through exercise (PLIE): a pilot clinical trial in older adults with dementia. *PloS one.* 2015;10(2):e0113367.
9. Wu E, Barnes DE, Ackerman SL, Lee J, Chesney M, Mehling WE. Preventing Loss of Independence through Exercise (PLIE): qualitative analysis of a clinical trial in older adults with dementia. *Aging & mental health.* 2015;19(4):353-362.
10. Eldridge LL, Masterman D, Knowlton BJ. Intact implicit habit learning in Alzheimer's disease. *Behav Neurosci.* 2002;116(4):722-726.
11. Garcia-Rodriguez B, Fusari A, Rodriguez B, Hernandez JM, Ellgring H. Differential patterns of implicit emotional processing in Alzheimer's disease and healthy aging. *J Alzheimers Dis.* 2009;18(3):541-551.
12. Laird KT, Paholpak P, Roman M, Rahi B, Lavretsky H. Mind-Body Therapies for Late-Life Mental and Cognitive Health. *Curr Psychiatry Rep.* 2018;20(1):2.
13. Marciniak R, Sheardova K, Cermakova P, Hudecek D, Sumec R, Hort J. Effect of meditation on cognitive functions in context of aging and neurodegenerative diseases. *Front Behav Neurosci.* 2014;8:17.
14. Smith SC, Murray J, Banerjee S, et al. What constitutes health-related quality of life in dementia? Development of a conceptual framework for people with dementia and their carers. *Int J Geriatr Psychiatry.* 2005;20(9):889-895.
15. Casey JJ, Harrison KL, Ventura MI, Mehling W, Barnes DE. An integrative group movement program for people with dementia and care partners together (Paired PLIE): initial process evaluation. *Aging & mental health.* 2019:1-7.
16. Harte R, Glynn L, Rodriguez-Molinero A, et al. A Human-Centered Design Methodology to Enhance the Usability, Human Factors, and User Experience of Connected Health Systems: A Three-Phase Methodology. *JMIR Hum Factors.* 2017;4(1):e8.
17. Nath PA, Sharp CD. A User-Centered Design Approach to Information Sharing for Older Patients and Their Families. *JAMA Intern Med.* 2015;175(9):1498-1499.
18. van der Cammen TJ, Albayrak A, Voute E, Molenbroek JF. New horizons in design for autonomous ageing. *Age Ageing.* 2017;46(1):11-17.
19. Logsdon RG, Gibbons LE, McCurry SM, Teri L. Assessing quality of life in older adults with cognitive impairment. *Psychosom Med.* 2002;64(3):510-519.
20. Cella D, Lai JS, Nowinski CJ, et al. Neuro-QOL: brief measures of health-related quality of life for clinical research in neurology. *Neurology.* 2012;78(23):1860-1867.
21. Hahn EA, Devellis RF, Bode RK, et al. Measuring social health in the patient-reported outcomes measurement information system (PROMIS): item bank development and testing. *Qual Life Res.* 2010;19(7):1035-1044.
22. Pendlebury ST, Welch SJ, Cuthbertson FC, Mariz J, Mehta Z, Rothwell PM. Telephone assessment of cognition after transient ischemic attack and stroke: modified telephone

interview of cognitive status and telephone Montreal Cognitive Assessment versus face-to-face Montreal Cognitive Assessment and neuropsychological battery. *Stroke.* 2013;44(1):227-229.
23. Ware J, Jr., Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Med Care.* 1996;34(3):220-233.
24. Centers for Disease Control and Prevention. *Measuring healthy days: Population assessment of health-related quality of life.* Atlanta: CDC; 2000.
25. Yap P, Luo N, Ng WY, Chionh HL, Lim J, Goh J. Gain in Alzheimer care INstrument--a new scale to measure caregiving gains in dementia. *Am J Geriatr Psychiatry.* 2010;18(1):68-76.
26. Yu J, Yap P, Liew TM. The optimal short version of the Zarit Burden Interview for dementia caregivers: diagnostic utility and externally validated cutoffs. *Aging & mental health.* 2019;23(6):706-710.
27. Mehling WE, Acree M, Stewart A, Silas J, Jones A. The Multidimensional Assessment of Interoceptive Awareness, Version 2 (MAIA-2). *PloS one.* 2018;13(12):e0208034.
28. Horowitz M, Adler N, Kegeles S. A scale for measuring the occurrence of positive states of mind: a preliminary report. *Psychosom Med.* 1988;50(5):477-483.
29. Lacey L, Bobula J, Rudell K, Alvir J, Leibman C. Quality of Life and Utility Measurement in a Large Clinical Trial Sample of Patients with Mild to Moderate Alzheimer's Disease: Determinants and Level of Changes Observed. *Value Health.* 2015;18(5):638-645.
30. Thorgrimsen L, Selwood A, Spector A, et al. Whose quality of life is it anyway? The validity and reliability of the Quality of Life-Alzheimer's Disease (QoL-AD) scale. *Alzheimer Dis Assoc Disord.* 2003;17(4):201-208.
31. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care.* 1992;30(6):473-483.
32. Salyers MP, Bosworth HB, Swanson JW, Lamb-Pagone J, Osher FC. Reliability and validity of the SF-12 health survey among people with severe mental illness. *Med Care.* 2000;38(11):1141-1150.
33. Huo T, Guo Y, Shenkman E, Muller K. Assessing the reliability of the short form 12 (SF-12) health survey in adults with mental health conditions: a report from the wellness incentive and navigation (WIN) study. *Health Qual Life Outcomes.* 2018;16(1):34.
34. Daley S, Murray J, Farina N, et al. Understanding the quality of life of family carers of people with dementia: Development of a new conceptual framework. *Int J Geriatr Psychiatry.* 2019;34(1):79-86.
35. Zarit SH, Reever KE, Bach-Peterson J. Relatives of the impaired elderly: correlates of feelings of burden. *Gerontologist.* 1980;20(6):649-655.
36. Higginson IJ, Gao W, Jackson D, Murray J, Harding R. Short-form Zarit Caregiver Burden Interviews were valid in advanced conditions. *J Clin Epidemiol.* 2010;63(5):535-542.
37. Mehling WE, Price C, Daubenmier JJ, Acree M, Bartmess E, Stewart A. The Multidimensional Assessment of Interoceptive Awareness (MAIA). *PloS one.* 2012;7(11):e48230.
38. Hughes JM, Ulmer CS, Gierisch JM, Mid-Atlantic VAMW, Howard MO. Single-Item Measures for Detecting Sleep Problems in United States Military Veterans. *J Gen Intern Med.* 2018;33(5):698-704.

39. Derogatis LR, Lipman RS, Covi L. SCL-90: an outpatient psychiatric rating scale-- preliminary report. *Psychopharmacol Bull.* 1973;9(1):13-28.
40. Amariglio RE, Donohue MC, Marshall GA, et al. Tracking early decline in cognitive function in older individuals at risk for Alzheimer disease dementia: the Alzheimer's Disease Cooperative Study Cognitive Function Instrument. *JAMA Neurol.* 2015;72(4):446-454.
41. Li C, Neugroschl J, Luo X, et al. The Utility of the Cognitive Function Instrument (CFI) to Detect Cognitive Decline in Non-Demented Older Adults. *J Alzheimers Dis.* 2017;60(2):427-437.

16 LIST OF PROTOCOL CHANGES

Protocol Version	Protocol Date	Description of Change	Date approved
V1.0	10/15/2020	n/a	n/a
V1.1	10/16/2020	n/a	10/16/2020
V1.2	3/10/2021	4.1. California residency removed as inclusion criteria 4.2. Current participation in another research study, dementia medication started in past 3 months, dementia medication change planned in next 6 months added as exclusion criteria	3/29/2021
V1.3	4/23/2021	n/a	n/a
V1.4	7/23/2021	4.1 Diagnosis of Alzheimer's or dementia unspecified no longer required; mild severity dementia still assessed using Quick Dementia Rating System (6.5 to 12.5) 4.3. Recruitment strategies expanded to include clinical colleagues, UCSF patients, key stakeholders, paid advertisements, and purchasing email distribution lists 5.2.5. Open-ended question added to monthly check-in surveys 7. Expanded administration options for monthly check-in surveys to include phone, email, text or online survey. 8.6 Added protocol violation and incident definitions and procedures	8/5/2021
V1.5	10/17/2021	Title page. Added RH Studio 2 OpCo 22 as new company name. Precis, 3.2, 4.1, 5.2.2, 10.2. Removed exploratory health utilization outcome in matched "no contact" control group and HIPAA authorization (not part of original grant). Study team roster. Replaced Wendy Hartogenesis with Fei Jiang as biostatistician. 3.2. Added clinicaltrials.gov number. 11.3.1. Removed list of Together's staff	11/4/2021
V1.6	2/21/2022	4.1. Added back requirement for diagnosis and expanded to include mild cognitive impairment (MCI) and a wider severity range (2.5 to 12.5); clarified that participants must reside in U.S. 16.0. Added list of protocol changes.	pending