Study Application (Version 1.15)

1.0 General Information

***Enter the full title of your study:**

Paired PLIE: An Integrative Movement Program for People with Cognitive Impairment and Care Partners

***Enter the study alias:**

Paired PLIE
* This field allows you to enter an abbreviated version of the Study Title to quickly identify this study.

2.0 Add departments

2.1 and Specify Research Location:

Is Primary?	Department Name
○	**UCSF** - *126607* - M_FCM-FamMed-Core-Programs
○	**UCSF** - *101001* - M_Osher Center
◉	**UCSF** - *133100* - M_Psychiatry

3.0 List the key study personnel: (Note: external and affiliated collaborators who are not in the UCSF directory can be identified later in the Qualifications of Key Study Personnel section at the end of the form)

3.1 *Please add a Principal Investigator for the study:

Barnes, Deborah E, PhD

Select if applicable

☐ Department Chair ☐ Resident

☐ Fellow

If the Principal Investigator is a Fellow, the name of the Faculty Advisor must be supplied below.

3.2 If applicable, please select the Research Staff personnel

A) Additional Investigators

Allison, Theresa, MD, PhD
Other Investigator
Chao, Linda, PHD
Other Investigator
Chesney, Margaret A, PhD
Other Investigator

Duffy, James M Other Investigator Mehling, Wolf MD, MD Co-Principal Investigator Nicosia, Francesca M Other Investigator Olsen, Pamela A Other Investigator Whitmer, Rachel A Other Investigator		
B) Research Support Staff		
Lee, Amanda Research Assistant Lee, Jennifer, BA Clinical Research Associate Martinez, Steven Research Assistant Tarasovsky, Gary Data Manager Woo, Michele Research Assistant		
3.3 *Please add a Study Contact		
Barnes, Deborah E, PhD Mehling, Wolf MD, MD The Study Contact(s) will receive all important system notifications along with the Principal Investigator. (e.g. The project contact(s) are typically either the Study Coordinator or the Principal Investigator themselves).		
3.4 If applicable, please add a Faculty Advisor/Mentor:		
3.5 If applicable, please select the Designated Department Approval(s)		
Add the name of the individual authorized to approve and sign off on this protocol from your Department (e.g. the Department Chair or Dean).		

4.0 Qualifications of Key Study Personnel

4.1 November, 2015 - NEW Definition of Key Study Personnel and CITI Training Requirements:

UCSF Key Study Personnel include the Principal Investigator, other investigators and research personnel who are directly involved in conducting research with study participants or who are directly involved in using study participants' identifiable private information during the course of the research. Key Personnel also include faculty mentors/advisors who provide direct oversight to Postdoctoral Fellows, Residents and Clinical Fellows serving as PI on the IRB application. **The IRB requires that all Key Study Personnel complete Human Subjects Protection Training through CITI prior to approval of a new study, or a modification in**

can be found on our website.

List the study responsibilities and qualifications of any individuals who qualify as Key Study Personnel (KSP) at UCSF and affiliated sites ONLY by clicking the "Add a new row" button. This information is required and your application will be considered incomplete without it.

KSP Name	Description of Study Responsibilities	Qualifications
Dr. Barnes, Deborah E, PhD	As PI, Dr. Barnes will oversee all aspects of the study	Deborah Barnes is a Professor of Psychiatry and Epidemiology & Biostatistics at UCSF, Research Health Science Specialist at SFVA, and Senior Investigator with Tideswell at UCSF. She led development and testing of the original PLIE intervention that serves as a foundation for Paired PLIE.
Dr. Mehling, Wolf MD, MD	As Co-PI, Dr. Mehling will work closely with Dr. Barnes to oversee the study. In addition, he will have primary responsibility for overseeing the intervention.	Wolf Mehling is Professor of Clinical Family and Community Medicine at UCSF. He and Dr. Barnes collaborated to develop and pilot-test both PLIE and Paired PLIE.
Chesney, Margaret A, PhD	As Co-Investigator, Dr. Chesney will contribute her extensive knowledge and expertise related to alternative approaches to health and well-being.	Margaret Chesney is Professor of Medicine at UCSF and the former Director of the Osher Center for Integrative Medicine. She was the Deputy Director of the NIH National Center for Complementary and Alternative Medicine and was Co-PI of the original PLIE intervention study.
Lee, Jennifer, BA	Jennifer Lee will serve as an exercise instructor.	Jennifer Lee is a certified Feldenkrais practitioner, a movement practice applicable for seniors. She is a key staff person in the PLIE study, where she is a member of the exercise instructor team.
Dr. Chao, Linda PhD, PHD	As Co-Investigator, Dr. Chao will oversee an imaging sub-study.	Linda Chao is a Professor of Radiology and Biomedical Imaging and in the Department of Psychiatry at UCSF. She has extensive expertise performing imaging studies in older adults including those with

Whitmer, Rachel A	As a Kaiser Co-Investigator, Dr. Whitmer will facilitate study procedures at Kaiser.	Dr. Whitmer was formerly an investigator in the Kaiser Permanente Northern California Division of Research and is currently a Professor at UC-Davis with expertise in aging epidemiology and predictors of cognitive decline and dementia.
Duffy, James M	As the Kaiser PI, Dr. Duffy will oversee study procedures at Kaiser.	Dr. Duffy is a Clinical Professor of Psychiatry at UCSF and was formerly an Integrative Neuropsychiatrist at Kaiser Permanente.
Tarasovsky, Gary	Gary Tarasovsky will be responsible for creating and maintaining the database in accordance with the approved study protocol.	Mr. Tarasovsky is an experienced database manager who has worked with Dr. Barnes on several of her prior studies.
Olsen, Pamela A	Mrs. Olsen will serve as interviewer and qualitative researcher in sub-study. She will co-conduct interviews, consent, record and analyze the interviews	Mrs Olsen holds a MA in Gerontology and is an experienced clinical research study coordinator and qualitative analyst.
Allison, Theresa, MD, PhD	Dr. Allison will serve as an additional investigator. She will be responsible for assisting with data analysis.	Theresa A. Allison, MD, PhD, is an Associate Professor of Medicine in the Division of Geriatrics, with a secondary appointment in Family and Community Medicine. She completed the MD in 2002 and PhD in Musicology in 2010, through the University of Illinois Medical Scholars Program. She completed family practice residency in 2005 and geriatric fellowship in 2007, at UCSF. Her primary appointment is in the San Francisco VA Health Care System, where she works in Home Based Primary Care Program (HBPC), as part of an interprofessional care team providing home-based medical care for vulnerable older veterans.

Nicosia, Francesca M	Dr. Nicosia will be assisting with qualitative data analysis and manuscript preparation.	Dr. Nicosia is a Research Health Science Specialist at SFVA and an Assistant Professor at the Institute for Health and Aging. As a medical anthropologist, she has extensive training and expertise in qualitative data analysis.
Lee, Amanda	Ms. Lee will be reviewing class videos, class notes, home visit reports and other participant data as part of her training as a PLIE instructor.	Ms. Lee has a masters degree in behavioral health and is a certified yoga instructor.
Martinez, Steven	Mr. Martinez may assist with data analysis and preparation of manuscripts and presentations.	Mr. Martinez has BS in psychological science and has worked for several years as a research assistant for a longitudinal study of neuroimaging in children.
Woo, Michele	Ms. Woo may assist with data analysis and preparation of manuscripts and presentations.	Ms. Woo is a psychology graduate student at Alliant University.

5.0 Initial Screening Questions - Updated 9/13

(Note: You must answer every question on this page to proceed). If you are converting to the new form, check questions 5.4, 5.6, 5.7, 5.8 and 5.10 before saving and continuing to the next section.

5.1 * Application type:

- ○ Full Committee
- ◉ Expedited
- ○ Exempt

5.2 * Risk level (Help Text updated 9/13):

- ◉ Minimal risk
- ○ Greater than minimal risk

5.3 * Subject contact:

- ◉ Yes (including phone, email or web contact)
- ○ No (limited to medical records review, biological specimen analysis, and/or data analysis)

5.4 * Funding (past or present):

- (●) Funded or will be funded (external sponsor, gift, program or specific internal or departmental funds)
- ( ) Unfunded (no specific funds earmarked for this project)
- ( ) Unfunded student project

5.5 * The Principal Investigator and/or one or more of the key study personnel has financial interests related to this study:

( ) Yes (●) No

If **Yes**, the Conflict of Interest Advisory Committee (COIAC) office may contact you for additional information.

5.6 * This is an investigator-initiated study:

(●) Yes ( ) No

5.7 * This study ONLY involves retrospective records review and/or identifiable biospecimen analysis:

( ) Yes (●) No

5.8 * This is a clinical trial:

(●) Yes ( ) No

Clinical Trial Registration
"NCT" number for this trial:

NCT02729311

5.9 * This is a multicenter study:

( ) Yes (●) No

5.10 * This application involves the study of unapproved or approved drugs, devices, biologics or in vitro diagnostics:

( ) Yes (●) No

5.11 * This application involves a Humanitarian Use Device:

- (●) No
- ( ) Yes, and it includes a research component
- ( ) Yes, and it involves clinical care ONLY

5.12 * This study involves human stem cells (including iPS cells and adult stem cells), gametes or embryos:

- (●) No
- ( ) Yes, and requires CHR and GESCR review
- ( ) Yes, and requires GESCR review, but NOT CHR review

○ Yes ◉ No

5.14 * This application includes a request to rely on another IRB (other than NCI CIRB):

○ Yes ◉ No

Note: If this request is approved, the CHR will **NOT** review and approve this study. Another institution will be the IRB of record.

6.0 Expedited Review Categories

6.1 * If you think this study qualifies for expedited review, select the regulatory category(ies) that the research falls under:

- ☐ Category 1: A very limited number of studies of approved drugs and devices
- ☐ Category 2: Blood sampling
- ☐ Category 3: Noninvasive specimen collection (e.g. buccal swabs, urine, hair and nail clippings, etc.)
- ☑ Category 4: Noninvasive clinical procedures (e.g. physical sensors such as pulse oximeters, MRI, EKG, EEG, ultrasound, moderate exercise testing, etc.)
- ☑ Category 5: Research involving materials (data, documents, records, or specimens) that were previously collected for either nonresearch or research purposes
- ☑ Category 6: Use of recordings (voice, video, digital or image)
- ☑ Category 7: Low risk behavioral research or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies

7.0 Funding

7.1 Identify all sponsors and provide the funding details. If funding comes from a Subcontract, please list only the Prime Sponsor: **Note: we require only a P Number *OR* an A Number for funding coming through UCSF. Please avoid these common errors in funding documentation:**

- **DO NOT add the A Number if a P Number was already provided OR update the A Number field when a new funding cycle begins. The IRB does NOT use this information or want these changes made.**
- **DO NOT add a grant continuation as a new funding source.**

External Sponsor:

View Details	Sponsor Name	Sponsor Type	Awardee Institution:	Contract Type:	Project Number	UCSF RAS System Award Number ("A" + 6 digits)
⊟	Alzheimer's Association, Inc.	07	UCSF	Grant	P0508185	

Sponsor Name:	Alzheimer's Association, Inc.
Sponsor Type:	07

Sponsor Role:	
Awardee Institution::	UCSF
Is Institution the Primary Grant Holder:	Yes
Contract Type:	Grant
Project Number:	P0508185
UCSF RAS System Award Number ("A" + 6 digits):	
Grant Number for Studies Not Funded thru UCSF:	
Grant Title:	Paired Integrative Exercise Program for People with Dementia and Caregivers
PI Name: (If PI is not the same as identified on the study.)	
Explain Any Significant Discrepancy:	

Gift, Program, or Internal Funding (check all that apply):

- [x] Funded by gift (specify source below)
- [x] Funded by UCSF or UC-wide program (specify source below)
- [ ] Specific departmental funding (specify source below, if applicable)

List the gift, program, or departmental funding source:

Drew and Ellen Bradley; Tideswell/Pepper Foundation UCSF-RAP grant; UCSF-RAP

7.2 If you tried to add a sponsor in the question above and it was not in the list, follow these steps:

- **If funding has already been awarded or the contract is being processed by the Office of Sponsored Research (OSR) or Industry Contracts Division (ICD), your sponsor is already in the system and the project has an eProposal Proposal or Award number. Check with your department's OSR Staff or ICD Officer to ask how the sponsor is listed in the UC sponsor list and what the Proposal or Award number is. Click here to find your OSR staff and here to find your ICD staff.**
- **If your sponsor is not yet in the list, enter it in the box below.**

(•) Sponsor not in list

Only if your sponsor is not yet in the list, type the sponsor's name:

UCSF-Osher Center RAP grant

If the funding is administered by the UCSF Office of Sponsored Research, your study will not receive CHR approval until the sponsor and funding details have been added to your application.

7.3 * This study is currently supported in whole or in part by Federal funding OR has received ANY Federal funding in the past (Help Text updated 9/13):

( ) Yes (•) No

If **yes**, indicate which portion of your grant you will be attaching:

- [ ] The Research Plan, including the Human Subjects Section of your NIH grant or subcontract

- [ ] For other federal proposals (contracts or grants), the section of the proposal describing human subjects work
- [ ] The section of your progress report if it provides the most current information about your human subjects work
- [ ] The grant is not attached. The study is funded by an award that does not describe specific plans for human subjects, such as career development awards (K awards), cooperative agreements, program projects, and training grants (T32 awards) OR UCSF (or the affiliate institution) is not the prime recipient of the award

8.0 Sites

8.1 Institutions (check all that apply):

- [x] UCSF
- [ ] China Basin
- [ ] Helen Diller Family Comprehensive Cancer Center
- [ ] Mission Bay
- [ ] Mount Zion
- [ ] San Francisco General Hospital (SFGH)
- [ ] SF VA Medical Center (SF VAMC)
- [ ] Blood Centers of the Pacific (BCP)
- [ ] Blood Systems Research Institute (BSRI)
- [ ] Fresno (Community Medical Center)
- [ ] Gallo
- [ ] Gladstone
- [ ] Institute on Aging (IOA)
- [ ] Jewish Home
- [ ] SF Dept of Public Health (DPH)

8.2 Check all the other types of sites not affiliated with UCSF with which you are cooperating or collaborating on this project (Help Text updated 9/13):

- [ ] Other UC Campus
- [ ] Other institution
- [x] Other community-based site
- [ ] Foreign Country

List the foreign country/ies:

1) Kaiser Permanente Oakland Dementia Caregiver Support Groups
2) Alzheimer's Services of the East Bay

8.3 Check any research programs this study is associated with:

- [ ] Cancer Center
- [ ] Center for AIDS Prevention Sciences (CAPS)
- [ ] Global Health Sciences
- [ ] Immune Tolerance Network (ITN)
- [ ] Neurosciences Clinical Research Unit (NCRU)
- [x] Osher Center
- [ ] Positive Health Program

9.0 Studies Involving Other Sites

9.1 UCSF is the coordinating center:

○ Yes ◉ No

If **Yes**, describe the plan for communicating safety updates, interim results, and other information that may impact risks to the subject or others among sites:

If **Yes**, describe the plan for sharing modification(s) to the protocol or consent document(s) among sites:

9.2 Check any other UC campuses with which you are collaborating on this research study:

- ☐ UC Berkeley
- ☐ UC Davis
- ☐ Lawrence Berkeley National Laboratory (LBNL)
- ☐ UC Irvine
- ☐ UC Los Angeles
- ☐ UC Merced
- ☐ UC Riverside
- ☐ UC San Diego
- ☐ UC Santa Barbara
- ☐ UC Santa Cruz

9.3 Are the above UC campuses requesting to rely on UCSF's IRB (check all that apply):

- ☐ Yes (Submit a reliance request through the UC IRB Reliance Registry)
- ☐ No (Complete IRB Approval Certification section)

10.0 Outside Site Information

10.1 Outside Site Information

Click "Add a new row" to enter information for a site. Click it again to add a second site again to add a third site, a fourth site, etc.

Outside Site Information

Non-UCSF affiliated site information:

Site name:

Alzheimer's Services of the East Bay

Contact name:

Micheal Pope, CEO and Executive Director

Email:

micheal@aseb.org

Phone:

(510) 644-8292

For Federally-funded studies only, corresponding FWA#:

*** The research at this site will be reviewed by:**

- ○ The non-affiliated site's IRB or a private IRB
- ○ The non-affiliated site is requesting UCSF to be the IRB of record for this study
- ◉ The non-affiliated site is not engaged in the human subjects research and has provided a letter of support

If the other site's IRB approval letter is available now, attach it to the application. If the IRB approval letter is not yet available, submit it once you receive it.

Or, if the other site is **not engaged** in human subjects research, attach the letter of support to your application.

Outside Site Information

Non-UCSF affiliated site information:

Site name:

Kaiser Permanente Oakland

Contact name:

Kitsy Schoen, LCSW

Email:

Kitsy.Schoen@kp.org

Phone:

510-752-7983

For Federally-funded studies only, corresponding FWA#:

*** The research at this site will be reviewed by:**

- ◉ The non-affiliated site's IRB or a private IRB
- ○ The non-affiliated site is requesting UCSF to be the IRB of record for this study
- ○ The non-affiliated site is not engaged in the human subjects research and has provided a letter of support

If the other site's IRB approval letter is available now, attach it to the application. If the IRB approval letter is not yet available, submit it once you receive it.

Or, if the other site is **not engaged** in human subjects research, attach the letter of support to your application.

11.0 Study Design

11.1 * Study design (Help Text updated 9/13):

We propose to perform a randomized, controlled trial (RCT) with a delayed start design to examine the effects of the Paired PLIÉ program in individuals with cognitive impairment and their care partners over 9 months. Study participants will be 60 pairs of individuals with mild-to-moderate cognitive impairment and their primary care partners. Study pairs will be enrolled in blocks of 10 and will be randomly assigned to Group 1 (immediate start, n=5) or Group 2 (3-month delayed start, n=5). Pairs randomized to Group 1 will participate together in the Paired PLIÉ program 2 days/week for 12 weeks (24 classes total) while pairs randomized to Group 2 will continue with their usual activities. After 3 months, Group 1 will transition into a maintenance phase, and Group 2 will participate in the Paired PLIÉ program 2 days/week for 12 weeks. Outcome data will be collected in all study participants at baseline and 3, and 6 months. We have partnered with local community-based organizations that have agreed to serve as study sites and to assist with recruitment efforts.
We will conduct a sub-study with semi-structured interviews in a sub-sample of our participants. The goal is to assess motivations and barriers for home practice of the exercises taught in the intervention classes and to develop improved support materials (brochures, video clips on DVD and/or YouTube) according to feedback from participants.

11.2 If this is a clinical trial, check the applicable phase(s) (Help Text updated 9/13):

- ☐ Phase I
- ☑ Phase II
- ☐ Phase III
- ☐ Phase IV

12.0 Scientific Considerations

12.1 Hypothesis (Help Text updated 9/13):

This study has a hypothesis:

◉ Yes ○ No

If yes, state the hypothesis or hypotheses:

Hypothesis 1: The immediate start group will experience significantly greater improvements in participant outcomes including cognitive function (Alzheimer's Disease Assessment Scale-cognitive subscale, ADAS-cog), independence (Disability Assessment for Dementia, DAD) and quality of life (Quality of Life in Alzheimer's Disease, QOL-AD) compared to the delayed start control group.
Hypothesis 2: The immediate start group will experience significantly greater reductions in caregiver burden (Caregiver Burden Inventory, CBI) and improvements in positive feelings about caregiving (Positive Aspects of Caregiving, PAC) compared to the delayed start control group.
There are no hypotheses for the sub-study.

12.2 * List the specific aims:

Aim 1. To determine whether Paired PLIÉ improves participant outcomes over 9 months.
Aim 2. To determine whether Paired PLIE improves caregiver outcomes over 9 months.
Sub-Study: To develop improved support material for home practice.

12.3 Statistical analysis:

All primary analyses will be performed using intent-to-treat principles. Baseline characteristics will be compared using descriptive statistics (e.g., frequency tables and percentages for categorical variables; means, medians, standard deviations, ranges for continuous variables), and p-values will be calculated using approrpriate statistical tests (e.g., chi-square, t-test, Mann-Whitney). Our primary analytic approach will be mixed effects linear regression which will enable efficient estimation of intervention effects and inclusion of all subjects in intent-to-treat analyses. Analyses will focus on differences in outcomes between the groups over time. Fixed effects terms will be included for group (immediate vs. delayed start), time (0, 3, 6 or 9 months), and the interaction between group and time, with time modeled as a dummy variable. Subjects and cohorts will be modeled as random effects. Models also will adjust for any baseline differences between groups that may occur by chance. Covariates will be included to adjust for any co-interventions that may occur (e.g., medication changes). Sensitivity analyses will be performed to determine the effects of compliance on intervention effects. Graphs and diagnostic tests will be used to assess for outliers and influence points. Line plots will be used to visually examine change over time by group.
Sub-Study: We will conduct qualitative analyses of the transcribed audio recordings from 10 interviews..

12.4 If this study has undergone scientific or scholarly review, please indicate which entity performed the review:

- [ ] Cancer Center Protocol Review Committee (PRC) (Full approval is required prior to final CHR approval for cancer-related protocols.)
- [ ] CTSI Clinical Research Center (CRC) advisory committee
- [ ] Departmental scientific review
- [x] Other:

Specify **Other**:

Alzheimer's Association peer review
Kaiser Permanente Northern California IRB

13.0 Background

13.1 Background:

More than 5 million Americans are currently living with Alzheimer's disease and related dementia (ADRD), and prevalence is expected to rise to 14 million by the year 2050.[1] Current dementia medications are associated with relatively small effect sizes[2,3] and are often discontinued due to side effects.[4] However, there is growing evidence that non-pharmacologic interventions can help reduce symptoms in those who are affected as well as caregivers.[5-8] The available evidence suggests that multi-domain programs—those that combine physical, mental and social stimulation with caregiver education—are more likely to impact multiple outcomes,[8] yet few multi-domain programs have been rigorously tested and disseminated to the community.

We recently developed a novel, multi-domain, non-pharmacologic program called Paired PLIÉ (pronounced 'plee-ay' and stands for Preventing Loss of Independence through Exercise). The original PLIÉ program was developed and tested at an adult day center with affected individuals and trained exercise instructors, where there was evidence of improvement with PLIÉ versus standard chair-based exercises.[9,10] Effect sizes were moderate to large in both affected individuals and caregivers (see below). Over the past year, we have adapted PLIÉ to be performed with affected individuals and their primary care partners (Paired PLIÉ), including creation of an illustrated booklet and videos to support home-based practice. **The primary objective of the proposed study is to test the efficacy of the Paired PLIÉ program on participant and caregiver outcomes over 9 months.**

Sub-Study: According to feedback from study participants, most dyads have difficulties performing regular exercises at home. The 30-minute video we had supplied did not seem to be effective in supporting home practice. We are now planning a qualitative sub-study to determine whether improving support material in form of brochures or shorter video clips can enhance the motivation and feasibility of home exercises.

13.2 Preliminary studies:

Our group has recently pioneered a novel, multi-domain program called Preventing Loss of Independence through Exercise (PLIÉ, pronounced 'plee-ay').[9,10] PLIÉ integrates physical activity (training of procedural memory for basic daily activities such as transitioning safely between sitting and standing), cognitive stimulation (mindful body awareness), social engagement (group movement and sharing of in-the-moment experiences), music, and caregiver education (monthly home-visit). We studied PLIÉ in individuals with mild to moderate dementia who were attending an adult day program in San Francisco, CA, and found evidence that those who participated in PLIÉ for 45 minutes, 2-3 days per week for 4 months (total: 26-39 hours) experienced improvements in a wide range of outcomes compared to a Usual Care (UC) control group that participated in standard chair-based exercises. Standardized, between-group effect sizes were moderate to large on validated measures of quality of life (0.83), cognitive function (0.76) and caregiver burden (0.49).[9,10]

Although PLIÉ was originally designed and tested in an adult day care setting, most people in the community do not have access to a day care center, are concerned about the stigma associated with day care or are unable to afford it. **There is a huge need for innovative, rigorously-tested programs that can be performed together by affected individuals and their care partners, either in group settings or at home.** The Paired PLIÉ Program was specifically designed to address this critical need in the community. Over the past year, we have systematically created the Paired PLIÉ program by adapting the original PLIÉ protocol to be performed by dyads of affected individuals and care partners.

13.3 References:

1. Alzheimer's Association. 2014 Alzheimer's disease facts and figures. *Alzheimers Dement.* 2014;10(2):e47-e92.
2. Rockwood K. Size of the treatment effect on cognition of cholinesterase inhibition in Alzheimer's disease. *J Neurol Neurosurg Psychiatr.* May 2004;75(5):677-685.
3. Smith M, Wells J, Borrie M. Treatment effect size of memantine therapy in Alzheimer disease and vascular dementia. *Alzheimer Dis Assoc Disord.* Jul-Sep 2006;20(3):133-137.
4. Birks J. Cholinesterase inhibitors for Alzheimer's disease. *Cochrane Database Syst Rev*. 2006 Jan 25;(1):CD005593.
5. Forbes D, Forbes SC, Blake CM, Thiessen EJ, Forbes S. Exercise programs for people with dementia. *Cochrane Database Syst Rev*. 2015 Apr 15;4: CD006489. [Epub ahead of print].

6. Aguirre E, Woods RT, Spector A, Orrell M. Cognitive stimulation for dementia: a systematic review of the evidence of effectiveness from randomised controlled trials. *Ageing Research Reviews.* Jan 2013;12(1):253-262.
7. Ueda T, Suzukamo Y, Sato M, Izumi S. Effects of music therapy on behavioral and psychological symptoms of dementia: a systematic review and meta-analysis. *Ageing Research Reviews* 2013;12:628-41.
8. Olazaran J, Reisberg B, Clare L, et al. Nonpharmacological therapies in Alzheimer's disease: a systematic review of efficacy. *Dement Geriatr Cogn Disorder* 2010;30:161-78.
9. Barnes DE, Mehling W, Wu E, Beristianos M, Yaffe K, Skultety K, Chesney MA. Preventing Loss of Independence through Exercise (PLIÉ): A pilot clinical trial in older adults with dementia. *PLoS One.* 2015 Feb 11;10(2):e0113367.
10. Wu E, Barnes DE, Ackerman SL, Lee J, Chesney M, Mehling WE. Preventing Loss of Independence through Exercise (PLIÉ): Qualitative analysis of a clinical trial in older adults with dementia. *Aging Ment Health.* 2015;19(4): 353-62.

If you have a separate bibliography, attach it to the submission with your other study documents.

14.0 Sample Size and Eligibility

14.1 Number of subjects that will be enrolled at UCSF and affiliated institutions:

60 dyads

14.2 Total number of subjects that will be enrolled at all sites (Help Text updated 9/13):

60 dyads

14.3 Estimated number of people that you will need to consent and screen here (but not necessarily enroll) to get the needed subjects:

100 dyads

14.4 Explain how and why the number of subjects was chosen (Help Text updated 9/13):

Sample size estimates and power calculations are based on a repeated measures design with 1 pre and 3 post measures using between-group effect size estimates from our pilot study, correlation between measures of 0.75 (based on our pilot data) and alpha=0.05. Sample size estimates at 80% power ranged from n=8/group to n=22 /group depending on the effect size. Conversely, power estimates using a sample size of 30/group ranged from 91% to 100%. Power will be >80% for all outcomes even with 20% attrition. We also estimate that 60% of those screened will be eligible and agree to participate based on our previous studies. There we anticipate screening a total of 100 dyads in order to reach our target sample size of 60 dyads.

14.5 * Eligible age range(s):

- [ ] 0-6 years
- [ ] 7-12 years
- [ ] 13-17 years
- [x] 18+ years

14.6 Inclusion criteria:

Affected individuals: cognitive impairment (mild to moderate severity based on Clinical Dementia Rating of 0.5, 1 or 2); ambulatory and able to take 2 steps without cane or walker; living in the community in a private home or apartment; English language fluency.
Caregiver/care partner: motivated to participate with affected individual; able to answer study questions related to the affected individual's functional status, mood, behaviors, falls, urinary incontience, and quality of life and their own feelings regarding caregiving; English language fluency.

14.7 Exclusion criteria:

Affected Individuals: behavioral or physical issues that would be disruptive or dangerous to themselves or others (e.g., active psychosis, drug abuse, severe behavioral issues); planning to move to a facility before the end of the study period; terminal illness (life expectancy < 1 year); non-stable dementia medication dose; current participation in another research study; unwilling to be video-recorded for quality control purposes.
Caregiver/care partner: planning to place affected individual in an institutional setting during the study period; terminal illness (life expectancy < 1 year); behavioral or physical issues that are disruptive or dangerous; unwilling to be video-recorded for quality control purposes.

14.8 There are inclusion or exclusion criteria based on gender, race or ethnicity:

○ Yes ◉ No

If **yes**, please explain the nature and rationale for the restrictions:

15.0 Other Approvals and Registrations

15.1 * Do any study activities take place on patient care units:

○ Yes ◉ No

If **Yes**, attach a letter of support for the study from the involved patient care manager(s).

15.2 * Does your protocol involve any radiation exposure to patients/subjects? The UCSF Radiation Safety Committee requires review of your protocol if it includes administration of radiation as part of standard of care OR research exposures:

○ Yes ◉ No

15.3 * This study may generate genetic data that may be broadly shared (e.g. submitted to NIH for Genome-Wide Association Studies (GWAS) in dbGaP, TCGA, etc):

○ Yes ◉ No

15.4 * This study involves administration of vaccines produced using recombinant DNA technologies to human subjects:

○ Yes ◉ No

15.5 * This study involves human gene transfer (NOTE: Requires NIH Recombinant DNA Advisory Committee (RAC) review prior to CHR approval):

○ Yes ◉ No

15.6 This study involves other regulated materials and requires approval and/or authorization from the following regulatory committees:

☐ Institutional Biological Safety Committee (IBC)

Specify BUA #:

☐ Institutional Animal Care and Use Committee (IACUC)

Specify IACUC #:

☐ Radiation Safety Committee

Specify RUA #:

☐ Radioactive Drug Research Committee (RDRC)

Specify RDRC #:

☐ Controlled Substances

16.0 Procedures

16.1 * Procedures/Methods (Help Text updated 9/13) For clinical research list all study procedures, test and treatments required for this study, including when and how often they will be performed. If there are no clinical procedures, describe the Methods:

1. Recruitment/Screening. We have partnered with local community-based organizations (see other study sites section) that have agreed to serve as study sites, provide space for the classes and assist with recruitment efforts. In addition, we will circulate flyers throughout the community in neighborhoods surrounding the study sites and will post announcements in newsletters and online (e.g., Facebook). Caregivers will be screened for eligibility by telephone. If the caregiver is not the legally authorized representative (LAR) for the affected individual, the LAR will be contacted separately regarding the affected individual's eligibility. We will mail a letter to the LAR or legal guardian and invite her/him to contact us by mail or phone to discuss the study and the consent process. If we do not get a response within 2 weeks we will call the LAR or legal guardian by phone assuming that she/he has received our letter. The screening and eligibility questions for the affected individual will then be completed with the LAR or legal guardian. The Clinical Dementia Rating (CDR) will be performed to assess level of severity of cognitive impairment. We will continue with enrollment only if the LAR permits the affected individual's study participation.

2. Informed consent. Verbal consent to be screened will be obtained over the telephone prior to collecting information on demographics and medical and psychiatric history. Written consent will be obtained with the affected individuals and caregivers/LARs together if possible, as described in more detail below. The consent forms will be reviewed and capacity to consent will be assessed in affected individuals based on responses to questions to determine level of understanding of study procedures, risks, benefits and rights. Participants who do not demonstrate capacity to consent will be asked to assent to study procedures and LARs will be asked to consent on their behalf. Separate consent will be obtained for public release of videos and future contact. After the consent process has been completed, the Montreal Cognitive Assessment (MoCA) will be administered to affected individuals to directly assess level of cognitive impairment. Consent procedures will take place at the study site, home or other location based on individual preferences. If consent is obtained at a location without a photocopier, we will send photocopies of signed consent and HIPAA documents to study participants by mail within 1 week of the consent visit. If there are errors or corrections on the consent or HIPAA forms, we will initial and date and send the updated forms to participants by mail.

Capacity to consent will be assessed by research assistants who will be extensively trained by the PI using a standardized procedure. We first provide the consent form to the affected individual

points of the form, pointing to the areas on the form where the information is described in more detail. We then ask a series of yes/no questions to assess understanding of the information in the form. If the participant cannot answer the questions, we review the material again and reassess their understanding. If they lack capacity to consent, we ask them if they would like to participate in the study to obtain their assent. We say that we are going to ask their LAR to sign the form on their behalf to obtain written consent. Most of our research assistants have a background in psychology and are highly sensitive to working with vulnerable individuals. We train new research staff by having them role play the consent process until senior personnel determine that they are adequately prepared. They then observe senior personnel performing the consent process on at least one study participant. Subsequently they are observed performing the consent process until senior personnel determine that they are competent. We also have weekly team meetings to discuss any difficulties that arise during consent or any other study procedure.

3. Randomization/Masking. The randomization sequence will be created in advance using a random number generator. Randomization will be performed in blocks that will vary in size (e.g., 2, 4 or 6) to ensure adequate balancing of the groups. The randomization sequence will be stored separately and securely and will be accessible only to the intervention team. Research staff involved with enrollment and assessment will be blinded and will be unaware of the randomization sequence.

4. Intervention: The intervention is an adapated version of the PLIÉ protocol, which we developed in consultation with experts worldwide who have experience performing different types of exercises in individuals with mild-to-moderate dementia, including physical therapy, occupational therapy, yoga, Tai Chi, Feldenkrais, Rosen and dance movement therapy. Specifically, we have identified exercises from each of these traditions that engage the muscles most needed to maintain independence--including lower body strength (to help with getting out of bed/chair), balance (to minimize risk of falls), upper body strength (to help with lifting), fine motor exercises (to help with activities such as eating and brushing teeth), and pelvic floor exercises (to help with continence)--and we have combined them into a unique integrative exercise program. These exercises are designed to be purposeful (i.e., to achieve a goal) and to build procedural ('muscle') memory. In addition, breathing and guided meditation exercises are included to promote in-the-moment body awareness, relaxation and well-being. Personally meaningful musical selections are also included to promote social connection and shared movement. Exercise instructors may perform an initial goals assessment to learn about preferences, motivators and concerns of caregivers and affected individuals. The intervention will be delivered for 1 hour, 2 days/week for 12 weeks (24 classes total) in a class setting with up to 5 dyads and at least 1 instructor per 5 individuals. In addition, a monthly home visit may be offered during the intervention period to facilitate practice at home (1 hour, 3 visits total). Caregivers will be provided with written materials about the program and will be asked to write weekly reflections of their thoughts and feelings about the content.

5. Assessments. We will perform a variety of standard measures in all participants and caregivers at baseline, 3, 6 and 9 months. Data will be collected separately in affected individuals and caregivers to maximize the validity of data collected (e.g., to ensure that caregivers do not 'help' affected individuals with answers to questions and feel comfortable providing information about issues such as difficult behaviors or levels of stress). Affected individuals assessments will take place at the study site. Caregiver assessments will primarily consist of questionnaires that can be self-administered. Therefore, these assessments may occur in person, by phone, or may be returned by email or standard mail, depending on caregiver preference. The first line of communication will be via telephone or in person to minimize the risk of loss of privacy. At the caregiver participant's request, further communication may be conducted via mail, email, fax or text. Caregivers will be informed that these modes of communication may increase their risk of loss of privacy. Mail, email, fax and text communications will include a confidentiality statement. The minimum amount of identifying information will be included in all communications. Study forms will include unique study ID numbers only.

5a. Affected Individuals:

Cognitive function will be assessed with the Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-cog) (Rosen 1984), which is the most commonly used primary outcome measure in AD treatment trials. It is an 80-point scale that includes direct assessment of learning (word list), naming (objects), following commands, constructional Praxis (figure copying), ideational Praxis (mailing a letter), orientation (person, time, place), recognition memory and remembering test instructions.

Physical performance will be assessed with the Short Physical Performance Battery (SPPB), which was developed by the National Institute on Aging to provide an objective tool for evaluating lower extremity functioning in older adults. The test includes repeated chair stands, tandem

balance testing and 8' walking speed (Guralnik 1994). Several additional items from the Senior Fitness Test (SFT) will be added to assess flexibility (sit-and-reach) and mobility (8-foot up-and-go) (Jones & Rikli 2002).

Fall-related self-efficacy will be assessed with the Falls Efficacy Scale (FES), which is a 10-item scale that has been validated in individuals with cognitive impairment (Hauer 2010). We are using a modified version that includes a 4-point Likert scale rather than a 10-point scale to increase ease of use.

Mood will be assessed with the Geriatric Depression Scale (GDS), a standard measure that includes 15 yes/no questions and has been validated in people with and without cognitive impairment (Sheikh and Yesavage, 1986)

Quality of life will be assessed with the Quality of Life Scale in Alzheimer's Disease (QOL-AD), which is a brief, 13-item measure that obtains input from both the individual and the caregiver (Logsdon 1999). Scores may range from 13-52 points.

Exploratory Outcome: Near Infrared Spectroscopy (no longer being performed). This assessment method has been developed in the past 30 years but is exploratory for our setting. The NIRS method has been used in combination with the Verbal-Fluency Task in Alzheimer's patients before, (M.J. Herrmann, A.-C. Ehlis, A.J. Fallgatter: Frontal activation during a verbal-fluency task as measured by near-infrared spectroscopy. Brain Research Bulletin 61 (2003) 51–560), but it has never been applied in a longitudinal study with our population. It will be done once at baseline and once with the other tests at the end of the 3-month intervention. It is a noninvasive measure that uses a small (1x2 inch) flexible patch that uses adhesive tape to stick to the forehead of the affected individuals. The patch is connected to a laser light source and a sensor that can measure regional brain oxygenation. The patch is connected by 2 lengthy thin cables to a monitor and a laptop where the data can be downloaded to an encrypted flash drive. The measure will be used in combination with the Verbal-Fluency Task. After the subjects seemed to be relaxed, a baseline measurement of approximately 60 s will be conducted. After a verbal request to open their eyes now, the participants will be instructed to pronounce in overt speech as many nouns as possible beginning with the letters "A," "F," and "S" or--after the exercise demonstration-- with the letters "E", "G" and "P".(Lezak, Muriel Deutsch (1995) . *Neuropsychological assessment*. Oxford [Oxfordshire]: Oxford University Press. **ISBN 0-19-509031-4**.) No repetitions or proper nouns are allowed. Each of these three conditions (different starting letters) will last 60 s. The correct verbal responses of the subjects are recorded and used as a measure of behavioral performance. (A more detailed description of the device is attached)

5b. Caregivers.

Affected Individual's physical function will be assessed with the Disability Assessment for Dementia (DAD) (Galinas and Gauthier, 1994), which is a standard measure that asks caregivers to rate the participant's disbility with 17 basic and 23 instrumental activities of daily living over the past 2 weeks. The DAD has high established validity and high test-retest reliability (ICC, 0.96), inter-rater reliability (ICC, 0.95), and internal consistency (Chronbach's alpha, 0.96).

Affected Individual's dementia-related behaviors will be assessed with the Neuropsychiatric Inventory (NPI), which is a 144-point informant-based questionnaire that assesses 12 behavioral domains common in dementia including frequency, severity and impact on caregiver distress (Cummings 1997).

Affected Individual's falls will be assessed based on caregiver report of number of falls in the previous 4 months.

Affected Individual's quality of life will be assessed with the Quality of Life Scale in Alzheimer's Disease (QOL-AD), which is a brief, 13-item measure that obtains input from both the individual and the caregiver (Logsdon 1999). Scores may range from 13-52 points.

Caregiver burden will be assessed with the Caregiver Burden Inventory (CBI), which is a 96-point scale that includes 24 items and 5 domains (Novak 1989).

Caregiver mood will be assessed with the GDS.

Positive feelings about caregiving will be assessed with the Positive Aspects of Caregiving scale, a standard measure that asks caregivers to rate their agreement/disagreement with 11 statements about positive aspects of caregiving on a 5-point Likert scale (disagree a lot .... agree a lot). (Tarlow 2004)

Caregiver health status will be assessed with the Medical Outcomes Study Questionnaire Short Form 36 Health Survey (SF-36), which includes 10 items that are used to create eight scaled scores related to vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning and mental health. The SF-36 has high reliability (0.8-0.9) and has been validated in numerous adult populations.

Affected individual's urinary incontinence will be assessed with questions about the frequency and severity of accidental urine leakage.

6. Qualitative data. Exercise instructors or other research staff may record qualitative observations of participants and/or caregivers including changes in movement abilities, emotional state, or cognitive function of participants within the class setting over time, and in response to specific exercise interventions as they are introduced. Comments made by participants and caregives related to the exercise class may also be recorded. Semi-structured interviews also may be conducted with caregivers to assess feasibility and acceptability of the program, barriers to home practice and suggestions for improvements.

7. Compliance, co-interventions and adverse events. Compliance will be assessed based on class attendance. In addition, caregivers will be asked to complete weekly reflection journals. Monthly check-in calls will be performed with caregivers to assess for adverse events, falls and co-interventions (e.g., changes to medications or daily routine) and to address issues related to non-compliance and barriers to practice. If caregivers request, monthly check-ins may be conducted via mail, email, fax or text. Caregivers will be informed that these modes of communication may increase their risk of loss of privacy. Mail, email, fax and text communications will include a confidentiality statement. The minimum amount of identifying information will be included in all communications. Study forms will include unique study ID numbers only.

8. Video-Recording. Some exercise classes and assessments may be video-recorded for quality control and educational purposes. Study participants will be able to consent to video recording for research and educational purposes (private viewing only) or public release of video recordings (public + private viewing). If any person who has not consented enters the video frame, this section will be deleted. Other persons may be staff at the study sites. Video recordings will be saved in a MyResearch folder only in the edited version (without any non-consented person in the frames). All other video recordings will be deleted from the camera after downloading on a secured server or an encrypted external hard drive stored in a secure locked file cabinet and will not be stored on any computers.

9. Post-intervention. Study participants will be provided with an illustrated booklet and access to videos (e.g., DVD or YouTube) to support home-based practice. Findings from the study may be provided to subjects and caregivers in aggregate form (i.e., without identifying individual subjects). Study participants will sign separate consent for future contact.

10. Qualitative Interview Substudy. Study participants who have completed the intervention and have agreed to future contact related to this research study will be contacted by telephone and asked if they would be interested in participating in a substudy that would involve semi-structured interviews conducted in their homes. Two reseach team members (including at least one exercise instructor) will conduct the home visits and interviews. This sub-study will require participants to sign a separate consent form and to consent/assent specifically for this sub-study. The topic of the interview is to solicit answers to (1) questions about motivators and barriers to home exercise practice and (2) questions about participants' wishes for written and/or electronic material that may support home practice. We will initially recruit 5 dyads for a 1-hour interview. Semi-structured interviews will follow an interview guide, will be audio-recorded and transcribed. We will develop new support material following the suggestions of the interviewees. We are planning to improve the exercise brochure and create a series of new and shorter video clips for DVD or YouTube according to the feedback of the participants. This material will be given to these participants for a month of home application followed by a second interview and asking for a written evaluation. Participants will also answer a brief questionnaire about facilitators and barriers for home practice and use a log for daily entries about their exercises and study-related movements. The second interview may prompt iterative revision of our support material, which we will provide to a second group of 5 dyads undergoing the same two interviews. Following the completion of all interviews, the support material will undergo a final professional production which we plan to include in a larger multi-site study of our Paired PLIE Program.

Audio recordings will be stored and--after study completion--deleted the exact same way as the video-recordings.

If you have a procedure table, attach it to the submission with your other study documents.

16.2 Interviews, questionnaires, and/or surveys will be administered or focus groups will be conducted:

(•) Yes ( ) No

List any standard instruments used for this study:

- Clinical Dementia Rating Scale (Morris, 1993)
- Montreal Cognitive Assessment (MoCA) (Nasreddine, 2005)
- Disability Assessment for Dementia (DAD) (Gelinas and Gauthier, 1994)
- Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-cog) (Rosen 1984)
- Physical Performance Battery (SPPB) (Guralnick 1994)
- Senior Fitness Test (SFT) (Rikli & Jones 2002)
- Neuropsychiatric Inventory (NPI) (Cummings 1997)
- Falls Efficacy Scale (FES) (Hauer 2010)
- Quality of Life Scale in Alzheimer's Disease (QOL-AD) (Logsdon 1999)
- Geriatric Depression Scale (GDS) (Sheikh and Yesavage, 1986)
- Caregiver Burden Inventory (CBI) (Novak 1989)
- Positive Aspects of Caregiving (PAC) (Tarlow 2004)
- Verbal Fluency Task (Lezak 1995)
- SF-36 (Ware 1992)

Attach any non-standard instruments at the end of the application.

16.3 Conduct of study procedures or tests off-site by non-UCSF personnel:

( ) Yes (•) No

If yes, explain:

16.4 Sharing of experimental research test results with subjects or their care providers:

(•) Yes ( ) No

If yes, explain:

Findings from the study may be shared with study participants or caregivers in aggregate form. Individual data will not be shared. Results may be shared by letter, email, in person or other means based on affected individual, caregiver or investigator preferences.

16.5 * Specimen collection for future research and/or specimen repository/bank administration:

( ) Yes (•) No

16.6 Time commitment (per visit and in total):

Affected Individual

- Consent/eligibility visit (1 hour)
- Baseline assessment (1 - 1.5 hours)
- Intervention (1 hour, 2 days/week for 12 weeks: 24 classes total)
- Home visits (1 hour, 3 visits total)

- Total: 33 hours over 12 months
- Home practice: additional 1-2 hours/week

Caregiver

- Consent/eligibility visit (1 hour)
- Baseline assessment (1 hour)
- Intervention (1 hour, 2 days/week for 12 weeks: 24 hours total)
- Home visits (3 visits, 1 hour each: 3 hours total)
- Monthly telephone check-ins (9 calls, 20 minutes each: 3 hours total)
- Post-intervention assessments (3, 6 and 9 months, 1 hour each: 3 hours total)
- Total: 36 hours over 12 months
- Home practice: additional 1-2 hours/week

Qualitative Interview Substudy:

- 2 interviews 1 hour each
- Questionnaire and daily log: 1-2 hours over 1 month
- Home practice: additional 1-2 hours/week for 1 month

16.7 Locations:

All study procedures will take place at Kaiser Permanente in Oakland and at ASEB in Berkeley, CA. Visits with caregivers may occur at an alternate location (e.g., home) if requested. Interviews for the qualitative substudy will be conducted in the participants' homes.

16.8 Describe the resources in place to conduct this study in a way that assures protection of the rights and welfare of participants:

The safety and welfare of study participants who are affected individuals will be ensured by performing all exercise-related study procedures and assessments with their caregivers together. Study personnel who assess for eligibility, obtain consent and administer study questionnaires are already extensively trained in how to work with individuals with mild-to-moderate dementia and caregivers in a sensitive and respectful manner. Class size will be limited to 5 dyads and 2 or more instructors to ensure the safety of study participants. Exercise instructors are certified in at least one type of exercise training and are extensively trained in how to safely work with individuals with mild-to-moderate dementia. Data and recordings will be maintained on secure servers or in locked file cabinets.

17.0 Risks and Benefits

17.1 * Risks and discomforts:

As with any program involving new exercises, study participants may experience injuries including muscle strain or soreness, joint pain, falls or other injuries. In addition, study participants may find the baseline or follow-up assessments or video-recording to be stressful. Loss to privacy may occur if information is released outside the study team.

17.2 Steps taken to minimize risks to subjects:

For our prior PLIE study, we have consulted with a wide range of experts who have experience leading exercise classes for individuals with mild-to-moderate dementia to ensure that the exercise program is safe and likely to be effective. These included local, national and international experts in traditional exercise programs as well as Tai Chi, Feldenkrais, and yoga. We will minimize stress during baseline and post-intervention assessments by having trained research staff to recognize and appropriately address signs of discomfort or stress when indicated (e.g., taking breaks, rescheduling appointment, skipping sections that cause undue discomfort). We will minimize risk of loss of privacy by having trained all research staff to maintain data in a secure manner and not to discuss study participants outside the research team. When it is necessary to carry private information offsite (e.g., names on class attendance logs, addresses for home visits), information will be caried in a locking device such as a briefcase. If caregivers request to communicate by mail, email, fax or text, they will be informed that this may increase the risk of loss of privacy. These communications will include a confidentiality statement, and the minimum

amount of identifying information necessary will be conveyed. Study forms will include unique ID numbers but not names or other identifying information. All research staff involved in this study have already been part of the PLIE study and are well trained. Recordings will be stored on a secured data server (MyResearch) and/or on an encrypted external hard drive stored in a secure locked file cabinet. Separate consent will be obtained for public release of video recordings and future contact.

Audio-recorded interviews for the substudy will be uploaded to MyResearch and subsequently deleted from the recorder.

17.3 Benefits to subjects:

(•) Yes ( ) No

If yes, describe:

Some affected individuals may experience improvements in physical, emotional or cognitive function, but this is not guaranteed. Caregivers may experience a reduction in caregiver burden or improved well-being, but this is not guaranteed.

17.4 Benefits to society:

This study will determine the impact of the Paired PLIE Program on function and well-being in individuals with mild-to-moderate cognitive impairment and their care partners. If this program is successful, it could substantially improve quality of life for individuals with dementia and their caregivers.

17.5 Explain why the risks to subjects are reasonable:

The risks to subjects are comparable to daily life experiences related to engaging in physical activity or in being assessed in a clinical setting.

18.0 Confidentiality and Privacy

18.1 Plans for maintaining privacy in the research setting:

Data will be entered into the MyResearch portal, which provides a secure web-based data management and storage system for UCSF investigators, and will not be stored electronically on computers or servers. Paper copies of data collection forms and video footage will be stored in locked files cabinets. Subjects will be identified by a unique participant identification number. Personal identifying information will be stored separately and securely. Video-recording will include identifiable faces and first names and will be stored electronically on the same secured server or an encrypted external hard drive stored in a secured locked file cabinet. No last names will be used and video-recordings will not be published or visible to anybody outside the research team or scientific meetings without additional written consent from study participants. At the caregiver participant's request, communication may be conducted via mail, email, fax or text. Caregivers will be informed that these modes of communication may increase their risk of loss of privacy. Mail, email, fax and text communications will include a confidentiality statement. The minimum amount of identifying information will be included in all communications. Study forms will include unique study ID numbers only.

18.2 Possible consequences to subjects resulting from a loss of privacy:

Loss of privacy could potentially result in stigma related to dementia diagnoses or test scores.

18.3 Study data are:

☐ Derived from the Integrated Data Repository (IDR) or The Health Record Data Service (THREDS) at SFGH

- [x] Added to the hospital or clinical medical record
- [ ] Created or collected as part of health care
- [ ] Used to make health care decisions
- [x] Obtained from the subject, including interviews, questionnaires
- [ ] Obtained from a foreign country or countries only
- [ ] Obtained from records open to the public
- [ ] Obtained from existing research records
- [ ] None of the above

If **derived from a medical record**, identify source:

18.4 Identifiers may be included in research records:

(•) Yes ( ) No

If **yes**, check all the identifiers that may be included:

- [x] Names
- [x] Dates
- [x] Postal addresses
- [x] Phone numbers
- [x] Fax numbers
- [x] Email addresses
- [ ] Social Security Numbers*
- [x] Medical record numbers
- [x] Health plan numbers
- [ ] Account numbers
- [ ] License or certificate numbers
- [ ] Vehicle ID numbers
- [ ] Device identifiers or serial numbers
- [ ] Web URLs
- [ ] IP address numbers
- [ ] Biometric identifiers
- [x] Facial photos or other identifiable images
- [ ] Any other unique identifier

* Required for studies conducted at the VAMC

18.5 Identifiable information might be disclosed as part of study activities:

(•) Yes ( ) No

If **yes**, indicate to whom identifiable information may be disclosed:

- [ ] The subject's medical record
- [ ] The study sponsor
- [ ] Collaborators
- [ ] The US Food & Drug Administration (FDA)
- [x] Others (specify below)
- [ ] A Foreign Country or Countries (specify below)

If **Others**, specify:

Medical personnel if study-related injury. Auditors.

18.6 Indicate how data are kept secure and protected from improper use and disclosure (check all that apply): NOTE: Whenever possible, do not store subject identifiers on laptops, PDAs, or other portable devices. If you collect subject identifiers on portable devices, you MUST encrypt the devices.

- [x] Data are stored securely in My Research
- [ ] Data are coded; data key is destroyed at end of study
- [x] Data are coded; data key is kept separately and securely
- [x] Data are kept in a locked file cabinet
- [x] Data are kept in a locked office or suite
- [x] Electronic data are protected with a password
- [x] Data are stored on a secure network
- [x] Data are collected/stored using REDCap or REDCap Survey
- [ ] Data are securely stored in OnCore

18.7 Additional measures to assure confidentiality and protect identifiers from improper use and disclosure, if any:

Research staff are HIPAA-trained and are instructed not to discuss or disclose information about study participants outside the research team.

18.8 This study may collect information that State or Federal law requires to be reported to other officials or ethically requires action:

- (•) Yes
- ( ) No

Explain:

Interviews with subjects or caregivers could potentially reveal information related to abuse or thoughts of suicide or homicide.

18.9 This study will be issued a Certificate of Confidentiality:

- ( ) Yes
- (•) No

19.0 Subjects

19.1 Check all types of subjects that may be enrolled:

- [ ] Inpatients
- [ ] Outpatients
- [x] Healthy volunteers
- [ ] Staff of UCSF or affiliated institutions

19.2 Additional vulnerable populations:

- [ ] Children
- [ ] Subjects unable to consent for themselves
- [ ] Subjects unable to consent for themselves (emergency setting)
- [x] Subjects with diminished capacity to consent
- [ ] Subjects unable to read, speak or understand English
- [ ] Pregnant women
- [ ] Fetuses
- [ ] Neonates

- [ ] Prisoners
- [ ] Economically or educationally disadvantaged persons
- [ ] Investigators' staff
- [ ] Students

Explain why it is appropriate to include the types of subjects checked above in this particular study:

The goal of the study is to determine whether the Paired PLIE program improves function and quality of life in individuals with mild-to-moderate cognitive impairment. Therefore, although study participants will have a diminished capacity to provide consent, findings from the study could potentially improve quality of life for some study participants and provide important data for others with mild-to-moderate cognitive impairment.

Describe the additional safeguards that have been included in the study to protect the rights and welfare of these subjects and minimize coercion or undue influence:

Informed consent will be obtained from both study participants--affected individuals and their caregivers/LARs--together if possible. Capacity to consent will be determined using a standard protocol that is based on the protocol used at the UCSF Memory and Aging Center. Subjects who are able to consent for themselves will do so. Subjects who do not demonstrate capacity to consent will be asked for assent and LARs will provide consent on their behalf.

20.0 Recruitment

20.1 * Methods (check all that apply):

- [ ] Study investigators (and/or affiliated nurses or staff) recruit their own patients directly in person or by phone.
- [ ] Study investigators recruit their own patients by letter. Attach the letter for review.
- [ ] Study investigators send a "Dear Doctor" letter to colleagues asking for referrals of eligible patients. If interested, the patient will contact the PI or the PI may directly recruit the patients (with documented permission from the patient). Investigators may give the referring physicians a study information sheet for the patients.
- [ ] Study investigators provide their colleagues with a "Dear Patient" letter describing the study. This letter can be signed by the treating physicians and would inform the patients how to contact the study investigators. The study investigators may not have access to patient names and addresses for mailing
- [x] Advertisements, notices, and/or media used to recruit subjects. Interested subjects initiate contact with study investigators. Attach ads, notices, or media text for review. In section below, please explain where ads will be posted.
- [ ] Study investigators identify prospective subjects through chart review. (Study investigators request a Waiver of Authorization for recruitment purposes.)
- [ ] Large-scale epidemiological studies and/or population-based studies: Prospective subjects are identified through a registry or medical records and contacted by someone other than their personal physician. (Study investigators request a Waiver of Authorization for recruitment purposes.)
- [ ] Direct contact of potential subjects who have previously given consent to be contacted for participation in research. Clinic or program develops a CHR-approved recruitment protocol that asks patients if they agree to be contacted for research (a recruitment database) or consent for future contact was documented using the consent form for another CHR-approved study.
- [x] Study investigators list the study on the School of Medicine list of UCSF Clinical Trials website or a similarly managed site. Interested subjects initiate contact with investigators.
- [x] Study investigators recruit potential subjects who are unknown to them through methods such as snowball sampling, direct approach, use of social networks, and random digit dialing.
- [x] Other

If **Other**, explain:

Study participants will be recruited using a variety of methods including: distribution of study fliers at caregiver support groups meetings (e.g., Kaiser, ASFB, Alzheimer's Association); posting

fliers in community settings (e.g., senior centers); posting fliers online (e.g., Facebook); and distributing letters and fliers to clinicians and other community members. Individuals who express interest in learning more about the study will be contacted by telephone by research staff, who will describe the study procedures and obtain verbal consent to be screened. Those who are eligible and interested will be scheduled for an in-person consent visit.

Qualitative sub-study participants will be recruited from current study participants who have completed the intervention and have provided consent to be contacted about this research study. Potential participants will be contacted in the order in which they were originally enrolled until our target sample size is reached.

20.2 * How, when, and by whom eligibility will be determined:

Caregivers who express interest will be contacted by telephone by research staff who will describe the study in more detail and will obtain verbal consent to be screened. Those who are interested and eligible will be scheduled for an in-person appointment to obtain written consent. The Clinical Dementia Rating will be administered by telephone to assess severity of cognitive impairment.

20.3 * How, when, where and by whom potential subjects will be approached:

Please see above.

20.4 * Protected health information (PHI) will be accessed prior to obtaining consent:

(•) Yes ( ) No

21.0 Waiver of Consent/Authorization for Recruitment Purposes

This section is required when study investigators (and/or affiliated nurses or staff) recruit their own patients directly.

21.1 * Study personnel need to access protected health information (PHI) during the recruitment process and it is not practicable to obtain informed consent until potential subjects have been identified:

(•) Yes

If **no**, a waiver of consent/authorization is NOT needed.

21.2 * A waiver for screening of health records to identify potential subjects poses no more than minimal risk to privacy for participants:

(•) Yes

If **no**, a waiver of authorization can NOT be granted.

21.3 * Screening health records prior to obtaining consent will not adversely affect subjects' rights and welfare:

(•) Yes

If **no**, a waiver of authorization can NOT be granted.

21.4 * Check all the identifiers that will be collected prior to obtaining informed consent:

- [x] Names
- [x] Dates
- [x] Postal addresses
- [x] Phone numbers
- [ ] Fax numbers
- [x] Email addresses
- [ ] Social Security Numbers*
- [ ] Medical record numbers
- [ ] Health plan numbers
- [ ] Account numbers
- [ ] License or certificate numbers
- [ ] Vehicle ID numbers
- [ ] Device identifiers or serial numbers
- [ ] Web URLs
- [ ] IP address numbers
- [ ] Biometric identifiers
- [ ] Facial photos or other identifiable images
- [ ] Any other unique identifier
- [ ] None

Note: HIPAA rules require that you collect the minimum necessary.

21.5 * Describe any health information that will be collected prior to obtaining informed consent:

During the telephone screening process, we will collect data to assess initial eligibility criteria including diagnoses of exclusionary medical conditions or contraindications to exercise. Verbal consent to be screened will be obtained prior to collecting this information.

Note: HIPAA requires that you collect the minimum necessary.

21.6 * Describe your plan to destroy the identifiers at the earliest opportunity consistent with the research or provide a health or research justification for retaining the identifiers, or indicate and explain that retention is required by law:

Personally identifying information for individuals who decline to participate will be destroyed (e.g., names, dates, contact information) after enrollment has been closed. Non-personally identifying information will be retained so that we may compare the characteristics of those who do and do not choose to participate.

22.0 Informed Consent

22.1 * Methods (check all that apply):

- [x] Signed consent will be obtained from subjects and/or parents (if subjects are minors)
- [x] Verbal consent will be obtained from subjects using an information sheet or script
- [ ] Electronic consent will be obtained from subjects via the web or email
- [ ] Implied consent will be obtained via mail, the web or email
- [x] Signed consent will be obtained from surrogates
- [ ] Emergency waiver of consent is being requested for subjects unable to provide consent
- [ ] Informed consent will not be obtained

22.2 * Process for obtaining informed consent:

Verbal consent to be screened will be obtained by telephone using a phone script. Those who are eligible and interested will then be scheduled for an in-person written consent visit. The affected individual and LAR/caregiver will sit together with research staff during the written consent process. Capacity to consent will be assessed by research assistants who will be extensively trained by the PI and co-investigators using a standardized procedure. We first provide the consent form to the patient and caregiver together if possible and allow them to review it. We then describe the key points of the form, pointing to the areas on the form where the information is described in more detail. We then ask a series of yes/no questions to assess understanding of the information in the form. If the participant cannot answer the questions, we review the material again and consider them to lack capacity to consent. We then ask them if they would like to participate in the study to obtain their assent. We say that we are going to ask their LAR to sign the form on their behalf to obtain written consent. Most of our research assistants have a background in psychology and are highly sensitive to working with vulnerable patients. We train new research staff by having them role play the consent process until senior personnel determine that they are adequately prepared. They then observe senior personnel performing the consent process on at least one study participant. Subsequently they are observed performing the consent process until senior personnel determine that they are competent. We also have weekly team meetings to discuss any difficulties that arise during consent or any other study procedure.
The assessment form is included for review. If the affected individual demonstrates capacity to consent, they will sign the consent form; if not, they will be informed that the LAR is being asked to sign on their behalf, and the affected individual will be asked to assent to study procedures. Because caregivers also will be actively participating in the study, they will sign a separate consent form. Finally, research staff will sign both forms and will indicate that an assent discussion was completed if appropriate.

Consenting for the video-recording will be performed in an identical manner. Although affected individuals may not be able to consent for themselves, they may express their opinions about the classes and the video tapes to provide assent. If they indicate in any way (e.g., saying 'no', shaking their head 'no', frowning, etc) that they do not want to participate in the classes or be video-taped, we will consider this to be an indication of lack of assent. Study participants will not be forced to engage in any study activities.

22.3 * How investigators will make sure subjects understand the information provided to them:

Research staff will ask affected individuals a series of yes/no questions to assess whether consent information was understood. The wording of the questions will be varied to ensure that participants cannot simply answer yes or no to all questions. Information not understood will be discussed again and understanding will be reassessed. If affected individuals are unable to answer questions after discussion, they will be considered unable to provide consent and will be asked to assent to study procedures by agreeing to have their caregiver provide consent on their behalf. Affected individuals who are unable to provide either consent or assent will be considered ineligible for the study.

23.0 Waiver of Signed Consent (Verbal/Electronic Consent)

23.1 * Select the regulatory category under which the CHR may waive the requirement to obtain *signed* consent:

- ○ 46.117(c) (1) The only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern
- ◉ 46.117(c) (2) The research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context

24.0 Surrogate Consent

24.1 Subjects are inpatients on a psychiatric ward or mental health facility, or on psychiatric hold:

- ◉ No

If **yes**, use of surrogate consent for research is NOT allowed in California.

24.2 This study is related to the cognitive impairment, lack of capacity, or serious or life-threatening diseases and conditions of the research subjects:

◉ Yes

If **no**, use of surrogate consent for research is NOT allowed in California.

24.3 Explain why use of surrogates is necessary for completion of this study:

The purpose of this study is to determine whether the Paired PLIE program can improve function and quality of life in individuals living with mild to moderate cognitive impairment and their care partners. Consequently, due to the nature and purpose of the study, it is likely that most affected individuals will have lost their capacity for decision making. A surrogate may be necessary for multiple reasons: A) to be able to provide consent should it be determined that the study participant does not have the capacity to make decisions and B) to provide reliable information regarding the participant's current level of functioning including mental and physical functioning, relevant to the study and C) to provide information on caregiver burden and well-being.

24.4 Plans for assessing the decision-making capacity of prospective subjects:

1. Attempts will be made to obtain informed consent directly from the subject.
2. To ensure the affected individual has the capacity to consent and is able to directly consent, decision making capacity will be assessed by interviewer who is thoroughly trained by the PI.
3. The affected individual's decision making capacity will be assessed by observations made during the consent and information sharing process. Observations made will be used to assess the subject's ability:
    1. to make and state a decision and
    2. to understand the study objectives, in particular the potential participant's ability to express his/her own understanding and rationale for decisions involving:
        - The nature of the research and relevant information including time in the study and procedures.
        - Consequences of not participating in the study
        - Alternatives to participation
4. A Capacity Assessment Record for Paired PLIÉ participants will be used to record the capacity to consent and will be kept with the research chart.
5. Should the investigator determine the subject lacks decision making capacity, the investigator will inform the affected individual and seek surrogate consent.
6. Surrogate will then be asked to fill out the Self-Certification of Surrogate Decision Maker form. The form will be kept in the participant's research chart.
7. Consent form will be reviewed again with surrogate and affected individual.
8. Consent will be obtained from surrogate
9. Assent will be obtained from affected individual
10. Should the affected individual not assent, she/he will be excluded from the study despite the surrogate's consent.

24.5 Plans for obtaining consent from subjects who regain ability to consent after a surrogate has given initial consent:

Dementia progression is typically assessed in clinical and research settings every 6 to 12 months. Because our study is low-risk and relatively brief, we will not reassess capacity to consent in participants. However, a subject's resistance or objection to engaging in study procedures at any point will be taken as evidence of refusal or withdrawal.

24.6 Requirements for any study involving surrogates for obtaining informed consent. Check to acknowledge:

- [x] Research takes place in California. All surrogates will complete the "Self-Certification of Surrogate Decision Makers for Participation in Research" form.
- [x] Conscious subjects will be notified of the decision to contact a surrogate. If subjects object to study participation, they will be excluded even if their surrogate has given consent.
- [x] Surrogates will not receive any financial compensation for providing consent.
- [x] If a higher-ranking surrogate is identified at any time, the investigators will defer to the higher-ranking surrogate's decision regarding the subject's participation in the research.

For research taking place outside of California, explain how investigators will confirm that surrogates are legally authorized representatives:

n/a

24.7 VA Studies Only
Provide any additional information to explain comply with the additional VAMC requirements for use of surrogates in research:

n/a

25.0 Financial Considerations

25.1 Subjects payment or compensation method (check all that apply):

Payments will be (check all that apply):

- [x] Subjects will not be paid
- [ ] Cash
- [ ] Check
- [ ] Debit card
- [ ] Gift card
- [ ] Reimbursement for parking and other expenses
- [ ] Other:

Specify **Other**:

25.2 Describe the schedule and amounts of payments, including the total subjects can receive for completing the study. If deviating from recommendations in Subject Payment Guidelines, include specific justification below.

25.3 Costs to Subjects: Will subjects or their insurance be charged for any study procedures?

- ○ Yes
- ◉ No

If **yes,** describe those costs below, and compare subjects' costs to the costs associated with alternative care off-study. Finally, explain why it is appropriate to charge those costs to the subjects.

26.0 CTSI Screening Questions

26.1 * This study will be carried out at one of the UCSF Clinical Research Services (CRS) centers or will utilize CRS services. CRS centers are at the following sites:

- **SFGH Clinical Research Center**
- **Moffitt Adult Clinical Research Center**
- **Moffitt Hospital Pediatrics & NCRC**

- **Tenderloin Center**
- **CHORI Children's Hospital Pediatrics & Adult Clinical Research Center**
- **Kaiser Oakland Research Unit**
- **SF VA Medical Center Clinical Research Unit**

Please note: Effective 3/1/14, the CRS form will no longer be completed and submitted in iRIS. The CRS budget request form can be found at: https://accelerate.ucsf.edu/files/crs/BudgetRequest2015.docx. Follow the instructions on the form to submit. Even if you click 'Yes' to this question, the form will no longer proceed to the Clinical Research Services (CRS) Application Form section.

○ Yes ◉ No

26.2 This project involves community-based research:

◉ Yes ○ No

26.3 This project involves practice-based research:

○ Yes ◉ No

27.0 End of Study Application

27.1 End of Study Application Form

To continue working on the Study Application: Click on the section you need to edit in the left-hand menu. Remember to save through the entire Study Application after making changes. If you are done working on the Study Application: Click Save and Continue. If this is a new study, you will automatically enter the Initial Review Submission Packet form, where you can attach consent forms or other study documents. Review the Initial Review Submission Checklist for a list of required attachments. Answer all questions and attach all required documents to speed up your approval.