STUDY PROTOCOL AND STATISTICAL ANALYSIS PLAN

NCT02350127

Preventing Loss of Independence through Exercise (PLIÉ) in Persons with Dementia

Version 1.34

Approved September 10, 2019

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Background Information

The University of California San Francisco (UCSF) Institutional Review Board (IRB) Study Application was used as the Study Protocol of Record for this study. The IRB-approved Study Application includes information about the overall study design, specific aims and hypotheses, statistical analysis plan, inclusion/exclusion criteria, study methods and procedures, and data and safety monitoring plan. The Study Application was originally approved by the UCSF IRB on November 20, 2014 (V1.1). Protocol changes made prior to study initiation and after study initiation are summarized in the table below. The most recently approved version of the Study Application (V1.34, approved September 10, 2019) is included here along with the Data and Safety Monitoring Plan from the originally approved version (V1.1, approved November 20, 2014).

List of Protocol Changes

Changes made prior to study initiation	**Version Number**	**Date approved**
Study design: changed from 12-month parallel-group randomized, controlled trial (RCT) with 6-month intervention and 6-month follow-up periods (assessments at baseline, 6 months, 12 months) to 8-month waitlist RCT with 4-month immediate start and 4-month delayed start groups (assessments at baseline, 4 months, 8 months)	V1.4	5/19/2015
Sample size: changed from 16/site, 9 sites (n=144) to 20/site, 6 sites (n=120)	V1.4	5/19/2015
Eligibility criteria: expanded to include diagnoses of memory loss as well as dementia; restricted severity to mild-to-moderate (Clinical Dementia Rating [CDR] 1 or 2); expanded to include veterans and non-veterans in the community	V1.4	5/19/2015
Outcome measures: Added Falls Efficacy Scale; added Positive Aspects of Caregiving Scale; replaced Functional Independence Measure with Disability Assessment for Dementia	V1.4	5/19/2015
Changes made after study initiation	**Version Number**	**Date approved**
Eligibility criteria: expanded to include mild cognitive impairment diagnosis or CDR 0.5	V1.10	1/13/2016
Outcome measures: Anonymous satisfaction survey added	V1.16	7/18/2016
Outcome measures: Added Perceived Stress Scale and open-ended questions about impact of California wildfires.	V1.27	11/21/2017

Study Application (Version 1.34)

1.0 General Information

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

Preventing Loss of Independence through Exercise (PLIE) in Persons with Dementia

***Enter the study number or study alias**

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

2.0 Add Department(s)

2.1 List the departments associated with this study. The Principal Investigator's department should be Primary.:

Primary Dept?	Department Name
○	**UCSF** - *101001* - M_Osher Center
◆	**UCSF** - *133100* - M_Psychiatry
○	**UCSF** - *147100* - M_Radiology

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

Abrams, Gary M MD
Other Investigator
Boscardin, W. John PhD, PhD
Other Investigator
Chao, Linda, PHD
Other Investigator

Chesney, Margaret A, PhD
Other Investigator
Mehling, Wolf MD, MD
Other Investigator
Nicosia, Francesca M
Other Investigator
Yaffe, Kristine MD
Other Investigator

B) Research Support Staff

Fung, Kathy
Biostatistician
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 which KSP are being added. More information on the CITI training requirement**

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 Principal Investigator, Dr. Barnes will oversee all aspects of this study.	Dr. Barnes is a Mental Health Research PI at SFVA and a Professor of Psychiatry and Epidemiology & Biostatistics at UCSF. As an epidemiologist, Dr. Barnes has extensive training and expertise in research study design and methodology. She has previously led two clinical trials of behavioral interventions in older adults with cognitive impairment, and she was PI of the PLIÉ pilot study that served as the foundation for the current study.
Dr. Yaffe, Kristine MD	As Co-Investigator, Dr. Yaffe will provide expertise related to dementia diagnosis and progression. In addition, she will participate in monthly leadership meetings, interpretation of results and publication of findings.	Dr. Yaffe is Chief of Neuropsychiatry and Director of the Memory Disorders Clinic at SFVA and a Professor of Psychiatry, Neurology and Epidemiology & Biostatistics at UCSF. She is an international leader in identification of risk factors for cognitive decline and dementia and has been PI or site-PI of several clinical trials in individuals with cognitive impairment or dementia. She was a co-investigator on the PLIÉ pilot study.
Abrams, Gary M MD	As Co-Investigator, Dr. Abrams will contribute expertise related to rehabilitation methods and outcomes and will also participate in monthly leadership meetings, interpretation of results and publication of findings.	Dr. Abrams is the Rehabilitation Section Chief at SFVA, Director of the Neurorehabilitation Clinic at UCSF, and Professor of Clinical Neurology at UCSF. He has extensive expertise related to techniques for neural compensation and repair, particularly related to the functional consequences of acquired brain injury.
Tarasovsky, Gary	Mr. Tarasovsky will serve as the data manager.	Mr. Tarasovsky is an NCIRE employee. He is an experienced data manager who has worked with Dr. Barnes on several of her prior studies.
Fung, Kathy	Ms. Fung will perform data analyses.	Ms. Fung is a VA employee. She is an experienced programmer who supports many PIs at SFVA.

Dr. Boscardin, W. John PhD, PhD	Dr. Boscardin will provide senior-level biostatistical oversight.	Dr. Boscardin is a biostatistician and Professor of Medicine and Epidemiology & Biostatistics at UCSF with a WOC SFVA appointment. He and Dr. Barnes have collaborated on numerous projects.
Chesney, Margaret A, PhD	As Co-Investigator, Dr. Chesney will provide expertise related to integrative exercise. In addition, she will participate in monthly leadership meetings, interpretatin of results and publication of findings.	Dr. Chesney is a UCSF Professor of Medicine, the Osher Foundation Distinguished Professor in Integrative Medicine and the Director of the Osher Center for Integrative Medicine at UCSF. She was Deputy Director of the National Center of Complementary and Alternative Medicine at the National Institutes of Health from 2003-2008 and has extensive knowledge and expertise related to alternative approaches to health and well-being. She was Co-PI of the PLIÉ pilot study.
Dr. Mehling, Wolf MD, MD	As Co-Investigator, Dr. Mehling will oversee management of exercise instructors, including participation in weekly intervention team meetings. He will also participate in monthly leadership meetings, interpretation of results and publication of findings.	Dr. Mehling is a Professor of Family and Community Medicine and a faculty member at the Osher Center for Integrative Medicine at the University of California, San Francisco (UCSF). He participated in the development and pilot-testing of the PLIÉ program, has more than 35 years of clinical experience with mind-body medicine, and has led three randomized, controlled trials (RCTs) of mind-body therapies and pain.
Lee, Jennifer, BA	Ms. Lee will serve as a PLIÉ exercise instructor and will provide oversight of other exercise instructors.	Ms. Lee, GCFP, is certified in the Feldenkrais Method of Somatic Education both in the US and Europe. She has a private somatic practice, teaching movement to adults, infants, seniors and those with complex cognitive, orthopedic and/or neurological issues individually and in groups for 17 years. She is also trained in Clinical Hypnotherapy, Process Work and Patient Navigation. She helped develop and pilot-test the PLIÉ exercise program.
Dr. Chao, Linda PhD, PHD	Dr. Chao will serve as Principal Investigator of a neuroimaging ancillary study.	Dr. Chao is a Professor of Radiology at UCSF with extensive experience performing neuroimaging

		studies in older adults including those with neurodegenerative diseases.
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:

NCT02350127

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

5.13 * This is a CIRB study (e.g. the NCI CIRB will be the IRB of record):

( ) 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:	UCSF RAS "P number" or eProposal number	UCSF RAS System Award Number ("A" + 6 digits)
⊟	US Dept of Defense	01	NCIRE	Grant		

Sponsor Name:	US Dept of Defense
Sponsor Type:	01
Sponsor Role:	Funding Monitoring
CFDA Number:	
Grant/Contract Number:	AZ160019
Awardee Institution:	NCIRE

Is Institution the Primary Grant Holder:	Yes
Contract Type:	Grant
UCSF RAS "P number" or eProposal number:	
UCSF RAS System Award Number ("A" + 6 digits):	
Grant Number for Studies Not Funded thru UCSF:	
Grant Title:	
PI Name: (If PI is not the same as identified on the study.)	
Significant Discrepancy:	

⊟ US Dept of Veterans Affairs	01	SF VAMC Research Office	Grant

Sponsor Name:	US Dept of Veterans Affairs
Sponsor Type:	01
Sponsor Role:	Funding
CFDA Number:	
Grant/Contract Number:	TBD
Awardee Institution:	SF VAMC Research Office
Is Institution the Primary Grant Holder:	Yes
Contract Type:	Grant
UCSF RAS "P number" or eProposal number:	
UCSF RAS System Award Number ("A" + 6 digits):	
Grant Number for Studies Not Funded thru UCSF:	
Grant Title:	
PI Name: (If PI is not the same as identified on the study.)	
Significant Discrepancy:	

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

- ☐ Funded by gift (specify source below)
- ☐ 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:

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:

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):

- ☐ 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

☑ Other community-based site

☐ Foreign Country

List the foreign country/ies:

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)
☑ 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:

Marin Adult Day Health Center

Contact name:

Holly Rylance

Email:

hrylance@lifelongmedical.org

Phone:

415.897.6884 x4911 or 11

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:

Catholic Charities of Santa Rosa

Contact name:

Lindsey Hazlewood

Email:

lhazlewood@srcharities.org

Phone:

707-528-8712 x.184

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:

Alzheimer's Services of the East Bay

Contact name:

Micheal Pope

Email:

micheal@aseb.org

Phone:

510-644-8292 x325

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:

Bayview Hunters Point Multipurpose Senior Services, Inc.

Contact name:

Sheila Hembury, LCSW

Email:

sheila.hembury@bhpmss.org

Phone:

415-826-4774 x 1006

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:

Primrose Day Club

Contact name:

Lauri Connors

Email:

DCDSR@primrosealz.org

Phone:

(707) 578-8360

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 test the efficacy of the Preventing Loss of Independence through Exercise (PLIÉ) program by performing a randomized, controlled trial (RCT) at adult day health centers that have current contracts with the San Francisco Veterans Affairs Medical Center (SFVA) or other local VA facilities. We propose to enroll participants in cohorts of 20 at a given center at a time and randomize them in blocks to Group 1 (n=10) or Group 2 (n=10) using a waitlist design. Veterans will be prioritized for enrollment. Study participants randomized to Group 1 will participate in the PLIÉ program at least 2 days/week, 1 hour/day for a 4-month intervention period while study participants randomized to Group 2 will engage in usual activities. After 4 months, Group 1 will 'graduate' and will be encouraged to engage in maintenance activities while Group 2 participates in PLIÉ at least 2 days/week, 1 hour/day for 4 months. Outcomes and potential mediators will be assessed in all study participants at baseline, 4 and 8 months to examine the effect of the intervention in both groups as well as maintenance of intervention effects post-intervention in Group 1. Study sites will include: Marin Adult Day Health Center in Novato, CA; Institute on Aging, San Francisco, CA; Catholic Charities, Santa Rosa, CA; and Alzheimer's Services of the East Bay, Oakland, CA. Other study sites will be added to the protocol over time.

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:

1. Study participants will experience significantly greater improvements on the co-primary outcomes of cognitive function (Alzheimer's Disease Assessment Scale-cognitive subscale, ADAS-cog), physical performance (Short Physical Performance Battery, SPPB) and quality of life (Quality of Life in Alzheimer's Disease, QOL-AD) when participating in PLIÉ versus Usual Care (UC).
2. Caregivers will experience significantly greater reductions in caregiver burden (Caregiver Burden Inventory, CBI) and improvements in positive feelings about caregiving (Positive Aspects of Caregiving, PAC) when participating in PLIÉ versus UC.
3. The benefits of PLIÉ on participant and caregiver outcomes will be maintained from 4 to 8 months in Group 1.

12.2 * List the specific aims:

Aim 1. To determine whether PLIÉ improves participant outcomes over 4 months compared to Usual Care (UC).
Aim 2. To determine whether PLIÉ improves caregiver outcomes over 4 months compared to UC.
Aim 3. To determine whether the effects of PLIÉ are maintained over 4 months post-intervention.

12.3 Statistical analysis:

All primary analyses will be performed using intent-to-treat principles. All variables will first be assessed for evidence of outlier values or skewed distributions. Baseline characteristics and potential confounders will be summarized for participants randomized to Group 1 versus Group 2 using standard methods such as means/standard deviations and medians/inter-quartile ranges for continuous variables and frequencies with percentages for categorical variables. Differences between the groups at baseline will be statistically tested using t-tests for continuous variables or non-parametric alternatives as indicated and Chi-square tests for categorical variables. Any differences detected will be adjusted for in multivariable models. Our primary analytic approach will be mixed effects linear regression which will enable efficient estimation of treatment effects, inclusion of all study participants in intent-to-treat analyses, and the same analytic approach to be used for all three Aims. Analyses will focus on differences in outcomes when participating in PLIE vs. UC. Fixed effects terms will be included for treatment (PLIE vs. UC), sequence (Group 1 vs. Group 2), time (baseline, 4 months, 8 months) and the interaction between treatment*time. Subjects will be modeled as random effects. Models also will adjust for any baseline differences in demographic factors or confounders that may occur due to chance. Covariates will be included to adjust for any co-interventions that occur (e.g., medication changes), and sensitivity analyses will be performed excluding participants who experience co-interventions. Standard diagnostic tests will be performed to examine model assumptions and distributions of residual values and to assess for potential leverage and influence points. To minimize the risk of Type I error due to multiple comparisons with co-primary outcomes, we will adjust p-values using bootstrapping (SAS Proc Multtest).

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**:

Department of Veterans Affairs; SFVA R&D Committee

13.0 Background

13.1 Background:

Dementia is common in older Veterans, affecting nearly 1 in 10 of those age 65 years or older (~1 million individuals), and prevalence is expected to rise as Korean and Vietnam-era Veterans grow older. Currently available dementia medications are associated with small improvements in cognitive and physical function (standardized effect sizes, 0.11-0.33) but have many adverse effects and do not stop or slow the disease course.[1-3] In addition, several new medications that initially appeared promising have recently failed in Phase III clinical trials.[4-8] In contrast, there is growing evidence that behavioral interventions such as physical, mental and social activity are beneficial in individuals with dementia and have minimal adverse effects.[9-11] We have recently developed a novel, integrative exercise program called Preventing Loss of Independence through Exercise (PLIÉ) that focuses on training procedural memory (unconscious learning of procedures, which is relatively well-preserved in individuals with dementia) to build the strength and capacity to perform the movements that are most needed for daily function (e.g., standing up from sitting) while also increasing mindful body awareness and facilitating social connection.[12,13] **The objective of this study is to perform a randomized, controlled trial to test the efficacy of PLIÉ for improving function and quality of life and reducing caregiver burden in individuals living in the community with dementia.**

13.2 Preliminary studies:

We performed a pilot-test of PLIÉ at an adult day health center in San Francisco, CA.[12,13] Study participants were 12 individuals with mild to moderate dementia attending an adult day health program in San Francisco, CA, and their primary caregivers. Participants in the PLIÉ group (n=7) attended the program for 45 minutes, 2 to 3 days/week (depending on their daily attendance at the center) for 18 weeks while participants in the Usual Care (UC) group (n=5) engaged in standard chair-based exercises at the center. Outcomes were assessed at baseline and 18 weeks and included standard measures of cognitive function (Alzheimer's Disease Assessment Scale – cognitive subscale, ADAS-cog), physical performance (Short Physical Performance Battery, SPPB), quality of life (Quality of Life Scale in Alzheimer's Disease, QOL-AD); and caregiver burden (Caregiver Burden Inventory, CBI).

Feasibility was assessed based on enrollment and retention. A total of 22 individuals were invited to participate in the study; of these, 8 declined (primarily due to lack of time/interest), 2 withdrew prior to the baseline assessment and 12 (55%) enrolled. Of the 12 who enrolled, 1 (PLIÉ) withdrew prior to the 18-week assessment (92% completion rate).

Effect sizes were estimated based on the mean standardized difference between PLIÉ and UC from baseline to 18 weeks (i.e., mean change from baseline to 18 weeks in PLIÉ group minus mean change from baseline to 18 weeks in UC group divided by the baseline standard deviation [SD] in both groups combined). We observed evidence of clinically meaningful between-group differences (≥0.25 SDs) for measures of cognitive function (ADAS-cog), physical performance (SPPB), quality of life (QOL-AD, participant and caregiver) and caregiver burden (CBI). **These effect sizes are substantially larger than has been observed with current dementia medications and affect a broader range of outcomes than current behavioral interventions.** These pilot data demonstrate convincingly that: 1) we can work successfully with community-based adult day health centers; 2) we can enroll and retain individuals with dementia and their caregivers in an integrative exercise intervention study; 3) we can successfully deliver the PLIÉ program to individuals with mild to moderate dementia; and 4) a larger study of the PLIÉ program is highly likely to find significant improvements in physical performance, cognitive function and quality of life and reduction in caregiver burden relative to usual care.

18-Week Change and Effect Size (ES) Calculations from PLIÉ Pilot Trial

Measure	PLIÉ	UC	Baseline SD	Standardized ES†
Participant Measures				
Cognitive function (ADAS-cog)*	-4.6	2.4	9.2	**+0.76**
Physical performance (SPPB)	1.0	0.2	2.4	**+0.34**
Quality of life (QOL-AD)	6.0	2.6	4.1	**+0.83**
Caregiver Measures				
Participant quality of life (QOL-AD)	2.2	0.0	7.2	**+0.33**
Caregiver burden (CBI)*	-5.5	1.8	14.2	**+0.49**

* lower scores reflect better performance. † + values reflect better outcomes with PLIÉ; values ≥0.25 considered clinically meaningful.

13.3 References:

1. Hansen RA, Gartlehner G, Lohr KN, Kaufer DI. Functional outcomes of drug treatment in Alzheimer's disease: A systematic review and meta-analysis. *Drugs & aging.* 2007;24(2):155-167.
2. Rockwood K. Size of the treatment effect on cognition of cholinesterase inhibition in Alzheimer's disease. *Journal of neurology, neurosurgery, and psychiatry.* May 2004;75(5):677-685.
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4. Bezprozvanny I. The rise and fall of Dimebon. *Drug news & perspectives.* Oct 2010;23(8):518-523.
5. Fagan T. Clinical Trials of Intravenous Bapineuzumab Halted. *Alzheimer Research Forum online*August 8, 2012.
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8. Zakaib GD. Phase 3 Solanezumab Trials "Fail" - Is There a Silver Lining? *Alzheimer Research Forum online*August 24, 2012.
9. 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.
10. Guzman-Garcia A, Hughes JC, James IA, Rochester L. Dancing as a psychosocial intervention in care homes: a systematic review of the literature. *International journal of geriatric psychiatry.* Dec 7 2012.
11. Potter R, Ellard D, Rees K, Thorogood M. A systematic review of the effects of physical activity on physical functioning, quality of life and depression in older people with dementia. *International journal of geriatric psychiatry.* Oct 2011;26(10):1000-1011.
12. 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 [in press].
13. 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 & Mental Health, DOI: 10.1080/13607863.2014.935290.

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:

120

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

120

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

218

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

Although our primary analytic approach will be mixed effects linear regression models using a waitlist design, sample size estimates and power calculations are based on the simpler (and more conservative) situation of a repeated measures design with 1 pre and 2 post measures using effect size estimates from our pilot study, correlation between measures of 0.75 (based on our pilot data) and estimated alpha=0.03 (to account for multiple comparisons for our three co-primary outcomes). Sample size estimates at 80% power ranged from n=12/group to n=59/group depending on the effect size. Conversely, power estimates using a sample size of 60/group ranged from 81% to 100%. Power ranged from 71% to 100% for all outcomes even with 20% attrition. We estimate that we will need to contact and screen 218 potential study participants in order to enroll our target sample of 120 based on our pilot study response rate of 55%.

Sample Size and Power Estimates	***Effect Size***	***Sample size, 80% Power***	***Power, N=60/ Group***	***Power, 20% Attrition***
Co-Primary Outcomes				
Cognitive function (ADAS-cog)	0.76	12	1.00	1.00
Physical performance (SPPB)	0.34	59	0.81	0.71
Quality of life (QOL-AD)	0.83	10	1.00	1.00
Secondary Outcomes				
Caregiver burder (CBI)	0.49	29	0.97	0.92

14.5 * Eligible age range(s):

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

14.6 Inclusion criteria:

We propose to enroll 120 dyads of individuals with dementia and their primary caregivers, with a goal of 20 dyads per intervention site. Veterans with dementia who are current clients at the site will be prioritized for enrollment. If we are unable to enroll our target sample of 20 Veterans with dementia at a given site, enrollment will be opened to non-Veterans with dementia at the site as well as Veterans and non-Veterans with dementia who are not currently clients at the site but are living in the community near the site and willing to attend for the study. Caregivers are not required to be Veterans, but their participation is necessary because they are providing care to the primary participants, many of whom will be Veterans.

Inclusion criteria, primary participant:

- diagnosis of memory loss or dementia
- mild to moderate severity (defined as Clinical Dementia Rating of 0.5, 1, or 2)
- English language fluency
- attendance or willingness to attend adult day health center at least 2 days/week on days that PLIÉ will be offered

Inclusion criteria, caregivers:

- Provide care for primary participant
- Able to answer study questionnaires related to participant's functional status, dementia-related behaviors, quality of life and their own feelings about caregiving
- English language fluency

14.7 Exclusion criteria:

Exclusion criteria, primary participant:

- Plans to change days of attendance during the study period so that participant would no longer be attending on at least 2 PLIE days/week
- Planning to leave the facility during the study period and not willing to come for PLIE classes at least 2 days/week
- Severe vision or hearing impairment (e.g., unable to see or hear well enough to follow instructions)
- Several physical impairment (e.g., paralysis or hemi-paralysis; wheel-chair or bed bound)
- Severe mental health condition (e.g., uncontrolled depression, PTSD, bipolar disorder)
- Limited life expectancy (e.g., enrolled in or eligible for hospice; metastatic cancer)
- Started dementia medication (cholinesterase inhibitor or memantine) in past 3 months
- Planning to change dementia medication during the study period
- Current participation in another research study
- Lack of legal supporting documentation for HIPAA (e.g., durable power of attorney, court ordered legal guardianship, advance health directives), If determined to lack capacity to consent.
- Lack of consent/assent to study procedures

Exclusion criteria, caregivers:

- Severe vision or hearing impairment (e.g., unable to see or hear well enough to follow instructions)
- Several physical impairment (e.g., paralysis or hemi-paralysis; wheel-chair or bed bound)
- Severe mental health condition (e.g,. uncontrolled depression, PTSD, bipolar)
- Limited life expectancy (e.g., enrolled in or eligible for hospice; metastatic cancer)
- Lack of consent

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:

Schedule of Evaluations. The table below provides an overview of study procedures and the schedule of evaluations. Briefly, screening will be performed by telephone and will include assessment of demographics and eligibility criteria. The consent visit will be performed in person with the participant and legally authorized representative (LAR) together; detailed consent procedures are provided in the Informed Consent section. After consent has been obtained, global cognitive function will be assessed in participants. The LAR may serve as the study caregiver or may designate someone else (e.g., other family member, paid caregiver) to play this role. The baseline, 4-month and 8-month visits will be performed with the participant and caregiver separately and will include measurement of participant and caregiver outcomes and potential confounders and mediators. Adverse events and co-interventions (e.g., medication changes) will be assessed during monthly caregiver check-ins during the intervention period. Each visit is described in more detail below. All of these research-related activities will be performed by our research team. Staff at the study sites will NOT be engaged in research and will be responsible for referring potential participants to our research team for screening; escorting study participants to and from the exercise intervention space; assisting study participants who need to use the toilet; and providing space for our exercise instructors to deliver the intervention.

Overview of Study Procedures and Schedule of Evaluations

	Screening	Consent	Baseline	4 Months	8 Months	Monthly CG Check-ins
Eligibility	X					
Demographics/ medical history	X					
Capacity to Consent		X				
Informed Consent		X				
Global cognitive function		X				

Outcomes			X	X	X	
Confounders/ mediators	nnn	nnn	X	X	X	
Adverse events						X
Co-Interventions						X

Screening (telephone, LAR/CG). Legally authorized representatives (LARs) of potential participants who have expressed interest in being contacted will be screened for eligibility over the telephone. Basic demographic and medical history information also will be collected after obtaining verbal consent. This information will be collected during screening in order to compare characteristics of those who choose to participate or not to assess for potential selection biases. Those who are eligible and interested will then be scheduled for an in-person consent visit. LARs may also serve as the study caregiver or may designate someone else (e.g., other family member, paid caregiver) to play this role. If an alternate study caregiver is designated, they will be screened and consented separately or consented with the LAR and potential participant if possible.

Consent Visit (in person, participant and LAR together). Similar to our pilot study, informed consent will be obtained with the participant and LAR together at a location of their choosing (e.g., home, SFVA, adult day center). Detailed consent procedures are provided in the Informed Consent section. In addition, the Montreal Cognitive Assessment (MoCA) will be administered to participants to measure global cognitive function. The MOCA is often used in clinical settings and will be used as a descriptive measure for clinical audiences to characterize dementia severity and also in exploratory analyses to determine whether baseline cognitive status acts as a confounder or effect modifier of the effects of PLIÉ. If an alternate CG is designated, they may be consented with the primary participant or at another time and place.

Baseline Assessment (with participants and caregivers separately). The baseline assessment may be performed immediately after the consent visit or scheduled for a later date. Participants and caregivers will provide data separately so that their answers do not influence each other. Participants will be directly assessed by research staff while caregivers will be provided with self-administered forms when feasible or may complete the assessment in person, by phone or mail-in.

Baseline Assessments in Participants
- Cognitive function (Alzheimer's Disease Assessment Scale – Cognitive Subscale, ADAS-cog). Cognitive function will be measured using the Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog). The ADAS-cog is one of the most commonly used outcome measures in dementia drug treatment trials and is one of the measures considered by the Food and Drug Administration for approval of dementia medications. It includes direct assessment of learning (10-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 and is scored on an 80-point scale with higher scores reflecting worse cognitive function. Prior studies have found the ADAS-cog to be valid and reliable with Cronbach's alpha greater than 0.8 and test-retest reliability above 0.9.
- Physical performance (Short Physical Performance Battery (SPPB). The SPPB was developed by the National Institute on Aging to provide an objective tool for measuring physical performance in older adults. **Lower body strength** is assessed based on time to complete 5 chair stands without using arms. **Balance** is assessed based on the ability to hold different stands for 10 seconds, including the side-by-side, semi-tandem and full tandem stands. **Mobility** is assessed based on usual walking speed over a 3-meter walking course. The **total SPPB score** is the sum of the 3 component scores and may range from 0 to 12. Prior studies have found that the SPPB is valid and reliable and associated with important outcomes including disability and mortality. A recent systematic review concluded that the SPPB was one of the best tools available to measure physical performance in older adults based on reliability, validity and responsiveness.
- Quality of life (Quality of Life Scale in Alzheimer's Disease, QOL-AD). The Quality of Life Scale in Alzheimer's Disease (QOL-AD) is a standard quality of life measure that asks parallel questions of affected individuals and caregivers and was used in our pilot study. Current quality of life is rated 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, friends, self as a whole, ability to do chores around the house, 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 0.84 for patient reports and 0.86 for caregiver reports and interrater reliability based on Cohen's kappa values >0.70.
- Falls Efficacy Scale. A standard measure of falls efficacy that can be administered to people with cognitive impairment or caregivers and asks about concern about the possibility of falling doing 10 daily tasks (e.g., taking a bath or shower) on a 4-point likert scale (not at all, somewhat, fairly or very concerned).
- Near-Infrared Spectroscopy (NIRS). A non-invasive optical method that measures blood oxygenation changes in the brain tissue. The NIRS method will be used in combination with the Verbal-Fluency Task, a cognitive task that is known to activate frontal brain areas. A few studies have used the Verbal Fluency

Task with NIRS (Herrmann, Ehlis, & Fallgatter, 2003), including in individuals with Alzheimer's disease (Fallgatter, Sitzmann, Heidrich, Mueller, & Strik, 1997).

Baseline Assessments in Caregivers
- Caregiver burden (Caregiver Burden Inventory, CBI). The Caregiver Burden Inventory (CBI) is a standard measure that includes 24 items and 5 domains. Caregivers are asked to rate how often each statement describes their feelings (never, rarely, sometimes, quite frequently, nearly always). The total score may range from 0 to 96 with higher scores reflecting greater feelings of burden. The CBI has good internal consistency (Cronbach's alpha, 0.73-0.86), and it was sensitive to change in our pilot study.
- Participant function (Disability Assessment for Dementia, DAD)**.** The impact of the intervention on functional independence will be assessed with the Disability Assessment for Dementia (DAD), which is a standard measure that asks caregivers to rate the participant's disability 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).
- Participant dementia-related behaviors (Neuropsychiatric Inventory (NPI). The NPI assesses the frequency, severity and level of distress caused by 12 common dementia-related behaviors (delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, aberrant motor behavior, sleep and appetite/eating). The NPI has good test-retest reliability (0.79-0.86) and good internal consistency (Cronbach's alpha, 0.87-0.88).
- Participant quality of life (QOL-AD). As described above, the QOL-AD is a standard quality of life measure that asks parallel questions of affected individuals and caregivers and was used in our pilot study.
- Participant urinary incontinence. Urinary incontinence in participants will be assessed with questions about the frequency, amount and distress caused by accidental urine leakage.
- Participant Falls Efficacy Scale. A standard measure of falls efficacy that can be administered to people with cognitive impairment or caregivers and asks about concern about the possibility of falling doing 10 daily tasks (e.g., taking a bath or shower) on a 4-point likert scale (not at all, somewhat, fairly or very concerned).
- 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).
- Geriatric Depression Scale - short form. Depressive symptoms in caregivers will be measured based on self-report with the GDS-short form, a 15-item yes/not scale that is valid in people with and without dementia.

Randomization. Study participants will be enrolled in one study site at a time in blocks of 20, and the randomization sequence will be generated in advance in blocks of 20 (10 Group 1, 10 Group 2) using a random number generator on a computer. The sequence will be stored in a secure location accessible only to intervention staff, and research staff who enroll study participants and collect outcome data will be unaware of the randomization sequence.

Blinding. Because we are using a waitlist design with usual care as the control condition, it will not be possible to blind study participants or their caregivers. However, research staff who collect outcome data will be blinded to group assignment. Every effort will be made to ensure that blinding is maintained including: 1) having interviewers remind study caregivers not to discuss any aspect of the study or ask any questions related to the study prior to scheduling or performing assessments*; 2)* excluding interviewers from staff meetings that discuss details of the intervention; and 3) maintaining the group assignment list separately from other study documentation. Interviewers also will be asked to guess which group participants were in to assess the adequacy of the blinding procedures.

Intervention. The PLIÉ program has been rigorously developed and pilot-tested by our team over the past four years. It capitalizes on recent discoveries in neuroscience and experimental psychology, which have found that, although explicit memory (the ability to consciously learn and remember new information) is impaired in people with dementia, implicit memory (unconscious learning that typically occurs through repeated exposure) is relatively preserved, particularly procedural memory (unconscious learning of procedures). PLIÉ therefore focuses on training procedural memory for the ability to perform the movements that are most needed for daily function (e.g., transitioning safely from sitting to standing) while also increasing mindful body awareness and encouraging social connection. It combines elements from a wide range of Eastern and Western exercise modalities, including occupational therapy, physical therapy, yoga, tai chi, Feldenkrais, Rosen Method, dance movement therapy and mindfulness meditation. The **PLIÉ Core Exercise Sequence** is repeated at every class and includes: Greetings (5 minutes); Body awareness warm-up (5 minutes); Seated exercises (15 minutes); Sit-to-stand and standing exercises (15 minutes); and Closing & appreciations (5 minutes). In addition, the program is guided by the **PLIÉ Guidin g Principles** (see below) for relating to class members, teaching exercise movements and utilizing goals and preferences. The PLIÉ program will be offered at each center for 1-hour sessions at least two days /week. Exercise instructors will prepare the exercise space and clean up after class as needed. Based on our prior experience, class size will be restricted to a maximum of 5 participants per instructor to ensure safety. In addition, participants will be offered a montly home visit to help them incorporate movements

from the classes into their daily lives. Caregivers may participate in home visits, and support materials (e. g., instructional booklets, iPad minis with access to instructional videos on the PLIE website) may be provided. iPad minis will not be used to access the UCSF or VA networks.

PLIÉ Guiding Principles	Rationale	Exercise Approaches Integrated
1. Repetition with variation	The same basic sequence of events is repeated in each class, providing a structure that becomes familiar over time and is designed to promote procedural learning. Specific movements are varied to maintain engagement based on moment-to-moment participant responses and to include variations introduced by participants.	Physical therapy, occupational therapy, yoga, tai chi, dance movement therapy
2. Progressive, functional movements	Specific movement sequences are selected to be related to important daily functional activities such as standing safely from a seated position. Simpler movements build slowly toward more complexity.	Physical therapy, occupational therapy, Feldenkrais, Rosen
3. Slow pace and step-by-step instructions.	Movements are performed slowly to enable participants to fully process instructions. Step-by-step instruction and modeling are utilized to minimize the cognitive demands and promote procedural learning.	Occupational therapy, yoga, tai chi, Feldenkrais, Rosen, dance movement therapy
4. Participant-centered goal orientation.	A goals assessment is performed before beginning the program. Participants are motivated by relating movements to personal interests and goals.	Physical therapy, occupational therapy
5. Body awareness, mindfulness, and breathing	Periods of rest are included between movements. Participants are encouraged to breathe deeply; notice how their bodies feel aided by sensory stimulation such as tapping, touching and naming body parts; and share their observations with the group.	Yoga, tai chi, Feldenkrais, Rosen
6. Social interaction	Participants sit in a circle, and many movements involve reaching across the circle to touch hands or elbows, or standing in a circle holding hands and moving together to facilitate social connection.	Dance movement therapy, occupational therapy, Rosen
7. Positive emotions	The program promotes positive emotions by creating a warm, loving, non-judgmental, non-coercive environment in which participants are encouraged to move in ways that feel good to them. Brief musical selections are used to enhance positive emotions.	Occupational therapy, yoga, tai chi, Feldenkrais, Rosen method, dance movement therapy

Goals Assessment. Prior to beginning the PLIÉ program, exercise instructors will meet individually with study participants and caregivers to discuss their personal goals and interests. Goals may range from concrete objectives (reaching down to tie shoes) to more general objectives (remembering appointments). Prior studies have found that rehabilitation tends to have better outcomes when patients are involved with setting their own goals. Exercise instructors will also ask about hobbies and interests of study participants as well as potential barriers and facilitators to engaging in a group exercise program. Information gathered will be used in the class setting to help tailor exercises to address individual goals and interests and to

imbue exercises with greater meaning (e.g., this exercise may help you reach down to tie your shoes; being more aware of your body and the things around you may help you remember upcoming appointments).

Usual Care (UC) Control. Those participants attending the adult day program will participate in usual activities at the center, while those from the community will continue to engage in usual activities at home. All adult day programs include some type of group physical activity (usually seated) or individualized physical therapy. Whenever feasible, we will strive to offer PLIÉ classes at the same time as usual exercises at the center. We will document usual care activities by collecting monthly activity schedules from study sites and by asking caregivers about usual activities over the past month during check-ins to assess for potential co-interventions or contamination. This will enable us to perform exploratory analyses to assess the effects of different usual care activities on study outcomes.

Follow-Up Assessments (participants and caregivers separately). Follow-up assessments will be performed at 4 months and 8 months for all study participants. Procedures and measures will be identical to those at baseline.

Adherence, Adverse Events and Co-Interventions. Adherence will be monitored using class attendance logs. Adverse events will be assessed by calling caregivers on a monthly basis using a standardized questionnaire. Caregivers will be asked to report changes to the participant's health status since the last contact, including any emergency room visits, hospitalizations, or injuries. For any symptoms or events reported, caregivers will be asked if they occurred during or shortly after participating in PLIÉ or usual activities. Events that are serious and unexpected will be reported to an independent Data Monitoring Committee (DMC) and the IRB within 5 working days. The DMC also will review the adverse event log on a biennial basis. Based on consultations with the SFVA Research Office, adverse events that are possibly, probably or definitely study-related that occur in SFVA patients will be entered as notes into the medical record. Co-interventions also will be assessed during monthly caregiver check-ins using a standardized questionnaire that asks about any changes since last contact that might affect study outcomes including changes in medications, caregivers, medical conditions, usual activities or other factors.

Video-recording. Some of the exercise classes or assessments will be video-recorded for quality control, research or educational purposes. Everyone must consent to the video-recording for quality control and training purposes. The participants will have the option to allow for (1) private viewing only – viewing limited to the research team, auditors, and monitoring committee, or (2) private and public viewing – viewing available to the public as videos will be included in the training manual, shown at research or educational meetings, and/or posted on the study website.

Participant options for video recording will be tracked together with the main consent; i.e., that tracking will be included in the current study database. More specifically, the database includes a Consent section, under which the main consent, video recording options, and future contact consent options will be entered. This will ensure that the research team are kept informed of participant choices for video recording. Participants may be contacted after study ends regarding information about the optional participation in ongoing community classes, Participants will be sent birthday cards, and--in case of death or hospitalization--sympathy cards.

PIs are permitted to sending annual research progress reports to funding agencies and research colleagues.

Other contact with study participants. To maintain good relationships with study participants, we may send birthday cards, get well cards and sympathy cards using IRB-approved templates. In addition, we may send periodic research progress updates using IRB-approved letters.

Implementation activities. We have received additional support from the Department of Veterans Affairs through the VA Innovators program to begin implementing PLIE as a new clinical program within VHA. To facilitate this process, we will be interviewing key VA stakeholders, patients, caregivers and clinicians regarding optimal implementation strategies; analyzing interviews to identify key themes; creating a 3-minute video 'pitch'; and drafting an implementation plan. In addition, we may offer PLIE classes at the Community Living Center, adult day programs that contract with VHA and through the YMCAs. This is considered a quality improvement project. However, some prior PLIE participants who are Veterans may be involved.

Additional measures to assess impact of North Bay fires: For caregiver participants at the Primrose site only, the Perceived Stress Scale will be administered at the mid-point and final assessments to measure the impact of the North Bay fires on general stress levels. In addition, an open-ended questionnaire will ask about the perceived impact of the fires on key study outcomes. A cover letter will inform caregivers that two new questionnaires have been added and will remind them that all study procedures are optional.

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:

Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-cog)
Short Physical Performance Battery (SPPB)
Quality of Life Scale in Alzheimer's Disease (QOL-AD)
Near-Infrared Spectroscopy (NIRS)
Caregiver Burden Inventory (CBI)
Disability Assessment for Dementia (DAD)
Neuropsychiatric Inventory (NPI)
Falls Efficacy Scale (FES)
Positive Aspects of Caregiving (PAC)
Geriatric Depression Scale - Short Form (GDS)
Perceived Stress Scale (Primrose caregiver participants only, Visits 2 and 3)

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:

The primary site for the proposed study is the San Francisco Veterans Affairs Medical Center (SFVA), which will oversee all study procedures and will maintain all study data. The intervention itself will take place off-site at adult day programs that have active contracts with SFVA or other local VA facilities. Study sites will include: Marin Adult Day Health Center, Novato, CA; Institute on Aging, San Francisco, CA; Alzheimer's Services of the East Bay, Oakland, CA; and Catholic Charities, Santa Rosa, CA. Other study sites will be added to the protocol over time. Some study procedures may occur at other off-site locations at the request of caregivers (e.g., caregiver home). All research-related activities will be performed by research staff, who may be employees of UCSF, SFVA or NCIRE. This will include: screening potential study participants for eligibility; scheduling visits; obtaining informed consent/assent; performing baseline and follow-up assessment; delivering the intervention; documenting research activities; and entering and analyzing data. Staff at the study sites will NOT be engaged in research and will be responsible for referring potential participants to our research team for screening; escorting study participants to and from the exercise intervention space; assisting study participants who need to use the toilet; and providing space for our exercise instructors to deliver the intervention.

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 phone, letter or in person based on participant, 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):

Participant with dementia

- consent: 1 hour

- baseline assessment: 1 hour
- intervention: 1 hour, 2-3 days/week, 4 months: 36-54 hours
- home visits: 1 hour, monthly, 4 months: 4 hours
- 4-month assessment: 1 hour
- 8-month assessment: 1 hour
- total: 44 to 62 hours over 10 months

Caregiver

- screening: 1 hour
- consent: 1 hour
- baseline assessment: 1 hour
- home visits: 1 hour, monthly, 4 months: 4 hours
- check-in calls: 15 minutes, monthly, 10 months: 2.5 hours total
- 4-month assessment: 1 hour
- 8-month assessment: 1 hour
- total: 11.5 hours over 10 months

16.7 Locations:

As described above, the primary site for this study is the San Francisco Veterans Affairs (SFVA), which will oversee all study procedures and will maintain all study data. The intervention itself will take place off-site at adult day programs that have active contracts with SFVA or other local VA facilities. In addition, some study procedures may occur at other off-site locations at the request of caregivers (e.g., caregiver home).

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 will be ensured by performing study procedures at adult day programs that study participants are already attending or are willing to attend or at locations chosen by caregivers (e.g., home). Study personnel who assess for eligibility, obtain consent and administer study questionnaires will be extensively trained in how to work with individuals with dementia and caregivers in a sensitive and respectful manner. Class size will be limited to 10 participants with 2 instructors to ensure the safety of study participants. Exercise instructors will be certified in at least one type of exercise training and will be extensively trained in how to safely work with individuals with dementia. Data will be maintained on secure VA or UCSF servers, VA-encrypted laptops, VA-approved thumb drives, VA-approved video recorders or in locked file cabinets. Subject identifiers will be used rather than personally identifying information on study forms whenever possible.

17.0 Risks and Benefits

17.1 * Risks and discomforts:

Subjects will be assigned to a group by chance that will determine the order in which they receive the intervention and control programs. These programs may be less effective or have more side effects than other available programs. This will not be known until after the study is completed and the data have been analyzed. As with any program involving new exercises, participants with dementia may experience exercise-related injuries including muscle strain or soreness, joint pain or falls. The primary participant may find the video-recorded sessions of the study to be stressful or uncomfortable. In addition, participants with dementia or caregivers may find the baseline or follow-up assessments to be psychologically or emotionally distressing. Loss of privacy may occur if research data are viewed by individuals outside the research team. There also may be risks that are unforeseeable.

17.2 Steps taken to minimize risks to subjects:

Minimizing risk of exercise-related injury: The PLIÉ program was specifically designed to be safe for individuals with dementia. Class size is restricted to a maximum of 10 participants with 2 instructors, so that exercise instructors can carefully attend to each participant as needed. Movements are broken down into their component elements and slowly increase in difficulty and complexity over the course of the program. Step-by-step instruction is provided to minimize the cognitive demands of the program. Participants are never forced to do anything, and their individual choices and preferences are respected.

Instructors encourage pleasurable, comfortable, pain-free, relaxed movements, and exercises are stopped or modified if there is evidence of pain or discomfort (e.g., based on holding of breath, constricted movement, facial expression or verbal statements). All adult day health centers also have standard procedures for dealing with medical emergencies. B. Minimizing risk of psychological or emotional distress related to research assessments or video-recording. Research staff who administer baseline and follow-up assessments will be carefully trained using standard procedures on strategies for working with individuals with dementia and their caregivers in a sensitive and respectful manner. Participants and caregivers will not be forced to answer any questions. Staff will be trained to recognize and appropriately address signs of discomfort or stress when indicated (e.g., by taking breaks, rescheduling appointment, skipping sections that cause undue discomfort). Participants will have the option to choose between private viewing (available only to research staff, auditors, and monitoring committee) or private/public viewing (available to private viewers and also public, such as being included in the training video, study website, and/or presentations). C. Minimizing risk of loss of privacy. We will minimize risk of loss of privacy by training all research staff to maintain data in a secure manner and not to discuss study participants outside the research team. Research data will be stored in locked file cabinets or on VA-approved devices (e.g., VA-encrypted laptops, VA-approved thumb drives, VA-approved video recorder) or secure VA or UCSF servers. Study forms will include unique ID numbers but not names or other identifying information whenever possible.

17.3 Benefits to subjects:

(•) Yes ( ) No

If yes, describe:

Some study participants may experience improvements in cognitive function, physical function, quality of life or reduced caregiver burden, but this is not guaranteed.

17.4 Benefits to society:

Knowledge gained from the study may aid with development and implementation of programs to enhance function and quality of life in individuals living in the community with dementia.

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:

Minimizing risk of loss of privacy and ensuring data security. All research staff will be trained to maintain data in a secure manner and to not discuss study participants outside the research team. Research data will be stored in locked file cabinets or on password-protected computers or secure servers behind the VA or UCSF firewall. All laptops and other transportable media devices (e.g., laptops, thumb drives, video camera) will be VA compliant. Study forms will be labeled using unique personal identification numbers (PIDNs) rather than personally identifying information whenever possible, and the code linking names with PIDNs will be stored separately and securely. If it is necessary to carry personally identifying information off-site (e.g., name and address for off-site assessment), the minimum amount of information necessary will be carried in a locked device (e.g., briefcase) and the information will be returned to SFVA as soon as possible and filed securely.

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] Derived from a medical record (e.g. APeX, OnCore, etc. Identify source below)
- [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:

SFVA electronic medical record

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
- [x] 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:

- [x] The subject's medical record
- [x] The study sponsor
- [x] Collaborators

- [ ] The US Food & Drug Administration (FDA)
- [x] Others (specify below)
- [ ] A Foreign Country or Countries (specify below)

If **Others**, specify:

Medical personnel if injuries; study auditors; Human subjects review committees

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
- [ ] 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 will be 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
- [x] 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 proposed study is specifically designed to improve functional status and quality of life in individuals with dementia. Although study participants have either a diminished capacity to consent or are unable to consent for themselves, the intervention is a very low risk exercise program that could potentially have beneficial effects in some study participants and, if successful, could be implemented more broadly.

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 study participants and their legally authorsized representatives (LARs) together. 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. Subjects who demonstrate dissent at any time (e.g., shaking head 'no'; walking away) will not be forced to engage in study activities.

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.
- [x] 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.
- [x] 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.
- [x] 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.

☑ Other

If **Other**, explain:

A variety of methods will be used to recruit potential participants for the study. 1) Veterans who are current clients at adult day programs where the intervention will occur will be recruited first. Staff at the facility will identify Veterans who meet initial eligibility criteria. Facility staff will then contact legally authorized representatives of potential participants either in person or by phone or by providing them with a CHR-approved brochure or letter to make them aware of the study. LARs may contact the research team directly or may tell facility staff that they are willing to be contacted. Those who express interest will be contacted by telephone by research staff, who will describe the study procedures and obtain verbal consent to be screened. 2) After all eligible Veterans at the site have been offered an opportunity to participate, a similar process will be used to recruit non-Veterans who are current clients. 3) Enrollment will be opened to Veterans with dementia living in the surrounding community who are not current clients but would be willing to come to the center at least 2 days/week on days that PLIE will be offered to participate in the study. These Veterans will be recruited using a variety of strategies including: providing SFVA clinicians with a Dear Doctor or Dear Patient letter that describes the study; posting advertisements and notices in public areas such as SFVA clinic waiting rooms and neighborhoods surrounding the study sites; posting information about the study on clinical trials websites; and by providing staff at the site with study brochures. In addition, we will send recruitment letters to legally authorized representatives of Veterans with a dementia diagnosis in their medical records who live in the community surrounding the study sites, providing them with an opportunity to 'opt out/in' by contacting research staff directly or returning a study postcard. 4) If we are not able to enroll an adequate number of study participants using the methods above, enrollment will be opened to non-Veterans living in the community surrounding the study site using the recruitment methods listed above.

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

For potential study participants who are current clients at the study site, initial eligibility (days of attendance, dementia diagnosis, English language fluency) will be determined by facility staff. LARs 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. For potential study participants who are not current clients at the study site, initial eligibility will be determined by SFVA clinicians, electronic medical records or self-referral.

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
- [ ] Email addresses
- [x] 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:

Names, telephone numbers and addresses will be obtained for legally authorized representatives of potential participants who indicate that they are willing to be contacted by our research team to learn more about the study. During the telephone screening process, we will collect data to assess initial eligibility criteria. Verbal consent to be screened will be obtained prior to collecting this information. In addition, we will search electronic medical records for Veterans with a dementia diagnosis who are living in the community surrounding the study site (e.g., based on zip code) and will send a recruitment letter to their legally authorized representative.

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:

We will store information collected for this study in accordance with VHA RCS-10.

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)
- [ ] 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:

The participant and LAR will participate together in the consent process. Research staff will review the key points of the consent documents and will ask if the participant or LAR have any questions. Research staff will then ask questions of the participant to assess their capacity to consent. The assessment form is included for review. If the participant 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 participant will be asked to assent to study procedures. The LAR may participate as the study caregiver or may designate another person (e.g., another family member, paid caregiver) to participate on their behalf. Because caregivers also will be actively participating in the study (by providing information about the participant behaviors, stress, etc.), they will sign a separate consent form. If the LAR is unable to participate in the consent visit in person (e.g., lives remotely), the consent forms may be mailed to them, reviewed with the research team over the phone, signed and mailed back; however, the participant must still provide assent. The study caregiver may also choose to have the consent form mailed to them, reviewed by phone, signed and mailed back. Finally, research staff will sign both forms and will indicate that an assent discussion was completed if appropriate.

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

Consistent with the procedures used successfully in our pilot study, research staff will ask participants 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 participants are unable to answer questions after two discussions, they will be considered unable to provide consent and will be asked to assent to study procedures by agreeing to have their LAR provide consent on their behalf. Participants who appear to dissent to study procedures (e.g., shake heads no, appear agitated or distressed) will be considered ineligible for the study even if their LAR provides consent.

23.0 Surrogate Consent

23.1 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.

23.2 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.

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

The purpose of this study is to test the efficacy of a novel, integrative exercise program to improve function and quality of life in individuals with dementia. Therefore, it is likely that some participants will no longer have the capacity to consent for themselves due to the nature of their condition. A surrogate may be necessary to: a) provide consent should it be determined that the study participant does not have the capacity to make decisions; b) 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 resulting from the loss of independence of the participant.

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

We have developed a standardized procedure to assess the decision-making capacity of potential study participants.

1. The informed consent process is performed with the individual with dementia (participant) and their surrogate decision-maker together.
2. The participant and surrogate decision-maker are given copies of the approved, stamped consent form to review.
3. Research staff then highlight the key elements of the consent form and ask if there are any questions.
4. Research staff assess for capacity to consent using the Consent Verification Form, which asks a series of yes/no questions to determine whether the participant understands: that they are being asked to participate in a research study, the key procedures involved, risks, benefits, whether participation is voluntary, whether they can stop, and whether they want to participate.
5. If the participant is unable to answer any of the questions correctly, the correct information is provided, and the questionnaire is readministered.
6. Capacity to consent is determined based on four criteria: whether the participant a) made a choice to participate; b) showed understanding of the research study procedures; c) demonstrated the ability to reason regarding whether or not to participate; and d) showed an appreciation for the risks /benefits of participating.
7. If the participant demonstrates capacity to consent based on these four criteria, they are asked to sign the consent form for themselves.
8. If the participant does not demonstrate capacity to consent for themselves, they are asked to assent to participation in the study, and the surrogate decision maker is asked to sign the consent form on the participant's behalf. The surrogate decision maker is also asked to complete the Self-Certification of Surrogate Decision Makers form and, if eligible, to sign the HIPAA form on the participant's behalf.
9. If the participant appears to dissent, they are not eligible to participate in the study, even if the surrogate signs the consent form. Signs of dissent may include verbal statements as well as non-verbal cues such as shaking their head no or appearing to be agitated or distressed.
10. The process of assessment of capacity to consent is documented on the Capacity Assessment Form.

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

Dementia is a progressive, neurodegenerative disease. Once capacity to consent has been lost, it is highly unlikely that it will be regained. Therefore, we do not plan to reassess capacity to consent. However, we will continuously assess assent to study participation. Participants will never be forced to participate in the exercise classes or other study procedures. They may decline to attend the exercise classes on a given day or may leave the room if they do not want to continue. In addition, assessment of outcomes will be discontinued if there is evidence of distress or lack of assent.

We will use the following hierarchy if the primary participant, legally authorized representative or caregiver differ regarding their desire to continue participation. 1) If the primary participant wishes to stop participating in the study (i.e., no longer consents/assents), the dyad will be withdrawn, regardless of the preferences of the caregiver or legally authorized representative. 2) If the primary participant does not demonstrate capacity to consent and the legally authorized representative wants the primary participant to stop participating in the study (i.e., withdraws consent on their behalf), the dyad will be withdrawn, regardless of the preferences of the primary participant or the caregiver. 3) If the caregiver wishes to stop participating in the study but the primary participant wishes to continue and, if the primary participant does not demonstrate capacity to consent, the legally authorized representative agrees (e.g., paid caregiver no longer wishes to be involved), then the primary participant will be allowed to continue without the caregiver's involvement.

23.6 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:

not applicable.

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

All study procedures will conform to the guidelines in VHA Handbook 1200.05, including section 36 on surrgate consent and section 49 on research involving persons who lack decision-making capacity.
Surrogate Consent (section 36)
a) Assessment of Capaciy. Detailed procedures are provided above describing our procedures for assessment of capacity to consent.
b) Investigators' Responsibilities for Surrogate Consent. Prior to engaging in the consent process, we will inform all LARs about their roles and obligations. Specifically, that their obligation is to try to determine what the potential participant would do if they were able to make their own decision; and that if they are unsure, then they should determine what is in the potential participant's best interests.
c) LARs. Consistent with VA guidelines, we will use the following order of priority to identify the most appropriate LAR: health care agent (i.e., individual named in Durable Power of Attorney for Health Care); legal guardian; next of kin in the following order: spouse, child, parent, sibling, grandparent, grandchild; or close friend.
d) Dissent or Assent. As described above, all study procedures will be explained to potential participants, and we will seek their assent to participate if they are unable to consent for themselves. Study participants who show evidence of dissent (e.g., shaking head no, appearing agitated or distressed) or who resist participating will never be forced to participate, even when the surrogate gives consent.
e. Fluctuating Capacity. As described above, dementia is a progressive, neurodegenerative disease. Once capacity to consent has been lost, it is highly unlikely that it will be regained. Therefore, we do not plan to reassess capacity to consent. However, we will continuously assess assent to study participation. Participants will never be forced to participate in the exercise classes or other study procedures. They may decline to attend the exercise classes on a given day or may leave the room if they do not want to continue. In addition, assessment of outcomes will be discontinued if there is evidence of distress or lack of assent.

Research Involving Persons Who Lack Decision-Making Capacity (section 49)
a) IRB Review and Approval: Individuals who lack decision-making capacity will not participate until the IRB has approved their participation
b) Criteria for Decision-Making Capacity: We will consult with the adult day health facility director at each site about each individual's decision-making capacity before proceeding with the informed consent process.
c) Temporary or Fluctuating Lack of Decision-Making Capacity: Please see above.
d. Criteria for Enrollment. The study entails minimal risk, and the potential for benefit is greater than the potential for risk. In addition, the disorder that has caused the participants' lack of decision-making capacity is being studied, and the study cannot be performed with only people who have decision-making capacity.
e. IRB Determination. The study includes appropriate procedures for obtaining assent and assessing dissent on an ongoing basis.

If the participant lacks capacity, the HIPAA can only be signed by the durable power of attorney, advance health directive agent, or legal guardian.

24.0 Financial Considerations

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

Payments will be (check all that apply):

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

Specify **Other**:

24.2 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.

Participants will not be paid to participate in the study.The PI received feedback from participants that incentives are not important factors for their participation in the study. Additionally, the research team has encountered significant challenges with procuring these incentives, and we are no longer able to utilize the same mechanism for obtaining the incentives. Between these challenges and the feedback we received from the study participants, the research team is removing the incentives all together.

24.3 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.

25.0 CTSI Screening Questions

25.1 * 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**
- **Mount Zion Hospital Clinical Research Center**
- **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

25.2 This project involves community-based research:

◉ Yes ○ No

25.3 This project involves practice-based research:

○ Yes ◉ No

26.0 End of Study Application

26.1 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.

18.0 Data and Safety Monitoring Plan

18.1 Describe the plan for monitoring data and safety (Help Text updated 9/13):

Serious or unexpected adverse events will be reported to CHR within 5 working days as required by CHR guidelines (**http://www.research.ucsf.edu/ch**
Approval_Reporting.pdf). In addition, an independent Data Monitoring Committee (DMC) will be established to provide external oversight and to ensure
and protocol adherence. The DMC will include 3 members to reflect different perspectives and will include: 1) clinician with expertise in dementia symptoms
biostatistician with expertise in clinical trial data analysis; and 3) adult day health center representative. The primary responsibilities of the DMC will be to
safety and study integrity. To achieve these responsibilities, the DMC will meet prior to beginning enrollment to review all study materials and procedures.
at least biennially thereafter to review study progress including enrollment, retention and adverse events. An agenda will be circulated prior to each meetin
be circulated after each meeting, amended as needed and approved by all members.

18.2 This study requires a Data and Safety Monitoring Board:

- (•) Yes
- ( ) No or not sure

If **yes**, press **SAVE and CONTINUE** to move to the next section of the application.

18.3 If No, provide rationale:

- ( ) Social/Behavioral research

19.0 Data and Safety Monitoring Board

19.1 Provide details from the Data and Safety Monitoring Board's charter, including meeting frequency, and affiliations and qualifications o

An independent Data Monitoring Committee (DMC) will be established to provide external oversight and to ensure participant safety and protocol adherenc
3 members to reflect different perspectives and will include: 1) clinician with expertise in dementia symptoms and care; 2) biostatistician with expertise in
analysis; and 3) adult day health center representative. The primary responsibilities of the DMC will be to ensure participant safety and study integrity. To a
responsibilities, the DMC will meet prior to beginning enrollment to review all study materials and procedures. They will also meet at least biennially therea
progress including enrollment, retention and adverse events. An agenda will be circulated prior to each meeting and minutes will be circulated after each m
needed and approved by all members.

19.2 All of the members of the Data and Safety Monitoring Board are independent of the sponsor:

(•) Yes ( ) No