Title: Dementia Caregiver Rehabilitation: Enhancing Veteran and Family-Centered Care
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2a. Research Plan

2.A.1. Background and Significance

2.A.1.A. Importance of the Problem to World Health

Worldwide, an estimated 24.3 million people suffered from dementia in 2005 with 4.6 million new cases of dementia developing every year [1]. Global estimates project the number of people with dementia will double every 20 years and reach 81.1 million by 2040 [1]. According to the latest report from the U.S. Department of Health and Human Services, Alzheimer's disease (AD), Parkinson's disease (PD), and cerebrovascular disease (CVD) all rank among the leading causes of death in the United States [2] and, per the World Health Organization, these diseases account for over 13% of all deaths in developed nations [3]. Ultimately, neurodegenerative conditions lead to the development of cognitive decline and have a large impact on quality of life in both patients and families [4], costly long-term care (LTC) placement [5], and patient [6] and caregiver [7] mortality.

2.A.1.B. Importance of the Problem to Veteran Health

According to VHA estimates for FY12, 485,423 Veterans suffer from dementia [8]. While VA estimates of dementia prevalence demonstrate a gradual decline in the near future, yearly prevalence is expected to remain over 400,000 for the next ten years. Specific comorbid conditions with elevated prevalence in the Veteran population confer additional risk for the development of dementia including posttraumatic stress disorder (PTSD) [9, 10], traumatic brain injury [11, 12], and vascular risk factors [13]. Furthermore, prevalence of risk factors for dementia (e.g., PTSD, depression, vascular risk factors including hypertension, diabetes) are increasing [14] in the veteran population.

2.A.1.C. Types of Dementia

Alzheimer's disease (AD)
In addition to AD being the most common global cause of dementia, it is the most prevalent cause of dementia in Veterans accounting for 44.6% of dementia cases in VA [15]. While causes of death with modifiable primary risk factors are on the decline (e.g., heart disease and stroke), AD-associated deaths increased by 66% from 2000 to 2008 [16]. According to the Alzheimer's Association [16], in 2012, payments for health care, LTC, and hospice services for people age ≥65 years with AD and other dementias are expected to be $200 billion (not including the contributions of unpaid caregivers). In 2011, more than 15 million family members and other unpaid caregivers provided an estimated 17.4 billion hours of care (valued at over $210 billion) to people with AD and other dementias.

Parkinson's disease dementia (PDD)
PDD ultimately develops in approximately 75% of PD patients [17] and leads to decreased survival [18]. Worldwide prevalence of PD is expected to double by 2030 [19]. In 2010, PD was added as a presumed service-related condition for Veterans potentially exposed to Agent Orange. At present, the Veterans Benefits Administration estimates it will cost $3.5 billion to care for Agent Orange exposed Veterans with PD over the next 10 years (75 FR 53202), on top of unknown costs for non-exposed Veterans. Evidence indicates the largest expenditures in PD care come from LTC, inpatient care, and medication [20, 21]. As Vietnam-era Veterans approach the mean age of onset for PD, VA will experience significant service utilization and cost burden associated with PD and PDD-related care, particularly related to LTC placement. PDD significantly increases caregiver burden and decreases quality of life in PD family caregivers [22]. During FY09-10, 56,332 Veterans were treated for PD within VA.

Dementia with Lewy bodies (DLB)
DLB shares a common pathology (e.g., synucleinopathy) with PDD and likely represents a spectrum of disease that is shared with PD and PDD. DLB is less common than other causes of dementia previously discussed (e.g., AD, VaD). However, DLB presents particular challenges for Veterans and caregivers given the large psychiatric component (i.e., hallucinations) of its presentation. Prior work involving AD [23] and DLB [24] caregivers indicate burden in DLB caregivers may be 45% greater than in AD caregivers. During FY09-10, 3,564 veterans diagnosed with DLB were treated within VA.

Vascular dementia (VaD)
VaD is the second leading cause of dementia and its prevalence doubles every 5.3 years [25]. VaD creates significant burden for family caregivers, particularly in the early stages of the disorder [26]. From 1996 to 2001, VaD accounted for 12% of all VA dementia cases [15]. However, there is significant overlap between AD and vascular dementia (VaD) comorbidity and risk factors. Subsequently a large proportion of dementia cases are likely comprised of mixed causes, including AD and VaD.

2.A.1.D. Patient- and Family-Centered Dementia Care

Dementia treatment: lack of progress on slowing disease progression
While behavioral/lifestyle changes and their effects show some promise in reducing dementia risk [27], current treatments lack significant prognostic improvement for those who do develop the disease. Despite significant governmental and pharmaceutical industry investments in research and development of treatments for various causes of dementia including tauopathies (e.g., Alzheimer's disease) and synucleinopathies (e.g., dementia with Lewy bodies, Parkinson's disease), no drug has been brought to market that demonstrates promise for preventing or halting disease progression. Subsequently, with little promise for "curative" treatments on the horizon, a growing number of family caregivers are left to cope with the progressive, deleterious effects of dementia on their loved ones.

Dementia caregiving: overt and hidden costs
The Alzheimer's Association reports that last year more than 15 million family members and other unpaid caregivers provided an estimated 17.4 billion hours of care (valued at over $210 billion) to people with AD and other dementias. In addition to the overt costs of lost time and earnings due to caregiving roles [28], family caregivers also bear significant physical, mental, and emotional burdens associated with care provision. Serving as a caregiver and experiencing caregiver strain has been associated with increased mortality risk [7]. Of particular importance to this application, recent research indicates a high prevalence of unmet caregiver needs, social isolation, and depression in caregivers of Veterans with dementia [29].

Dementia caregiving: modifiable caregiver variables and care recipient **[[hospitalization]]** and long-term care placement
In addition to the clinical presentation of dementia care recipients, clinically relevant factors associated with dementia caregiving have a significant impact on dementia outcomes. Caregiver burden has consistently been shown to increase the risk of [[hospitalization]] [30, 31] LTC placement [32, 33] for persons with dementia. Additional evidence indicates that spousal caregiver depression persists after care recipient institutionalization [34] highlighting the need for coping skill-building in caregivers.

Long-term care placement and mortality in dementia
Permanent placement in LTC has significant ramification on prognosis for persons with dementia [35]. For example, one study of mortality in nursing homes discovered that, at admission, while only 1.1% of advanced dementia patients had a life expectancy of < 6 months, 71% died within that time frame [36].

Patient- and Family Centered Dementia Care: Summary
- With little promise for "curative" dementia treatments on the horizon, a growing number of family caregivers are left to cope with the progressive, deleterious effects of dementia on their loved ones.
- Recent research indicates a high prevalence of unmet caregiver needs, social isolation, and depression in caregivers of Veterans with dementia [29].
- Caregiver burden has consistently been shown to increase the risk of costly hospitalization and LTC placement for persons with dementia [30-33].

- Prognosis is poor for persons with advanced dementia after they transition to costly LTC.

2.A.1.E. Unmet Need: Low-cost, Clinically Translatable Interventions for Dementia Caregivers

Interventions applicable to caregivers of all-cause dementia
Numerous intervention strategies [5, 37-40], including one specific to Veterans [23], have aimed to improve dementia caregiver quality of life/mental health and several outcomes among care recipients suffering from dementia. Various aspects of both caregivers and care recipients mediated or moderated the effects of these interventions including caregiver and care recipient demographics (e.g., age, ethnicity), intervention modality, intervention participation burden, and proximity of skill-building to time identified concerns.

The bulk of these interventions were design for (or, specifically investigated in) caregivers of specific dementia subtypes (e.g., AD) and excluded additional dementia subtypes. Meanwhile, though some differences between dementia subtype presentations do exist, there is abundant symptom overlap between AD, VaD, DLB, PDD, and other dementing processes. Interventions designed to educate and build skills in dementia caregivers could be applied to more inclusive samples. ***Interventions designed to improve caregiver outcomes for care recipients of all-cause dementia are needed to enhance clinical translatability. While limitation of caregiver intervention to those caring for someone with a specific type of dementia may increase result specificity, it hampers broad-scale implementation and creates the resource-heavy need to create new, or test old, interventions for caregivers of other dementia subtypes. This need is particularly poignant in the VA population as a large proportion of VA medical care system users (approximately 40%) carry diagnoses of varying, non-specific causes of dementia [15].***

Dementia caregiver interventions with long-term follow-up
Arguably, one of the most successful and advanced dementia caregiver interventions to date has been the Resources for Enhancing Alzheimer's Caregiver Health (REACH-II) study [40]. REACH-II was a comprehensive dementia caregiver intervention study that investigated the impact of provision of information, didactic instruction, role playing, problem solving, skills training, stress management techniques, and telephone support groups on caregiver quality of life. Significant improvements were found in caregiver quality of life, moderated by caregiver ethnicity and relationship status.

As a significant step toward translation of research findings into clinical practice, a version of REACH-II was translated for use in the Veterans Health Administration (REACH-VA) [23] and deployed through home-based primary care teams from 24 facilities in 15 states. The intervention successfully decreased dementia caregiver burden and depression, amongst other caregiver and care recipient outcomes. Unfortunately, due to the nature of the REACH VA project, caregiver outcomes were only able to be assessed at 6-month follow-up.

While these two studies are prime examples of successful caregiver interventions, it is unknown if REACH intervention effects last more than six months. ***Future studies with follow-up periods beyond six months post-intervention will enable more complete assessment of care recipient outcomes including LTC placement and mortality***; events which typically occur more distally [5].

Multicomponent dementia caregiver interventions without high cost burdens
While REACH-II served as large step forward in improving family-centered dementia care, these effects came at high resource costs including 13.5 hours of in-home visits, 1.5 hours of telephone sessions, and five additional telephone support group sessions. The REACH-VA clinical translation project, while moderately effective, will also be costly to implement on a large scale. Official patient care costs for this translational study have not yet been reported. Simply using time as a measure of resource intensity, REACH-VA required: nine hours of individual home visits and 1.5 hours of individual telephone session for a total of 10.5 hours of individual care time per caregiver, on top of five hours of telephone support group sessions and staff travel time for home visits.

Alternatives to resource intensive interventions aiming to enhance Veteran- and family-centered dementia care are needed. Low-cost, pragmatic interventions can fill a void in VA dementia care by providing caregiver rehabilitation to a large number of family members without causing high staff,

resource, and cost burdens. Using recent and growing advances in VA technology such as video telehealth to provide care to more Veterans and families will increase access to care and decrease cost burden to the VA.

2.A.1.F. Advancement of Clinical Practice

We propose to improve Veteran, family, and VHA outcomes through the study of a group-based education and skill-building rehabilitation (ESBR) intervention, targeted specifically to address limitations of prior studies including narrow diagnostic inclusions, proximal follow-ups, and the use of costly, resource-intensive interventions.

The results of this project will determine the efficacy of a low-cost, pragmatic intervention for caregivers of Veterans with all-cause dementia and will be used to build upon prior findings indicating the efficacy of resource-intensive methods to rehabilitate caregivers of Veterans with AD. If this rehabilitative intervention proves successful, it will represent an ***approach to Veteran- and family-centered dementia care that can be pragmatically translated to practice throughout VHA with low staff, resource, and cost burdens.***

2.A.2. Preliminary Studies

2.A.2.a. Description of Career Development Award Team

This team of investigators is very well suited to perform the proposed work because of their expertise and productivity, as well as their established collaboration. The seeds of this proposal were planted in 2010 when the CDA-2 candidate, Dr. Scanlon, joined the VISN 21 Mental Illness Research, Education, and Clinical Center (MIRECC) as a fellow. Our MIRECC's integrated plan aims to enhance functional outcomes in aging Veterans and better match Veterans with the types of treatment to which they best respond. Our MIRECC focuses on the target areas of cognition, mood, and sleep, especially in the Vietnam-era Veteran population. This population appears to be at increased risk of incident dementia [9] and worse physical health [41]. The CDA-2 team members are summarized in the table below.

Investigative Team - Based at VA Palo Alto Health Care System (Buildings 4 & 5), Stanford University (Psychiatry and Behavioral Sciences), or New York University

Name	Service / Division	Role	Areas of Expertise
Blake K. Scanlon, PhD	Psychiatry / MIRECC	CDA-2 candidate	Neurodegenerative disease; neuropsychology
Jerome A. Yesavage, MD	ACOS Mental Health / Director MIRECC	Primary Mentor	RCTs; geriatric psychiatry; neurodegenerative disease; caregiving
Joy L. Taylor, PhD	Psychiatry / MIRECC	Secondary Mentor	Cognitive aging; dementia; Multivariate analysis / SAS
Lisa M. Kinoshita, PhD	Psychology / Neuropsychology	Secondary Mentor	Neuropsychology; cognitive/behavioral symptoms of dementia
[[Mary S. Mittelman, DrPH	**New York University / Psychiatry**	**Consultant**	**Dementia caregiver intervention; video telehealth intervention; caregiver and care receiver outcomes]]**
Betty Wexler, RN, MS, CNS, ACHPN,	Geriatrics and Extended Care / GRECC	Consultant	Dementia care; caregiving; video telehealth
Booil Jo, PhD	Stanford University / Psychiatry and Behavioral Sciences	Consultant	Longitudinal data analysis; clinical trials; missing data analysis; mixed models

2.A.2.b.1. Description of Clinical Experience that Identified the Need for the Current Project
Beginning with Dr. Scanlon's initial dementia care work at VAPAHCS with Dr. Kinoshita in 2008, he noticed that during family feedback sessions for Veterans who were assessed in the VA Memory Clinic many family caregivers presented with significant distress and frustration. Family caregiver burden was apparent and families were eager to learn more about dementia and how they could enhance their ability to provide care while minimizing distress and burden. At that time, there were minimal VA services available to caregivers of Veterans with dementia. Drs. Scanlon and Kinoshita provided referrals to community resources and national organizations to aid caregivers, but given the nature of the high clinical load in the Memory Clinic, continued follow-up with caregivers was not possible.

When Dr. Scanlon began his postdoctoral fellowship at the Sierra-Pacific MIRECC, he was afforded the clinical flexibility to offer caregiver services in conjunction with the VA Palo Alto Dementia Committee. He created and led an education and skill-building seminar for a large group of family caregivers of Veterans with dementia, as part of a Caregiver Support and Educational Series supported by Extended Care Service and the VA Palo Alto Dementia Committee. The exceedingly positive response from caregiver attendees was the initial impetus for this current research proposal. While the seminar and entire educational series was well-received, many caregivers noted that travel to VA Menlo Park, where the series was held, was burdensome.

Subsequent to the success of the Caregiver Support and Educational Series, the need for additional dementia caregiver services was discussed in VA Palo Alto Dementia Committee meetings.

2.A.2.b.2. Project Inception
In collaboration with Drs. Yesavage, Taylor, Kinoshita, and Ms. Wexler, and with support from the MIRECC, VAPAHCS Dementia Committee, VA Palo Alto Memory Clinic, Stanford/VA Aging Clinical Research Center, and the Department of Psychiatry and Behavioral Sciences at Stanford University School of Medicine, Dr. Scanlon began developing the ESBR intervention (see Sections 2.A.3.e.2.- 2.A.3.e.2e.) in May 2012.

2.A.2.c. ESBR Intervention Pilot
A version of ESBR was piloted beginning October 2012 as a "Dementia and Alzheimer's Disease Education Series." The series was offered on the four Fridays of the month of October from noon – 1:00pm in the MIRECC (see Appendix 2 for content samples). Participation was open to Veterans with mild cognitive impairment, Veterans with early stage dementia, adult family members of all Veterans, and was also open to Veterans without dementia. The pilot was designed to have open attendance, in that attendees were invited to come to as many or as few sessions as they were able (knowing the series would recur monthly for the next few months). We did not gather follow-up data on potential study outcomes as the aim of this intervention pilot was to test feasibility and acceptance of the intervention.

During this initial pilot month, 12 participants attended some or all of the sessions. Individual session attendance ranged from one to seven participants. Participants consisted of 11 family caregivers of Veterans with dementia and one Veteran with dementia who attended with his spouse. Attendees were asked to provide anonymous feedback through an evaluation form at the end of each session. Feedback was requested (1 = Strongly agree; 2 = Agree; 3 = Neutral; 4 = Disagree; 5 = Strongly Disagree) on the following topics:

- The seminar was well organized.
- The seminar format was effective.
- The seminar content was informative.
- I learned something useful today about [major topic of the session].
- The seminar met my expectations and learning needs.

Feedback for all four session was positive. Participants responded with "strongly agree" or "agree" to all questions. The evaluation forms also contained a section for comments. The following comments were written:

- "very useful and informative."
- "This is a big help, thank you!"
- "Excellent! Thank you so much!"
- "Big help!"
- "This is great. Thank you for all this information!"

[[Continuing with open attendance, in that attendees were invited to come to as many or as few sessions as they were able (knowing the series would recur monthly for the next few months), we continued to pilot the intervention content on a monthly basis (scaled back during the holiday season: December 2012 – January 2013) through April 2013, with individual session attendance ranging from one to eight participants. Four caregivers who lived near CBOCs phoned Dr. Scanlon to indicate their interest in the Series, but indicated that traveling to the main facility to attend was too difficult for them; video telehealth will enhance access to care for these types of caregivers. Two social workers (both from different CBOCs) also phoned Dr. Scanlon to request the intervention be extended to serve caregivers at their location.

Feedback from participants continued to be positive. Participants responded with "strongly agree" or "agree" to all evaluation questions.

The following additional comments were written:

- **"detailed information was great on the resources, their types of services offered, and easy access to them."**
- **"Very informative regarding interactions with doctors."**
- **"Very informative. Hope that we will find the resources needed for our family"**
- **"Looking forward to the next session"**
- **"May not only help me, but family and volunteer friends."**
- **"Better than Excellent"**
- **"Continue to let me know about similar classes, etc. ******@******.com"]]**

2.A.2.d. Summary of Preliminary Work

Our research team has a long record of accomplishment in the areas of neurodegenerative disease, cognitive decline, dementia, and caregiver health. Based on our preliminary work and pilot of ESBR, we anticipate that study recruitment goals will be met given the need for dementia caregiver education and skill-building both at VA Palo Alto and in surrounding areas served by the VAPAHCS. Caregivers of Veterans with dementia were accepting and appreciative of ESBR. Using video telehealth to deliver ESBR will enable broader access to dementia care services in more rural areas.

2.A.3. Research Design and Methods.

2.A.3.a. Approach

[[To test the efficacy of a group-based education and skill-building rehabilitation (ESBR) intervention in improving dementia caregiver and care recipient outcomes, our proposed trial will consist of 150 family caregivers coping with all-cause dementia. Fifty participants will be randomized to receive in-clinic ESBR (ESBR-i), 50 participants will be randomized to receive video telehealth ESBR (ESBR-v), and 50 participants will be randomized to receive usual care plus supplemental educational materials on dementia (UC).]]

The current proposed project will recruit family caregivers of Veterans with all-cause dementia to participate in a randomized, controlled trial of a group-based ESBR designed to enhance quality of life for caregivers of Veterans with all-cause dementia (Primary Aim 1), reduce caregiver depression (Secondary Aim 2), and **[[increase community tenure]]** and delay permanent long-term care placement and mortality of Veterans with all-cause dementia (Secondary Aim 3). Video telehealth technology (ESBR-v) or in-clinic contact (ESBR-i) will be used to deliver the caregiver intervention to family caregivers. ESBR groups will be compared to participants who receive usual care supplemented with educational materials on dementia (UC). Intervention effects will be examined longitudinally using mixed effects modeling and Cox proportional hazards models at six, 12, and 24 months post-intervention.

The results of this project will determine the efficacy of a low-cost, pragmatic intervention for caregivers of Veterans with all-cause dementia and will be used to build upon prior findings indicating the efficacy of resource-intensive methods to rehabilitate caregivers of Veterans with Alzheimer's disease.

The table below presents a general outline of the activities planned during the award period to ensure timely completion of the research plan, publication/presentation of results, preparation of future studies aiming to enhance Veteran- and family-centered care (i.e., VA Merit Award), and development of a dissemination/implementation plan for a successful intervention.

CDA-2 TIMELINE										
	Year 1		Year 2		Year 3		Year 4		Year 5	
Project Component										
Study preparation	X									
Recruit/screen participants	X	X	X							
Data collection		X	X	X	X	X	X	X	X	
Data analysis			X	X	X	X	X	X	X	
Manuscript preparation				X	X	X	X	X	X	X
Presentation of findings				X	X	X	X	X	X	X
Merit award preparation							X	X	X	X

2.A.3.b. Participants

Inclusion criteria -- Participants must:

- be adults (age ≥18)
- report distress associated with being the primary caregiver for a family member with all-cause dementia [23]
    - **[[reporting at least 2 of the following 6 items at baseline assessment: felt overwhelmed, felt like they often needed to cry, were angry or frustrated, felt they were cut off from family or friends, reported moderate to high levels of general stress, or felt their health had declined]]**
- **[[provide at least one hour of care (supervision or direct assistance) per week over the past 3 months (other sources of caregiving for the Veteran with dementia can also be utilized; e.g., respite, home health aide, other family members, etc.)]]**
- be proficient in spoken and written English
- be capable of providing informed consent

Exclusion criteria -- Potential participants will be screened and excluded for:

- current or lifetime history of any psychiatric disorder with psychotic features
- prominent suicidal or homicidal ideation
- having met DSM-IV criteria for drug or alcohol abuse or dependence (except nicotine) within the past six months
- presence of alcohol intoxication (by breathalyzer) or alcohol withdrawal (by exam) during study recruitment or participation
- diagnosis of probable or possible dementia
- a Telephone Cognitive Screen score of < 20
- participation in another caregiver intervention within the past year
- lack of regular access to a telephone
- illness that would prevent 24 months of study participation
- planned transfer of care receiver to another caregiver or nursing home within 12 months

2.A.3.c.1. Recruitment

We aim to recruit 150 participants who meet inclusion/exclusion criteria for the proposed project (ESBR-i: n = 50; ESBR-v: n = 50; UC: n = 50). Participants will be recruited primarily from the VA Palo Alto Health Care System (VAPAHCS), including major divisions (i.e., Palo Alto, Menlo Park, and Livermore) and community-based outpatient clinics (CBOCs) in the surrounding area (i.e., Capitola, Fremont, Modesto, Monterey, San Jose, Sonora, and Stockton). We anticipate primary referral sources to include: Sierra-Pacific Mental Illness Research Education and Clinical Center (directed by Dr. Yesavage); VAPAHCS Dementia Committee (chaired by Ms. Wexler, consultant); VA Memory Clinic (directed by Dr. Kinoshita); Geriatric Research, Education, and Clinical Center (Ms. Wexler, consultant, serves as Clinical Nurse Specialist at this Center); Stanford/VA Aging

Clinical Research Center (directed by Drs. Yesavage and Taylor); Stanford/VA Alzheimer's Research Center (co-directed by Dr. Yesavage); Psychology and Psychiatry Services (Dr. Yesavage is ACOS for Mental Health); and the War Related Illness and Injury Study Center (Dr. Adamson, see reference letter, serves as Director of Research). Based on clinical experience in the VA Memory Clinic, we also expect primary care clinics to serve as key referral resources. Dr. John Chardos, Associate Chief of Staff for Ambulatory Care at VAPAHCS, has designated resources to our team to aid with recruitment in Patient Aligned Care Team (PACT; i.e., primary care) clinics. Additional participants will be recruited from the Veteran community via word of mouth, an IRB-approved recruitment flyer, and public and private speaking engagements. These additional recruitment avenues have been highly successful in providing subject pools for prior studies from our group. Given our past history of participant recruitment at MIRECC and participant response to a pilot of the intervention (see Section 2.A.2.c.), we expect ample ability to meet recruitment goals from these resources. In the interest of maintaining recruitment of an adequate number of participants, we will supplement our veteran sample with non-Veterans, if necessary.

[[2.A.3.c.2. Retention

We will implement several procedures to enhance recruitment and study retention. First, we will provide remuneration for each study session/assessment ($25). We will also provide telephone and mail reminders of upcoming appointments. We will also be flexible in scheduling appointments to accommodate the participant's schedule. Furthermore, we will make a strong effort to "personalize" each participant's experience. For example, we will send out birthday cards to all participants and will make follow-up telephone calls to express gratitude for participation. We will follow procedures that we have successfully used in our previous research. These methods include continuing our close, collaborative relationships with recruitment sites (Section 2.A.3.c.1.).

We will also use an extensive locator sheet, with participant consent, which contains the names, addresses, and phone numbers of the participant's close friends or professionals who generally know the participant's whereabouts in the event that participants relocate over the follow-up period. When trying to locate the participant, every effort will be made to protect their confidentiality, and no mention will be made of the study. If a participant elects not to return for their follow-up appointment, the study coordinator will attempt to reach them to ascertain the reason for refusal.]]

2.A.3.d. Screening Procedures

Participant screening for eligibility and collection of basic demographic information will mainly occur during telephone interviews conducted by study staff. **[[Should caregivers prefer, face-to-face (in-person) screening/assessment will also be offered.]]**

Interview. A telephone interview will be conducted with caregivers to determine study eligibility. During this interview, study staff will explain the study, its requirements, and answer any questions the potential participant may have. Upon the potential participant's willingness to be screened, study staff will ensure all inclusion criteria are met and screen the potential participant for all exclusionary criteria followed by a brief cognitive screen (see T-CogS below). Basic clinicodemographic data (i.e., age, education, gender, marital status, income, geographic location, care recipient dementia diagnosis, and other relevant demographics) will be obtained during the initial telephone contact and reassessed for any changes at follow-up.

Telephone Cognitive Screen (T-CogS). The T-CogS was originally referred to as the Telephone Mini-Mental State Examination (TMMSE) [42]. The T-CogS is a 26-item, brief mental status examination that was designed to be administered over the telephone, based on the Mini-Mental Status Examination (MMSE) [43]. Scores range from 0-26. Scores on the T-CogS are strongly correlated with MMSE scores ($r = 0.88$, $p < 0.001$) [44]. An exclusion cutoff score of < 20 on the T-CogS was chosen to match a MMSE cutoff of < 23. A telephone cognitive screen was specifically chosen to reduce travel burden for caregivers. **[[Caregivers with a T-CogS score < 20 during screening, or any point during the study, will be offered referrals to the Stanford/VA Alzheimer's Research Center, with full support from Drs. Tinklenberg (Director) and Yesavage (Co-Director and CDA-2 Primary Mentor). The Center provides a comprehensive diagnostic evaluation, including cognitive assessment, by a multidisciplinary clinical research team at no cost to the patient.]]**

The results of all screening assessments will be review with Drs. Scanlon and Yesavage in consultation with Drs. Taylor and Kinoshita. After consensus determination of study eligibility, the Study Coordinator will contact the participant to schedule a Baseline assessment (if eligible), or provide appropriate referral (e.g., VA Caregiver Support Program) and explanation (if not deemed eligible). Both "screen failures" and eligible participants who drop out prior to receiving any intervention will be replaced.

2.A.3.e. Procedures Involving Eligible Participants

2.A.3.e.1. Enrollment, Randomization, and Baseline Measures

Enrollment and Randomization
Once participants pass screening, they will be invited by the Study Coordinator to participate in the study, if willing and able to provide informed consent [F]. At this point, the Data Manager will **[[randomize the participant to one of the three arms: ESBR-i, ESBR-v, or UC.]]** For randomization, a modification of the Efron procedure [45] developed by Dr. Helena Kraemer [46] will be implemented to assure the three groups are comparable at baseline in terms of dementia subtype. Participants who drop out after receiving any intervention will not be replaced, but their data will be used in mixed-effects analyses (as described in Section 2.A.3.e.8a.).

Baseline Assessment
Trained study staff, blind to the participants' ESBR/UC assignment, will administer a baseline assessment including clinicodemographic updates and measures of caregiver burden, depression, self-efficacy, and health-related quality of life, in addition to care recipient functional status (see section 2.A.3.e.6. for a detailed description of these measures). These assessments will mainly occur over the telephone. Our motivation for telephone assessment is to reduce study participation burden for the participants. Packets with assessment aids will be sent to the caregiver in the mail prior to each assessment. **[[Should caregivers prefer, in-person assessments will also be offered.**

Mental Health referrals to Stanford Outpatient Psychiatry Clinics will be offered to all participants who score 16+ on the CES-D at any assessment (see Section 2.A.3.e.6), in addition to participants who endorse symptoms of significant clinical concern, as determined by study staff. All participants are also provided information on accessing the VA Caregiver Support Program and the Veterans Crisis Line.]]

2.A.3.e.2. Education and Skill-Building Rehabilitation Intervention (ESBR)
Our ESBR intervention consists of four, 90-minute sessions over a 4-6 week period. **[[These four sessions are supplemented with booster sessions at 3 and 9 months post-intervention.]]** Each group session (≤ 10 participants) is attended either in-clinic or via video telehealth technology within the VAPAHCS.

As presented in the Summary of Section 2.A.1.D., the two modifiable risk factors for dementia care recipient placement in LTC are caregiver burden and depression.

Caregiver Burden
Our ESBR intervention consists of four, 90-minute sessions **[[(plus booster sessions at 3 and 9 months post-intervention)]]**. Each group (≤ 10 participants) session is attended either in-clinic or via video telehealth technology in place at community-based outpatient clinics, or other VA facilities, throughout VAPAHCS. ESBR is designed to decrease caregiver burden by altering caregiver perceptions of burden through education on dementia from several perspectives including: 1) simplified science that non-professionals care relate to and process; 2) reframing of cognitive, behavioral, and psychiatric symptoms of dementia as manifestations of damage to the brain of their loved one; and 3) understanding access to and being connected with VA, community, and national resources that can assist with reducing burden.

The ESBR intervention is also designed to enhance caregiver self-efficacy and ability to seek appropriate additional education and resources on their own (e.g., through respected national organizations, responsible and reliable internet information). ESBR specifically provides communication skill-building designed to enhance caregiver and care recipient interactions with health care providers. Communication skill training targeting

caregiver ability to seek assistance from family, friends, VA, other providers, and community resources is also a key tenet of the ESBR intervention. ESBR encourages and provides support for caregivers to seek social work referrals VA (e.g., VA Caregiver Support Program, PACT clinic, GRECC clinic) to ensure caregivers, and their care recipients, are supported with all services for which they are eligible (e.g., support groups, respite care, home telehealth, home-based primary care, adult day health care).

Assistance and direction with planning for future care needs (e.g., LTC options, end-of-life care) is integrated into the intervention with the goal of anticipating future needs and reducing future burden.

Self-care and stress awareness/management are large foci of the ESBR intervention and are interwoven into each session. Participants will learn relaxation techniques including guided imagery, deep breathing, and progressive muscle relaxation. Sleep hygiene practices are discussed and solutions that incorporate fragmented caregiving schedules are problem-solved. Rationale for planning pleasant activities is discussed and pleasant event implementation is fostered.

Skill-building exercises specifically tailored to each group and reported caregiving challenges are integrated throughout the intervention (e.g., care recipient wandering, perseveration, agitation).

Caregiver Depression

The ESBR intervention is designed to address symptoms of caregiver depression through multiple modalities including: 1) behavioral activation and pleasurable event scheduling; 2) sleep hygiene skill-building; 3) stress management skill provision and relaxation training; and 4) respite care opportunities.

[[Relaxation Training

The relaxation portion of each session is designed to teach participants different ways to relax themselves to reduce their arousal levels. Relaxation techniques have been found to reduce cortisol levels [47, 48], increase serotonin [49, 50] and lower catecholamine levels [51, 52] in a variety of populations. The psychoneuroendocrine loop evidenced by these studies, and others, provides the rationale for the addition of a relaxation component to the intervention.]]

[[2.A.3.e.2a. ESBR Session 1 – Dementia: what does it mean for me and my family?

Session 1 objectives are to:

- **increase caregiver knowledge about dementia (~20 minutes)**
- **build caregiving skills (tailored to the needs of each small group) (~40 minutes)**
- **emphasize the importance of self-care (stress awareness) (~15 minutes)**
- **introduce the relaxation technique of guided imagery (~15 minutes)**

Session 1 is designed to increase the caregiver's knowledge of dementia, its causes, and how disease impacts the brain to create symptoms of dementia. It simplifies the most common causes of dementia including AD, VaD, mixed dementia, DLB, PDD, and frontotemporal dementia into relatable, understandable information (information is adapted to the needs of each group based on care receiver diagnosis). This session explains common symptoms of dementia syndromes using concrete examples provided both by the leader of the session and caregiver participants. See Appendix 2 for content samples.

Targeted skill-building to address care recipient symptoms (and other stressors) elicited from participants is integrated into the session to maximize training in skills pertinent to the group. Discussion is focused around challenging symptoms of dementia experienced by participants and skills to address these symptoms are interwoven into the discussion. Prepared handouts are given to participants that focus on specific symptoms and behaviors elicited during group discussion (See Appendix 3 for examples).

Caregiver self-care is emphasized through group discussion of the following: stress warning signs, identification of specific stressors, and introduce appropriate use of problem-focused and emotion-focused coping for controllable and uncontrollable aspects of stressors.

The relaxation technique covered in Session 1 is guided imagery (See Appendix 4), including instruction and practice. Guided imagery audio segments are provided for use at home via the modality of caregiver preference (MP3 download, CD, or cassette tape). A variety of scenes are provided so that participants can choose their own scene (e.g., beach, forest, mountain stream, park). Continued home use is encouraged with participants setting self-made goals for implementation.

2.A.3.e.2b. ESBR Session 2 – Dementia: what resources are available to help me and my family?
Session 2 objectives are to:

- **increase caregiver knowledge of dementia resources (~30 minutes)**
- **build caregiving skills (tailored to the needs of each small group) (~30 minutes)**
- **emphasize the importance of self-care (sleep hygiene) (~15 minutes)**
- **introduce the relaxation technique of deep breathing (~15 minutes)**

Session 2 is designed to increase the caregiver's knowledge of resources available within VA, the local community, and on a national level. Participants' prior use of dementia resources is discussed and education is provided regarding additional available resources. Resources that are available 24/7 are highlighted (e.g., Veterans Crisis Line; VA Caregiver Support Line; Alzheimer's Association Helpline). Medical and mental health services are explained (e.g., primary care, psychiatry, psychology, neurology), other consultation services are identified (e.g., physical therapy, driver evaluation, respite care), and specialty centers are introduced (e.g., GRECC, Parkinson's Disease Research, Education, and Clinical Centers, academic medical centers). National organizations with missions dedicated to causes of dementia and caregivers are introduced and their services (e.g., support groups) are discussed. Contact information for all resources is made readily available to participants. Information is adapted to the needs of each group based on care receiver diagnosis. See Appendix 2 for content samples.

Targeted skill-building to address care recipient symptoms (and other stressors) elicited from participants is integrated into the session to maximize training in skills pertinent to the group. Discussion is focused around challenging symptoms of dementia experienced by participants and skills to address these symptoms are interwoven into the discussion. Prepared handouts are given to participants that focus on specific symptoms and behaviors elicited during group discussion (See Appendix 3 for examples).

Self-care activities from the previous session are briefly discussed and continued self-care is emphasized. Sleep hygiene education and discussion is included due to the fluctuations in sleep [53] most likely due to the demands of care provision and sleep problems [54, 55] in caregivers. Exercise commensurate with physician approval is also promoted due its effects on sleep [56] in addition to its general paucity in caregivers [57].

The relaxation technique covered in Session 2 is deep breathing (See Appendix 4), including instruction and practice sessions. Continued home use (instructional materials provided) is encouraged with participants setting self-made goals for implementation.

2.A.3.e.2c. ESBR Session 3 – Dementia: How can I best communicate with my sources of support?
Session 3 objectives are to:

- **build caregiver communication skills (~50 minutes)**
- **emphasize the importance of self-care (planned pleasant activities) (~20 minutes)**
- **introduce the relaxation technique of progressive muscle relaxation (~20 minutes)**

Session 3 is designed to enhance the caregiver's ability to communicate with family, friends, and health care providers (both those of their care recipient and their own). Targeted skill-building geared toward effective communication is the focus of this session. Role play is utilized to give participants practice using effective communication techniques for interactions with family and friends. Skill-building targeted at improving caregiver/health care provider communication is modeled after the National Institute on Aging publication *Talking with your doctor: a guide for older people* (participants are provided with a copy of the publication to supplement the session). Communication tools,

preparing for a healthcare appointment, getting information from healthcare providers, and partnering with healthcare providers to make decisions are addressed in detail. Assistance and direction with planning for future care needs is reviewed and social work referrals are encouraged. See Appendix 2 for content samples.

Self-care activities from the previous sessions are briefly discussed and continued self-care is emphasized. This session will specifically focus on planning pleasurable activities.

The relaxation technique covered in Session 3 is progressive muscle relaxation (See Appendix 4), including instruction and practice sessions. Continued home use (instructional materials provided; audio segments are provided for use at home via the modality of caregiver preference) is encouraged with participants setting self-made goals for implementation.

2.A.3.e.2d. ESBR Session 4 – Dementia: How can I cope with the challenges and stress caused by dementia?

Session 4 objectives are to:

- **build caregiver coping skills (~45 minutes)**
- **solidify the importance of self-care (review) (~15 minutes)**
- **review of learned relaxation techniques (~30 minutes)**

Session 4 is designed to improve the caregiver's coping skills, specifically targeted to address the challenges of being a dementia caregiver. Ways to manage common symptoms of dementia syndromes using concrete examples, provided both by the leader of the session and caregiver participants, are demonstrated and practiced in role play. The intervention leader will aid participants in reframing cognitive, behavioral, and psychiatric symptoms of dementia as manifestations of damage to the brain. See Appendix 2 for content samples.

Targeted skill-building to address care recipient symptoms elicited from participants is integrated into the session to maximize training in skills pertinent to the group. Non-pharmacological interventions for dementia symptom management from previous sessions are reviewed and consolidated (see Appendix 3 for examples).

Self-care activities from the previous sessions (stress awareness, sleep hygiene, and planned pleasant activities) are discussed and importance of continued self-care is solidified.

The relaxation techniques covered in Sessions 1-3 are reviewed and consolidated. Continued use post-intervention is encouraged with participants setting ongoing goals for implementation.

2.A.3.e.2e. ESBR Booster Sessions (3 and 9 months post-intervention)

Booster Session objectives are to:

- **review dementia and dementia resources (~20 minutes)**
- **polish caregiving skills (tailored to the needs of each small group) (~35 minutes)**
- **re-emphasize the importance of self-care (~15 minutes)**
- **highlight learned relaxation techniques (~20 minutes)**

The booster sessions are designed to briefly review dementia knowledge and resources available to dementia patients and their caregivers (i.e., within VA, the local community, and the nation). Caregiving skills, as they pertain to current stressors, are honed in a manner that is tailored to the small group's needs. The importance of continued self-care (specifically stress awareness, sleep hygiene, and planned pleasant activities) is accentuated. Intervention relaxation techniques (i.e., guided imagery, deep breathing, and progressive muscle relaxation) are revisited and continued use is fostered.]]

2.A.3.e.3. Method of Delivering ESBR as In-clinic or Video Telehealth

For the participants randomized to our ESBR intervention (n=50 in-clinic, ESBR-i; n=50 via video telehealth, ESBR-v), all ESBR sessions will be led by Dr. Scanlon in groups of ≤ 10 participants. Dates and times of the group intervention will be arranged to fit participant schedules. In general, Sessions 1-4 (described above) will

be completed within 4-6 weeks. Materials (e.g., print items, audio) for each session will be provided for each participant in each intervention arm.

In-clinic ESBR Delivery: Participants in the ESBR-i (in-clinic) group will meet in person with Dr. Scanlon to receive the ESBR intervention. They will come to the VAPAHCS medical center division (i.e., Palo Alto, Menlo Park or Livermore) or VAPAHCS community-based outpatient clinic (CBOC) in the proximal community (e.g., San Jose, Fremont) most convenient to them.

Video Telehealth ESBR Delivery: Participants in the ESBR-v (video telehealth) group will receive Dr. Scanlon's ESBR intervention via video telehealth technology (i.e., two-way audio and video). Clinics throughout the VAPAHCS are equipped with private rooms containing with audio/visual equipment (video camera, microphone, and display monitor) that will be used to deliver the ESBR intervention with the assistance of the local telehealth coordinator. Participants will attend the ESBR sessions at the medical center division or CBOC most convenient to them.

2.A.3.e.4. Usual Care (plus supplemental educational materials)
Participants randomized to the Usual Care (UC) group will receive supplemental educational materials (e.g., VA Caregiver Support Program, Veterans Crisis Line, National Institute on Aging publications "Caring for a Person with Alzheimer's Disease: Your Easy-to-Use Guide" and "Understanding Memory Loss").

2.A.3.e.5. Follow-up (at 6, 12, and 24 months post-intervention)
Trained study staff, blind to the participants' ESBR/UC assignment, will administer follow-up assessments at 6, 12, and 24 months after the conclusion of the intervention or assignment to usual care. These assessments will mainly occur over the telephone. Our motivation for telephone assessment is to reduce study participation burden for the participants. Packets with assessment aids will be sent to the caregiver in the mail prior to each assessment. **[[Should caregivers prefer, in-person assessments will also be offered.]]** The follow-up assessments include clinicodemographic updates and measures of caregiver cognitive status, burden, depression, self-efficacy, and health-related quality of life, in addition to care recipient functional, placement, and mortality status. (See section 2.A.3.e.6. for a detailed description of these measures).

[[2.A.3.e.6. Study Conclusion
At the conclusion of the study, all participants will be thanked for their participation. Similar to referral procedures implemented throughout the study, at the conclusion of the study all participants will be provided with referrals for services for significant stress, mental health challenges, or cognitive concerns. Mental Health referrals to Stanford Outpatient Psychiatry Clinics will be offered to all participants. Participants with cognitive concerns will be offered referrals to the Stanford/VA Alzheimer's Research Center. The Center provides a comprehensive diagnostic evaluation, including cognitive assessment, by a multidisciplinary clinical research team at no cost.]]

2.A.3.e.6. <u>Study Measures</u>
Study assessments will mainly occur over the telephone *τ*, conducted by the Study Coordinator. Our motivation for telephone assessment is to reduce study participation burden for the participants. Packets with assessment aids will be sent to the caregiver in the mail prior to each assessment. **[[Should caregivers prefer, face-to-face (in-person) *F* assessments will also be offered.]]**

<u>Primary Outcome: Caregiver Burden</u>
Zarit Burden Interview (ZBI) [58] *τ.* The ZBI is a 22-item self-report measure of caregiver burden. Several version of the ZBI have been used successfully as outcome measures in interventions for dementia caregivers [22, 23, 40]. Reliability of the ZBI ranges based on time intervals between tests, but can be assumed to have moderate reliability [59-61]. The ZBI contains questions related to emotional, physical, and social strains that result from caregiving. Scores for each item range from 0 (never) to 4 (nearly always) on questions such as "Do you feel embarrassed by your relative's behavior?." Total scores are calculated by summing all responses and range from 0-88.

Secondary Outcome: Caregiver Depression
Center for Epidemiological Studies-Depression (CES-D) [62] τ. The CES-D is a 20-item, self-report measure of frequency of depressive symptoms over a one week period. The CES-D is frequently used to assess depression in dementia caregivers and has been shown to be sensitive to changes in caregiver depression post intervention [37]. It has been demonstrated to show sufficient psychometric properties [62]. Scores for each item range from 0 (rarely or none of the time) to 3 (most or all of the time), with some items reverse coded. Total scores are calculated by summing all responses and range from 0-60. A cutoff score of > or = 16 is used to indicate depressive symptoms considered to be comparable to prevalent depression.

[[Secondary Outcome: Community tenure τ
Based on caregiver interview and available medical records, community tenure (i.e., amount of time spent living in the community and not hospitalized or placed in a facility) and number of incidents leading to non-community status will be ascertained.]]

Secondary Outcome: Long-term Care Placement τ
Based on caregiver interview, permanent placement of the care recipient in LTC will be ascertained at all follow-up time-points. Date and level of placement will be ascertained.

Secondary Outcome: Mortality τ
Based on caregiver interview, care recipient mortality status will be ascertained at all follow-up time-points. Date and cause of death will be ascertained.

Supplementary Outcomes
Global Deterioration Scale (GDS) [63] τ. The GDS is a semi-structured rating of functional status in degenerative dementia. It has been successfully used in prior studies of dementia caregiver intervention with adequate reliability [5]. Ratings will be assigned for care recipient status based on interview with the caregiver. Ratings will be assigned by Drs. Scanlon, Yesavage, and Kinoshita while remaining blinded to the participant's ESBR/UC assignment. Care recipients with all-cause dementia will have scores ranging from 4 to 7 on this 0-7 point scale.

Revised Scale for Caregiving Self-Efficacy (SCSE) [64] τ. The SCSE is a 15-item scale consisting of three subscales (self-efficacy for: obtaining respite; responding to disruptive patient behaviors; and controlling upsetting thoughts about caregiving). Items are rated from 0-100 to indicate how confident a caregiver is in their ability to do certain activities (e.g., "How confident are you that you can control thinking about unpleasant aspects of taking care of [insert care recipient]?").

Medical Outcomes Study Short Form Health Survey (SF-12) [65] τ. The SF-12 is a brief self-report measure of overall health-related quality of life. Items relate to physical limitations and the extent to which pain and emotional problems interfere with activities over the past 4 weeks. Scores are calculated for Physical and Mental Health Composites and range from 0 to 100. Higher scores indicate better health-related quality of life.

Telephone Cognitive Screen (T-CogS) τ. The T-CogS was originally referred to as the Telephone Mini-Mental State Examination (TMMSE) [42]. The T-CogS is a 26-item, brief mental status examination that was designed to be administered over the telephone, based on the Mini-Mental Status Examination (MMSE) [43]. Scores range from 0-26. Scores on the T-CogS are strongly correlated with MMSE scores ($r = 0.88$, $p < 0.001$) [44]. An exclusion cutoff score of < 20 on the T-CogS was chosen to match a MMSE cutoff of < 23. A telephone cognitive screen was specifically chosen to reduce travel burden for caregivers.

[[Assessment Timeline

An outline assessments and time-points at which they will be ascertained are show below:

Assessment	**Screening**	**Baseline**	**3 month Booster**	**Intervention Period**	**6 month Follow-up**	**9 month Booster**	**12 month Follow-up**	**24 month Follow-up**
Inclusion/Exclusion	X							
T-CogS*	X	X			X		X	X
Demographics	X	X			X		X	X
Primary Outcome								
ZBI*		X			X		X	X
Secondary Outcomes								
CES-D*		X			X		X	X
Community tenure		X			X		X	X
Long-term care placement					X		X	X
Mortality					X		X	X
Supplementary Outcomes								
GDS*		X			X		X	X
SCSE*		X			X		X	X
SF-12*		X			X		X	X

*Full measures available in Appendix 5
T-CogS = Telephone Cognitive Screen; ZBI = Zarit Burden Interview;
CES-D = Center for Epidemiological Studies-Depression; GDS = Global Deterioration Scale; SCSE = Revised Scale for Caregiving Self-Efficacy;
SF-12 = Medical Outcomes Study Short Form Health Survey

]]

2.A.3.e.7. Data Management Plan

The data management plan follows established VISN 21 MIRECC policies. In general, the Study Coordinator collects all data on hard copy, which enables audit of primary materials. All hard copies of data are stored in locked file cabinets in a locked office. Within one week of collection, the data are entered into a SAS database constructed in collaboration with the MIRECC Data Manager, Art Noda, M.S., who works in close collaboration with Dr. Booil Jo, the MIRECC Biostatistician. Data are double-entered to ensure accuracy. The data are entered directly into the SAS dataset through interactive SAS or Microsoft Access programs that provide relevant variable range-checks. Additionally, a SAS error-checking program is run to detect further errors within and across forms, such as incompatible answers or unlikely values. These data are stored in a server behind the VA firewall in a secure VA server room at VA Palo Alto.

All procedures have been audited by the VA Palo Alto Information Security Officer (ISO), Anthony Wallace. The data are backed up daily to separate disk drives in the secure VA server room and also backed up weekly to a separate off-site VA server located in Sacramento, California. All Center personnel have successfully completed VA, Stanford and Health Insurance Portability and Accountability Act (HIPAA) training, and abide by the Center's "Data Security Policy" document.

2.A.3.e.8. Data Analytic Plan

2.A.3.e.8a. Statistical Analyses

We will use mixed effects (growth curve) modeling [66, 67] to fully utilize outcome data repeatedly measured over time (baseline, 6, 12, and 24 month assessments) and to better handle missing outcome information in line with the intention to treat principle. For estimation of mixed effect models, maximum likelihood (ML) estimation from the Mplus program version 7.1 or above will be used [68]. Data points that are missing due to subject attrition or unusable imaging data will be handled assuming that data are missing at random (MAR) [69] conditional on observed information, which is less restrictive than missing completely at random (MCAR) [69] assumed in fixed effects analyses such as ANOVA and regression analysis. In mixed effects analyses, the change in caregiver burden will be modeled as the key dependent variable predicted by the group membership. The results of these longitudinal analyses can be easily converted to group effect at each assessment point to directly respond to our specific hypotheses. In particular, we are interested in the group difference at 12 month assessment, as this time-point extends six months beyond that examined by the REACH II [40] and REACH-VA [23] projects. Our project consultant, Dr. Booil Jo, is an expert in design and analysis of clinical trials, mixed effects modeling, and missing data approaches.

[[Primary Aim: Specific Aim 1
Hypothesis 1. Mixed effects modeling will be used to test the hypothesis that participants randomized to the intervention groups (ESBR-i and ESBR-v) will show decreased caregiver burden compared to UC over time. In mixed effects analyses, the change in caregiver burden (ZBI total score) will be modeled as the key dependent variable predicted by the group membership (ESBR-i and ESBR-v vs. UC).]]

Secondary Aim: Specific Aim 2
Hypothesis 2. Mixed effects modeling will be used to test the hypothesis that participants randomized to the intervention groups (ESBR-i and ESBR-v) will show decreased prevalence of clinical depression compared to UC over time. In mixed effects analyses, the change in prevalence of depression (CES-D score ≥ 16) will be modeled as the key dependent variable predicted by the group membership (ESBR-i and ESBR-v vs. UC).

[[Secondary Aim: Specific Aim 3
Hypothesis 3a. Mixed effects modeling will be used to test the hypothesis that participants randomized to the intervention groups (ESBR-i and ESBR-v) will show longer community tenure compared to UC over time. In mixed effects analyses, days of community tenure will be modeled as the key dependent variable predicted by the group membership (ESBR-i and ESBR-v vs. UC). The model will be adjusted for effects of care recipient gender, income, and disease stage (Global Deterioration Scale score). The effects of other potential covariates including caregiver and patient age, caregiver gender, dementia subtype, and caregiver burden and depression will also be explored.

Hypothesis 3b. Cox proportional hazards regression modelling [70] will be used to test the hypothesis that Veterans with family caregivers randomized to the intervention groups (ESBR-i and ESBR-v) will transition to LTC at a slower rate compared to UC. In proportional hazards regression analyses, time to permanent LTC placement (total time from caregiver randomization to permanent LTC placement of the care receiver) will be modelled as the key dependent variable predicted by the group membership (ESBR-i and ESBR-v vs. UC). The model will be adjusted for effects of care recipient gender, income, and disease stage (Global Deterioration Scale score). The effects of other potential covariates including caregiver and patient age, caregiver gender, dementia subtype, and caregiver burden and depression will also be explored.

Hypothesis 3c. Cox proportional hazards regression modelling [70] will be used to test the hypothesis that Veterans with family caregivers randomized to the intervention groups (ESBR-i and ESBR-v) will survive longer compared to UC. In proportional hazards regression analyses, time to death (total time from caregiver randomization to death of the care receiver) will be modelled as the key dependent variable predicted by the group membership (ESBR-i and ESBR-v vs. UC). The model will be adjusted for effects of care recipient gender, income, and disease stage (Global Deterioration Scale score). The effects of other potential covariates including caregiver and patient age, caregiver gender, dementia subtype, and caregiver burden and depression will also be explored.

Exploratory Aims:
Hypothesis 4. Mixed effects modeling will be used to examine whether participants who receive the intervention via video telehealth (ESBR-v) will show similar levels of caregiver burden compared to those that receive the intervention in-person (ESBR-i) over time. For this exploratory aim, we will focus on monitoring the clinical significance (effect size). We expect the effect size will be quite small (Cohen's *d* of 0.2 or less). In mixed effects analyses, the change in caregiver burden (ZBI total score) will be modeled as the key dependent variable predicted by the group membership (ESBR-i vs. ESBR-v).

Mixed effects modeling will be used to examine whether participants who receive the intervention via video telehealth (ESBR-v) will show similar levels of caregiver depression compared to those that receive the intervention in-person (ESBR-i) over time. For this exploratory aim, we will focus on monitoring the clinical significance (effect size). We expect the effect size will be quite small (Cohen's *d* of 0.2 or less). In mixed effects analyses, the change in caregiver depression (CES-D total score) will be modeled as the key dependent variable predicted by the group membership (ESBR-i vs. ESBR-v).

Mixed effects modeling will be used to test the hypothesis that participants who receive the intervention via video telehealth (ESBR-v) will have similar community tenure compared to those that receive the intervention in-person (ESBR-i) over time. For this exploratory aim, we will focus on monitoring the clinical significance (effect size). We expect the effect size will be quite small (Cohen's *d* of 0.2 or less). In mixed effects analyses, community tenure (time spent living in the community) will be modeled as the key dependent variable predicted by the group membership (ESBR-i vs. ESBR-v).

Cox proportional hazard modeling will be used to test the hypothesis that Veterans with caregivers who receive the intervention via video telehealth (ESBR-v) will show similar rates of LTC placement and survival compared to those that receive the intervention in-person (ESBR-i) over time. In Cox proportional hazard models, LTC placement or survival will be modeled as the key dependent variable predicted by the group membership (ESBR-i vs. ESBR-v).

Hypothesis 5. Clinico-demographic characteristics (e.g., caregiver age, dementia type/severity, socioeconomic status) will be evaluated as moderators of the effects of the ESBR intervention (i.e., Aims 1, 2, and 3). For this investigation, the MacArthur framework for moderator analysis [71] will be embedded in mixed effects and Cox proportional hazards models. The moderator effect will be tested in line with the eligibility and analytical criteria described in Kraemer et al. [71].]]

2.A.3.e.8b. Power Estimation
We estimated power based on the proposed mixed effects analyses considering the repeatedly measured outcomes. Based on these analyses, we converted the growth model parameter estimated to group difference in primary outcome at 12 month. Considering potentially nonlinear development of our outcomes, we allowed for nonlinear trend over time (specifically, we used a piecewise growth model). In our power estimation for primary hypothesis 1, over the 4 assessments, we assumed the attrition rate of 10% (6 month), 15% (12 month), and 20% (24 month). We assumed the reliability of the Zarit Burden Interview to be 0.7 based on prior studies demonstrating a range of intra-class correlation coefficients that vary based on time intervals between tests [59-61]. Prior studies of caregiver interventions, like many psychosocial interventions, have reported small to medium effect sizes. One such study specifically aimed to improve outcomes of caregivers of Veterans with all-cause dementia of the Alzheimer's type [23] and demonstrated effect sizes (Cohen's *d*) on caregiver burden and depression ranging from 0.26-0.33. Based on this study, we expect an effect size of *d*=0.3 on our primary outcome of caregiver burden, as measured by the Zarit Burden Interview [72], and designed our study to be powered accordingly assuming that mixed effects modeling will be used as the analysis method. Our primary hypothesis (Hypothesis 1) is that those in the intervention group (n=50 ESBR-i and n=50 ESBR-v) will show steeper decline in burden compared to the usual care (n=50 control) group. Under this scenario, the estimated power to detect the difference between the intervention (ESBR-i + ESBR-v) and the control group in terms of care burden is 0.83 (d=0.3, α=0.05, two-tailed) at the 12-month follow-up. For the secondary analysis, we will monitor both clinical (effect size) and statistical (p-value) significance, with more emphasis on clinical significance, which will inform future trials.

2.A.3.e.9. Implementation Plan

The table below presents a general outline of the activities planned during the award period to ensure timely completion of the research plan, publication/presentation of results, preparation of future studies aiming to enhance Veteran- and family-centered care (i.e., VA Merit Award), and development of a dissemination plan for a successful intervention.

CDA-2 TIMELINE										
	Year 1		Year 2		Year 3		Year 4		Year 5	
Project Component										
Study preparation	X									
Recruit/screen participants	X	X	X							
Data collection		X	X	X	X	X	X	X	X	
Data analysis			X	X	X	X	X	X	X	
Manuscript preparation				X	X	X	X	X	X	X
Presentation of findings				X	X	X	X	X	X	X
Merit award preparation							X	X	X	X

2.A.3.e.10. Dissemination Plan

If this form of ESBR were shown to be useful in improving outcomes in dementia caregivers or Veterans with all-cause dementia, it could easily be assimilated into our national roll-out program at the VISN 21 MIRECC. The Evidence-Based Therapy (EBT) roll-out started with cognitive-behavioral therapy for depression (CBT-D), then progressed to include CBT for insomnia (CBT-I). The program has now trained over 1,500 VA therapists nation-wide. The program staff consists of a national coordinator based in VACO, a coordinator based at VAPAHCS, and several staff at VAPAHCS who deal with screening mental health staff applicants for their eligibility to participate, scheduling courses, making sure all course materials are distributed, attending to the administrative arrangements for training sessions and payment of consultants. In general, a 3-day course is given for about 40 VA therapists from 3-4 VISNs in a convenient location. There they meet their “consultants” who will follow the trainee’s treatment of two training patients over a 3-4 month period. Taped recordings of trainees’ therapy sessions are used by consultants to follow trainee proficiency and patient outcomes obtained.

If the results of the proposed study are positive, group trainings (similar to those for CBT-D and CBT-I) of clinicians could be initiated using the same administrative mechanisms, 3-day course model, expert consultant model, and tape-recorded verifications. Thus, if ESBR were to prove useful, we could add this as another intervention disseminated through the EBT program.

2.A.3.e.11. Study Limitations and Potential Problems

Sample Size

One limitation of the current proposal is the relatively small sample size (ESBR-i: n = 50; ESBR-v: n = 50; UC: n = 50). Nonetheless, our power analyses (see Section 2.A.3.e.8b.) indicate we will have ample power to detect intervention effects on the primary outcome of caregiver burden at 12-month follow-up.

Control Condition

Another limitation of the current proposal is our control condition. While we would like to have offered the ESBR intervention (or something more substantial than printed educational materials and resource contact information) to all participants at some time during the study period, this would have made our aims of comparing ESBR to standard VA dementia care unobtainable.

Recruitment

One potential problem may be difficulty recruiting sufficient numbers of family caregivers of Veterans with all-cause dementia. As discussed in Section 2.A.3.c., a strength of our recruitment capability is the integrated network of recruitment support available in clinics and centers staffed/administrated by Key Personnel. Given our past history of participant recruitment/retention at MIRECC and participant response to a pilot of the intervention (see Section 2.A.2.c.), we expect ample ability to meet recruitment/retention goals from these resources. However, we will supplement our veteran sample with non-Veterans, recruited from the San Francisco Bay Area, including our academic affiliate, Stanford University School of Medicine, if necessary.

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