# Protocol

## 1. Project Title:
Nonpharmacologic Management of Challenging Behaviors in Veterans with Dementia

## 2. Investigator(s):
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## 3. Abstract:
Over 5 million Americans have Alzheimer's disease or related dementias, a progressive and irreversible neurodegenerative syndrome, with prevalence rates expected to reach close to 16 million individuals by 2050. As populations age worldwide, dementia will increase dramatically and reach epidemic proportions. Among Veterans 65 and older, prevalence rates are similar to the population at-large with 7.3% having dementia across all races, except for African-Americans for whom the rate is 50% higher. Prevalence rates across VISNs range from 5.8 to 9.4% with dementia associated with substantially higher Inpatient and outpatient service utilization relative to other VA patients.

A hallmark of dementia is neuropsychiatric symptoms (NPS) which include agitation, apathy, depression, mood lability, and aggressiveness. NPS are associated with increased health care costs, and reduced quality of life and daily functioning, heightened family caregiver burden, and nursing home placement. Standard care typically involves pharmacologic agents, but these are at best modestly effective, carry serious risks including mortality, and do not address behavioral symptoms families themselves consider most distressful or that prompt nursing home placement. Given the devastating effects of the disease and that a cure is not imminent, medical organizations nationally and internationally including the VA have urged for the development and testing of new approaches to manage NPS.

This proposed study addresses this call by testing the efficacy of a transformative patient-centric intervention designed to reduce the burden of NPS in Veterans with dementia who live at home with family caregivers. The innovative intervention, the Tailored Activity Program (TAP-VA), involves 8 sessions over 4 months in Veterans' homes. An occupational therapist conducts a systematic assessment to identify a Veteran's preserved capabilities and deficit areas, and previous roles, habits and interests from which to develop and introduce activities tailored to the Veteran's profile. Family caregivers are then trained to incorporate tailored activities into daily care routines. The intervention was pilot tested in an NIMH funded study with 60 community-living individuals with dementia. Findings from this pilot showed statistically significant and clinically meaningful reductions in NPS, specifically agitation and less time being on "duty" by family caregivers. Results of this pilot phase support moving forward with a full-scale Phase III efficacy trial. We plan to test TAP-VA in a randomized two-group parallel design in which 160 racially and ethnically diverse Veterans with dementia and their family caregivers (dyads) will be randomly assigned to receive TAP-VA or an attention control group. All dyads will be evaluated at baseline and 4-months (main trial endpoint), and then reassessed at 8-months to evaluate long-term treatment effects (baseline to 8 months), including continued activity use, caregiver well-being, and costs.

**4. Background:**
Over 5 million Americans have Alzheimer's disease or related dementias, a progressive and irreversible neurodegenerative syndrome, with prevalence rates expected to reach close to 16 million individuals by 2050. As populations age worldwide, dementia will increase dramatically and reach epidemic proportions. Among Veterans 65 and older, prevalence rates are similar to the population at-large with 7.3% having dementia across all races, except for African-Americans for whom the rate is 50% higher. Prevalence rates across VISNs range from 5.8 to 9.4% with dementia associated with substantially higher Inpatient and outpatient service utilization relative to other VA patients.

A hallmark of dementia is neuropsychiatric symptoms (NPS) which include agitation, apathy, depression, mood lability, and aggressiveness. NPS are associated with increased health care costs, and reduced quality of life and daily functioning, heightened family caregiver burden, and nursing home placement.[4,5] Standard care typically involves pharmacologic agents, but these are at best modestly effective, carry serious risks including mortality, and do not address behavioral symptoms families themselves consider most distressful or that prompt nursing home placement. Given the devastating effects of the disease and that a cure is not imminent, medical organizations nationally and internationally including the VA have urged for the development and testing of new approaches to manage NPS.

**5. Specific Aims:**
**Our primary study aim** concerns the Veteran with dementia and tests the immediate effect of TAP-VA at 4-months on NPS. Our *hypothesis* is that Veterans with dementia who receive TAP-VA will manifest lower total scores on the Neuropsychiatric Inventory (NPI), which assesses frequency and severity of 12 common neuropsychiatric symptoms, compared to Veterans assigned to an attention control group. We also propose **four secondary aims**. These are to: 1) Test the long-term effects of TAP-VA at 8-months on quality of life and neuropsychiatric behaviors of Veterans with dementia. *Hypothesis:* Veterans receiving TAP-VA will manifest higher quality of life and lower total NPI scores over time (baseline to 8-months) in comparison to Veterans in the attention control group; 2) Test the immediate effects of TAP-VA at 4-months and long-term effects at 8-months on caregiver burden, skill acquisition, efficacy using activities, and time spent providing care. *Hypotheses*: Caregivers receiving TAP-VA will report reduced burden, enhanced skills and efficacy using activities, and less time providing care compared to the control group at 4 and 8-months; 3) Examine whether caregivers receiving TAP-VA are using activities at 8 months; and 4) Examine whether TAP-VA results in reduced VHA health care use and costs for Veterans with dementia and their caregivers. Results from these secondary aims will provide further evidence of treatment efficacy, identify whether booster sessions are necessary, and inform dissemination efforts and translation of TAP-VA system-wide.

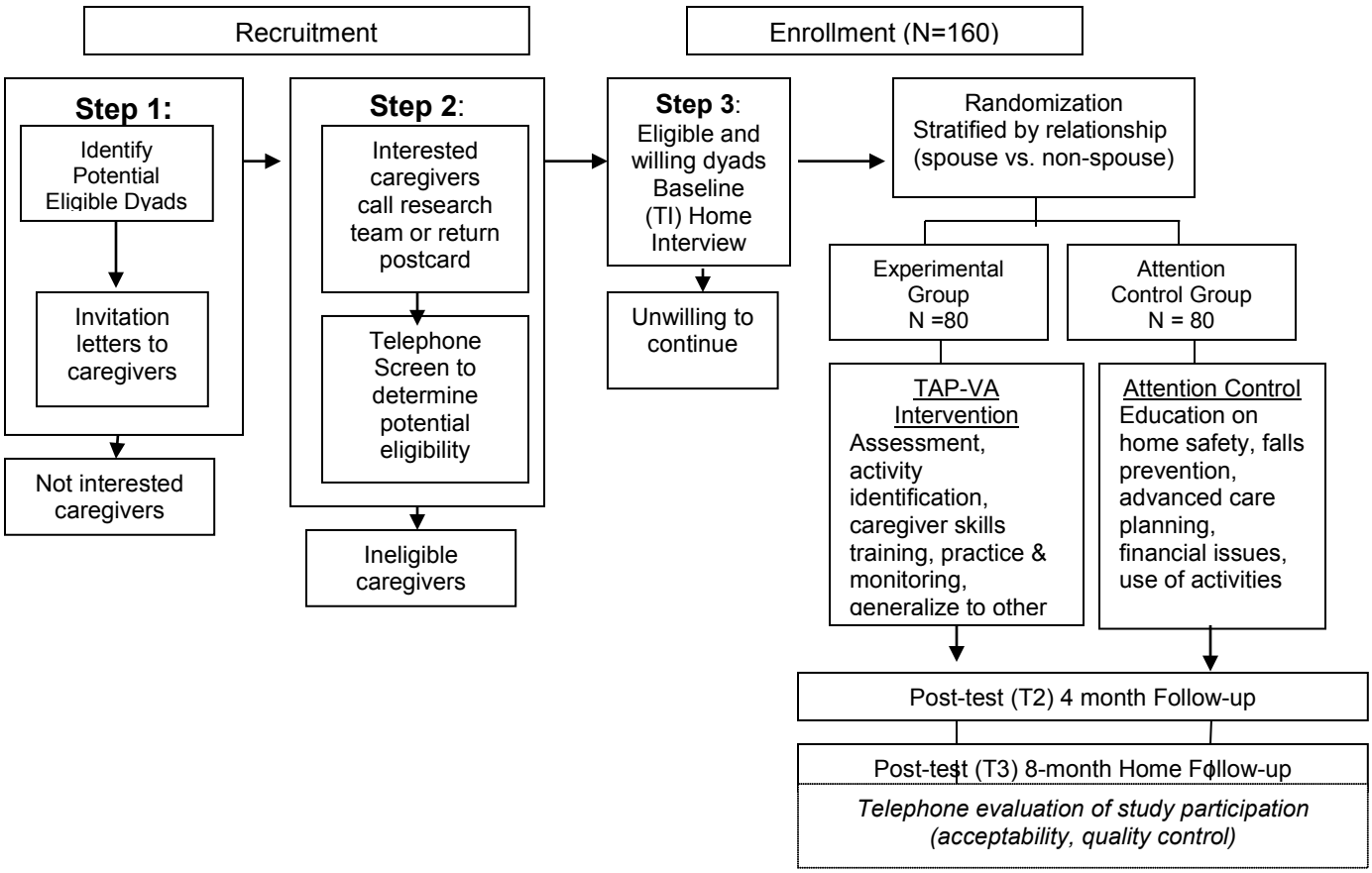
**Our long-term objective**, if proven efficacious, is to integrate TAP-VA into standard care practices within the VHA system as the first treatment choice to address NPS in Veterans with dementia living at home. This would transform the current paradigm of dementia care which relies on pharmacologic management.

**6. Research Plan:**
**Overview:** This study will test whether a targeted Veteran-centric intervention reduces NPS (NPI total score of frequency by severity) and, secondarily, whether it reduces burden by reducing time spent in care, and enhancing skill in family caregivers. We also seek to evaluate its cost savings in terms of health care utilization rates of both Veterans and family caregivers using a cost diary. We will enroll 160 Veterans with dementia whose caregivers report one or more NPS and are living at

home. Veterans with diagnosis codes 290.0, 290.2, 290.3, 331.2 (senile dementias), 290.4 (vascular dementia), 294.8 (dementia not otherwise specified), 331.0 (Alzheimer's disease), 331.1 (frontotemporal dementia), and 331.82 (Lewy body dementia) will be considered to have dementia diagnoses and eligible for study participation. Veterans with these diagnostic codes will be recruited from NF/SG VHS Geriatric Research, Education & Clinical Center (GRECC) and Geriatrics and Extended Care Service (GECS) outpatient services, including the Home Based Patient Care (HBPC) and Homemaker Home Health Aide program.

Eligible dyads will receive a baseline home interview (T1), and then be randomized to experimental (TAP-VA) or attention-control group conditions. Experimental dyads will receive up to 8 contacts with an occupational therapist (OT) interventionist over 4-months whereas caregivers in the attention control group will receive bi-monthly telephone contact (up to 8 contacts) in which education is provided and tailored to address unmet expressed informational needs of caregivers. Information concerning the value of activity and a list of activity ideas will also be provided. All dyads will be retested at 4-months from baseline (T2), main study endpoint, and 8-months from baseline (T3) at home to evaluate long-term effects. Interviewers will be masked to treatment assignment throughout the study (Figure 1). Each study component is described in more detail below.

**FIGURE 1**
**FLOW CHART OF STUDY DESIGN**



**Eligibility Criteria:** *Inclusion Criteria for Veterans with dementia* include: 1) English speaking; 2) diagnosed with dementia as above; 3) able to participate in at least two activities of daily living (ADLs - bathing, dressing, grooming, toileting, transferring from bed to chair); and 4) not currently participating in any other dementia-related intervention. If the Veteran with dementia is on any of four classes of psychotropic medications (antidepressant, benzodiazepines, antipsychotic, or anti-convulsant) or an anti-dementia medication (memantine or a cholinesterase inhibitor), we will require that he/she have been on a stable dose for 60 days prior to enrollment to minimize possible confounding effects of concomitant medications (the typical time frame used in clinical trials) and 5) 23 or less on the MMSE. *Caregivers* of Veterans must be: 1) English speaking, 2) self-identify as the primary member of the family caring (hands-on or supervision) for the Veteran and 21 years of age or older (male or female), Legal Authorized Representative (LAR), 3) living with the Veteran, 4) accessible by telephone to schedule interview, intervention sessions and follow-up interviews, 5) planning to live in area for 8 months (to reduce loss to follow-up), 6) indicate willingness to learn activity use, 7) report one or more NPS in the Veteran in the past month; and 8) not currently participating in any other caregiver-related intervention. Finally, we will require that caregivers taking a psychotropic medication (antidepressant, benzodiazepines, antipsychotic, or anti-convulsant) at time of telephone screen be on a stable dose of the medication for 60 days prior to enrollment. In the event more than one caregiver wishes to be involved in the study, the study team will obtain informed consent from each caregiver and will work with them as a caregiving unit.

**Recruitment Procedures:** Our recruitment and enrollment procedures primarily target the caregivers of VA patients in geriatric service programs that are directed by Dr. Nannette Hoffman, co-investigator on this project. Services include Home Based Patient Care (HBPC) and the Homemaker Home Health Aide program. Our recruitment strategy is based on over 20 years experience with and success in enrolling families managing dementia in clinical trials. It will involve mailings to families identified through the VA services. The mailing will include a letter from the medical director of the service (Dr. Hoffman) explaining study procedures and inviting study participation and it will also include a descriptive flyer about the study. Caregivers will be directed to either contact the research team by telephone or to return a post card in a self-addressed and stamped envelope that indicates an interest in being contacted by the study team to learn about the study. Caregivers contacting the research team either way will be explained study procedures; and if interested, they will complete a brief telephone screen to determine eligibility. For caregivers eligible and willing to participate, a baseline interview will be conducted by a trained interviewer within 2 weeks of determination of eligibility, and prior to randomization to study group. At the time of the interview, the Mini-mental Status Examination (MMSE) will be administered to the Veteran. For Veterans with MMSE scores>23, a follow-up telephone call with their physician to confirm a dementia diagnosis will be obtained. Dyads eligible and willing following the baseline interview will be randomized (see data analytic considerations) to treatment or attention control. Caregivers who do not respond to the initial mailing will receive a second, duplicate mailing several months after the first mailing. Subsequent recruitment letters, including the flyer, will be sent to the following facilities in the NF/SGVHS study area:

1. Altrusa House, Gainesville
2. All Saints Daycare Center, Jacksonville

3. The Sunshine Center, St. Augustine
4. Blessed Trinity Adult Elder Care Home, Ocala
5. Tallahassee Memorial Rehabilitation Center, Tallahassee
6. Hope Adult Day Care, Inc., Jacksonville Beach
7. VA Social Work Service, NF/SGVHS
8. VA Mental Health Clinic, NF/SGVHS
9. Al'z Place, Gainesville
10. Brooks Rehabilitation Hospital, Jacksonville
11. Park of the Palms, Keystone Heights

These letters will request nursing staff and social workers to ask Veterans or their caregivers who might benefit from or be interested in this study to call the study team at the toll free number listed on the flyer.

**Subject Accrual, Replacement Rule, Subject Attrition and Retention**: *Subject Accrual*: Recruitment procedures will be implemented in month 6 of project year 01 and continue to month 3 of year 04 for a total of 33 months with close to 5 dyads enrolled per month. Based on our previous caregiver studies, the typical response rate from a targeted mailing to families is 10%; of responders, typically over 80% are eligible to participate in our studies that have similar enrollment criteria as that proposed for this trial. Thus, as shown in Table 1, even with one mailing from the two primary VA recruitment sources, we would be able to obtain our target sample size of 160 even when a conservative estimate of a 60% eligibility rate is applied. The numbers in the table were based on projections developed from actual new patients in each NF/SG VHS service over the past two years, with data provided by the GRECC. Thus, we do not anticipate difficulties obtaining the desired sample size dyads.

**Techniques:** The intervention is designed to tap into spared or residual abilities and provide an environment supportive of these abilities. The OTs select activities that build on preserved capabilities but do not tax areas of cognition that are most impaired (e.g., memory, new learning). In designing activities, OTs simplify activity and structure it to focus on single rather than multiple or complex tasks, thereby minimizing errors. The activity environment is set up to provide auditory or tactile cues to facilitate recall and guide initiation and sequencing. By grading activities to match the Veteran's capabilities, the OT minimizes demand that may heighten stress (e.g., high functioning individuals will be introduced to more goal-directed and multi-step activities, whereas lower functioning individuals will be introduced to activities that are based on repetitive motion (e.g., washing windows, folding towels) and integrate multi-sensory stimulation (e.g., soft music, objects pleasant to touch). Whereas previous activity interventions emphasized new learning, our approach does not, although it may entail some procedural learning if appropriate.

TAP provides caregivers with the requisite knowledge and skills to use activities. Caregivers are instructed in specific skills such as ways to simplify activities, the environment and their communication, and how to help the Veteran initiate and follow a sequence. The overall goal is to provide predictability, familiarity and structure in the daily life of Veteran and caregiver and establish a level of environmental stimulation appropriate to Veteran abilities. Three clinical elements are used to enhance caregiver receipt and enactment of intervention strategies: 1) the OT engages caregivers (vs being prescriptive), 2) the caregiver is provided repeated opportunities for practice and modification of techniques, and 3) the OT uses validation and actively demonstrates techniques within the context of their use. Caregivers are provided concrete knowledge as to what the Veteran is capable of doing (e.g., can grasp object such as a plate) and his/her specific limitations (e.g., needs verbal cueing to place dish in cabinet). With this knowledge, interventionists can help caregivers cognitively restructure their expectations, behavioral goals and reactions to the Veteran.

During treatment sessions, caregivers are taught to: 1) recognize capabilities and deficits, 2) translate capabilities into objective activity goals, and 3) generate specific steps to set up activities and help caregivers initiate/sequence.

**7. Possible Discomforts and Risks:**

This study involves the delivery of an online caregiving training and telephone support for CGs of elderly Veterans with dementia.

If a research staff member encounters a medical emergency over the telephone, we identify whether another individual is in the home, the person is put on hold and we call 911 immediately. If the situation occurs within the home, then the staff person calls 911 immediately, and stays with participant until help arrives. The PI is informed within 24 hours of the event. PI then contacts individual as a follow-up within two days. Research staff member completes alert form and provides to PI.

If a research staff person encounters a situation in which the person (Veteran or CG) threatens to hurt self immediately, then staff person stays with person (on phone or in home), calls 911 and stays with individual until help arrives. If the person (Veteran or caregiver) is determined to not be an immediate threat to self, then the person is actively encouraged to contact physician or contact is made for the person if they allow that. An agreement is obtained with the person that they will not hurt themselves. The research staff person also informs the person that a member of the research team will be contacting him/her shortly to follow-up. Immediately at the conclusion of the interview, the PI is notified of the situation. The PI contacts the person to obtain further information and encourages immediate action be taken (e.g., physician referral). PI consults about case within 24 hours of event and consultation with the team's geriatrician will occur to review next steps. Research staff person involved fills out Alert form and provides to PI.

If caregiver scores in the high depressed range on the CES-D (>15 on 10-item version) in an interview, the PI contacts the caregiver to inform them of their elevated score and that they should follow-up with their physician. Consultation by the team's geriatrician will be obtained if necessary. Research staff person involved completes Alert form and provides to PI.

Evidence of physical abuse is as follows:

1) Caregiver or Veteran with dementia states to research staff that abuse occurs;
2) or research staff observes physical evidence (black eye, black and blue marks on arms/legs)

Research staff member informs participant that a senior member of the research team will contact him/her later that day. Staff member informs PI immediately upon completion of interview or intervention session. PI (or designate) contacts participant to obtain further information. Participant is strongly encouraged to call his/her physician and/or Adult Protective Services (phone number will be provided). Based on the situation, the PI may notify Adult Protective Services and consult with team's geriatrician. PI (or designate) completes Alert form.

The DSMB will be responsible for reviewing the safety of study participants during the conduct of this study and provide recommendations to the research team on specific aspects of the research protocol as it pertains to safety, potential study alerts and adverse events. Specific responsibilities

of the DSMB will be to: a) provide an independent periodic review of recruitment and enrollment progress; b) review adverse events (AEs) including serious events and offer recommendations regarding the trial based on such observed events; c) serve in a consultative capacity to the research team regarding study procedures to address ethical dilemmas (e.g., reporting of abuse), safety of subjects in the trial, and appropriateness of all study procedures.

*Composition of the DSMB:* The DSMB will be an independent multi-disciplinary group consisting of biostatistical and research and clinical experts who collectively have experience in the treatment of depression, dementia and the environment, and the conduct and monitoring of randomized clinical trials that are community/home-based and nonpharmacologic. The 5-member board has no apparent conflict of interest with the study including financial, scientific or regulatory in nature. DSMB members are not employed by VHS and are not paid consultants on any related study of the principal investigator or that conducted by other members of the research team. DSMB members will be responsible for advising the principal investigator of any changes in their relationship and/or financial interests that occur during the course of the trial. The DSMB and PI will be responsible for deciding whether these changes create a conflict of interest. Any DSMB member who develops a conflict of interest during the course of the trial will be asked to resign from the DSMB and another person with similar areas of expertise will be sought. Otherwise, DSMB membership is to be for the duration of the trial.

*DSMB Meetings, Documentation:* The DSMB will have one face-to-face meeting prior to entering into the field for the trial and one tele-conference call each subsequent year unless the DSMB decides otherwise at its first organizational meeting. More frequent meetings or teleconferences may be held to review serious adverse events from the trial at the discretion of the DSMB. At the initial meeting in year 01 (anticipated to occur in month 3 prior to entry into the field), the DSMB will review all study procedures including data collection forms, intervention protocol and oversight plan. At this meeting, the DSMB will agree on whether there should be interim analyses of efficacy endpoints and, if so, the stopping rules and interim analysis plan that avoids potentially biasing the investigative team. Modifications to protocols based on the DSMB review will be made prior to entering the field. At subsequent conference calls, the DSMB will review the progress of the study (accrual rate, protocol deviations and interim study analyses if recommended) and make recommendations. A representative of the research team will keep minutes of these meetings. A copy of the minutes approved by the DSMB will be shared with the IRB -01. The minutes will include recommendations of the DSMB. Meetings of the DSMB will be open unless the DSMB requests otherwise. A closed meeting of the DSMB may be requested if it is deemed necessary to review efficacy data. The DSMB chair or his/her designate will take meeting notes of closed sessions.

*Provision of Data for DSMB Review*: Interim Analyses: We have elected to not consider interim analyses in this study due to the extended time for recruitment and the low likelihood of a sufficiently large effect that would make it possible to stop early. However, we will revisit this decision with the DSMB at its first organizational meeting.

**8. Possible Benefits:**

Participants may learn about dementia and may be able to apply that knowledge in their daily CG activities. A better understanding of the responsibilities and varied activities of CGs of elderly Veterans with dementia will further research on the Veteran CG role: responsibilities, benefits and value.

**9. Conflict of Interest:**

There is no conflict of interest for the investigators.