STAR Caregivers – Virtual Training and Follow-up

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SIGNATURE PAGE

Signatures constituting approval of this protocol and the attachments and providing necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and guidelines.

Signatories for this protocol are:

Robert Penfold, PhD – Principal Investigator

Senior Investigator

Kaiser Permanente Washington Health Research Institute

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LIST OF ABBREVIATIONS

ABCs	Antecedent, Behavior, Consequence
ADRD	Alzheimer's Disease and Related Dementias
BPSD	Behavioral and Psychological Symptoms of Dementia
CG	Caregiver
CMS	Caregiver Master Scale
DPOA	Durable Power of Attorney
DSRS	Dementia Severity Rating Scale
EHR	Electronic Health Record
FAQ	Functional Activities Questionnaire
GAD	7 item General Anxiety Disorder scale
GEE	Generalized Estimating Equations
HIPAA	Health Insurance Portability and Accountability Act
HITECH	Health Information Technology for Economic and Clinical Health Act
ICD-10	International Classification of Diseases, 10th Revision
IRB	Institutional Review Board
KPWA	Kaiser Permanente Washington
KPWHRI	Kaiser Permanente Washington Health Research Institute
LAR	Legally Authorized Representative
MHRN	Mental Health Research Network
NACDA	National Archive of Computerized Data on Aging
NIA	National Institute on Aging
PHQ8	8-item Patient Health Questionnaire
PLWD	Person Living With Dementia
REDCap	Research Electronic Data Capture [software]
RMPBC	Revised Memory and Problem Behavior Checklist
SFT	Secure File Transfer
STAR-VTF	Staff Training in Assisted living Residences – Virtual Training and Follow-up

PROTOCOL SUMMARY – SUAY PRAGMATIC EFFECTIVENESS TRIAL

Title:	*STAR Caregivers – Virtual Training and Follow-up*
Précis:	The STAR-Caregivers program is an education, training, and support intervention demonstrated efficacious in reducing the behavioral and psychological symptoms of dementia. The investigators propose to test a 6-session, self-directed, online version called STAR-virtual training and follow-up (STAR-VTF) that leverages secure email within the member portal at Kaiser Permanente Washington, an online learning management system, and 6 30-minute coaching telephone calls to improve access to training, fidelity to the STAR principles, and to lower the cost of the program. Outcomes in the intervention arm will be compared to an attention control group that receives printed materials and links to online training resources but does not receive coaching.
Objectives:	Test the effectiveness of the intervention training vs. attention control in a practical clinical trial involving one hundred caregiver-person living with dementia dyads at Kaiser Permanente Washington.
Populations:	Persons living with dementia and their informal caregivers (spouses and adult children)
Site:	Kaiser Permanente Washington
Description of Intervention:	This study evaluates the effectiveness of a caregiver outreach, self-directed online training, and support program for caregivers of people with dementia who are using an antipsychotic medication to manage agitation/aggression. The Investigators will conduct a randomized trial of the caregiver program compared to a control group to measure differences in caregiver burden and discontinuation of antipsychotic medication use. The results will help in expanding access to and delivery of empirically supported behavioral health services for caregivers and persons living with dementia.
Trial Duration:	18 months
Subject Participation Duration:	6 months
Estimated Time to Complete Enrollment:	12 months

1 KEY ROLES AND CONTACT INFORMATION

Principal Investigator:	Robert Penfold, PhD, Scientific Investigator III Kaiser Permanente Washington Health Research Institute (KPWHRI) 1730 Minor Avenue, Suite 1600 Seattle, WA 98101 *Robert.B.Penfold@kp.org* (206) 287-2232
Program Director:	Lisa Onken, NIA
Institutions:	Kaiser Permanente Washington University of Washington
Co-Investigators:	Linda Teri, PhD, University of Washington Susan McCurry, PhD, University of Washington

2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 *Background Information*

Alzheimer's Disease and related dementias (ADRD) are debilitating conditions affecting more than 5 million Americans in 2014.(1, 2) With aging of the population it is projected that 8.4 million people will be diagnosed with ADRD over the next 15 years(3, 4) and health care costs attributable to ADRD are projected to be more than 1.2 trillion by 2050.(2) Behavioral and Psychological Symptoms of Dementia (BPSD) (anxiety, agitation, depression) are common and often involve aggressive behavior towards family caregivers (CG) in response to unmet needs, discomfort, or frustration. BPSD are disturbing and frequently lead to CG seeking medication to control patient symptoms. Antipsychotic use in persons living with dementia (PLWD) more than doubles mortality risk;(5) however, many caregivers are willing to accept those risks. The Choosing Wisely Guidelines from the American Psychiatric Association(6) and American Geriatrics Society(7) both recommend against prescribing antipsychotics as a first-line treatment for BPSD. STAR-Caregivers is an efficacious first-line behavioral treatment, endorsed by the Administration on Aging,(8) that involves caregiver training to manage BPSD.(9-16) However, the program has not been implemented widely – partly due to the cost of the programs,(17) difficulty conducting outreach,(18, 19) and modality of training (in person with written materials). Adequate caregiver training and commensurate reduction in caregiver burden are the mediators (mechanisms) we will engage in this Stage III trial to reduce BPSD and discontinue antipsychotic medication use by PLWD.

2.2 *Rationale and Objectives*

The STAR-Caregivers program is an education, training, and support intervention demonstrated efficacious in reducing BPSD.(9, 10, 20, 21) The original program involved 8 face-to-face, in-home training sessions and 4 follow-up phone calls. The condensed version involves 4 in-home sessions with 2 phone follow-ups.(18) Neither of these is feasible from a payer perspective due to the cost and, more recently, the COVID-19 pandemic makes home visits risky. We will test a self-directed, online version called STAR-virtual training and follow-up (STAR-VTF) that leverages weekly telephone calls and secure email within the member portal at Kaiser Permanente Washington to improve access to training, fidelity to the STAR principles, and to lower the cost of the program.

This trial will ascertain the feasibility and acceptability of STAR-VTF in which (a) caregiver training materials are delivered electronically and learning is self-directed, (b) caregivers have 7 telephone calls with a social worker and (c) where caregivers receive ongoing support from a social worker via secure messaging in the web-based portal (My Kaiser Permanente). We will compare outcomes in the STAR-VTF group to an attention control group that receives mailed material from the Alzheimer's Association and National Institute of Mental Health plus generic secure messages. Our specific aims are:

AIM 1: Assess the feasibility and acceptability of conducting caregiver outreach, training, and support via social workers and licensed mental health counselors including: (1) willingness of caregivers to interact through secure messaging (contact rates) and telephone; and (2) willingness of caregivers to complete self-directed training (training completion rates).

AIM2: Assess the feasibility and acceptability of the program from the payer perspective including: (1) average time spent per orientation visit; (2) average time per month spent responding to caregiver emails and coordinating care with primary care physicians; and (3 differences in face-to-face primary care, urgent care, and emergency department visit rates by PLWD.

AIM 3: Test the hypotheses that (H1) caregiver participants in STAR-VTF will have lower levels of caregiver burden at 8 weeks and 6 months compared to an attention control group; and (H2) PLWD participants in STAR-VTF will have lower rates of antipsychotic medication use at 6 months compared to control. Secondary outcomes are: caregiver depression, caregiver stress and caregiver self-efficacy. We propose to recruit 100 CG-PLWD dyads (50 per arm).

This will be the first study to test a low intensity, self-directed caregiver training program with remote support from social workers. It will also be the first study to measure changes in antipsychotic medication use by PLWD after CG training. Kaiser Permanente is an ideal setting because we have access to the complete EHR, prescription medication use, health care use, and demographic data. We will be able to identify and enroll participants in real-time using an automated data algorithm as we have done previously.(22) This study will be an important step in expanding access to training and support in a format that could be implemented within integrated delivery systems with capitated payments (i.e., Accountable Care Organizations). Growing use of EHR portals in these organizations will further increase demand for web-based care management/support. Demand will also increase as today's near-retirees, familiar with web-based applications, develop ADRD. Kaiser Permanente has pioneered such efforts and is the lead site in the Mental Health Research Network (MHRN). Findings from this study will inform a future multi-site pragmatic trial across the 13 health systems and 12 million enrollees in the MHRN.

3 OUTCOME MEASURES

Outcome measures will be collected regardless of the extent to which intervention arm caregivers or families accepted or utilized interventional components. That is, we will follow an intent-to-treat approach and encouragement trial methods.

3.1 *Primary Outcomes*

The following primary quantitative outcome measures for the trial will be assessed for the grant deliverables:

(1) **Change in caregiver burden at 8 weeks and 6 months**. Self-reported caregiver burden will be assessed by the Disruption subscale on the Revised Memory and Behavior Problem Checklist (RMBPC) questionnaire. The range in subscale scores is 0 to 32 with higher scores representing a worse outcome.

3.2 *Secondary Outcomes*

The following secondary outcome measures for the trial will be assessed:

(1) **Antipsychotic medication Use**. Proportion of participants will at least one antipsychotic prescription refill after initial medication dispensing, using automated system pharmacy data.
(2) **Change in caregiver depression.** Self-reported caregiver depression assessed by the 8-item Patient Health Questionnaire (PHQ-8). The PHQ-8 is an eight-item measure of depression that assesses symptoms over the last two weeks. The total sum of the 8 responses from the PHQ-8 ranges between 0 and 24 with higher scores indicating worse outcome. In general, a total of 10 or above is suggestive of the presence of depression.
(3) **Change in caregiver self-efficacy**. Self-reported caregiver self-efficacy assessed by the Caregiver Mastery Scale. Total scores can range from 7 to 35, with higher scores reflecting greater caregiver mastery. The Caregiver Mastery Scale is a 7-item measure of self-efficacy. is a 7-item self-report scale, indicating the extent to which respondents agree (5) or disagree (1) with each item. Three items with negative statements are reverse-scored. Total scores can range from 7 to 35, with higher scores reflecting greater caregiver mastery.
(4) **Change in caregiver stress**. Caregiver stress will be measured on the Kingston Caregiver Stress Scale. This is a 10-item measure with respondents rating the level of stress between 1 (coping fine, no stress) to 5 (extreme stress, feeling at the end of rope). Total scores vary between 10 and 50.
(5) **Response rates for baseline, 8-week, and 6-month measures**. We will assess participants' willingness to complete study measures using the REDCap online survey by the proportion completing study measures at each time point.
(6) **Training Completion rate**. We will report training completion rates as a measure of feasibility. Completion will be defined as viewing all 6 online training modules, conducting at least 3 phone calls with a study coach and sending at least one secure message to a study coach in the baseline to 8-week period and one message in weeks 9 through 24.
(7) **Primary care visit rates**. Measured as the number of primary care visits per eligible study participant during the study period.

(8) **Urgent care visit rates**. Measured as the number of urgent care visits per eligible study participant during the study period.

(9) **Emergency department visit rates**. Measured as the number of emergency department care visits per eligible study participant during the study period.

(10) **Case management time**. We will estimate the time spent responding to ad hoc secure messages and phone calls by caregivers in order to inform the feasibility of the intervention from a payer perspective.

4 TRIAL DESIGN

We will conduct a parallel, two-arm pragmatic clinical trial comparing the intervention and attention control groups. The follow up period for the trial will be 6 months.

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 *Inclusion and Exclusion Criteria for Persons Living with Dementia*

The investigators will identify and recruit PLWD-CG dyads in which the PLWD has filled a new prescription for an antipsychotic medication. The study programmer will identify potential PLWD-CG dyads using an automated data algorithm that queries claims data and electronic health record (EHR) data on a weekly basis.

Because we will enroll dyads, there are inclusion/exclusion criteria for both persons living with dementia and their caregivers.

Persons with dementia inclusion criteria:

- Aged ≥ 65 years
- Diagnosis of Alzheimer's Disease or related dementia (ADRD)
- Expected to live >= 6 months from enrollment

Persons with dementia exclusion criteria:

- A diagnosis of bipolar disorder or schizophreniform disorder
- The primary care physician's opinion is that the person with dementia is expected to live less than 6 months.
- Primary language is not English (patient requires a translator).

5.2 *Inclusion and Exclusion Criteria for Caregiver Subjects*

Potentially eligible caregivers are identified by the family contact information in the electronic medical record.

Caregiver inclusion criteria:

- Aged ≥ 21 years
- Lives with person with dementia or within 8 miles
- Provides at least 8 hours of care per week

Caregiver exclusion criteria:

- Diagnosis of Alzheimer's Disease or related disorders.
- Caregiver is not the spouse or adult child of the person living with dementia
- Primary language is not English (caregiver requires a translator).

5.3 *Randomization Assignment Procedures*

5.3.1 Randomization Procedures

The study biostatistician will create a randomization schedule and this will be uploaded into a REDCap database. Caregivers who remain eligible for the study after screening will be randomized within REDCap following the pre-set randomization schedule. All eligible caregiver-patient dyads will be block randomized to ensure comparable numbers of dyads enrolled in each study arm. Caregivers will be categorized according to age (<75 years, >=75 years), sex, and spouse/non-spouse.

R, an open-source statistical computing software, will be used to generate an even number of control and intervention assignments within each block.

5.3.2 Blinding

Study staff will be blinded to study arm when verifying subject eligibility.

STAR Caregiver coaches interact with both intervention and control arm subjects. Group assignment is therefore known to these study staff. For the control group, coaches will conduct the consent process and orient participants to the printed and online materials available from the Alzheimer's Association.

The PI will remain blinded to arm assignment until follow-up is complete. Only the study biostatistician, programmer, and project manager will be un-blinded to arm when preparing reports for the Safety Officer. The PI will be un-blinded for reporting any serious adverse events or incidental deaths to the Safety Officer and NIA staff, should such events occur during the course of the trial.

5.4 *Withdrawal*

Caregivers are free to withdraw from study activities at any time. However, we will still measure antipsychotic medication utilization rates between intervention and control. A waiver of consent to access PLWD medical records after withdrawal will be obtained.

5.5 *Control arm*

We will use an attention control arm. PLWD-Caregiver dyads randomized to the control arm will receive paper-based information from the Alzheimer's Association and National Institute on Aging including links to online training resources. Control arm participants will also receive 3 scripted secure messages (one at 4 weeks, one at 8 weeks and one at 6 months following randomization) to remind them to read the provided materials, check the provided web links to training resources, and check in with their primary care physician if they have concerns about the PLWD.

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6 INTERVENTION ARM

6.1 *Intervention Arm*

Randomized PLWD-CG dyads are offered:

- A telephone orientation visit with a study coach to acquaint the caregiver to the 6-session STAR-VTF program and online learning environment.
- A paper-based and electronic manual to identify priority behaviors, develop plans for addressing behaviors, and make plans for pleasant events.
- 6 weekly telephone coaching visits lasting 30 minutes and corresponding to each of the 6 training modules.
- Secure message (email) support within the patient portal, as needed, with the coach to help with personalizing the STAR-VTF curriculum for up to 6 months, as initiated by the caregiver.

We anticipate that self-directed caregiver training with support from social workers will enhance caregivers' sense of competence and self-efficacy. Training caregivers on good communication and the ABCs of dementia problem-solving will lead to decreased activation of behavioral triggers, lower incidence of problem behaviors, and lower caregiver stress in response to behaviors. Assisting caregivers to engage in higher levels of pleasant activities will enhance PLWD and caregiver mood and create a more positive care environment. With increased insight into the natural disease history, caregivers will be able to reframe behaviors as symptoms of dementia rather than insensitivity, rudeness, or deliberate provocation. We hypothesize that changes in the physical and psychosocial environment that reduce triggering events and improve caregiver-PLWD dyadic interactions will reduce the need for and use of antipsychotic medication.

6.2 *Eligibility Confirmation*

Once a PLWD is identified using the automated algorithm, a REDCap database is populated with the potential participants once per week. There are three steps to confirming eligibility.

- A study staff person will review the PLWD medical record to confirm that the person has a diagnosis of ADRD, an emergency contact or other family/friend is listed in the record, and that the PLWD does not live in an adult family home, skilled nursing facility, or memory facility.
- If eligible after medical record review, the staff person will contact a study coach (clinician) who will send a staff message within the EHR to the physician who prescribed the antipsychotic medication to the PLWD. The prescribing clinician will be asked:
    - Is [PLWD] capable of making health care decisions for themselves? [YES/NO/SOMETIMES]
    - Do you believe [PLWD] will live at least 6 months from today? [YES/NO]

- Was [antipsychotic medication] prescribed for behavioral/psychological symptoms of dementia? [YES/NO]
- Is there any other reason to NOT invite this patient and family caregiver to be in the research study? [YES/NO]

Recruitment will not proceed without a response to these questions by the prescribing clinician.

In the third stage, a study staff person will mail an invitation letter to the PLWD-CG dyad. This is followed by a screening phone call approximately 3 business days later. The purpose of the screening call is to determine:

- Willingness to take part in the study regardless of the randomization group.
- Ability to read and speak English.
- Determine whether the CG has ever been diagnosed with Alzheimer's disease or related dementia
- Confirm the PLWD does not live in an adult family home, assisted living facility, skilled nursing facility, or memory facility.
- Whether the caregiver is 21 years or older.
- Whether the caregiver lives in the same household as the PLWD or within 8 miles (30 minutes).
- Whether the caregiver spends at least 8 hours providing care to the PLWD
- Whether the caregiver is the DPOA and if not who that person is.
- Whether the caregiver is the spouse or adult child of the PLWD
- Caregiver access to a computer or other device where the caregiver can access the patient portal, personal email and websites to complete the online training.
- Whether the caregiver uses MyChart – the Kaiser Permanente patient portal - to email the doctors that care for the PLWD
- Administer the Short Portable Mental Status Questionnaire to the caregiver.

If the PLWD-CG dyad remains eligible after the 3-step verification process then a study staff person will randomize the dyad in REDCap and schedule an orientation telephone visit.

If the caregiver is not the DPOA and the PLWD is unable to consent, the study staff person will request the contact information of the person who is DPOA. If the dyad is otherwise eligible, the DPOA will be contacted to obtain verbal consent on behalf of the PLWD.

6.3 *Consent*

6.3.1 Verbal Consent for screening questions

Following the recruitment packet mailing, two things may happen:

1. Potential participants may call our study line and express interest in participating or decline to participate. Those expressing an interest will receive a phone call from a Research Specialist and those who decline to participate will be coded as such and not contacted.

2. If we have not heard from the potential caregiver participant, we will follow-up with a phone call to assess interest and eligibility.

During the screening phone call, the Research Specialist will describe the study, answer any questions, and administer a phone screening questionnaire to assess eligibility after verbal consent is given.

6.3.2 Verbal Consent for participation in study

If the PLWD-CG dyad is eligible after the phone screening questionnaire, an orientation phone visit will be scheduled. A study coach will obtain verbal informed consent from the caregiver on the day of their orientation phone visit prior to any study activities. The coach will read the consent forms to the caregiver and PLWD, emphasizing that study participation is voluntary and that if the caregiver or PLWD decides not to participate, the decision will have no impact on the care of the PLWD. The coach will also explain that the caregiver or PLWD can stop the consent process or the study at any point if they decide they no longer want to participate. The caregiver and PLWD will have an opportunity to ask questions prior to giving verbal consent. The caregiver and PLWD will have a copy of the consent forms mailed to them with the invite letter and will instructed to have these in front of them during the call.

6.3.3 Caregiver is not the DPOA or Priority Person

If the caregiver is not the DPOA or priority person, and either the doctor or the caregiver have indicated that they believe the PLWD is unable to consent for themselves, we will contact the DPOA or priority person to obtain verbal consent for the PLWD to participate in the study prior to scheduling the orientation phone visit. A study staff member will contact the DPOA/LAR, describe the study in detail, and answer any questions. The study staff member will get verbal consent from the DPOA or legally authorized representative (LAR) for the PLWD to participate. The study staff member will mail a copy of the consent form to the DPOA/LAR following the phone call. If the DPOA/LAR gives verbal consent for the PLWD to participate, study staff will then call the caregiver to schedule the orientation phone visit. The purpose of this is to avoid scheduling a phone visit and randomizing a dyad should the DPOA not give consent for the PLWD to participate.

The consent process will vary depending on the following factors:

(1) The PLWD is able to consent for themselves. The PLWD's provider will inform the study coach as to his/her medical opinion to the PLWD's incompetence (the provider's response to this question is required in order for the PLWD and caregiver to participate).

(2) The PLWD is not able to consent for themselves and the caregiver IS either the DPOA or the priority person authorized to make decisions on the PLWDs behalf.

(3) The PLWD is not able to consent for themselves and the caregiver is **not** the DPOA or the priority person authorized to make decisions on the PLWDs behalf.

Under Case #1, the PLWD gives consent on their own behalf. Under case #2, the caregiver gives verbal consent on behalf of the PLWD. If possible, we will get verbal assent from the PLWD as well. Under case #3, prior to the visit study staff will speak with the DPOA or the priority person authorized to make decisions on behalf of the PLWD and get verbal consent for the PLWD to participate in the study. A copy of the consent form will be mailed to the DPOA or priority person for their records.

6.4 Orientation Call

The purpose of the orientation telephone call is to:

- Make introductions
- Review consent forms and obtain informed consent
- Orient the caregiver to the baseline measures survey site (online) and confirm their ability to login and complete the baseline measure survey
- Confirm the caregiver has received the printed materials corresponding to their study arm

6.4.1 Intervention Arm only

Participants randomized to the intervention arm will also be oriented to the online learning modules. A study coach will give caregivers an overview of the program and assist the caregiver to:

- Navigate to the Kaiser Permanente School learning modules site
- Login using their credentials
- Give an overview of the learning modules, the cadence of completion (one per week), and required homework
- Schedule the first 30-minute check-in regarding Session One of the program.

6.5 Online Learning Modules

There are 6 self-directed learning modules for intervention arm participants to complete. Modules consist of text, figures and audio describing the principles of the STAR Caregivers program. The modules are:

(1) Introduction to STAR-Caregivers, Overview of Dementia, Principles of Communication

(2) ABCs of Problem Solving

(3) Review of ABCs and Modifying Plans

(4) Pleasant Events

(5) Review of Pleasant Events, ABCs, Practical Communication

(6) Pleasant Events for Caregivers

Each module takes between 30 and 45 minutes to complete and participants are expected to complete one module per week. Participants complete the homework and reading assignments following completion of each module. Study coaches review problem solving plans, pleasant events schedules and any questions about the material or individual needs during follow-up phone calls.

6.6 Weekly Coach Phone Calls

Caregivers are invited to participate in weekly, 30-minute phone calls with a study coach to review material from the relevant training session. Coaches will provide ad hoc advice on the nature and disease process of ADRD, realistic expectations for PLWD behavior, practical communication, how to complete/revise ABC problem solving plans, how to complete/revise the pleasant events schedule, and how to obtain formal and informal respite from caregiving.

6.7 Secure Messaging (Email in the patient portal)

Caregivers will be invited to communicate with their coach via email at the completion of the 6-week training program and up to the end of the 6-month follow-up period. Coaches will only respond to messages initiated by caregivers. Telephone support will be given only as necessary.

6.8 Procedures for Training Study Coaches and Fidelity Monitoring

Drs. McCurry and Teri are clinical psychologists and the original developers of the STAR Caregivers training program. They will train study coaches on the STAR Caregivers curriculum and consultation best practices.

Drs. McCurry and Teri will meet by regular conference call with study coaches to discuss fidelity to the STAR Caregivers program by anonymously discussing case examples.

The study coaches will keep weekly progress notes that include a checklist confirming what content areas are covered from the protocol during the telephone sessions, information about the types of ABC and pleasant event plans developed by caregivers, and the frequency and content of secure messages initiated. Therapist quality control will be assured through a sample of in-person observed sessions overseen by Drs. Teri and McCurry.

7 STATISTICAL CONSIDERATIONS

7.1 *Sample Size Considerations*

We anticipate enrolling 100 PLWD-CG dyads in the trial (50 per arm), with up to 90 remaining enrolled at 6 months of follow-up (i.e., 10% lost to follow-up).

7.1.1 Statistical Power for Primary Outcome.

We calculated effect sizes for the impact of STAR-C on the Subjective Caregiver Burden scale (d=0.77) and the Revised Memory and Behavior Problem Checklist (d=0.68) based on the p-values reported for t-tests comparing the STAR-C mean with the routine medical care group mean in prior research. We will power on the RMBPC (primary outcome) and assume a loss of effect size due to the lower intensity of the intervention. Assuming an effect size of 0.65, type-I error of 0.05, power of 80%, and equal sample sizes, we will require 39 dyads in the STAR-VTF arm and 39 dyads in the control arm (n=78). We additionally assume it will be necessary to adjust for baseline covariate imbalance and sample attrition, thus, we will inflate our recruitment targets by 30% as we have done in the past. The final recruitment target will be 50 PLWD-CG dyads in each arm.

7.2 *Analysis Plan*

Data will be collected from project tracking systems, the Epic EMR, and other health system data systems for analysis. Baseline, 8 week, and 6 month measures will be collected via an online survey using REDCap functionality.

Data validation and quality assurance checks will be undertaken to ensure data collection during the study is sufficiently reliable.

7.2.1 Statistical Analysis Plan

All analyses will be conducted under intention-to-treat principles.

7.2.2 Aim 1. Feasibility/Acceptability

We will measure response rates for follow-up data collection using the online survey functionality in REDCap. We will use descriptive statistics to characterize response rates by study arm and demographic characteristics. We will use generalized estimating equations (GEE) with a working correlation matrix to estimate a logistic regression model for response vs. non-response. We will estimate separate models for the 8-week and 24-week outcome periods. Models will be adjusted for PLWD stage of dementia (DSRS), PLWD FAQ score, PLWD age and sex, caregiver relationship (spouse, non-spouse), caregiver age and sex, caregiver highest level of education attained, PLWD residential status (living with caregiver full-time versus not) and study arm.

7.2.3 Feasibility/Acceptability - Completion of Training.

We will use descriptive statistics to characterize completion rates by study arm and demographic characteristics. We will use generalized estimating equations (GEE) with a working correlation matrix to estimate a logistic regression model for completion vs. non-completion. Models will be adjusted for PLWD stage of dementia (DSRS), PLWD FAQ score, PLWD age and sex, caregiver relationship (spouse, non-spouse), caregiver age and sex, and caregiver highest level of education attained, and study arm.

7.2.4 Assess the feasibility and acceptability from the payer perspective.

We will use descriptive statistics to characterize the effort required by coaches to facilitate caregiver training. These measures are (1) time reading secure messages, (2) number of exchanges per message thread, (3) number of ad hoc phone calls required (i.e., other than the 6 scheduled calls).

7.2.5 Primary Care, Urgent Care and Emergency Department Use.

We will use longitudinal, generalized estimating equations (GEE) to estimate a Poisson regression model for adjusted mean monthly visit rates (separately by visit type) in the STAR-VTF arm compared to the attention control arm in the 6 months following randomization. Models will be adjusted for PLWD stage of dementia (DSRS), PLWD FAQ score, PLWD age and sex, caregiver relationship (spouse, non-spouse), caregiver age and sex, and caregiver highest level of education attained, and study arm. We will use the robust sandwich estimator to calculate standard errors to account for repeated (i.e. 6 monthly) observations within people and the misspecified variance in the Poisson model.

7.2.6 Effect of STAR-VTF on CG burden and PLWD antipsychotic medication use.

We will measure overall caregiver burden using the Revised Memory and Problem Behavior Checklist (RMPBC). We will use GEE with a working correlation matrix to estimate the regression model, using robust sandwich estimators to calculate standard errors accounting for within person correlation. We will adjust for baseline pre-randomization covariates: PLWD stage of dementia (DSRS), PLWD FAQ score, PLWD age and sex, caregiver relationship (spouse, non-spouse), caregiver age and sex, and caregiver highest level of education attained.

We will use generalized estimating equations (GEE) with a working correlation matrix to estimate a logistic regression model for refill (versus no refill) of the initial antipsychotic medication. Models will be adjusted for PLWD stage of dementia (DSRS), PLWD FAQ score, PLWD age and sex, caregiver relationship (spouse, non-spouse), caregiver age and sex, and caregiver highest level of education attained, study arm. We will again use GEE with a working correlation matrix to estimate a logistic regression model for daily versus “less than daily” use of antipsychotic medication (as reported to the coach). Models will again be adjusted for pre-randomization variables listed above.

7.2.7 Caregiver depression, stress and self-efficacy.

Caregiver depression will be measured using the PHQ-8. Caregiver self-efficacy will be measured using the Caregiver Mastery Scale. Caregiver stress will be measured using the Kingston Caregiver Stress Scale. We will again use GEE to compare the mean PHQ-8, CMS and Kingston scores in the STAR-VTF and attention control arms. Models will be adjusted for pre-randomization variables as above.

7.3 *Handling of Missing Data*

Preventing missing data is superior to statistical treatment. We will make every effort to collect data on all study participants. If there are substantial missing data or significant loss-to-follow-up, we will use inverse probability weighting(23) to rebalance the STAR-VTF and attention control group. Inverse probability weights are used to rebalance groups on prognostic factors when the treatment and control groups become unbalanced over time, post-randomization, due to study drop out. If we find intermittent missing data, we will instead use multiple imputation(24) via chained equations to address the problem, using at least 10 imputed datasets and combining results using Rubin's rules.

8 PRAGMATIC TRIAL OVERSIGHT

8.1 *Data Safety Monitoring by Safety Officer*

Dr. Elizabeth Phelan will act as the Safety Officer for the Phase 3 pragmatic trial.

The Safety Officer and PI will advise NIA of its findings and reports will be shared with the KPWHRI IRB, as required. We will be responsive to additional specific requests for data reports that may be requested by the Safety Officer or NIA program staff.

Confidentiality will be maintained during all phases of review and deliberations.

A separate data safety monitoring plan accompanies this protocol.

9 QUALITY CONTROL AND QUALITY ASSURANCE

9.1 *Study Procedures*

Standard operating procedures for the study will be detailed in the Manual of Procedures. An overview of procedures is provided in this protocol.

9.2 *Protocol Deviations*

Staff will immediately report protocol deviations to the Project Manager, who will inform the PI. Any deviations will be considered noncompliance with this protocol or Good Clinical Practice. Protocol deviations will include privacy breaches, and IT-related problems that lead to errors in protocol adherence.

Protocol deviations that may impact patient safety or study data integrity will be immediately reported to the PI and PM. The Safety Officer will be informed within 5 business days of study staff becoming aware of a protocol deviation impacting patient safety or study data integrity.

Staff will report all other protocol deviations. The KPWHRI IRB will be notified of deviations per reporting requirements. The NIA program director and Safety Officer will review protocol deviations in the regular data reports.

Events not considered protocol deviations: Due to the pragmatic aspects of the study, the failure of a provider or patient to adhere to the protocol (e.g., not responding to request for information on a patient, not completing training), are not considered protocol deviations. These uncontrolled and expected events are of scientific interest due to the pragmatic nature of the study.

10 ETHICS/PROTECTION OF HUMAN SUBJECTS

10.1 *Ethical Standard*

The investigator will ensure that this research study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, as drafted by the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6.

10.2 *Potential Risks and Benefits*

None of the individual interventional components of this study are experimental in nature. All components have been tested and demonstrated effective elsewhere. No medications or other treatments are withheld or delayed. Prescribers are not advised to stop antipsychotic medications and remain free to exercise their own clinical judgment.

10.2.1 Potential Risks

One component of the skills training is to brainstorm strategies for reducing problem behaviors. For example, PLWD may become oppositional/defiant when asked to get dressed or bathe. This brainstorming process involves some trial-and-error and it is possible that caregivers, with the best of intentions, may make problem behaviors temporarily worse as they experiment with their personalized strategies (A-B-C problem solving plan). This experience may be distressing and/or frustrating for both caregiver and PLWD.

10.2.2 Potential Benefits

There is potential for improvement in mental health and quality of life of the caregiver due to practicing the skills taught as part of the intervention and coaching received. The skills are designed to reduce interpersonal conflict between caregiver and PLWD as well as to increase participation in pleasant activities.

It is anticipated that this research will yield important new information regarding alternatives to antipsychotic medication use in persons with dementia. The results of this study will also serve to give doctors and caregivers of this population with more effective tools for managing troublesome and stressful behavior problems in this group of patients

10.3 *Institutional Review Board*

The protocol and project materials for providers and patients and caregivers have been submitted to the KPWHRI IRB and approved. Amendments require review and approval by the IRB before the changes are implemented.

10.4 *Subject Confidentiality*

Appropriate steps will be taken to safeguard participant confidentiality. This includes the following:

- All project data will be maintained on secure, password protected servers at clinical sites. Only project staff needing this information for their work will have access. Members of the study team include Epic programmers from the delivery system;
- Participants will be identified using only subject ID in any study analytic database(s) at each site;
- The protocol, documentation, data and all other identifying information will be held in strict confidence. No information about the project will be released without prior approval of NIA. Authorized representatives of the NIA may inspect records, as needed.

10.5 *Future Use of Identifiable Data*

Identifiable information will be destroyed within 5 years of the end of the study, consistent with funding, HIPAA and IRB requirements.

We have no plans to retain identifiable information beyond this period. If this plan changes, we will obtain appropriate IRB approval.

11 DATA HANDLING AND RECORD KEEPING

11.1 *Data Management Responsibilities*

Both institutional and application level access granted by the local information security office and simultaneous knowledge of both a valid username and password are required to access data collected in electronic records. Any paper records generated with patient identifying information will be kept in locked filing cabinets in secured office buildings.

No participant data shall be overwritten by project staff. As necessary, variables may be recoded into new variables for analyses, so as to preserve the original record. All changes will be documented.

Final datasets will be saved electronically, clearly labeled and stored in a secure project folder on the KPWHRI server accessible only to project staff.

11.2 *Data Capture Methods*

The majority of data for this pragmatic study is captured electronically in REDCap, including study enrollment, note taking by coaches, and collection of baseline and outcome measures. All information entered into the REDCap questionnaires by participants is stored behind the KPWRHI firewall.

Cost and utilization data will be collected from the KPWHRI virtual data warehouse.

All electronic records will be kept in a 21 CFR Part-11 compliant data capture system, which includes password protection.

11.3 *Study Records Retention*

Identifying information and linking files will be destroyed within 5 years of the conclusion of the project unless consent to retain these files is granted by the IRB. Following this time, no other records will be destroyed without the consent of NIA. It is the responsibility of NIA to inform the investigator when these documents no longer need to be retained.

12 DATA SHARING PLAN

Data and resource sharing are an integral part of the STAR-VTF research program.

12.1 *Data Sharing Experience*

We at KPWHRI have a long history of sharing data with investigators locally and at other institutions and strongly support NIA's effort to promote data sharing of results of publicly funded research to scientists in the US and elsewhere, with due respect for confidentiality and privacy. Our success supporting these projects is built on the understanding that effective data sharing means providing more than just data – it means offering programmatic and scientific support through an iterative process tailored to the needs of our external collaborators to help them understand and appropriately interpret data. Our data sharing philosophy ensures the highest quality science while safeguarding the protection of data on STAR-VTF participants.

12.2 *Data and Resource Sharing Plan*

Completely de-identified datasets will be available for download. These will be based on published STAR-VTF papers and include documentation needed to ensure reproducibility. These data sets will be easily accessible with clear documentation of included variables. Custom datasets will be available upon request from the STAR-VTF team to support ancillary studies, collaborative meta-analyses, and external studies.

Below we describe how we meet the five elements of NIA's Guidance on Data Sharing.(25)

12.2.1 Access - STAR-VTF Repository and Data Sharing Capacity

We will make completely de-identified study data available on the National Archive of Computerized Data on Aging (NACDA)(26) following the Guide to Social Science Data Preparation and Archiving(27). We will transform SAS files into comma delimited text files so that the data can be used in a variety of statistical software packages.

Each participant will have a unique study identification number linking tables for demographic data, item and total scores for standardized instruments, healthcare utilization, and pharmacy utilization. All dates will be transformed to "days relative to randomization". Cost data will be standardized to the Medicare fee-for-service fee schedule to protect financial data.

We will also publish a data dictionary providing metadata descriptions in accompanying excel and pdf formats. Each variable will have a unique name, English language description, and description of its type (string, numeric) and length.

12.2.2 Timetable for Data Release

We will make the study data available prior to the online publication of the primary outcomes manuscript.

12.2.3 Restrictions to Data Sharing

We do not share data in any manner that may be deemed commercial or seen as selling data. Prior to downloading data, investigators will be required to make written application for our approval. Such approval shall not be unreasonably withheld provided the data will be used for public interest research or for the purposes of validating our reported findings.

Clinical notes that interventionists use to coach study participants will not be included in the publicly available data.

12.2.4 Data Deidentification Procedures

Respecting privacy and minimizing risk of identifiable information disclosure of participants is of utmost importance. We have well-developed internal policies and procedures in place to make sure that confidentiality is maintained. We will build on KPWHRI's existing secure data architecture and management systems to accommodate new data. When data are transferred NACDA, the PI will work closely with the Director of Data Programming and IT and the KPWHRI IRB to ensure data are protected to be compliant with HIPAA and IRB requirements. Prior to transfer from KPWHRI, a dedicated programmer and biostatistician pair with knowledge of the data will pre-review files to ensure compliance with regulations, alignment of data elements with permissions, and use of strategies to mitigate re-identification risk. Structured data extracted from source data will be transferred as either comma delimited text or SAS files.

Unique identification numbers are assigned to all participants. Only the PI and designated programmer will have access to the participant's actual identification on an as-needed basis. All data collected for analytic purposes will be filed separately from clinical information, which may include participant names. Participant privacy and confidentiality will be protected through the creation of limited data sets and, where possible, data sets that are de-identified in accordance with the HIPAA Privacy Rule. Data will be transferred via KPWHRI's web-based secure file transfer (SFT) application, which uses the 128-bit Secure Sockets Layer encryption protocol, the standard for secure Internet information transfer, and meets the 2009 HIPAA HITECH safe harbor standard. Data will be maintained locally in password protected files located in a secure server with restricted access.

Within KPWHRI, only authorized project staff can access identifiable data. EHR data from KPWA systems and research data from other Cores will be stored in the KPWA Data Warehouse with unique anonymous encrypted identifiers that cannot be linked to KPWA identifiers without specific programming. Data handling procedures will be clearly documented and comply with KPWA guidelines for data storage, transfer, and destruction.

12.2.5 Data Curation and Documentation

We will employ robust quality processes to identify and correct errors for STAR-VTF Repository elements. Structured data from the KPWHRI virtual data warehouse, captured as electronic health record (EHR) data from KPWHRI's instance of Clarity, or study data collected via REDCap will undergo comprehensive quality assurance to: (1) confirm that values fall within valid ranges and are internally consistent with related variables; (2) quantify levels of missing responses, accounting for complex skip patterns when relevant; and, (3) visualize temporal patterns in data elements to uncover unexpected trends, for instance from ICD-10 coding changes. Data quality concerns will be investigated fully by the study programmer and biostatistician in partnership with the PI and project manager. Corrective actions will be taken, and data rechecked to confirm issue resolution before certification.

Once clean structured data elements are procured for each data domain, the programmer and biostatistician pair will collaborate with the PI and project manager to derive, validate, and provide detailed documentation of analytic variables relevant to address all project aims. Documentation in each case will include an exhaustive, user-friendly data dictionary that describes variable definitions, coding, construction, and usage. This documentation will guide all potential users in efficiently and appropriately using the data for analysis and sharing.

Data files will be accompanied by statistical summaries of key features of the data and a curated suite of SAS programs that can be used and adapted to produce other potential summaries of interest or to generate different types of analysis-ready files. These summaries and documentation of variables and linked datasets will be available on the NACDA website. This process ensures that accessible and easy-to-use data can be leveraged to produce transparent and reproducible analyses with the most up-to-date and quality-controlled information available.

12.3 *Data Sharing Summary*

In summary, we agree with the NIA that the best means to maximize the value of investments made in this study is to share the data as widely as possible. We are thoroughly committed to data sharing, are proud of our accomplishments to date in this area and look forward to continuing to broadly collaborate and share KPWHRI data and resources under the STAR-VTF project.

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