Systematic Multi-Domain Alzheimer's Risk Reduction Trial (SMARRT)

[formerly: Multi-domain Alzheimer's Risk Reduction Study (MARRS) Pilot]

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PRÉCIS

Study Title

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Objectives

The primary goal of this study is to pilot-test a personalized, pragmatic, multi-domain Alzheimer's disease risk reduction intervention in an integrated healthcare delivery system. Our innovative pilot trial could provide critically needed information to support a future multi-site RCT, with the ultimate goal of delaying or preventing cognitive decline leading to Alzheimer's disease or other dementia in higher-risk individuals. This scalable healthcare system-based intervention targets personalized lifestyle and medical risk factors that also affect overall health.

Design and Outcomes

SMARRT is a randomized pilot study to test a personalized, pragmatic, multi-domain Alzheimer's disease risk reduction intervention in a US integrated healthcare delivery system. We will randomize 200 higher-risk older adults to a two-year Alzheimer's risk reduction intervention (SMARRT) or a Health Education (HE) control.

The primary outcome is two-year cognitive change on a cognitive test composite score. Secondary outcomes include: a) improvement on Alzheimer's risk factors, b) components of the global cognitive composite score, c) quality of life, and d) incidence of mild cognitive impairment (MCI) and Alzheimer's disease and dementia. Changes made to the protocol due to Covid-19, i.e., switching to telephone data collection, may limit our ability to examine cognitive change effectively, as several of the most important cognitive tests cannot be administered via telephone. Additionally, the onset of Covid-19 may affect the ability of participants to achieve risk factor reduction.

Interventions and Duration

Eligible participants will be randomized to either SMARRT or HE control. Participants randomized to the SMARRT group will receive personalized interventions related to their risk factors. Participants in the HE control group will receive typical health education information about risk factors for Alzheimer's disease. All participants will receive a screening phone call, a baseline visit, and three follow-up visits with blinded assessors (to assess outcomes) at approximately 6, 12, and 24 months, and the option of a telephone assessment or a questionnaire by mail at 18 months.

Sample Size and Population

200 higher-risk older adults (age 70-89 with low normal performance on cognitive screen and ≥ two modifiable risk factors that will be targeted by our intervention) at baseline will be eligible for randomization. 100 will be randomized to SMARRT, and 100 to HE

control. Randomization will be stratified by clinic and blocked by race (white, non-white) and age (70-79, 80-89) to ensure balance in these groups. Study participants will be recruited from selected primary care clinics of Kaiser Permanente Washington (KPWA).

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1 STUDY OBJECTIVES

1.1 Primary Objective

To collect pilot data on the effect of SMARRT compared to Health Education (HE) control for our primary outcome of two-year cognitive change. We will obtain critical information for estimating sample sizes required for a larger multi-site trial.

Changes made to the protocol due to Covid-19, i.e., switching to telephone data collection, may limit our ability to examine cognitive change effectively, as several of the most important cognitive tests cannot be administered via telephone.

1.2 Secondary Objectives

To compare changes in Alzheimer's risk factors over two years in those randomized to SMARRT vs HE. The results will determine if SMARRT can have a meaningful impact on cognition by demonstrating significantly greater risk factor change than HE.

To gather preliminary data on the impact of SMARRT vs HE on components of the global cognitive composite score, quality of life and incidence of mild cognitive impairment (MCI) and Alzheimer's disease.

2 BACKGROUND AND RATIONALE

2.1 Background

Alzheimer's disease prevalence is growing, creating a critical need for prevention. The number of people in the U.S. living with Alzheimer's disease and related dementias is expected to rise from 5 million today to 13 million by 2050(1). Current medications do not change the disease course, and several drugs have recently failed Phase III trials; thus, there is growing interest in strategies to prevent Alzheimer's disease. We have estimated that up to 30% of Alzheimer's disease may be attributable to modifiable risk factors (2, 3) including physical inactivity, low education, smoking, diabetes, hypertension, depression, and obesity. Our estimates are now being supported by several large population-based cohort studies, which are finding that Alzheimer's disease prevalence is actually decreasing in parallel with population-level changes in risk factors, such as better education, lower smoking and better control of cardiovascular risk factors. In addition, multidomain prevention trials in Europe have found that targeting these risk factors in older adults slows cognitive decline and reduces cognitive impairment. (4) These studies raise hope that multimodal risk reduction interventions in higher-risk older adults may delay the onset of Alzheimer's disease.(5)

2.2 Study Rationale

Despite growing evidence and tremendous promise, to date there has not been a single multi-domain Alzheimer's risk reduction trial in the US. In addition, multi-domain risk

reduction trials performed in other countries have all involved relatively intensive interventions that would be difficult to implement in real-world settings. An integrated healthcare setting provides an important potential venue to promote Alzheimer's prevention and risk reduction because the goals of the intervention are consistent with the goals of the healthcare system. This study will enable us to test the feasibility of this approach for motivating behavior change in older adults with an increased risk of Alzheimer's.

SMARRT is a randomized pilot study to test a personalized, pragmatic, multi-domain Alzheimer's disease risk reduction intervention in a US integrated healthcare delivery system. We will randomize 200 higher-risk older adults (age 70-89 with low normal performance on cognitive testing and ≥ two modifiable risk factors that will be targeted by our intervention) to a two-year Alzheimer's risk reduction intervention (SMARRT) or a Health Education (HE) control.

3 STUDY DESIGN

This study is a pragmatic, single-blind, randomized controlled pilot trial. We will randomize 200 higher-risk older adults to a two-year Systematic Multi-domain Alzheimer's Risk Reduction Trial (SMARRT) intervention or a Health Education (HE) control. The SMARRT team will work with participants to develop a tailored action plan to address risk reduction. Targeted areas will include: increasing physical, mental and social activities; controlling cardiovascular risk factors (diabetes, hypertension); quitting smoking; reducing depressive symptoms; improving sleep; neuroprotective diet; and decreasing use of potentially harmful medications. Our novel intervention uses a personalized, pragmatic risk reduction program in an integrated healthcare delivery system and state of the art technology to maximize feasibility and risk reduction.

Primary outcome is two-year cognitive change on a cognitive test composite score. Secondary outcomes include: a) improvement on Alzheimer's risk factors, b) components of the cognitive score, c) quality of life, and d) incidence of mild cognitive impairment (MCI) and Alzheimer's disease and dementia. Changes made to the protocol due to Covid-19, i.e., switching to telephone data collection, may limit our ability to examine cognitive change effectively, as several of the most important cognitive tests cannot be administered via telephone. Additionally, the onset of Covid-19 may affect the ability of participants to achieve risk factor reduction.

3. 1 Setting

Kaiser Permanente Washington (KPWA) is an integrated healthcare delivery system with about 710,000 members in the Northwest United States that provides members with both insurance coverage and healthcare. Because KPWA provides insurance coverage, we have complete information about members' healthcare utilization as well as diagnosis and procedure codes and medication fills. About 2/3^{rds} of KPWA members receive all or nearly all clinical care from KPWA physicians at KPWA-owned clinics. For those members we also have information on clinical measures such as vital signs (e.g. blood pressure values) and laboratory test results. This study will only recruit

members who are receiving their clinical care within KPWA's healthcare system. The University of California, San Francisco (UCSF) will provide study oversight.

3.2 Regulatory Review and Approval

All study procedures have been reviewed and approved by Institutional Review Boards (IRBs) at KPWA and UCSF, and the study will be registered on ClinicalTrials.gov. All study participants will provide written, informed consent before participating in assessments or intervention activities. We received a consent and Health Insurance Portability and Accountability Act (HIPAA) waiver to use electronic health records (EHR) to identify and recruit potential participants. HIPAA is a national privacy regulation in the US that requires all research study participants to review and sign a form that describes what type of information is being collected and how it will be used prior to participating in a study. IRBs can provide researchers with permission to use patient data for research without their prior approval when certain conditions are met, such as the research involves no more than minimal risk and is of sufficient importance to outweigh intrusion into the privacy of research subjects. Consistent with federal and state laws, all KPWA patients are provided with a Notice of Privacy Practices stating that their information may be used for research. Patients who have previously requested not to be contacted or have their records reviewed for research studies will be excluded.

4 INCLUSION/EXCLUSION CRITERIA

4.1 Inclusion Criteria

Participants must meet all the inclusion criteria to participate in this study. Age 70-89 years (to target a population at increased risk of experiencing cognitive decline that is still able to participate fully in a two-year intervention study); English language fluency; low-to-normal performance as compared to participants enrolled in the Adult Changes in Thought (ACT) Study (median 30) on a brief telephone cognitive screen (Cognitive Abilities Screening Test [CASI] short version); and ≥ two additional risk factors that will be targeted by our intervention (the table below has additional details on definitions).

Initial eligibility criteria using electronic health records (EHR) data will be based on having at least one targeted risk factor.* We will recruit among those with at least one targeted risk factor (rather than two) because not all risk factors of interest can be identified from the EHR (e.g., physical activity). We expect many individuals initially identified as having one risk factor will ultimately have two or more based on information collected on the telephone interview. The final inclusion criteria of at least two risk factors will be determined via a combination of EHR data (for hypertension, diabetes and contraindicated medications) and phone screening (for the remaining risk factors).

*Note: The targeted risk factors are defined in the table below. In addition to the targeted risk factor of poorly controlled hypertension as measured by elevated blood pressure

twice in the prior 6 months, we also selected for initial eligibility people who had a hypertension diagnosis in the past 2 years. This is not a change to the definition of the risk factor, but rather a way of broadening the pool of sampled participants who are screened for eligibility. Many people have not been to their clinic twice in the past 6 months to have documented elevated blood pressures, but do still have poorly controlled hypertension. They would still need to have 2+ of the targeted risk factors below to be enrolled in the study, so the criteria for eligibility is unchanged.

Table. Inclusion criteria for SMARRT Trial		
Inclusion Criteria	**Definition**	**Data source**
Older age	70-89 years	EHR
Language	Fluent in English	EHR and telephone screen
KPWA enrollment status	≥ 12 months (allow 3-month gap)	EHR
Low-to-normal cognitive performance on cognitive screen, excluding top performers	Brief CASI score 25 to 32, inclusive	Telephone screening
≥2 targeted risk factors		
o Poorly controlled hypertension	Systolic blood pressure ≥ 140 and/or diastolic blood pressure ≥ 90 twice in the past 6 months	EHR
o Poorly controlled diabetes, with evidence of either hyperglycemia or hypoglycemia	Hyperglycemia: ≥ 1 HbA1c ≥ 8.0 in past 12 months Potential hypoglycemia: Diabetes, taking insulin (at least one fill in past 6 months) and one or more of the following: 1) most recent A1c in past 12 months ≤ 6.0; 2) diagnosis code for hypoglycemia in past 1 year	EHR
o Elevated depression symptoms	Initial recruitment (EHR): Score of ≥ 3 on Patient Health Questionaire-2 (PHQ-2) screen in past 12 months Final eligibility: Score of ≥ 10 on PHQ-8 on telephone screen	EHR (initial) Telephone screening (final eligibility)
o Sleep difficulty	Initial recruitment: Diagnosis code for sleep disorder and/or ≥ 2 fills for a sleep medication in the past 12 months Final eligibility: Scoring above the cut-off on the sleep questionnaire in phone screening (problems with sleep 3+ nights/week and bothered "somewhat" or more)	EHR (initial) Telephone screening (final eligibility)
o Risky medications	≥ 2 fills for medications in a given class of risky medications in past 6 months, per modified Beers criteria.	EHR

o Low physical activity	< 30 minutes moderate intensity most days (<150 minutes/week, Surgeon General guidelines)	Telephone screening
o Social isolation	Rarely or never get social and emotional support needed (scoring ≥ 6 out of 9 possible points)	Telephone screening
o Smoking	Initial recruitment: EHR evidence of current use of any tobacco Final eligibility: self-reported current smoking on telephone screen	EHR (initial) Telephone screening (final eligibility)

4.2 Exclusion Criteria

Any candidates meeting any of the exclusion criteria during EHR review or the screening phone call will be excluded from study participation. For initial determination of eligibility, we will rely on information recorded in the EHR, such as International Classification of Diseases 10 (ICD-10) diagnosis codes and medication fills. We will exclude those who are currently residing in a skilled nursing or rehabilitation facility; receiving palliative care or hospice services (based on clinic encounters, past 2 years); Charlson comorbidity index score > 5 (based in ICD-10 diagnoses, past year, to exclude severe comorbidity likely to interfere with ability to participate in the study); bipolar illness or schizophrenia (any ICD-10 code, past 2 years, or receiving two or more fills for antipsychotic medications, past 6 months); current alcohol or drug use disorder (any ICD-10 code, past 2 years); receiving chronic opioid therapy (enough supplied to have taken 20 mg in morphine equivalents each day for at least 70 days out of the last 90 day period); Parkinson's disease, amyotrophic lateral sclerosis, or multiple sclerosis (any ICD-10, past 2 years); requested not to be contacted or not to have their medical record reviewed for research studies (KPWA Health Research Institute database); had clinical visits with the study co-investigators; and evidence of dementia (based on ICD10 codes, past 2 years, or prescription fills for dementia medications such as donepezil or memantine, past 2 years. If two participants from the same household are eligible, only one will be randomly selected for invitation.

Additional exclusion criteria will be determined as part of telephone screening and will include: severe hearing impairment (unable to complete telephone screen); inability to come in for assessments; inability to participate in an intervention and outcomes assessments conducted in English; plans to disenroll from KPWA or move out of the area in the next 2 years; current enrollment in the Adult Changes in Thought (ACT) study; answering 'yes' to the question "have memory problems contributed to a decline in your ability to care for yourself over the past year;" short CASI scores ≤24 (suggestive of cognitive impairment) or ≥33 (low likelihood of experiencing cognitive decline over 2 years); or inability to provide informed consent.

5 STUDY PROCEDURES

5.1 Schedule of Evaluations

Assessment	Screening	Baseline	Health Coach Sessions (SMARRT Group Only)	Health Education (HE Control Only)	6 Month Assessment	12 Month Assessment	18 Month Assessment	24 Month Assessment
Inclusion/Exclusion Criteria	X							
Informed Consent Form		X	X (first session)					
ActiGraph		X				X		X
Physical Function Tests		X			X	X		X
Blood Pressure and Height/Weight		X			X	X		X
Questionnaire packet		X			X	X	X	X
Neuropsychological Test Battery		X			X	X	X*	X
Cognitive Abilities Screening Instrument (CASI)		X			X	X	X*	X
Mailed Education Forms				X				
Meet with Interventionist			X					
Risk Factor Review			X (at 6 months)					
Adverse Events		X	X	X	X	X	X	X
Medication Questionnaire and Script								X
***Option for phone assessment at 18 months, to include subset of neuropsychological tests, and telephone CASI.**								

5.2 Description of Evaluations

5.2.1 Recruitment

Our goal is to target higher-risk individuals who will be motivated to make medical and behavioral changes to reduce their Alzheimer's risk. Initial eligibility will be determined using medical risk data from the EHR. Final eligibility will be determined during telephone screening.

Initial eligibility criteria using EHR data will be based on age, KPWA enrollment status, fluency in English, lack of exclusion criteria (described above), and ≥one targeted risk factor. We will recruit among those with ≥one targeted risk factor (rather than ≥two) to increase the size of the pool of people screened and minimize the risk of missing potentially eligible individuals who have risks that are not documented in the EHR. The final inclusion criteria of ≥two risk factors will be determined via phone screening. All potential participants will have EHR risk factor data (demographics, diagnoses, laboratory values and medications). In order to achieve greater diversity, we will use race-ethnicity information available from KPWA demographic files to oversample potential participants who are Hispanic or non-white, with a goal of having at least 30% of study participants from diverse backgrounds.

5.2.2 Mailing

Using standardized procedures that have been successfully applied in numerous research studies at KPWA Health Research Institute (KPWHRI), a research specialist within the Survey Research Program will mail recruitment letters describing the study to current KPWA members who meet initial eligibility criteria. Recruitment letters will include a phone number participants can call to opt out of being contacted for recruitment into this study.

5.2.3 Screening Evaluation

Approximately one week after letters have been mailed, potentially eligible study participants will be called and study interviewers will describe the study activities, randomization, and risks and benefits of the study. They will confirm understanding and invite any questions. They will obtain verbal informed consent to collect demographic information, to continue with the screening process, and (for those eligible for the study) to wear the ActiGraph activity monitor for a week. Once verbal consent has been given, they will give a detailed description of the study and determine final eligibility with a standardized screening questionnaire.

Because our goal is to enroll people with low normal cognitive function, we will also perform the short telephone version of the CASI. Enrollment will be restricted to those whose scores fall between 25 and 32 inclusive (see inclusion criteria section for rationale). Individuals who are eligible and interested will then be scheduled for in-person written consent and baseline assessment, and will be sent an accelerometer by

mail to obtain a measure of baseline levels of physical activity.

5.2.4 Baseline and Randomization

Consenting Procedure

At the written consent and baseline measurement visit, the assessor will discuss the nature of the study and review the written consent and HIPAA authorization form. Adequate time will be allowed to ensure comprehension and answering any questions. The assessor will obtain written consent from the participant and will also sign the consent form. A copy of the dually signed consent form will be given to the participant. The original will be stored in a locked filing cabinet in KPWHRI's locked offices. The consent forms will be stored separately from study ID and measures.

Baseline Assessments

All participants will complete the assessments listed below at baseline and three four follow-up visits spaced over 24 months (approximately 6, 12, and 24 months). Details of the assessments are below, in section 5.3.

- ActiGraph: objectively measures physical activity (worn for a week before baseline visit)
- Physical Function Tests
  - Short Physical Performance Battery
- Vital Signs
  - Height and weight
  - Blood pressure
- Questionnaire packet
  - Memory and Thinking Questionnaire (Cognitive Function Instrument)
  - Health Questionnaire (PROMIS Global Health)
  - Exercise Questionnaire (Rapid Assessment of Physical Activity in Older Adults: RAPA)
  - Social Activities Questionnaire (PROMIS Satisfaction with Participation in Discretionary Social Activities)
  - Leisure Activities Questionnaire (Cognitive Activities Questionnaire)
  - Alcohol and Smoking Questionnaire (AUDIT-C and Smoking Use)
  - Diet Questionnaire (MIND Diet)
  - Mood Questionnaire (Center for Epidemiological Studies Depression Scale: CES-D)
  - Sleep Questionnaire (Pittsburgh Sleep Quality Index: PSQI)
- Neuropsychological Test Battery
  - Verbal memory (WMS-R Logical Memory)
  - Verbal memory (CERAD Word List)
  - Attention/Working memory (WAIS-R Digit Span)
  - Speed (WAIS-R Digit Symbol)
  - Speed/Executive (Trail Making Test)

- Speed/Executive (Stroop Test)
- Language (Category Fluency Test)
- Language/Executive (Phonemic Fluency)
- Cognitive Abilities Screening Instrument (baseline, 6, 12, and 24 months; Telephone CASI at 18 months for phone assessments)

Randomization

Study participants will be randomized after the baseline visit in a 1:1 ratio to treatment and control, using procedures described below in Section 9.2.1. The study intervention will begin within eight weeks of randomization. If an appointment with the interventionist has not been scheduled within eight weeks of randomization, a case review will take place between the clinical support team and the intervention team to decide the best way to continue with the participant.

5.2.5 Follow-up and Final Visits

Assessments given at baseline will be repeated three times over the following 24 months (approximately 6, 12, and 24 months*), plus the option of a phone assessment or a mailed questionnaire at 18 months.

*Participants who are unable to or decline to complete follow up in-person visits will be given the option to complete an abbreviated assessment by phone/mail. These participants will still be given the $50 incentive.

All Follow-up Visits and 24-Month (Final) Visit
- ActiGraph (not at 6-month visit)
- Physical Function Tests
- Vital Signs
- Questionnaire packet
- Neuropsychological Test Battery*
- Adverse Events
- Medication Questionnaire (24-month only)***

* Several integral tests in the Neuropsychological Test Battery could not be administered via telephone, so those were not collected post-March 2020, when Covid-19 interrupted the study.

*** The medication questionnaire will be pilot tested at the 24-month timepoint in 10-15 participants**.** After study team debriefing for QA and additional training/clarification, we will implement for all future visits.

The study team will notify all participants once their participation has ended at two years and when the overall study has ended. The team will mail a letter thanking each person for their participation. The letter will include a 1-page summary of study

findings in lay language, a "graduation" certificate, and a reference to the first article resulting from the study.

The study does not plan to terminate anyone's participation early. They will continue in the study if they develop dementia, for as long as they and their legally authorized representative are willing to continue. For people unable to attend follow-up evaluations, we will offer a phone follow-up (CASI, neuropsychological tests, survey questions, AEs). Possible reasons for early withdrawal include medical event, illness, too busy, etc. If a participant asks to withdraw, we will first ask them if we can contact them again in a few months. If they are unwilling, we will ask permission to follow via medical records only.

Exit Interview (Optional)
After completing the study, participants may be invited to complete an exit interview by phone about their experience with the program and any feedback they have. This will help us improve the program. Participation in the exit interview is optional; if they agree to participation, we will ask to audio-record and transcribe the interview, but audio-recording is also optional.

5.3 Outcomes

Primary Outcome: Two-year Cognitive Change (Composite Score): Cognitive function will be measured by a global composite score from the modified Neuropsychological Test Battery (mNTB), a comprehensive battery including tests of memory (WMS-R Logical Memory, Consortium to Establish a Registry for Alzheimer's Disease [CERAD] Word List); attention (WMS-R Digit Span); executive functioning/processing speed (Trail Making Test, Stroop Test, WAIS-R Digit Symbol); and language [Category Fluency Test; Phonemic Fluency (FAS)].

Outcome measures in Alzheimer's risk reduction trials need to be sensitive to detecting subtle cognitive changes. We selected the mNTB to meet this need based on several lines of evidence for its strength as an outcome measure. Specifically, the original NTB,(6) on which the mNTB builds, is well-validated with strong test-retest reliability,(6,7) ability to distinguish between individuals at different clinical stages (i.e., normal cognition, MCI, AD),(7) and sensitivity to detecting cognitive change in early stages of Alzheimer's.(6)

Changes made to the protocol due to Covid-19, i.e., switching to telephone data collection, may limit our ability to examine cognitive change effectively, as several of the most important cognitive tests cannot be administered via telephone.

Secondary outcomes:

a) Improvement on Alzheimer's risk factors. Because this is a pilot study, one of our goals is to quantify the number and type of Alzheimer's risk factors each person has at baseline as well as change in each risk factor over two years in response to the SMARRT intervention. This will be accomplished using a combination of validated

objective and self-report measures as well as EHR data. We chose to use individual measures rather than an AD risk score so that we could examine each risk factor independently. In addition, current AD risk scores do not include all of the risk factors being targeted in this study. Specific measures include:

- Self-reported physical activity (Rapid Assessment of Physical Activity for Older Adults (RAPA): a validated 9-item self-report inventory assessing physical activity, which is designed for use with older adults and based on CDC recommendations for physical activity.
- Objectively measured physical activity (Actigraphy): participants will wear an ActiGraph wGT3X+ (Pensacola, FL) waist-worn accelerometer for 7 days prior to measurement visits at baseline, 12 months, and 24 months. Data from the ActiGraph will be aggregated using ActiLife software with counts over 1040 per minute used as the threshold for moderate or higher intensity activity (a cut point that appears to be valid for older adults).
- Leisure / Social Activity (PROMIS Satisfaction with Participation in Discretionary Social Activities): 12-item questionnaire which asks individuals to rate how satisfied they have been with their engagement with social and other leisure activities and social connectedness in the past 7 days on a 5-point Likert scale (not at all … very much).
- Cognitive activity (Cognitive Activity Questionnaire): 11-item questionnaire which asks how often an individual engages in activities such as reading the newspaper, playing games (e.g., crosswords, puzzles), playing a musical instrument, and other cognitively stimulating hobbies/leisure activities on a 6-point Likert scale (once a month/never … every day).
- Control of cardiovascular risk factors (hypertension, diabetes): Blood pressure and HbA1c values will be ascertained from the KPWA EHR.
- Smoking: Participants will be asked to self-report current tobacco usage, including questionnaire items: “Have you smoked even a puff in the last 7 days?” and if yes, “How many cigarettes have you smoked in the last 7 days?”.
- Diet (MIND diet score): The Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet combines elements of the Mediterranean and the Dietary Approach to Systolic Hypertension (DASH) diets. The15-item questionnaire assesses frequency of consumption of specific food types (e.g., green leafy vegetables, red meat) over the past 6 months.
- Depressive symptoms (Center for Epidemiologic Studies – Depression Scale, CES-D): 20-item questionnaire that assess both positive and negative affect over the last week rated on a scale from 0 (rarely or none of the time) to 4 (most or all of the time).
- Sleep quality (Pittsburgh Sleep Quality Index, PSQI): 19 item questionnaire that assesses sleep quality and disturbances over the past month (not at all, less than once a week, once or twice a week, three or more times a week).
- Potentially harmful medications (identified from KPWA pharmacy database): based on a detailed list of contraindicated medications developed for the intervention (see Intervention section). Additionally, a medication questionnaire will assess the use of over-the-counter [OTC] medications containing ingredients that increase risk of cognitive impairment/dementia.

b) Individual cognitive domain scores
c) Quality of life (PROMIS Global Health): 10-item self-report inventory which asks individuals to rate their quality of life including in terms of their overall physical and emotional health.
d) Incidence of MCI and Alzheimer's disease: While the incidence of clinically significant cognitive impairment is anticipated to be low, we will hold consensus conferences to identify MCI and dementia including Alzheimer's in people who meet one of the following criteria: 1) Full-length CASI score < 86 (or < 27 on the abbreviated telephone CASI for those unable to complete in-person) or 2) assessors observe or ascertain a noticeable decline in function. For these individuals, we will follow standard guidelines developed and used since 1994 in the ACT study to determine cognitive status using DSM-IV criteria for determination of the presence and diagnostic subtype of dementia. The diagnosis of Alzheimer's disease will be based on type of dementia according to current NINCDS-ADRDA diagnostic criteria for Alzheimer's and other types of dementia. We will define MCI broadly based on the Petersen criteria for MCI. We will further define MCI based on cognitive domain of deficit in order to yield categories of amnestic MCI, single non-memory impairment MCI and multiple domain MCI.

6 STUDY INTERVENTIONS

6.1 Interventions, Administration, and Duration

SMARRT Intervention Arm

After baseline assessments have been completed, the intervention team (including a nurse care manager and a behavioral interventionist) will use a standardized procedure to develop an individualized Alzheimer's Risk Profile for each patient randomized to the SMARRT intervention arm. This will include a graphic display of the targeted risk factors showing areas where the participant is doing well (green), areas where they can continue to improve (orange), and areas that are of particular risk for them (red). Patients will then meet in-person with an interventionist to review their risk profile and develop a personalized risk reduction action plan. Interventionists will elicit participants' values and motivators to reduce Alzheimer's risk and will use a decisional balance process informed by motivational interviewing and confidence ratings to help them choose 1-3 specific, achievable risk reduction steps that they are most ready to adopt. Participants will be provided with tools to track their progress. At each subsequent visit, interventionists will review progress, problem-solve barriers, and set new goals as needed. Targeted areas will include: increasing physical, mental and social activities; quitting smoking; healthy diet; controlling cardiovascular risk factors (diabetes, hypertension); reducing depressive symptoms; improving sleep; and decreasing use of potentially harmful medications. Following detailed protocols, the intervention team will provide counseling if participants experience distress related to being informed of their Alzheimer's risk.

Interventionists will provide participants with a menu of options for each targeted risk factor, and goals will be individualized to preferences, barriers, and motivators up front to optimize intervention adherence (see Table below). For each target, there are options that

leverage technology as appropriate for the participants' interest and skill level. Non-technology-based options are provided for each target as well.

For management of medical conditions (e.g., hypertension, diabetes, depression, sleep disorders), a "treat-to-target" approach will be used. This will involve setting discrete goals for targeted conditions (e.g., blood pressure, HbA1c, depressive symptoms) in consultation with the primary care team, systematically monitoring patient progress, adjusting treatment as needed (treat-to-target) and supporting patient self-care. Each week, the intervention team will meet with the clinical support team (MDs and clinical psychologists) for case reviews. Treatment algorithms will be based on standard KPWA treatment recommendations synthesized from national guidelines. Approval to exercise will be obtained from primary care physicians (PCPs) to ensure participants can safely engage in exercise prior to receiving interventions. Those who are approved and interested will be encouraged to gradually increase their physical activity levels, focusing on walking. In addition, our protocol includes strategies to reduce sitting behavior as an alternative in those who are not interested or able to increase physical activity levels. The SMARRT study physician or nurse will make recommendations to the participant and their PCP about management of targeted medical conditions and use of specific high-risk medications via Epic messaging, a secure, electronic, internal messaging system that enables clinical staff to communicate with each other about patient care. A detailed list of contraindicated medications including generic and brand names was developed using the 2015 updated Beers criteria for potentially inappropriate medications in older adults and a Kaiser reference for high-risk medications in the elderly, focusing on medications that impact cognitive function. Examples of targeted medications include those with strong anticholinergic properties, such as some antihistamines (e.g., diphenhydramine), some antidepressants (e.g., amitriptyline, paroxetine), and sedative-hypnotics (e.g., alprazolam, lorazepam). Nurses will work collaboratively with the primary care team to deprescribe contraindicated medications, and health coaches will work with participants on behavioral approaches to manage underlying conditions such as depression or insomnia.

Interventionists will follow a standard protocol for delivering the SMARRT intervention that allows for personalization of the specific risk reduction action plan; these plans will evolve over time according to participant progress, motivation and preferences or newly identified risk factors. Staff will use a tracking database to record information for each participant, including date and time of session, identified risk factors, motivational barriers and important values, and the outcome of discussions around developing goals. For each participant, the exact number and mode (phone or in-person) of contacts will differ, but we will aim to have at least 1 contact per month with each participant. Best practice will include in-person meetings twice a year during the 2-year intervention period. Even if a participant has relatively fewer risk factors, or successfully addresses all of their risk factors, interventionists will continue to check in with them to ensure that they are maintaining their healthy behaviors over time.

Table. Targeted Risk Factors and Approaches and Outcomes in SMARRT			
Risk Factor	**Goal**	**Menu of Options Tailored to Individual Preferences & Abilities**	**Outcome Measures**
Poorly controlled hypertension	<140/90 (<130/90 in patients with 10-year atherosclerotic cardiovascular disease risk ≥10%	Exercise, diet, medication changes using stepped care "treat to target" approach with primary care provider (PCP)	Blood pressure (study visits; EHR)
Poorly controlled diabetes	HbA1c between 7 and 8	Exercise, diet, medication changes using stepped care "treat to target" approach with primary care	HbA1c (EHR)
Physical inactivity	Increase by 2500 steps per day or maintain if they are over 10,000 steps/day, or work up to 8,000 steps per day	KPWA covered programs (e.g., Silver Sneakers, EnhanceFitness), community programs (e.g., YMCA, mall walking), smart phone apps (e.g., Apple Health, MyFitnessPal, MapMyWalk), wearable devices (e.g., pedometer, Fitbit), protocol to reduce sitting	Rapid Assessment of Physical Activity (RAPA) for Older Adults; Actigraphy
Lack of mental stimulation	Increase engagement in cognitively stimulating activities that are enjoyable	Senior center activities, local college classes, crossword puzzles and games, cognitive training web programs, smart phone apps (e.g., Lumosity, Brain HQ), on-line classes, volunteering; mindfulness	Cognitive Activities Questionnaire
Social isolation	Increase social engagement	Senior center activities, group exercise, social networking websites (e.g., Facebook), video chat tools, volunteering	PROMIS – Satisfaction with Participation in Discretionary Social Activities
Depressive symptoms	Fewer depressive symptoms	Behavioral activation, referral to behavioral health for CBT, antidepressant medication via PCP, smart phone apps based on CBT (e.g., MoodKit) or mindfulness (e.g., Mindfulness Coach)	Center for Epidemiologic Studies – Depression Scale
Sleep difficulty	Improvement on self-reported sleep quality and	Sleep hygiene and sleep restriction education, CBT for Insomnia (CBT-I), smartphone apps (e.g. Sleepio),	Pittsburgh Sleep Quality Index

	sleep duration	physical activity, behavioral activation	
Smoking	Reduction/cessation	Referral to Quit for Life, comprehensive program at no cost to KPWA members delivered by phone, web, and/or smart phone app; mobile tools (NCI QuitPal)	Self-reported current tobacco usage
Unhealthy diet	Increase adherence to MIND diet	Education about neuroprotective foods, self-monitoring neuroprotective food intake with paper food logs or websites/apps (e.g. Fitbit, MyFitnessPal, MyPlate)	Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) Diet Score
Contraindicated medications	Elimination/minimization	Education on alternatives, including nonpharmacologic therapy	Contra-indicated medications for cognition (2015 Beers criteria and KPWA list)

Health Education Control Arm

In this pragmatic pilot trial, our goal is to compare the personalized SMARRT intervention to what is currently 'usual care' in the healthcare system, while also providing enough interaction to maintain retention and blinding. Therefore, participants randomized to the Health Education (HE) group will receive mailed materials (typically 1-2 pages) every 3 months: general information on Alzheimer's and dementia risk reduction using materials from sources such as the Alzheimer's Association and educational materials commonly provided as part of routine care at KPWA. The general information provided will address factors that will be targeted in the SMARRT intervention, including physical, mental and social engagement; management of cardiovascular risk factors; quitting smoking, healthy diet; depression; sleep; and contraindicated medications. HE participants will not be provided with personalized information about their Alzheimer's and dementia risk.

Included in the mailings every 3 months will be a form asking if the HE participant has experienced a serious adverse event in the prior 3 months, and if so, a description, date(s), whether the participant has recovered, treatment plan if any, and whether we can call the participant later to see how they are doing. This approach will allow for more standardized, routine collection of SAEs among the control group.

We may contact the primary care providers of Health Education program participants, for example if the blood pressure results or cognitive test results at a measurement visit are outside of the expected range.

6.2 Handling of Study Interventions

Interventionists will follow a standard protocol for delivering the SMARRT intervention that allows for personalization of the specific action plan. Staff will use a tracking database to record information for each participant, including date and time of session, identified risk factors, motivational barriers and important values, and the outcome of discussions around developing goals. Also documented in the tracking database will be notes about participants' follow-through on recommendations and weekly case review recommendations with the clinical support team to supply information about intervention adherence.

6.3 Concomitant Interventions

6.3.1 Allowed Interventions

Unless specifically targeted for intervention, participants will remain on medication and dosages as prescribed by their primary care provider.

6.3.2 Prohibited Interventions

As dementia at baseline is an exclusionary disorder, dementia medications at baseline (such as donepezil or memantine) will be prohibited. These medications will be allowed

if they are newly prescribed during the 24-month follow-up period.

6.4 Adherence Assessment

Interventionists will use the tracking database to carefully document each contact with participants, including the type (in person, phone) and outcome (risk factor targeted, goal, whether the goal was met, comments). This will enable us to determine the total number and type of contacts per participant, the number and types of risk factors targeted, and the extent to which goals were achieved. Interventionists also will document weekly case review recommendations with the clinical support team to supply information about intervention adherence. In the control arm, there is no active intervention (only passive materials, usual care) so we cannot assess adherence or engagement.

7 SAFETY ASSESSMENTS

7.1 Adverse Events and Serious Adverse Events

An adverse event (AE) is defined as a not serious condition (e.g., muscle aches from physical activity, abnormal lab values) that occurs during the study.

A serious adverse event (SAE) is defined as a serious (defined as death, life-threatening event, hospitalization, or significant disability) or unexpected (defined as new or more severe than expected) and possibly, probably or definitely study-related (e.g., occur during or shortly after study-related activities) condition occurring during the study period.

We expect AEs associated with this intervention to be minimal and consistent with daily risks (e.g., anxiety caused by assessments, muscle aches from physical activity); AEs will be tracked in the study database. AEs may be detected through reports or contact with study participants, from survey data, and from data in the EHR. All participants will be prompted to report AEs and SAEs at their measurement visits (approximately 6, 12, 18, and 24 months). All participants will be asked to respond to an SAE form sent in the mail every three months (approximately months 3, 9, 15, and 21) when new health education materials are sent. Those in the SMARRT group may also report AEs during check-ins with their health coach. SAEs will be reported immediately to the project PIs and to the IRB and DSMB as described below.

Any activities that result in participant distress or serious physical activity-induced injury will be reported to the project PIs. The PIs will discuss all such events with co-investigators and the IRB and take other action(s) as appropriate (e.g., providing information about relevant community services to distressed participant). Summary reports of any such adverse events and subsequent actions taken will also be provided to the DSMB and NIA.

7.2 Reporting Procedures

Serious Adverse Events (SAEs): SAEs will be reported to NIA and the Data and Safety Monitoring Board (DSMB) members by the PIs or their designees by email within 24 hours of learning of deaths, and 48 hours of learning of non-deaths. Official reports will be

submitted within five business days. The DSMB will request additional information as needed and will determine whether changes to the study protocol are warranted.

Adverse Events (AEs): AEs will be reported to NIA and the DSMB in aggregate form prior to the biannual DSMB meetings.

7.3 Follow-up for Adverse Events

Unresolved AEs will be followed until resolved or considered stable. The health coaches will follow up during subsequent contact until the AE is resolved for participants in the intervention. For those in the HE group, the study nurse will follow-up via phone or EHR until the AE is resolved. For occurring SAEs, the MDs will triage for appropriate medical care within the KP system. The study nurse will follow-up with the participant and through medical records until the condition is stable or resolved.

7.4 Safety Monitoring

This study will be monitored by a DSMB, which will act in an advisory capacity to the NIA and the Principal Investigators, Dr. Kristine Yaffe and Dr. Eric Larson, to monitor participant safety, data quality, and the progress of the study.

8 INTERVENTION DISCONTINUATION

Subjects may withdraw voluntarily from participation in the study at any time and for any reason. Participants will continue to be followed, with their permission, even if the study intervention is discontinued. Follow-up measurement visits will continue to be scheduled if the participant is agreeable. If not, we'll follow-up via phone calls and/or medical record review, as allowed by the participant.

9 STATISTICAL CONSIDERATIONS

9.1 General Design Issues

The primary outcome will be a global cognitive function composite score. To calculate the composite score, each raw test score will be standardized based on the mean/standard deviation from all participants at baseline. Then, the resulting z-scores will be averaged across tests. Secondary outcomes will include change in Alzheimer's risk factors, components of the cognitive composite score, and quality of life. Changes made to the protocol due to Covid-19, i.e., switching to telephone data collection, may limit our ability to examine cognitive change effectively, as several of the most important cognitive tests cannot be administered via telephone. Additionally, the onset of Covid-19 may affect the ability of participants to achieve risk factor reduction. Our hypotheses include the following:

1. We hypothesize that composite cognitive function scores among participants randomized to the SMARRT intervention arm will show better scores, relative to those in the HE control arm. We also hypothesize that the component scores will be improved by the intervention.

2. We hypothesize that participants in the SMARRT intervention will show improvements on Alzheimer's risk factors during the intervention, relative to those in the HE control arm.
3. We hypothesize that additional outcomes including components of the global cognitive function composite and quality of life will be improved by the intervention. We also hypothesize that incidence of MCI and Alzheimer's will be lower among participants in the SMARRT arm.

9.2 Sample Size and Randomization

Because this is a pilot trial, our goal is to estimate effect sizes for a larger trial. Therefore, sample size estimates are based primarily on considerations of precision rather than power and effect size. For our primary outcome, our sample size of 200 will enable us to estimate the effect size with a precision of +/- 0.08 SDs, assuming loss to follow-up of 10%, and ICC of 0.6, based on data from the FINGER trial (4). This estimate will be used in combination with a consensus clinically meaningful effect, based on the literature and investigator expertise. For secondary outcomes, we estimate that precision will range from +/- 0.06 SDs to +/- 0.08 SDs, depending on the ICC. We anticipate that conversion to MCI/AD in this two-year trial will be low (<10%); therefore, this outcome is considered exploratory.

9.2.1 Treatment Assignment Procedures

Randomization will be implemented using randomly permuted blocks of size two, stratified on clinic, age (70-79 vs. 80-89), and race/ethnicity (white vs. non-white), This will maximize blinding of outcome assessors and achieve balanced groups that accurately reflect the underlying composition of the study population, as a primary aim of the study is to lay the groundwork for future large, multisite trials in integrated healthcare systems in the US. The randomization sequences will be generated in advance by the study statistician, securely stored electronically, and accessible only to intervention staff.

Research staff who enroll study participants and collect outcome data will be unaware of the randomization sequence and will be blinded to group assignment. Staff will be instructed not to seek information about study group. Outcome assessors will be blinded to group assignments. The content of interviewer scripts will be designed to deliberately reduce the chance of disclosure, using procedures and language that Dr. Rosenberg used in an R21 pilot RCT with blinded assessors. Assessors will document if they become unblinded; a different blinded assessor will perform any further follow-up assessments. Data analysts will also be blinded as to group assignment by using codes for randomization groups.

If unblinding occurs, the following will be recorded:
- The ID of the unblinded participant
- The reason for unblinding
- The study staff person responsible for unblinding
- A list of person(s) who have been unblinded

- Future assessments will be performed by team members who remain blinded.

9.3 Interim analyses and Stopping Rules

Because this is a pilot study, no interim analyses are planned. The DSMB may request that an interim analysis be performed if there are concerns about participant safety. The interim analysis results will be reviewed in closed session and may be presented in blinded or unblinded format at the DSMB's request. If interim analyses are requested, criteria for stopping the study will be clearly defined in advance by DSMB.

9.4 Data Analyses

We will first assess balance on baseline characteristics of the SMARRT and HE groups using graphical and tabular checks for overlap, and statistical comparisons using t-tests, Wilcoxon, chi-square, and Fisher's exact tests as appropriate. All analyses will use intent-to-treat principles.

Aim 1. To estimate the effect of SMARRT compared to HE on our outcome, repeated measures of the composite cognitive function score obtained at 6, 12, 18, and 24 months, we will use a linear mixed model (LMM), with fixed effects for the baseline score, time, treatment, and the time-by-treatment interaction, as well as random intercepts and slopes. Exploratory analyses will be performed within the intervention group to determine whether there is evidence that the magnitude of the effect varies based on the number or types of risk factors targeted, the extent to which goals are achieved, or the number or type of interventionist contacts. These analyses will be restricted to the intervention group because among controls, the number and type of risk factors targeted will not be assessed, achievement of goals will be undefined, and the number and type of contacts will differ systematically by design. Hence these results will be descriptive and will not estimate effect modification, mediation or dose-response, respectively. We also will use multiple imputation to explore the impact of missing data.

Aim 2. Similar methods will be used to assess the effect of the intervention on continuous Alzheimer's risk factors over two years. Because this is a pilot study, we chose not to pre-specify the benchmarks for change/improvement for each risk factor. Instead, we will quantify the amount of change achieved for each risk factor. Generalized linear mixed models (GLMMs), also with fixed effects for the baseline value, time, treatment, and the time-by-treatment interaction, and random intercepts and slopes, will be used as appropriate to assess treatment effects on binary, count, ordinal, and multinomial risk factors, including the number of risk factors.

Aim 3. LMMs and GLMMs also will be used to compare the impact of SMARRT vs. HE on individual components of the global cognitive score and quality of life. Finally, Cox proportional hazards models will be used to analyze intervention effects on time to MCI and Alzheimer's.

Based on data from prior Alzheimer's risk reduction trials, differences in intervention effect by gender or by race/ethnicity are not expected. Because the study was not designed to examine potential differences in intervention effect between gender and

racial/ethnic subgroups, the recruitment of women and minorities for the proposed project is expected to reflect the underlying composition of the aged 70+ population enrolled in the KPWHRI health network. As a result, we expect that our study population will not include gender and racial/ethnic subgroups large enough for comparisons of the intervention effect to have high statistical power for detecting clinically meaningful differences.

10 DATA COLLECTION AND QUALITY ASSURANCE

10.1 Data Collection Forms

Outcome assessments will be performed by trained Research Specialists who will be blinded to group assignments; if an assessor becomes unblinded, a different assessor will perform any further follow-up assessments. Assessors will receive periodic observations to ensure fidelity and completeness. Most measures during the outcome assessments will be collected using paper forms. The data from these forms will be entered by the assessors into a secure, web-based system overseen by UCSF. Questionnaires will be administered with the participants answering directly via a tablet computer. The participants' responses will be automatically scored and entered into the web-based database. Telephone assessment forms will be completed via direct entry into the secure web-based UCSF database, or onto fillable pdf forms stored separately from PHI on the KPWHRI secure file transfer site.

All study forms are described in detail in the Manual of Procedures (MOP).

10.2 Data Management

Data will be collected and stored separately for enrollment and intervention activities and outcomes activities (secure, web-based data entry system overseen by UCSF; no PHI). All data will be collected by KPWHRI staff in KPWA facilities. The following is a list of study data management responsibilities which will be undertaken by the clinical site (KPWHRI) to ensure protection of participant privacy:

Electronic files and paper forms – Identifiable data (PHI or PII) will be stored in a separate file from study data, all in a secure location. Computers are password-protected and filing cabinets are kept locked.

Computer security – Computers are password-protected with multiple levels of permissions and systems knowledge required to access study data. Users receive security training, including annual compliance trainings. The system is routinely backed up in an off-site server to prevent loss of data.

Data listings and distribution – No PHI or PII will be included in any published data listing. It will not be distributed without proper institutional agreements and IRB approval in place.

Access and storage – Participant records will not be accessible to persons outside of KPWHRI and UCSF without the express written consent of the participant. KPWHRI

offices are locked at all times to protect computer records and paper files locked in filing cabinets. Guests must be escorted. Precautions will be maintained during and after the study period for as long as the records are retained.

Data disposal – After the appropriate retention period passes, study files will be disposed of in an appropriate manner. Computer files will be deleted. Paper files will be placed in a locked confidential shred bin.

KPWHRI (Clinical Site) study staff control the data entry into UCSF's secure web-based data entry site, called REDCap. UCSF (Coordinating Center) controls the return of data via KPWHRI's Secure File Transfer site.

The Coordinating Center (UCSF) will receive a limited dataset (outcomes data, including cognitive testing and risk factor data) labeled by study ID; no PHI will be entered. This data will be stored in UCSF's secure web-based data entry system, REDCap. Outcomes data from REDCap will be transmitted back via KPWHRI's Secure File Transfer. Additionally, UCSF will receive audio recordings of selected cognitive testing batteries for the study neuropsychologist to monitor. These recordings, although coded, are considered PHI.

10.3 Quality Assurance

10.3.1 Training

All study staff will be trained by the same lead person in the same manner. Dr. Kaup will train KPWHRI staff in administering neuropsychological tests. Dr. Rosenberg will train staff in ActiGraph initialization and download, as well as conducting the anthropometric and physical function portions of the measurement visits. Drs. Rosenberg, Adams, Ludman, and Balderson will train the interventionists. Each lead will also monitor performance and provide feedback to ensure consistency.

Interventionists will have master's degrees in relevant health-related areas (e.g. public health, social work) and will be trained by two licensed clinical psychologists to deliver motivational interviewing, problem solving treatment, and general health coaching for all health behaviors. They will be trained using didactic techniques, role-play, and direct observation of at least two initial sessions and two follow-up sessions with corrective feedback. The Project Coordinator or Co-Investigators will observe new staff members during mock sessions as well as their first three interactions with research participants (e.g., screening/consent/baseline visits for enrollment and outcomes).

All interviewers, nurses, and other study staff will be trained to identify potentially adverse events. These would include subject, family member, or physician complaints; threats to withdraw or actual withdrawals from the study; and responses to questionnaire items indicating risk of serious consequences.

10.3.2 Metrics

Data for a random sample of 10% of study participants will be double-entered to determine the extent of data entry error and adjust if indicated.

10.3.3 Protocol Deviations

Any deviations in study protocol will be documented and reported in accordance with Kaiser Permanente Washington's IRB requirements.

10.3.4 Monitoring

The programmer and project manager, supervised by the PIs, will enact and monitor data quality control checks. Data quality control checks will be included to identify potential data anomalies such as:

- Missing data or forms
- Out-of-range or erroneous data
- Inconsistent and illogical dates over time
- Data inconsistency across forms and visits
- Not completing all fields of a "completed form" or no reason for missing data is provided

The data entry forms will include logic and range checks to minimize the possibility of missing or invalid entries. Electronic data entry forms will mirror paper case report forms. Calculations will be automated whenever possible. Audio will be recorded during the cognitive testing battery. The first few sessions and a random selection of other visits will be monitored for accuracy and consistency by the study neuropsychologist.

Prior to the end of each measurement visit, assessors will review their own forms and the participants' self-report surveys for any incomplete or illegible sections. This will allow clarification before the session ends. If incomplete or illegible sections are discovered later, those variables will be data entered as missing.

11 PARTICIPANT RIGHTS AND CONFIDENTIALITY

11.1 Institutional Review Board (IRB) Review

This protocol and the informed consent document (Appendix I) and any subsequent modifications will be reviewed and approved by the IRB.

11.2 Informed Consent Forms

A signed consent form will be obtained from each participant. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy will be given to each participant.

11.3 Participant Confidentiality

All KPWHRI employees, including full- and part-time employees of the Survey Research

Program, sign agreements to maintain confidentiality of data and research information. As a condition of employment, all members of the KPWHRI workforce must complete training in Health Insurance Portability and Accountability Act (HIPAA) requirements. All forms and study procedures are reviewed by KPWA's IRB for compliance with HIPAA and human subjects protections. Any data that will be accessed or disclosed outside KPWA will meet HIPAA requirements, through the use of business associate agreements, data use agreements, de-identification, and/or accounting of disclosures, as applicable.

All KPWHRI computers require passwords to access the network and the electronic mail system. Access to the Institute's data warehouse also requires special authorization.

KPWHRI policies and procedures ensure controlled access to computers and physical space for secure storage of data and confidentiality information. Access to KPWHRI's work areas is restricted by locked doors. Entry requires either a key card or a punch code that changes on a regular basis. Key cards or keys are required to enter the building, elevator, and KPWHRI floors during off-hours. Visitors must check in with designated staff to gain entry. A roster of persons authorized to enter the area is maintained by administrative personnel. KPWHRI requires employees to wear employee badges at all times and unfamiliar persons are required to state their purpose.

Study documents will be retained for the longest applicable period. Signed consent forms that include HIPAA authorizations will be retained six years from the date of creation or the date last in effect, whichever is later. Identifiable study data will be retained for 10 years after the study's end date. Other study forms will be retained for three years after the study's end date.

11.4 Study Discontinuation

The study may be discontinued at any time by the IRB, the NIA, the OHRP, or other government agencies as part of their duties to ensure that research participants are protected.

12 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by the policies and procedures of UCSF, KPWA, and NIA.

13 REFERENCES

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14 SUPPLEMENTS/APPENDICES

I. Informed Consent Form/ HIPAA Authorization