

FULL PROTOCOL TITLE

Identifying and supporting patients with undiagnosed dementia using the EHR Risk of Alzheimer's and Dementia Assessment Rule (eRADAR): a pilot clinical trial

PROTOCOL SHORT TITLE

The Brain Health Study: A Pragmatic, Patient-Centered Trial

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PRÉCIS

Background

Dementia is typically diagnosed relatively late in the disease process, and studies estimate that nearly half of people currently living with dementia are undiagnosed. Earlier detection of dementia could potentially improve clinical care and quality of life for patients and family members by connecting them with appropriate treatments and supportive services. The National Institute on Aging (NIA) issued RFA-AG-20-051 to support research into low-cost approaches to detect cognitive decline in clinical settings and, in particular, pragmatic trials of tools that can be incorporated into electronic health records (EHRs).

With pilot funding from NIA (R56 AG056417), we developed a low-cost tool for detecting patients at risk of having undiagnosed dementia called eRADAR (electronic health record Risk of Alzheimer's and Dementia Assessment Rule). eRADAR utilizes structured EHR data elements that are readily accessible in most healthcare systems and may reflect markers of high risk for dementia. To inform successful implementation of eRADAR, we conducted extensive interviews with patients, families, clinicians, and health system leaders. They felt it would be critical to implement a tool such as eRADAR as part of a process within primary care that will better support patients, family members, and clinical staff to minimize burden and potential for unintended harm. This proposal builds on our development work by performing a pragmatic trial of eRADAR implementation as part of a targeted, supported outreach process in primary care. The initial study site will be Kaiser Permanente Washington (KPWA), an integrated healthcare delivery system, with independent replication in the University of California, San Francisco (UCSF), an urban academic medical center.

Study Title

Low-cost detection of dementia using electronic health records data: validation and testing of the eRADAR algorithm in a pragmatic, patient-centered trial.

Objectives

- 1:** To determine whether implementing eRADAR through a supported outreach process increases dementia detection rates compared to usual care.
- 2:** To explore the impact of eRADAR implementation on healthcare utilization and experience of patients and family members.

Design and Outcomes

This study is a pragmatic, randomized controlled trial (RCT) set within two healthcare systems. It will include three KPWA primary care clinics serving about 18,000 patients age 65 years or older, with independent replication in three UCSF primary care sites (comprised of 5 clinics) serving about 9,000 patients. Randomization will occur at the level of the primary care physician (PCP). Within each clinic, half of the PCPs will be randomly allocated to have their high-risk patients (defined based on their eRADAR

score) undergo outreach and dementia assessment, while the other half will receive usual care. The eRADAR score will be calculated for all eligible patients including those in the usual care and intervention arms. The eRADAR score used to define “high risk” (cut-point) will be determined with input from patient and clinician advisors and will likely represent 5-15% of patients. Outcomes for this study include dementia diagnosis rates; measures of healthcare utilization (e.g., lab tests and imaging); and patient, family member and clinician experience and satisfaction.

Interventions and Duration

The primary intervention involves calculating eRADAR risk scores for all patients and then inviting patients with a high eRADAR score whose PCP was randomly allocated to the intervention group, to meet with a clinical research interventionist for a brain health assessment visit. Clinical research interventionists will reflect current health care system roles (e.g., nurses or clinical social workers); they will be embedded in the primary care clinics and work closely with the primary care teams randomized to the intervention group. The brain health visit will take 30-60 minutes and will include taking a history and assessing cognitive status and self-reported functioning. Patients will be encouraged to bring a family member or other trusted individual to provide support and additional information during the visit, although this will not be required. The research interventionist will summarize results of the visit in a clinic note to the PCP along with standardized recommendations for next steps if further workup is needed. We expect that most participants will have normal findings and will not require follow up care. The PCPs will be responsible for ordering follow-up tests and making final diagnoses. The research interventionist will offer to meet with patients who are subsequently diagnosed with dementia and their care partners to provide support and connect them with healthcare system and community services. All eligible participants, regardless of group assignment or participation in the brain health visit, will be followed for up to 18 months through the EHR to assess for new dementia diagnoses and healthcare utilization.

Sample Size and Population

The target study population includes people over 65 receiving care at participating primary care clinics who do not have a prior diagnosis of dementia or use of dementia medications. We will conduct analyses separately for the two sites, KPWA and UCSF (which is considered the replication site). At KPWA, the study will take place at three clinics with about 75 PCPs and about 18,000 patients. The population for primary analyses will be individuals with a “high-risk” eRADAR score (cut-off to be determined). If a cut-off of 15% (top 15% of scores) is used, this population will be about 2,700 individuals. At UCSF, the study will take place at five clinics serving about 9,000 patients, so the population for analyses using a cut-off of the top 15% would consist of about 1,350 individuals.

STUDY TEAM ROSTER

Multiple Principal Investigator: Sascha Dublin, MD, PhD

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Main responsibilities/Key roles: As multiple PI, Dr. Dublin will lead the KPWA study team and will work closely with Dr. Barnes and the UCSF team to conduct the research plan described in this study protocol. Specifically, Dr. Dublin will be responsible for overseeing a team whose responsibilities will include: submission of all KPWA IRB materials; ensuring that Data Use Agreements are fully executed; and overseeing all aspects of the proposed work at KPWA including study design, data collection, data analysis, interpretation of results, and presentation and publication of findings. This will include: extracting KPWA EHR data for calculation of eRADAR scores; identifying local stakeholders including patients, clinicians, and healthcare system leaders and obtaining their input on study materials and procedures; participating in team meetings; reviewing and providing feedback on study-related materials; hiring and training clinical research staff; delivering the intervention to KPWA study participants with high eRADAR scores randomized to the intervention arm; conducting a formative evaluation that will involve observing and recording a subset of patient interactions with research staff and semi-structured interviews with patients, family members and clinical staff; assisting with rapid qualitative review and coding; extracting outcome data from the EHR; sending, checking, and entering patient satisfaction surveys; and analyzing data and interpreting and publishing results. She will ensure that the study is submitted for initial and continuing IRB review and that all reporting requirements are met, including reporting unanticipated events to the sponsor and Data Safety and Monitoring Board (DSMB) as appropriate. She will work with Multiple PI Dr. Barnes to ensure reporting of all changes to research and unanticipated problems involving risks to subjects and not make any changes without IRB approval except where necessary to eliminate immediate hazards.

Multiple Principal Investigator: Deborah E. Barnes, PhD, MPH

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Main responsibilities/Key roles: As multiple PI, Dr. Barnes will lead the UCSF study team and will work closely with Dr. Dublin and the KPWA team to conduct the research plan described in this study protocol. Specifically, Dr. Barnes will be responsible for overseeing communications with the single IRB (sIRB); overseeing submission of all UCSF IRB materials; ensuring that Data Use Agreements are fully executed; and overseeing all aspects of the proposed work at UCSF including study design, data collection, data analysis, interpretation of results, and presentation and publication of findings. This will include: extracting UCSF EHR data for calculation of eRADAR scores; securely transferring relevant data to KPWA to enable

retrospective validation analyses; identifying local stakeholders including patients, clinicians, and healthcare system leaders and obtaining their input on outreach materials and procedures; participating in team meetings; reviewing and providing feedback on study-related materials in a timely manner; hiring and training clinical research staff; delivering the intervention to UCSF study participants with high eRADAR scores randomized to the intervention arm; conducting a formative evaluation that will involve observing and recording a subset of patient interactions with research staff and semi-structured interviews with patients, family members and clinical staff; assisting with rapid qualitative review and coding; extracting outcome data from the EHR; sending, checking, and entering patient satisfaction surveys; securely transferring data to KPWA for analysis; and interpreting and publishing results. She will ensure that the study is submitted for initial and continuing IRB review and that all reporting requirements are met, including reporting unanticipated events to the sponsor and DSMB as appropriate. She will work with Multiple PI Dr. Dublin to ensure reporting of all changes to research and unanticipated problems involving risks to subjects and not make any changes without IRB approval except where necessary to eliminate immediate hazards.

Kaiser Permanente Washington Health Research Institute Team

Co-Investigator: Yates Coley, PhD

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Main responsibilities/Key roles: Dr. Coley is the lead biostatistician on the project. They will contribute to development of data specifications and analysis plans. They will lead and oversee analyses of primary and secondary outcomes in both healthcare systems. They will be responsible for randomization procedures. They will help develop plans for data quality checking and will oversee preparation of DSMB reports.

Co-Investigator: Clarissa Hsu, PhD

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Main responsibilities/Key roles: Dr. Hsu is the lead for all qualitative data collection and analysis. She will lead development of materials for qualitative data collection such as interview guides, observation checklists, etc. She will design and lead a formative evaluation that will involve observing and recording a subset of patient interactions with research staff. She will also lead the summative analysis which will include semi-structured interviews with patients, family members and clinical staff. She will train and supervise study staff who conduct rapid qualitative

review and coding. She will lead development of the patient satisfaction surveys and assist with analyzing data and interpreting and publishing results.

University of California, San Francisco Team

Co-Investigator: Leah Karliner, MD, MAS

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Main responsibilities/Key roles: Dr. Karliner will oversee intervention activities at UCSF including hiring and training intervention team members, delivering the intervention, and facilitating interactions with the healthcare delivery system. In addition, she will participate in team meetings and contribute to study design, data collection, data analysis, interpretation of results, and presentation and publication of findings.

Co-Investigator: Kristine Yaffe, MD

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Main responsibilities/Key roles: Dr. Yaffe will assist with developing and implementing standard protocols for assessing patients for cognitive impairment and dementia and follow-up recommendations. In addition, she will participate in team meetings and will contribute to study design, data collection, data analysis, interpretation of results, and presentation and publication of findings.

Co-Investigator: Sei Lee, MD, MAS

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Main responsibilities/Key roles: Dr. Lee will provide expertise in geriatric medicine and clinical risk prediction modeling. He will participate in team meetings and will contribute to study design, data collection, data analysis, interpretation of results, and presentation and publication of findings.

PARTICIPATING CLINIC SITES

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2. Kaiser Permanente, Seattle, Northgate Medical Center
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Seattle, WA 98115

3. Kaiser Permanente, Seattle, TBD
Seattle, WA 98
4. UCSF Medical Center at Mount Zion
1545 Divisadero St
San Francisco, CA 94115
5. Women's Health Primary Care Clinic
2356 Sutter St., Third and Fourth Floors
San Francisco, CA 94143
6. Primary Care at China Basin
185 Berry St., Lobby 2, Suite 130
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1 STUDY OBJECTIVES

1.1 Preliminary work

We would like to note that we are currently performing preliminary work that will provide information needed for the main eRADAR RCT. Specifically, we are performing a retrospective cohort study using EHR data from KPWA and UCSF to examine the performance of the eRADAR algorithm for identifying patients with dementia diagnoses to help guide choice of cut-points for “high risk” that we will use to identify participants for this study. This work has been approved by local IRBs at KPWA and UCSF and is underway now. We do not provide a detailed description of these analyses here but mention it to provide context, as we refer to it elsewhere in this protocol.

1.2 Primary Objective

Conduct a pragmatic randomized controlled trial to assess the impact of implementing the eRADAR algorithm and the supported outreach process on dementia detection rates.

1.3 Secondary Objective

Explore the impact of eRADAR implementation on healthcare utilization and patient experience.

2 BACKGROUND AND RATIONALE

2.1 Background on Underdiagnosis of Alzheimer's Disease and Dementia

There are currently 5.8 million people in the U.S. living with Alzheimer's disease and related dementias (ADRD).^{1,2} Studies estimate that only about half have received a diagnosis.²⁻¹⁰ Barriers to dementia diagnosis in primary care settings include lack of curative treatments, concern about stigma, prioritizing management of other medical conditions, failure to recognize early symptoms, and lack of training. Many clinicians identify insufficient time as a key barrier.^{2,11-17} Several studies have identified the need for standardized tools and information technology resources to address these barriers and support earlier diagnosis.^{2,11,16,18}

Although the U.S. Preventive Services Task Force (USPSTF) does not recommend for or against routine screening of older adults for dementia due to lack of evidence that early detection improves patient outcomes,¹⁹ organizations such as the Alzheimer’s Association and the Gerontological Society of America advocate for early detection so that patients and families can be provided with adequate support and education throughout the disease process.^{20,21} In addition, the 2010 Affordable Care Act mandated that clinicians detect cognitive impairment as part of the Annual Wellness Visit (AWV) for Medicare recipients, although uptake of the AWV to date has been limited.²² NIA issued RFA-AG-20-051 to increase the evidence base for early dementia detection by supporting pragmatic trials of low-cost strategies in real-world clinical settings.

We have been leaders in development of dementia risk scores for the past decade.²³⁻³⁰ Such risk scores can be used to identify older adults at the highest risk for dementia so they can be targeted for outreach and intervention. In 2017, we were invited to present our prior work at the NIA-sponsored meeting “Cost-Effective Early Detection of Cognitive Decline” that led to this RFA. We subsequently received NIH pilot funding (R56 AG056417) to develop the electronic health record (EHR) Risk of Alzheimer’s and Dementia Assessment Rule (eRADAR) risk score, which uses easily accessible EHR data elements to identify patients with an elevated risk of undiagnosed dementia.²³ Our final eRADAR predictive model includes diagnoses for dementia risk factors (e.g., stroke, diabetes, traumatic brain injury); dementia-related symptoms (e.g., depression, being underweight); use of certain medication classes; and patterns of sub-optimal healthcare utilization (e.g., recent emergency department [ED] visits).

As described in RFA-AG-50-051, earlier detection of cognitive impairment has many potential benefits, including providing patients with appropriate treatment and support.^{20,21} However, there are also potential harms of earlier detection, particularly if implemented without an appropriate support process.^{31,32} These include anxiety, depression, stigma, social isolation, loss of driving privileges, and denial of long-term care insurance. In the recently completed Indiana University Cognitive Health Outcomes Investigation of the Comparative Effectiveness of Dementia Screening (IU CHOICE) trial—a randomized, controlled trial (RCT) that examined the benefits and harms of routine dementia screening of all older patients—33% of those who were eligible declined to participate, and 66% of those who screened positive, declined diagnostic testing and follow-up care.³³ The primary barriers to screening included perceived emotional distress and fear of losing independence. Other studies have identified similar barriers.^{31,32,34-37} Taken together, these studies highlight that any effort to improve dementia detection in clinical settings will need to also address patients’ fears and concerns to be successful.

As part of our development work, we collected qualitative data to inform pragmatic implementation of eRADAR. We conducted focus groups with diverse patients and caregivers (60% non-White) and clinicians and interviewed healthcare system leaders. Patients strongly preferred that outreach be initiated through their primary care providers (PCPs) and that they be provided with ongoing support rather than simply receiving a diagnosis. Clinicians emphasized that they also would need support to implement a tool such as eRADAR given their other clinical demands. In contrast, in the CHOICE trial, patients were screened by research assistants over the telephone, and those who screened positive were referred to a separate dementia care program for follow-up testing and care. Our hypothesized mechanism of action is that patients and clinicians will be more likely to accept dementia assessment if it is targeted at higher-risk patients and implemented in a familiar setting with appropriate support. In addition, we propose

to refine all outreach, assessment, and follow-up procedures with input from patients and clinicians to maximize acceptance rates.

2.2 Study Rationale

eRADAR was developed using data from the Adult Changes in Thought (ACT) study (U01AG006781),³⁸ an NIA-funded prospective cohort study of dementia set within the Kaiser Permanente Washington (KPWA) integrated healthcare delivery system. In ACT, community-dwelling KPWA members are screened for dementia every two years, and those who screen positive

undergo a gold-standard dementia diagnostic process.^{39,40} Because ACT is embedded within KPWA, it is possible to compare the timing of dementia diagnoses made through ACT with those made through routine clinical care. We classified ACT participants' status at each follow-up visit as 1) no dementia, 2) diagnosed dementia or 3) undiagnosed dementia (if the EHR did not include any diagnosis codes or medication fills indicating dementia.) We then developed a prediction model to differentiate between no dementia and undiagnosed dementia. Key predictors from the final model are shown in Table 1.

Discrimination based on the c statistic was good (training: 0.78; 95% CI: 0.76, 0.81; test: 0.81; 95% CI: 0.78, 0.84). The estimated sensitivity, specificity, and positive and negative predictive values (PPV and NPV) at different cut-points are shown in Table 2.

In 2018, we conducted five focus groups (n=40) including patients with dementia or mild cognitive impairment (MCI), patients with neither diagnosis, and caregivers (60% Hispanic or non-white). Topics included participants' experiences with dementia, preferences about timing of diagnosis, and use of EHR-based tools to screen for undiagnosed dementia. Participants generally supported early diagnosis; however, they wanted information about their dementia risk to come from a trusted provider such as their PCP, and they emphasized that diagnoses should be paired with ongoing support. Our current proposal addresses these issues by embedding our intervention in primary care as part of a supported process.

We also conducted two focus groups with KPWA clinicians (n=12), mostly from primary care,

Table 1. Key Predictors in the eRADAR Model		
Characteristic	No dementia,* % (N=15,640)	Undiagnosed dementia,* % (N=498)
<u>Dementia Risk Factors</u>		
Congestive heart failure	12	28
Cerebrovascular disease	11	21
Diabetes	7	13
Traumatic brain injury	1	4
Gait abnormality	8	17
<u>Dementia-Related Symptoms</u>		
Psychosis	2	7
Antidepressant fill	12	26
Underweight (BMI<18.5)	2	4
<u>Healthcare Utilization</u>		
≥1 Emergency Dept visit	26	46
*The unit of analysis for this table is the study visit, not the patient.		

Table 2. eRADAR's Performance at Varying Cut-points				
Risk cut-off (percentile*)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
≥ 95 th	23	96	16	98
≥ 90 th	36	92	12	98
≥ 85 th	47	87	10	98
≥ 75 th	66	78	8	99
≥ 50 th	91	52	5	99

and interviewed 10 delivery system leaders. Most delivery system leaders and providers favored making dementia diagnoses early in the disease process to allow for patient planning and to improve care management. There was broad consensus that implementing a tool such as eRADAR would need to be accompanied by additional resources and training for care teams. We propose to address these concerns by incorporating a pre-implementation phase to enhance clinic readiness.

3 STUDY OVERVIEW

This is an embedded, pragmatic randomized controlled trial. At each primary care clinic, we will randomize half of the primary care providers (PCPs) to the intervention or to a “usual care” control group. After applying inclusion and exclusion criteria, we will calculate eRADAR scores for the patients in each arm of the study to identify a subset of patients at risk of having undiagnosed dementia. The specific cut-point used to define the high-risk group will be determined with input from patient and clinician advisors. Study analyses will include the subset of patients with high eRADAR scores in each arm. Patients with high eRADAR scores whose PCPs are randomized to the intervention group will be invited to a brain health assessment visit. They will be encouraged to bring a care partner with them to provide additional information, but a care partner will not be required. Patients with high eRADAR scores whose PCPs are randomized to the control group will not be contacted by the research team and will receive usual care.

At the brain health assessment visit, the research interventionist will assess whether the patient has any concerns about memory loss or thinking, challenges with daily activities, or depressive symptoms, and will also administer a brief cognitive screening test. The research interventionist will then write a summary of the visit with recommended guidelines for next steps for the PCP. Patients whose results are consistent with dementia or who have evidence of another illness or condition needing treatment (e.g., unrecognized or undertreated depression) will be advised to follow up with their PCP. PCPs will order follow-up tests if needed and will meet with patients and care partners to conduct additional evaluation and assign a diagnosis, if appropriate. We expect that most patients will have normal findings and will not require follow up care. All patients who participate in a brain health assessment visit will receive a brief satisfaction survey after the visit.

For patients newly diagnosed with dementia, the research interventionist will reach out to offer a visit for post-diagnosis support. S/he will assess what kinds of help and resources they need and ensure they are receiving all available and applicable support. S/he will collaborate with other clinic team members within each healthcare system. The research interventionists will provide patients and family members with educational materials and referrals to community resources (e.g. the local Alzheimer’s Association) as appropriate.

We will audio- or video-record a subset of the initial brain health assessment visits at KPWA and UCSF to help us refine the visit process. In addition, a subset of intervention group patients and care partners will be invited to provide additional qualitative data at 1 month and 4 months post-assessment visit via in-depth interviews. We also will conduct semi-structured interviews with a subset of PCPs to seek their perspective on the impact of the intervention on patient care and workload.

We hypothesize that the eRADAR intervention will increase dementia recognition and diagnosis compared to usual care. In order to test our primary hypothesis, we will compare dementia diagnosis rates among high-risk patients in the intervention arm (including those who decline an assessment visit, following “intent to treat” principles) with high-risk patients in the “usual care” arm. Dementia diagnoses will be assessed from the EHR based on standard ICD-10 codes. The primary outcome will be dementia diagnoses in the 12 months following the “index date,” that is, the date on which the patient’s eRADAR score was calculated and categorized as high risk or not high risk. As secondary outcomes, we will examine rates of dementia diagnosis over 6 and 18 months following the index date.

The study will take place at 3 Kaiser Permanente Washington outpatient clinics (Capitol Hill, Northgate and TBN) and 3 UCSF outpatient sites (Mount Zion, Women’s Health, and China Basin) that together comprise 5 clinics. The study population at all sites/clinics will include current patients of participating PCPs who are age 65 and older, do not have a dementia diagnosis or take dementia medications, and have enough historical data to calculate eRADAR scores.

4 SELECTION AND ENROLLMENT OF PARTICIPANTS

This study involves several different categories of participants (patients, care partners, and providers), each of which has different inclusion/exclusion criteria and different study procedures.

4.1 Inclusion/Exclusion Criteria

Patient Participants

- Age 65 years or older
- No prior diagnosis of dementia and not receiving medications for dementia
- Active patient at KPWA or UCSF participating clinic
- Have adequate EHR data to calculate eRADAR score (e.g., at KPWA, meeting prespecified criteria for length of enrollment; at UCSF, meeting prespecified criteria for number of visits over a set time period)
- Not currently receiving hospice care
- UCSF participants must have English, Spanish, Cantonese, or Mandarin as their preferred language in their medical record.

Care Partners

- 18 years or older
- Family member or other individual selected by patient to accompany them to the assessment visit

Providers

- Primary care provider at participating clinic
- Panel of patients includes older adults

- Clinic chiefs will have the option to exclude certain providers, such as those very recently hired or close to retirement
- Not a locum tenens or “panel replacement” provider (temporary provider in a clinic)
- Not a medical resident (physician in training)

4.2 Study Enrollment Procedures

4.2.1 Randomization and Blinding

The study biostatistician will create a computer-generated sequence to randomize eligible PCPs to the intervention vs. usual care groups. We will stratify randomization by clinic and block by the number of eligible patients on each PCP’s panel (broadly grouped). The rationale for blocking by number of eligible patients is that this characteristic may correlate with physician practice patterns and their engagement with and learning from the intervention, influencing the intervention’s effectiveness. Due to the nature of the intervention, we will not be able to blind PCPs or patients to their treatment assignment. However, study outcomes derived from EHR data will be extracted in a blinded manner.

4.2.2 Assignment of “Index Date”

At each site, an experienced programmer will extract relevant data from the EHR to determine which patients at a given clinic meet eligibility criteria. For those who are eligible, the programmer will calculate eRADAR scores and generate a ranked list with percentiles. Those who are assigned to a PCP in the intervention group and have a high eRADAR score (above the chosen threshold) will be selected to receive outreach. Because it will not be possible for interventionists to reach out to all high-risk patients in a given clinic at the same time, we will identify groups of eligible participants in blocks. For example, we might extract a block of 1,100 eligible patients, of whom 110 would be considered “high risk” using a cut-point of the top 10%. Of these, we would estimate that about 55 would be patients of PCPs who were previously randomly assigned the intervention group. All high-risk patients will be assigned an “index date” that will be used for enrollment and follow-up purposes. The “index date” will be defined as the date on which their eRADAR score was calculated and they were categorized as “high risk” and eligible for outreach in the intervention group. PCPs in the intervention group will have the option to review their list of patients with high eRADAR scores prior to outreach and to indicate any patients who should not be contacted (e.g., patients with a terminal illness). However, these patients will still be included in intention-to-treat analyses, since PCPs in the usual care group will not have a similar opportunity to exclude specific patients.

4.2.3 Outreach to Eligible Intervention Patient Participants

Study staff will mail a letter with an information sheet to eligible intervention group patients describing the program and inviting them to meet with the interventionist for a brain health assessment visit. Patients will be requested to bring a spouse, family member or friend (“care partner”) if possible, but this will not be mandatory. Patients will be given information allowing them to opt out of any further contact, or to call the study team to express interest. The letter also

may include a link to a secure online portal for patients who prefer to respond electronically. Patients will be given at least a week to respond, after which they will receive a follow up phone call from a research team member to describe the program, answer any questions and schedule the visit.

A study screening log will be used to document outreach efforts, including number, type, and outcome of contacts made. Because we are following “intention-to-treat” principles, all eligible patients will be included in study analyses, regardless of randomization group or participation in the intervention. We will also use the screening log to document reasons that eligible patients decline to participate so that we can make adjustments to outreach materials if needed. If we have difficulty reaching patients or scheduling them for brain health assessment visits, we also will consider alternative outreach procedures, such as identifying upcoming primary or specialty visits and coordinating outreach to coincide with those visits. For example, for patients with upcoming visits, we could alert their PCP who could either 1) initiate an evaluation of cognitive and functional status themselves, if appropriate and acceptable to the patient, or 2) provide the patient with information about the study and encourage them to connect with the research team.

5 STUDY INTERVENTION

5.1 Pre-Intervention Phase

We will begin by establishing relationships within each clinic and assessing clinic readiness for eRADAR implementation. We will collect information from providers, staff, and leadership about their comfort level providing dementia evaluation and care. We will attend existing clinic meetings and facilitate discussions with groups of PCPs and clinic staff. After gaps have been identified, clinicians on the research team (Drs. Dublin or Grace at KPWA and Drs. Karliner and Yaffe at UCSF) will provide additional training as needed, emphasizing existing guidelines, processes and EHR-based tools. During this phase, we will also leverage existing KPWA Epic SmartSets for dementia care to build the same tools at UCSF.

5.2 Brain Health Assessment Visit

Research interventionists will be trained and licensed health practitioners (e.g., social workers, registered nurses). At the brain health assessment visit, the research interventionist will take a brief history and then assess cognitive and functional status. Where possible, we will use standardized

Table 3. Instruments Used for Assessment of High-Risk Patients	
Domain	Instrument
Instrumental Activities of Daily Living (IADLs)	Selected and modified Lawton IADLs ⁴¹
Depressive Symptoms	PHQ-2; if positive, progress to PHQ-9. ⁴² Assess for suicidal ideation if indicated.
Memory and Cognition	Montreal Cognitive Assessment (MoCA) ⁴³
Care Partner Perspective (if available)	AD8 ⁴⁴

instruments that are part of routine clinical care at the study sites, such as the Montreal Cognitive Assessment (MoCA)⁴³ for cognition and the two-item Patient Health Questionnaire (PHQ-2) for depressive symptoms (Table 3). The brain health assessment visit may occur virtually or in person and will take between 30 to 60 minutes.

5.2.1 History

The history will involve asking about the patient's current living situation (e.g., whether they live alone or have family or other support nearby), difficulty with vision or hearing, education, sleep, falls, and subjective changes in memory or thinking or daily activities/hobbies.

5.2.2 Functional Status

Functional status will be assessed using a modified version of Lawton's Instrumental Activities of Daily Living (IADLs), focusing on independence in medications, finances, driving/transportation, shopping, and meal preparation.

5.2.3 Depressive Symptoms

The PHQ-2 will be used to screen for major depressive disorder. If the PHQ-2 is positive (defined as a score of 2 or higher on either screening question), then the full PHQ-9 will be administered. If the score on item 9 (suicidal ideation) is 2 or 3, then Columbia Suicide Severity Risk Assessment (CSSRA)⁴⁵ will be administered. When administering the CSSRA, the interventionist will stop after the first question where the patient answers "No". All research interventionists will be thoroughly trained in how to assess for and address any suicidal thoughts.

5.2.4 Cognitive Function

We will screen for cognitive impairment using a standard, validated tool. We are currently planning to use the MoCA.⁴³ The MoCA includes items to assess attention and concentration, executive functions, memory, language, visuo-constructional skills, conceptual thinking, calculations, and orientation. For the in-person version, scores may range from 0 to 30, and an additional point is added for those with 12 or fewer years of education. Scores of 26 or greater are considered normal, scores of 18-25 are consistent with mild cognitive impairment (MCI) or possibly dementia (depending on functional status), and scores less than 18 are consistent with dementia.

At the end of the visit, all patient participants will be provided with a standard brochure about maintaining brain health.

5.2.5 Care Partner Participation in Brain Health Assessment Visit

All participants will be encouraged to bring a family member or other trusted individual (care partner) with them to the brain health assessment visit. The research interventionist will include them in the conversation about the participant's cognitive and functional status (for example, by asking if they have noticed any changes in the participant's memory, thinking, mood, or ability to manage daily tasks). In addition, care partners may be asked to complete the AD8 Dementia Screening Interview, a validated measure that asks whether the participant has experienced a change in the last several years (yes/no) caused by problems with memory or thinking in eight areas such as judgement, hobbies, or repeating things.⁴⁴ Scores of 0 or 1 are consistent with normal cognition, and scores of 2 or greater are consistent with cognitive impairment.

5.3 Notification of Results

The research interventionist will enter results into the EHR, where possible using flowsheets or SmartForms (tools that support the entry of patient data in a structured format, facilitating retrieval and visualization). S/he will also write a chart note using a standardized template developed for this research study. It will include history and test results. For patients whose results suggest dementia, we will reach out to the PCP to alert them, provide interpretation of the findings, and suggest next steps based on standard guidelines at the healthcare system. We will direct PCPs to existing SmartSets (decision support tools) in use at the healthcare system. We will either route the chart note to the PCP or use a Staff Message in Epic to convey recommendations; the choice will be determined by input from clinician stakeholders in the healthcare system as to what is most effective when follow up is needed.

It is expected that a large proportion of patients will have normal cognitive scores and report no impairment in cognition, daily functioning, or depressive symptoms. These patients will be notified by the research interventionist at the end of the visit that their results are normal and that there are no concerns about cognitive impairment at this time.

Patients whose results are consistent with dementia (abnormal cognitive score with report of functional limitations due to memory or cognition) will be told that the next step is to schedule a follow-up visit with their PCP. PCPs will be provided with information about probable diagnoses and recommended next steps for each patient as well as information about SmartSets (order sets) within Epic that provide decision support on laboratory testing, imaging, and specialty referrals. PCPs will be responsible for ordering all follow-up tests and meeting with patients to make final diagnoses of dementia, MCI, or other disorders.

Patients who during the assessment visit are found to have other health problems needing treatment (e.g. depressive symptoms that are moderate or more severe, defined as a PHQ-9 score ≥ 10) will also be advised to follow up with their PCP, and the PCP will be notified about this finding via Staff Message within Epic.

For patients whose results are consistent with dementia, research interventionists will periodically review the Epic chart to confirm that a follow up visit with the PCP has occurred. If one month after the brain health assessment visit, a patient does not have a follow up appointment with their PCP scheduled yet, research interventionists will reach out to the patient to determine why and attempt to help problem-solve if the patient is open to this. They will also note the reason(s) that follow up did not occur in the research file.

5.4 Intervention Follow-Up Visit

Research interventionists will reach out to patients who are newly diagnosed with dementia to schedule a follow-up visit. As with the brain health assessment visit, patients will be strongly encouraged to bring a family member or other trusted individual to serve as a care partner. The research interventionist will work with the patient's primary care team to connect patients and care partners with appropriate resources within the healthcare system and in the community.

6 STUDY PROCEDURES

Because this is a pragmatic trial, there are relatively few study visits or procedures other than the

brain health assessment visit. Section 6.1 below details other planned study activities and their anticipated timeframes.

6.1 Overview of Data Collection and Evaluations

Here we provide an overview of each data collection time-point other than the brain health assessment visit, with additional details provided in the next section.

Intervention group, subset of high-risk patients and care partners:

- Observation/recording of selected brain health assessment visits: 30 or more patients at each site. Both patients and care partners will be observed and recorded during this process.
- Semi-structured interviews: About 24 patients and care partners from each site who agree to observation/recording of their brain health assessment visit will be purposively selected and invited to undergo a semi-structured interview. Timing: 1 and 4 months following brain health assessment visit.

Intervention group, all high-risk patients who complete brain health assessment visit

- A post-visit evaluation survey will be sent to all patients who complete the brain health assessment visit to seek their feedback on the process. Data from initial surveys will be used to refine the outreach process (formative evaluation). Data from later surveys will be used to assess patient satisfaction (summative evaluation).

All high-risk patients (intervention and control groups)

- EHR data extraction for baseline characteristics and patient outcomes: Our primary outcome is dementia diagnoses 12 months following each patient's "index date." Sensitivity analyses also will examine dementia diagnoses at 6 and 18 months.

Primary care providers and other clinical team members:

- Semi-structured interviews: About 20 PCPs or other clinical team members will be selected and invited to undergo a semi-structured interview to assess their experience and satisfaction with the eRADAR intervention and how it affected their workflow and burden of clinical responsibilities.
- Debriefs: Group debrief sessions/discussions will take place quarterly while the eRADAR study is active in a clinic. Those who will participate in debriefs include the study research interventionists and clinic staff who are interfacing often with the eRADAR study. This may include individuals in roles such as: CRS (Community Resource Specialist), clinic social worker, and other supporting clinic staff (medical assistants, nurses, etc.) identified by the study research interventionist as potentially impacted by the study visit workflow.

6.2 Detailed Description of Data Collection and Evaluations

6.2.1 Observation/Recording of Selected Brain Health Assessment Visits (Subgroup of Patients and Care Partners)

A subgroup of patients and care partners that attend the brain health assessment visit will be asked for permission to observe and either audio or video record their visit during the startup phase in each health care system. Participants are free to decline to be observed or recorded. The purpose of the observations is 1) to identify any patient distress, so we can improve the

intervention to minimize distress; and 2) to monitor fidelity to study procedures (improving validity of the study). Members of the study qualitative research team who are observing and/or listening to the recordings will fill out a brief notes template that includes the outcomes of the visit, key questions raised, any signs of emotional distress and any feedback provided by patients and family members. Participants agreeing to be observed will be asked for permission to recontact them in the future (so that we can invite them for a semi-structured interview) and their preferred mode of contact (telephone, letter, email or text.)

6.2.2 Post-Visit Survey (Patients)

This survey activity has two goals: 1) results in the early months of the intervention will be used to refine and improve study activities, to improve the patient experience (that is, a formative evaluation); and 2) results will be used at the end of the study for summative analyses to describe patients' satisfaction with the study intervention. Within one week after the brain health assessment visit, each patient participant will receive a brief evaluation survey that can be completed either by mail or online using a secure online link. The survey will ask about their perceptions of and satisfaction with the outreach and assessment process and will include structured questions as well as room for free text comments. Surveys from the first ~40 patients at each site will be used for the formative evaluation; the survey will continue throughout the trial, and results will also be used in Aim 3 to assess patient experience. Participants who complete the survey will be paid \$5. If the patient is unable to fill out the survey on their own, they will be instructed in the cover letter that they can have a friend or family member help them fill it out.

6.2.3 Semi-Structured Interviews (Patients and Care Partners)

From those patients and care partners agreeing to have their brain health assessment visit observed and recorded for the study, a purposive recruitment approach will be used to recruit 20 patients and up to 20 care partners (10 per site) for in-depth interviews at 1 month and 4 months after study enrollment. Patients whose assessment visit results indicate cognitive impairment or dementia will be oversampled. We will also oversample people of color, if possible, based on the composition of the group participating.

The selected group of participants will receive an invitation via the communication mode they have previously indicated that they prefer, including by telephone, mail, email or text. They will be invited to complete semi-structured interviews that explore perspectives on their experiences with the brain health assessment program, including outreach, the assessment visit, the process of clinical evaluation leading to a final diagnosis, and how their experience has affected their planning and decision making, especially emotional and/or practical impacts of the program. The 4-month follow-up interview will explore longer-term impacts including any impact on planning or decision making. These interviews may occur remotely or face-to-face at the study site. Participants who agree to the interview will be paid \$50.

If the initial sample of participants whose visits were observed and recorded does not include enough patients with cognitive impairment or dementia, we will expand the sample and also invite some participants whose assessment visits were not observed and recorded, because we place a high value on interviewing people found to have abnormal cognitive results. A similar

targeted sampling approach may be used if we find that specific groups such as people of color (racial or ethnic minority groups) are under-represented in the sample of participants who agree to have their visits observed and recorded.

6.2.4 Semi-Structured Interviews (Providers)

We will interview 20 primary care team members (10 per site) whose patients received the intervention. These interviews will be about 30 minutes in length and will explore their awareness of the eRADAR process, input on the workflow and communication between the eRADAR interventionist and the primary care team, and the interactions that PCPs have had with patients about the intervention, particularly those with abnormal cognitive findings. If PCPs are permitted to complete these interviews during normal work hours, then no incentive will be provided. If PCPs are required to complete the interviews on non-work time, we will pay them \$75 for participating.

6.2.5 Extraction of EHR Data for Baseline Characteristics, New Diagnoses and Healthcare Utilization (All High-Risk Patients)

We will extract baseline data on all high-risk patients so that we can describe their demographic characteristics and adjust for medical conditions in analyses. We will also use the baseline data to describe characteristics of people who agree to participate in the brain health assessment visit compared to those who do not participate.

The primary and secondary study endpoints will be identified by extracting data from the EHR. We will define outcomes as of 6, 12 and 18 months following each patient's index date. The primary time point is the 12-month point, but we will also analyze data for outcomes defined at 6 and 18 months following index date for sensitivity analyses.

Our study population for the primary analysis is all eligible patients whose PCPs meet eligibility criteria and whose eRADAR scores are above the selected cut-point. Because only these “high-risk” individuals are invited for an assessment visit, eRADAR's impact should only be seen in this group; limiting analyses to this group (rather than all patients in the base population) should improve our power. We will compare outcomes among high-risk patients in the intervention arm (including those who decline an assessment visit, following intention-to-treat principles) with outcomes among high-risk patients in the usual care arm. To follow intention-to-treat principles, it is necessary to include patients who did not come in for an assessment visit, or else the resulting bias might threaten the validity of the study.

The primary outcome for **Aim 1** will be the rate of new dementia diagnosis over 12 months. We hypothesize that the eRADAR intervention will increase dementia recognition compared to usual care. Dementia diagnoses will be assessed from the EHR based on standard ICD-10 codes.⁴⁶

In **Aim 2** we will explore the impact of the eRADAR intervention on healthcare utilization (based on EHR data; see **Table 4**).

Table 4: Aim 2 Outcomes Identified from EHR Data	
Description of Category	Measures
Healthcare utilization or burden potentially resulting from eRADAR intervention	• Number of PCP visits in the 6 months following the index date • Laboratory tests performed (e.g., Thyroid Stimulating Hormone, vitamin B12) • Neuroimaging (e.g. brain Magnetic Resonance Imaging) • Referrals (e.g. to Speech, Language and Learning or Neurology) • New prescriptions for dementia medications
Healthcare utilization measures that could improve with better detection and support of patients	• PCP visits in 1 year following the index date • Urgent care or Emergency Department visits in 1 year • Inpatient stays in 1 year, especially for Ambulatory-Care Sensitive conditions • “No shows” for clinic visits • Medication adherence (measured as Proportion of Days Covered)^{47,48}

7 SAFETY ASSESSMENTS

7.1 Risks and Discomforts

7.1.1 Risks Associated with Use of EHR Data

We will use EHR data for several aspects of this study. Specifically, we will use EHR data to identify patients who meet eligibility criteria; to recruit eligible patients who are randomly allocated to the intervention group; and to assess outcomes and safety in both groups. Use of health records for these purposes may increase the risk of violating patient/participant privacy or confidentiality.

7.1.2 Risks of the Intervention

This study is embedded in primary care, and all study procedures are consistent with standard geriatric care and best clinical practices. For example, the Affordable Care Act requires “detection of cognitive impairment” as part of Annual Wellness Visits for all older adults, and most of the tools we are using in the assessment visit are part of routine clinical care in our healthcare systems. The research team will have only a few points of contact with most intervention group participants: 1) an invitation letter; 2) one or more scheduling phone calls/emails; 3) the brain health assessment visit; 4) post-visit evaluation survey; and 5) for the subgroup found to have dementia, a follow up visit. A relatively small number also will have their brain health assessment visits observed and will be invited for in-depth interviews. The primary “experimental” aspect of this study is use of an EHR-based algorithm to identify high-risk patients to target for clinical outreach and assessment.

This targeted outreach approach has several risks. Some patients may experience emotional distress related to the outreach or brain health assessment processes. Patients who ultimately receive a dementia diagnosis may experience additional emotional distress. This emotional distress could potentially lead to depression and, in rare but extreme cases, suicidal ideation. These risks are comparable to things that could occur in the course of usual clinical care, in the absence of any intervention.

We also will be putting results from the assessment visit into the EHR. These results will be factual and will include patient-reported history, functional status, depressive symptom scores

(PHQ2/9), and cognitive test scores (MoCA, AD8 if administered). PCPs will be responsible for interpreting results, ordering follow-up tests if needed, and making any final diagnoses.

It is expected that the brain health assessment visit will have downstream consequences for some patients who are found to have undiagnosed dementia. For example, receiving a dementia diagnosis could affect a patient's ability to obtain long term care insurance, the cost of their premiums for health insurance or long term care insurance, driving privileges, and living situation. Healthcare providers caring for the patient will be able to see the brain health assessment visit results and any subsequent dementia diagnoses recorded in the chart, which could affect future care provided to the patient. We consider these to be risks primarily from the presence of dementia, more so than of the intervention, but we acknowledge that the intervention itself is increasing the likelihood of this information being put into the medical record.

7.2 Strategies to Reduce Risks

7.2.1 Reducing Risks Associated with Use of EHR Data

The study programmer/analyst at each site will maintain a list of participant identifiers linked to study identifiers. These lists will be stored in directories in each health system's HIPAA/HITECH compliant computer networks. Access to these networks requires a user ID and password, and access to study folders is restricted to designated team members. Identifiable information will only be available to study staff with clear need to know (for example, programmer/analysts who need them to pull data; study investigator responsible for reviewing medical records for serious adverse events; intervention clinicians; members of the Qualitative sub-team who need them to conduct patient interviews; etc.). Analytic datasets will be limited datasets, that is, containing dates and ages > 89 but no other identifying information.

7.2.2 Reducing Risks Associated with Sharing or Accessing Identifiable Data

For certain study activities, identifiable data will be shared between sites. For example, KP Washington study team members will conduct some observations of brain health visits and semi-structured interviews involving UCSF patients and/or clinicians. Transcripts of interviews and brain health visits will be shared between sites. While we do not intentionally collect identifiers during interviews, the recordings and transcripts may contain identifiers such as names of the participant or care partner. We will put in place appropriate agreements such as Data Use Agreements or Data Transfer Agreements to govern data sharing. We will create a Data Sharing Checklist for study staff to use before transferring data. Data that may contain identifiable information will be shared using secure transfer methods such as the KP Washington Secure File Transfer site.

Certain study activities may also involve research team members at one site accessing, hearing or viewing identifiable data for the other site. For example, both teams participate together in meetings where cases are discussed. While we do not intentionally share identifiers during this meeting, it is possible that identifiable information could be inadvertently shared as part of the case reviews. Research team members at one site may also be granted approval to access secure research databases at the other site if access is needed for them to do their jobs. For example, qualitative team members may need to access research databases to obtain identifiable information such as participant names and contact information to perform semi-structured interviews. We will reduce the risks of these activities by reminding all research team members

to disclose identifiable information only when necessary and by restricting access to team members with a “need to know.”

7.2.3 Reducing Risks of the Intervention

We are incorporating many strategies to minimize potential risks associated with the intervention and are also including procedures to identify potential unintended harms:

- 1) We have convened a Patient Advisory Committee to review and provide feedback on outreach procedures and processes.
- 2) The interventionist will document participant responses to the outreach and evaluation process, and this information will be reviewed at weekly team meetings. Materials and processes will be revised iteratively to address concerns as they are raised.
- 3) An evaluation survey will be sent to all individuals who undergo a brain health assessment visit to gather information on satisfaction with the process and unintended consequences. Results will be entered into a database, and responses will be reviewed monthly by the research team.
- 4) In the first few months of the intervention, we will perform a formative evaluation in which a subset of brain health assessment visits will be directly observed, recorded and reviewed by research team members to identify negative responses not directly reported by the interventionist or patients. Findings will be reviewed at research team meetings, and materials and processes will be further revised to address issues identified.
- 5) In-depth interviews will be conducted with a subset of patients and caregivers one and four months after the initial assessment to gather information on their experiences, including any longer-term adverse consequences.

Results of these activities will be summarized and reviewed every six months by the Data and Safety Monitoring Board (DSMB) convened by the NIA.

7.3 Specification of Safety Parameters

7.3.1 Safety Parameters in the Control Group

We will have no contact with participants in the usual care group and, therefore, it will not be possible to monitor individual patient safety in this group.

7.3.2 Safety Parameters in the Intervention Group

In the intervention group, we will monitor the following safety parameters, which are summarized in Table 5.

Participant complaints. We will track participant complaints received related to the intervention in several ways:

- 1) We will document any complaints or incidents reported in response to the outreach letter or scheduling process.
- 2) We will document any complaints received related to the brain health assessment or follow-up visit, including complaints about the observation process.

3) We will send a post-visit survey to all individuals who participate in a brain health assessment visit that will ask whether they agree or disagree with statements such as “I felt the invitation letter was clear” and “I felt upset or concerned because of the visit.” The survey will also have open ended questions asking them if anything did not go well during their visit.

4) We will conduct in-depth semi-structured interviews with a subset of participants and their care partners/family members to gain deeper insight into the impact of our targeted outreach and assessment approach. The qualitative team will document participant and care partner complaints reported during these interviews.

Depression and suicidal ideation: At all brain health assessment and follow up visits, the research interventionist will use the PHQ-2 to screen for depressive symptoms. If the PHQ-2 is positive (score of 2 or higher on either screening question), then the full PHQ-9 will be administered. If depressive symptoms are moderate to severe (PHQ-9 score ≥ 10), participants will be advised to follow up with their PCP, and the PCP will be notified about this finding via Staff Message within Epic. In addition, if the response for item 9 (suicidal ideation) is 2 or higher, the Columbia Suicide Severity Risk Assessment (CSSRA)⁴⁵ will be administered. This cut-point was chosen to be consistent with current KPA guidelines for clinical practice in primary care. When administering the CSSRA, the interventionist will stop after the first question where the participant answers “No”. If the CSSRA reveals high risk of self-harm (“yes” to all items), the interventionist will work with the participant to arrange appropriate follow-up care. Depending on the urgency of the situation, this might include providing resources such as Crisis Line numbers, connecting with Behavioral Health care, or assessment in the emergency department or by a local 24-hour mobile crisis team. All clinical research team members will receive annual trainings in suicide risk assessment and prevention. Clinical supervisors also will be available for as-needed clinical consultation.

We will monitor and track the number of patients who at their follow up visit are found to have depressive symptoms that are moderately severe or severe (defined as PHQ-9 score ≥ 15), the number reporting suicidal ideation (PHQ-9 question 9 score of 2 or greater), and the number and outcomes of patients who are administered the CSSRA.

Deaths: Intervention group participants in this study have relatively few interactions with the research study team (recruitment and scheduling calls; brain health assessment visit; follow-up visits in subset newly diagnosed with dementia; interviews in small subgroup 1 and 4 months after the brain health assessment visit). Therefore, the research team has few opportunities to identify individual participants who have died. In the unlikely event that we learn that a participant has died (for example, when trying to schedule a follow-up visit or interview), we will review the medical record to determine the cause of death. We will classify the death as expected if it is due to an underlying health condition or due to a health condition or illness that is not related to the study (such as infectious disease). The only deaths that could plausibly be caused by this study are suicide and, possibly, accidents.

7.3.3 Group-Level Safety Parameters

This study does not include any drugs or devices and is not expected to impact patients’ physical health. We are not conducting any laboratory testing or physical examinations and thus will not

be detecting any health conditions or worrisome findings with respect to medical conditions. Nonetheless, we will use automated EHR data to assess for group-level differences in key safety parameters including new diagnoses of depression or prescriptions/fills for new anti-depressant medications; diagnoses of suicidal ideation or self-harm (defined from automated diagnosis data using ICD-10 codes); death; and hospitalizations (Table 5). We will compare patients with high eRADAR scores randomized to the intervention and control groups (following intention-to-treat principles).

We also will look at rates of these events specifically in the subset of patients randomized to the intervention who participated in the assessment visit and will compare them with rates in patients in the control arm, using weighting to account for differences between those who choose to participate in the visit and those who do not. It is important to look for safety signals within the subset of people offered the intervention who actually participated in the assessment visit because otherwise, if the response rate is low, we could miss a safety signal. People who agree to participate in a visit are not a random sample, so it would not be appropriate to compare their rates of safety events to the entire control arm without weighting. In the treatment arm, we can calculate the probability of coming to the appointment conditional on patient characteristics such as the eRADAR risk score, Elixhauser comorbidity score, age, race, ethnicity, and sex. We will already have collected data on all of these factors because they are needed to calculate the initial eRADAR score and/or to evaluate the intervention's impact accounting for censoring. We can then re-weight all patients in the control arm so that they have the same distribution of all the covariates used in the weighting model as the distribution observed among patients in the treatment arm who did attend an assessment visit. We will use that same weighting to estimate adjusted rates of new depression diagnoses, new starts of anti-depressant medication, suicidal ideation, self-harm, death, and hospitalization in the control arm and compare that to event rates observed in the treatment arm among patients who attended the brain health assessment visit.

It is important to note that our intervention is designed to identify underlying depression or suicidal ideation as part of the evaluation, and so it is likely to result in increased documentation of these conditions in the intervention group. In the brain health assessment visit, we specifically assess depressive symptoms, and if substantial symptoms are found (PHQ-9 score ≥ 10), we will recommend follow up with their primary care doctor for evaluation and treatment as appropriate. This will likely result in more diagnoses of depression and/or more new anti-depressant medication prescriptions/fills being recorded for the intervention group than the control group, who are not receiving screening or assessment related to depression. In other words, increased recognition and treatment of pre-existing depression is a potential benefit of our intervention, not necessarily a safety signal. Using automated diagnosis and medication data alone, we will not be able to distinguish depression diagnoses that reflect improved recognition and treatment of preexisting depression from diagnoses that indicate new-onset depression as a consequence of the intervention.

Table 5: Safety Parameters for this Study

Safety event	Level of monitoring	How monitored
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Participant complaint	Individual level, intervention group only	Complaints received in response to outreach or as part of brain health assessment visits, observations, post-assessment surveys, or semi-structured interviews
Depression	Individual level, intervention group only	Assessed at all brain health assessment and follow up visits with research interventionist using PHQ-2 and, if positive, PHQ-9
Suicidal ideation and suicide risk assessment	Individual level, intervention group only	Assessed at brain health assessment and follow up visits for patients with a positive PHQ-2 (indicating possible depression) using the PHQ-9 (item 9) and, if item 9 is positive, further assessed using Columbia Suicide Severity Risk Assessment (CSSRA) ⁴⁵
Deaths	Individual level, intervention group only	Incidentally discovered during study contacts/outreach for participants who participated in a brain health visit. For these deaths, a study physician will review medical records and characterize the death as expected vs. unexpected.
Depression and antidepressant use	Group-level comparisons	Routine assessment every 6 months from EHR - Incident diagnosis of depression (assessed from diagnosis codes) - New starts of an antidepressant medication (determined from pharmacy dispensing data at KPWA and medication orders at UCSF)
Diagnoses of suicidal ideation or self-harm	Group-level comparisons	Routine assessment every 6 months from EHR (diagnosis codes only)
Death	Group-level comparisons	Routine assessment every 6 months from automated EHR and/or mortality data (however, we note that there is likely to be incomplete capture of deaths and significant data lag)
Hospitalizations (any cause)	Group-level comparisons	Routine assessment every 6 months from automated EHR data

7.4 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

The multiple PIs will meet weekly with research team members throughout the study to review progress and discuss and address any safety issues that arise. This will include reviewing all participant complaints, depression, and suicidal ideation that occur in response to the outreach process or during a brain health assessment or follow up visit. The qualitative analysis team also will report any observations of emotional distress, depression, or suicidal ideation that occur during observed visits or semi-structured interviews during team meetings.

In addition, our study programmer will create summary reports for DSMB meetings that will include PHQ-2/9 and CSSRA scores in the intervention group as well as summaries of suicidal ideation, self-harm, hospitalization, and death in the intervention vs. control groups, and in patients in the intervention group who participate in the brain health assessment visit vs. the weighted sample of controls.

7.5 Adverse Events and Serious Adverse Events

7.5.1 Availability of Data Regarding Potential Adverse Events

In contrast to adverse event data collected and reported by traditional clinical trials, data regarding adverse events in this pragmatic trial will be limited in detail and delayed in time. Data regarding diagnoses of suicidal ideation, self-harm, hospitalizations, and death will be extracted from health system administrative databases regarding encounter diagnoses and insurance claims. Given that these data are collected under a waiver of consent and waiver of HIPAA authorization, investigators are only allowed to extract and store the minimum information necessary to address study hypotheses. Because we will extract group-level rather than individual-level data, these data will be limited in detail. Because insurance claims data may be submitted up to three months following a health care encounter, data regarding suicide attempt diagnoses from insurance claims may be delayed by up to three months. Because suicide deaths are most often identified by linkage with state death certificate data, data regarding suicide deaths may be delayed by 1 year or longer.

7.5.2 Definition and Reporting of Adverse Events (AEs) and Serious Adverse Events (SAEs)

As described above, the research team has relatively few points of contact with intervention group participants, and no contact with the usual care control group. We are not conducting any laboratory testing or physical examinations and thus will not be detecting any health conditions or worrisome findings with respect to medical conditions. Therefore, there will be few opportunities to assess for individual-level AEs or SAEs in the intervention group, and none in the control group.

Adverse Event (AE): An AE can be defined as any untoward or unfavorable medical occurrence in a clinical research study participant, including any abnormal sign (e.g. abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the participants' involvement in the research, whether or not considered related to participation in the research. For this study, we will assess for AEs in the intervention group by asking closed- and open-

ended questions about negative effects of the brain health assessment visit on the post-visit survey and during in-depth interviews. AEs reported will be summarized for DSMB reports.

Serious Adverse Event (SAE): SAEs are typically defined as AEs that result in death, life-threatening event, hospitalization, or significant disability. For this study, we will extract data on suicidal ideation, self-harm, death, and hospitalization and provide group-level summaries for DSMB reports. If we learn that an intervention group participant has died due to suicide or accident during the follow up period, we will report the event to the NIA PO, DSMB, and IRB within 48 hours of PI awareness.

7.6 Protocol Violations and Research-Related Incidents

We will track and report the following types of protocol violations and research-related incidents.

Protocol Violations: Any unapproved changes, departures or deviations from the study design or procedures of the research project that are under the investigator's control and have not been reviewed and approved by the IRB.

Major (Reportable) Protocol Violations: Any protocol violations that affect the participant's rights, safety, or well-being, or the completeness, accuracy and reliability of the study data. Criteria for defining major violations include any of the following:

- The violation has harmed, or posed a significant or substantive risk of harm, to the research participant.
- The violation resulted in a change to the participant's clinical or emotional condition or status.
- The violation has damaged the completeness or soundness of the data collected for the study
- The violation is evidence of willful or knowing misconduct on the part of the investigator(s)
- The violation involves serious or continuing non-compliance with federal, state, or local guidelines.

Major (Reportable) Incidents: Any problematic or unanticipated events involving the conduct of the study or study participants that affects the rights, safety, or well-being of participants or others, or the completeness, accuracy and reliability of the study data. Examples include:

- Significant complaint or concern received from a potential or enrolled study participant.
- Inappropriate behavior of study participants and/or research personnel.
- Problems during study recruitment or the informed consent process.
- Potential breach of study participant's privacy or confidentiality
- Withdrawal or significant reduction in resources necessary to safely and adequately conduct study activities
- Changes to the protocol to eliminate or reduce an apparent immediate hazard to the safety of research participants or others.

7.7 Safety Monitoring

The multiple PIs (Sascha Dublin, MD, PhD, and Deborah Barnes, PhD, MPH) will be responsible for overseeing participant safety. The DSMB will act in an advisory capacity to the NIA Program Officer (PO) to monitor participant safety, evaluate the progress of the study, and review procedures for maintaining the confidentiality of data and the quality of data collection, management, and analyses.

DSMB Responsibilities

Prior to and at the beginning of DSMB meetings, DSMB members will confirm they have no conflicts of interest with investigators or key personnel. The DSMB will be responsible for: reviewing the Study Protocol and Manual of Procedures (MOP) with regard to participant safety, recruitment, randomization, intervention, data management, quality control and analysis and the informed consent materials; recommending changes as needed; approving the content and format of DSMB reports; recommending initiation of participant recruitment; reviewing DSMB and other safety reports as needed; reviewing masked and unmasked data as needed; determining whether additional safety data are needed; periodically reviewing data on safety and endpoints and proposing additional analyses as needed; recommending for or against trial continuation; reviewing and make recommendations regarding proposed protocol changes; providing advice on issues related to any data discrepancies identified; and reviewing manuscripts if requested by the Board or NIA.

Frequency of Data and Safety Monitoring

The DSMB has been constituted by the NIA. DSMB meetings will be held every six to nine months at the call of NIA or the DSMB Chair. The multiple PIs will jointly oversee the study team in preparing DSMB reports that will be distributed by email at least 7 to 10 calendar days before the meetings.

8 INTERVENTION DISCONTINUATION

The “intervention” in this case consists of being randomized to the intervention arm; we plan to include in final analyses all participants invited for an assessment visit, whether or not they attend. Thus, the concept of “discontinuation” is not applicable in its traditional sense.

We recognize that many patients may choose not to attend the assessment visit; those who do choose to do so may also choose to terminate the visit before it is completed. Most patients are expected to have only a single study assessment visit, and thus there will not be further procedures expected that they would have the opportunity to discontinue. A small proportion who go on to receive a dementia diagnosis in primary care will be invited back for a follow up visit to offer them support and resources. Participants will have a choice whether to participate or not.

If a participant chooses to withdraw at any point, we will not contact them further. However, we will use information collected before they withdrew, and we will not be able to destroy information that was entered into their medical record before their withdrawal. Consistent with intention-to-treat principles, we will include all participants who were randomized in final analyses of study endpoints, which will involve extraction of EHR outcome data regardless of

enrollment status. In addition, we will continue to include participants who have withdrawn in data and safety monitoring reports.

We will track the following information related to discontinuation and report it to the DSMB:

- Proportion of individuals offered the brain health assessment visit who decline to participate
- Among those attending the visit, the proportion who choose to stop it early
- Among those who qualify for a follow up visit with the research interventionist (due to a new dementia diagnosis), the proportion who do not participate in the follow up visit.

9 STATISTICAL CONSIDERATIONS

9.1 General Design Issues

We hypothesize that patients whose PCPs are randomized to the eRADAR supported outreach intervention will be significantly more likely to be diagnosed with dementia than the usual care control group.

This pragmatic randomized trial in two healthcare systems will provide data on whether implementing eRADAR improves dementia detection while minimizing harms. Having parallel groups within two distinct healthcare systems with differences in data capture will provide valuable information about the transportability of eRADAR across diverse healthcare systems. Separate analyses will be conducted in each health care system. The portion of the study carried out at UCSF is considered the “replication” phase of the study.

The primary outcome will be the rate of new dementia diagnosis in the 12-month period following the “index date.” We will identify new dementia diagnosis from diagnosis codes recorded in the EHR, in keeping with the pragmatic nature of this study. Secondary analyses will examine dementia diagnoses over 6 months and 18 months. Secondary outcomes also include other events that matter to stakeholders including patients, family members/care partners, clinicians, and healthcare systems, including healthcare utilization (e.g., additional laboratory testing or imaging studies), hospitalizations and patient and provider satisfaction. Healthcare utilization measures will be identified from EHR data, in keeping with the pragmatic nature of this study.

We will conduct “intention-to-treat” analyses. The intervention group will include all individuals with high-risk eRADAR scores whose PCP was randomized to the intervention, regardless of whether these individuals chose to participate in a brain health assessment visit. This is critical for avoiding bias, which could arise if analyses were limited to individuals who chose to participate in the brain health assessment visit. People who decline this assessment may differ in important and systematic ways from those who accept; they could either be more likely to have undiagnosed dementia, or less likely, we cannot predict which.

9.2 Sample Size and Randomization

We calculated power to detect an increase in the rate of new diagnoses of dementia, assuming a baseline rate of 3% per year. Based on our prior work, we estimate that the positive predictive value (PPV) of the eRADAR risk score will be 0.15 using a cut-point of 5%, 0.12 using a cut-point of 10%, and 0.10 using cut-point of 15%. At KPWA we assume a sample size of 18,000 patients and 75 providers, while at UCSF we assume a sample size of 9,000 patients and 175 primary care providers. We have varied the assumptions about the proportion of patients accepting assessment (50 or 75%), the intraclass correlation coefficient (0.01 or 0.05), and the cutoff for the eRADAR score (top 5, 10 or 15% of patients invited for assessment). Because this trial will randomize providers, we used the R package “clusterPower” to account for clustering. We will have power $\geq 90\%$ at both KPWA and UCSF under scenarios with a range of assumptions. From our calculations, power is 0.90 or higher even under the most pessimistic scenario of 50% participation, ICC of 0.05, and using a 5% cut-point to define “high risk” based on eRADAR scores.

9.2.1 Treatment Assignment Procedures

Eligible PCPs will be randomized to the intervention or to usual care through a computer-generated sequence created by the biostatistician. Randomization will occur at the PCP level. We carefully considered what unit of randomization would be most appropriate: the individual patient, the PCP, or the clinic. We sought to randomize at the level of the smallest unit possible (to increase effective sample size and study power) while balancing this against the risk of contamination. We decided not to randomize at the level of the individual patient because this would be very likely to result in contamination. If an individual PCP had patients in both the intervention and control arm, it might change their practice considerably over the course of the study and affect dementia diagnosis rates in patients in their panel who were not randomized to the intervention. We considered whether randomizing PCPs in the same clinic to different study arms would lead to contamination and concluded that there would be a low likelihood of contamination, based on practice patterns at KPWA and UCSF.

Randomization will be stratified by clinic and blocked by the number of eligible patients on each PCP’s panel (broadly grouped, e.g. 0-49, 50-99, etc.). The rationale for blocking by number of eligible patients is that this characteristic may correlate with physician practice patterns and their engagement with and learning from the intervention, influencing the intervention’s effectiveness. To ensure that interventionists have a reasonable patient panel size for outreach, and so that outreach can occur promptly after patients are categorized as “high risk,” we also will identify groups of eligible participants in blocks and will assign them an “index date” to use for recruitment and follow-up. As discussed above, this index date will be defined as the date on which their eRADAR score was calculated and categorized as high risk vs. not high risk.

9.3 Interim Analyses and Stopping Rules

We will not perform an interim analysis for the study.

9.4 Outcomes

9.4.1 Primary Outcome

The primary outcome will be the rate of new dementia diagnoses during 12 months following the index date, identified from the EHR using a prespecified set of ICD-10 codes.

9.4.2 Secondary Outcomes

Secondary outcomes include the rate of new dementia diagnoses during 6 or 18 months after index date. They also include process outcomes, such as the proportion of patients offered an assessment visit who accept, and the positive predictive value or “yield” of the eRADAR algorithm, estimated by calculating the proportion of those who are assessed who ultimately are diagnosed with dementia. We will also calculate the proportion diagnosed with MCI and the proportion found to have another diagnosis, such as depression, during the assessment visit.

Other secondary outcomes relate to healthcare utilization (see Table 4).

Finally, we will conduct qualitative and quantitative analyses of patient and care partner satisfaction and experience. We will also collect qualitative information about the experience of clinicians with this intervention. These data will come from surveys mailed to all patients participating in the assessment visit, and from semi-structured interviews with patients, care partners, and clinicians.

9.5 Data Analyses

Aim 1: Our primary analysis for Aim 1 will compare the rate of new dementia diagnosis by treatment arm. We will conduct an intention-to-treat analysis fitting a modified Poisson generalized estimating equations (GEE) regression (with log link) to estimate the relative rate of dementia diagnosis following randomization comparing eligible patients with high-risk eRADAR scores of PCPs randomized to the intervention versus control arm.

Secondary analyses will explore the impact of different specifications of the outcome (e.g., using dementia diagnoses made within 6 or 18 months, or including MCI diagnoses). We will also explore whether the effects of the eRADAR intervention differ across subgroups such as age, sex or race/ethnicity by performing stratified analyses as well as formally testing for differences by including an interaction term with the grouping variable in the model.

Aim 2: Analyses for Aim 2 also will be limited to patients with high-risk eRADAR scores. We will use GEE regression with the appropriate distribution and link function (e.g., log link for binary and count outcomes, identity link for continuous outcomes) to examine differences in healthcare utilization and diagnoses of other conditions (e.g., depression) between the intervention and control arms. Similar to Aim 1, we will explore whether eRADAR’s impact differs by subgroup (e.g., sex or race/ethnicity) by performing stratified analyses and testing for interactions.

For surveys and process outcomes, quantitative data (e.g., satisfaction ratings) will be

analyzed with standard descriptive statistics (e.g., means, standard deviations, proportions) and qualitative data (e.g., perceptions and impact of process) will be analyzed using a template analysis approach.

10 DATA COLLECTION AND QUALITY ASSURANCE

10.1 Data Collection Forms

10.1.1 Brain Health Assessment Visit

We will create a research dashboard within Epic that research team members will use to track interactions with study participants. In addition, we will create a structured note template for the brain health assessment visit that research interventionists will use to capture key data elements (e.g., patient history, functional status, depressive symptoms score(s), MoCA scores). Using this template, research interventionists will generate a standardized note summarizing the visit findings. Some information will be summarized in free text in the visit note (e.g., self-reported memory symptoms and complaints), while results from standardized questionnaires will be documented separately using Flowsheets (SmartForms), e.g. the PHQ-2. Study programmers have the ability to extract data recorded in Flowsheets for later analyses.

10.1.2 Notes Template for Brain Health Assessment Visits that are Observed and/or Recorded

For the subset of brain health assessments visits that are observed and/or recorded, we will use a notes template that has both closed and open-ended fields for observers to complete as they listen to or view the visit to document key insights and learnings. Topics on the form include but are not limited to: descriptions of the overall tone or feel of the visit, key questions raised by the participant and care partner, examples of engagement in the process, and any concerns raised by the participants. These forms will be labeled with the participant's study ID and will not contain any identifying information such as people or places.

10.1.3 Post-Visit Surveys

Following the brain health assessment visit, we will send each participant a brief evaluation survey. The survey may be returned by mail using a pre-addressed and stamped envelope or may be completed online using a secure link to an approved tool such as REDCap. Surveys returned by mail will be entered manually into the research database.

10.1.4 Semi-Structured Interviews

All semi-structured interviews will be performed by trained qualitative team members at KPWA and UCSF. Each interview will be audio-recorded and transcribed, with interviewers documenting key takeaway messages using a uniform notes template to allow for rapid review and feedback of findings from the interviews for formative purposes.

10.2 Data Management

KPWA and UCSF will be the settings for data collection and will be responsible for secure storage of all research data. Internal policies and procedures will be put in place to make sure confidentiality is maintained. Electronic data will be maintained in files that are stored on secure servers; access to the network requires an approved user ID and password. Study folders will be

restricted, with access only allowed for the project team working on this study. Electronic data may also be collected via a secure online platform such as REDCap with secure storage behind the firewalls at each site. Data that will be transferred between KPWA and UCSF will be transferred via KPWA's Secure File Transfer site after executing a Data Use Agreement.

Paper copies of data collection forms such as brain health assessment visit notes, paper copies of evaluation surveys, and hand-written notes from observations and semi-structured interviews will be stored in locked file cabinets.

Audio and video recordings will be saved directly on to a secure server and will only be viewed or listened to by study staff and the transcription vendor. For transcription, files will be uploaded using secure file transfer.

10.3 Quality Assurance

10.3.1 Training

All research staff from both KPWA and UCSF will review the study protocol and successfully complete HIPAA and human subjects protection training prior to interacting with participants.

Research interventionists will be trained to deliver the intervention by: 1) reviewing written protocols; 2) role-playing with experienced team members and patient advocates; 3) observing experienced team members or clinical providers interact with study participants or patients; and 4) being observed by experienced team members until competency is demonstrated. All research interventionists will complete the official online training to become certified to perform the MoCA.

All clinical research team members will also receive annual trainings in suicide risk assessment and prevention.

10.3.2 Fidelity Assessment

We will ensure fidelity to the intervention by: 1) having weekly intervention team meetings, in which we review and problem-solve interactions with participants during the previous week; 2) having a senior research team member review a 5% random sample of research interventionist notes for thoroughness and accuracy; 3) having an annual review of research interventionist best practices; and 4) sharing observation insights with staff in a timely manner. If any issues are identified, they will be reviewed with the research interventionist and, if necessary, a larger sample of notes will be reviewed and updated if indicated.

10.3.3 Monitoring

The Multiple PIs will oversee and monitor protocol compliance and data quality at both KPWA and UCSF. They will ensure that procedures are in place to review records and identify data anomalies such as:

- Missing data or forms
- Inconsistent and illogical dates over time
- Inconsistent data entry across surveys, forms and visit documents
- Inaccurate coding of interviews

- Incomplete data entry on forms

For surveys that are completed online, there will be data checks to identify missing, invalid or out of range responses. While they are completing the survey, participants will be prompted if they skip a question or enter an invalid response. Similar data checks will be conducted when study team members are entering data from surveys that are returned by mail.

10.4 Data Sharing and Future Use

We may use study data for future analyses, and we will share deidentified study data and transcripts with researchers if requested, as required by and following the NIA's guidance. Deidentified or limited datasets and transcripts containing individual-level data on which publications are based will be made available to qualified researchers for specified analyses. Safeguards will be put in place to protect participants' confidentiality and privacy.

Data will be maintained on secure servers behind the firewalls at the two study sites: Kaiser Permanente Washington (KPWA) and the University of California, San Francisco (UCSF). There are two main types of data generated by the study that will be available to outside researchers for additional analyses: data extracted from electronic health records for approximately 18,000 people at KPWA and 9,000 people at UCSF, and qualitative data collected through semi-structured interviews.

The final EMR based dataset may include medical diagnoses, vital signs, healthcare utilization, laboratory test results, and medications as well as data from assessments consisting of screenings for cognitive or functional impairment and from a subset of study participants who agree to assessment visits. The final dataset will be limited: it will not include most identifiers but may include age and specific dates such as dates of death or dementia diagnosis to enable replication of analyses. Although the dataset may be summarized and parsed (to prevent re-identification), there remains the possibility of deductive identification of subjects with unusual characteristics. Thus, we will make the data available to users who have fulfilled certain regulatory requirements (described below) under a data-use agreement (DUA) that includes:

- (1) A commitment to using the data only for pre-specified research purposes and not for any analyses not specified in the DUA;
- (2) A commitment not to attempt to re-identify any individual participant;
- (3) A commitment the data will not be used for commercial purposes and will not be redistributed to third parties;
- (4) A commitment to securing the data using appropriate computer technology; and
- (5) A commitment to destroying or returning the data after analyses are completed.

11 PARTICIPANT RIGHTS AND CONFIDENTIALITY

11.1 Institutional Review Board (IRB) Review

Advarra will serve as the single IRB (sIRB) of record. The same study protocol will be implemented within the primary care clinics in the KPWA integrated health delivery system and the UCSF healthcare delivery system. All patient-facing materials such as information sheets, recruitment materials, and intervention-related scripts including telephone scripts will be reviewed and approved by the sIRB. Modifications of these documents will be reviewed and

approved by the sIRB prior to using them with study participants.

11.2 Approach to Informed Consent

11.2.1 Consent Strategies for Main Study Groups

To develop our plans related to consenting patients, the eRADAR study team consulted with the Regulatory and Ethics Committee of the NIA's IMbedded Pragmatic Alzheimer's disease and AD-related dementias Clinical Trials (IMPACT) Collaboratory. This committee consists of researchers who have expertise in geriatrics, ethics, and health services research, particularly related to pragmatic trials embedded in healthcare systems that seek to enroll people living with dementia. We also consulted with representatives of Advarra and our Patient Advisory Committee to inform our approach to consent/assent for this study. Based on these discussions and guidance, we are requesting a waiver of consent for some activities and patient groups in this study and a waiver of written consent for the main study intervention and for other specified activities in sub-groups.

11.2.2 Waiver of Consent to Identify and Characterize Eligible Patients and Calculate eRADAR Scores

We are requesting a waiver of consent to use EHR data at both KPWA and UCSF to identify and characterize potential study participants, apply inclusion/exclusion criteria, and calculate eRADAR scores to identify high-risk individuals. These activities are necessary to identify patients for outreach. In addition, we need to obtain baseline demographic and medical data so that we can describe our study population and perform analyses adjusting analytically for any differences between groups (e.g., to calculate appropriate control group weights for DSMB reports). We will also use the baseline data to describe characteristics of people who agree to participate in the brain health assessment visit compared to those who do not participate.

This use of EHR data poses minimal risk to participants, apart from breach of confidentiality or invasion of privacy. It is not feasible to reach out to approximately 27,000 patients to obtain consent to use their EHR data to determine eligibility and identify the high-risk group. It would not be possible to perform this research study without being able to calculate eRADAR scores. For the validity of the study, it is critical that we be able to calculate eRADAR scores and identify the high-risk subgroup within the control (usual care) group as well as the intervention group. Our proposed analyses will compare outcomes in the high-risk group targeted by the intervention with outcomes in the analogous group in the "usual care" arm. It would not be scientifically appropriate to compare outcomes in the high-risk group targeted by the intervention with all patients in the "usual care" arm, or to compare all patients in the intervention vs. usual care arms, because the intervention is only expected to have an impact on patients identified as "high risk" based on their eRADAR risk score.

11.2.3 Waiver of Consent to Identify Study Outcomes

We also request a waiver of consent to use EHR data to identify study outcomes (such as new dementia diagnoses and healthcare utilization) in both the usual care and intervention arms of the study. It is not feasible to reach out to patients in the "usual care" arm to obtain consent, both because of the very large number and because we will not have any contact with these patients for the study. We also request a waiver of consent to identify study outcomes from the EHR for the intervention group, because for results to be valid, we need to extract and analyze outcomes for all patients whose PCP was randomized to the intervention, not only those who accept the

study assessment visit – in other words, we need to perform analyses based on the principle of intention-to-treat. If we were required to obtain informed consent and only include in final analyses those who choose to come in for the assessment visit, this would be a biased sample of the intervention group. People who choose not to participate in the assessment visit are likely to be systematically different from those who do participate, and specifically, they might have a substantially higher (or lower) likelihood of having dementia. This selection process occurs only in the intervention group and not the usual care group, and thus an analysis comparing consenting patients from the intervention group with all patients in the usual care group would be problematic. Thus, in keeping with intention-to-treat principles, it is vital for the study that we collect EHR outcome data for all high-risk patients, regardless of randomization group or participation status, which requires a waiver of consent. We will notify patients in the intervention group in the recruitment letter that we plan to use data from all invited patients in our final analyses, whether or not they accept the invitation for an assessment visit.

We believe it is ethical to follow all high-risk patients in both the intervention and control groups for outcomes using EHR data for several reasons. First, patients will not be harmed by this use of their data for research purposes. Outcomes will be compared between groups, and we will be unaware of individual patient identities when performing analyses. Second, the goal of this study is to improve patient care. If we are unable to use patient data as proposed, our study could potentially yield biased results, which could have a negative impact on patient care. Third, patients' rights and healthcare will not be affected by our extracting information from automated healthcare data. Because we are already sending a letter to participants in the intervention group with high eRADAR scores, we will inform them that we plan to use their health records to follow the group as a whole for study outcomes regardless of whether they participate in the brain health visit. We will have no contact with the control group.

11.2.4 Waiver of Consent to Perform Safety Monitoring for Reporting to DSMB

For this study, we propose to periodically extract data from the EHR to monitor certain safety outcomes, such as hospitalization, self-harm, or suicidal ideation. The frequency will be determined by the DSMB but probably this will occur about every 6 months. We will extract these data for both the usual care and intervention arms, including for patients in the intervention arm who choose not to undergo the assessment visit (with whom we do not have contact, and thus do not have the opportunity to seek consent.) It is possible that the invitation letter itself could lead to increased anxiety and/or depression in patients in the intervention group, and some of them may choose not to undergo an assessment visit. If so, then the only way we could learn of AEs in this group is through the EHR. As described in section 11.2.3, there is self-selection of patients into the assessment visit, which could make them a biased sample of the intervention arm. Even for patients in the intervention arm who accept an assessment visit, most will have a small number of contacts with the research team, and it is likely that any safety events (such as anxiety or depression leading to suicidal ideation) would take place after the brain health assessment visit rather than before it. Thus, we would not have an opportunity to learn of these adverse outcomes without extracting EHR data. The same issues around self-selection and biased sampling that were discussed in section 11.2.3 apply here; to get a comprehensive and unbiased view of potential harms of the study, we need to be able to extract data on patients in both the usual care and intervention arms, and for those who choose to participate in an assessment visit

as well as those who do not. To minimize risks or harms from this data extraction, we will access the minimum data necessary to identify potential AEs, and we will analyze and present data for groups of patients rather than specific individuals.

11.2.5 Waiver of Written Consent for Brain Health Assessment and Follow Up Visits in Intervention Group

We are requesting a waiver of written consent for the assessment and follow up visits that patients in the intervention arm will have with the research interventionist, during which their cognitive and functional status will be assessed. This research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context. Therefore, we will obtain verbal consent/assent using an information sheet.

We will take several steps to provide information to participants about the intervention, ensuring that they understand that the visits are part of a research study and are completely voluntary. We will also include procedures to assess their capacity to understand the information and to consent to participate. If patients are found not to have capacity to consent, we will seek consent from a Legally Authorized Representative on their behalf. Below we describe the steps in the consent process and our approach to ascertaining capacity.

First, we will send eligible patients an invitation letter that describes the brain health assessment visit and provides them with an opportunity to decline if they wish. This mailing will also contain an information sheet describing the key study procedures, risks and benefits. It will be written in plain and simple language. It will clearly state that this activity is part of a research study and that results will be recorded in the medical record.

Next, we will reach out to patients for a recruiting/scheduling call. The research team member will go over key points from the letter and information sheet. If the patient expresses interest in participating, the team member will ask several brief simple questions to assess understanding and capacity to consent. These will include questions such as, “Are we asking you to participate in a research study?” and “What will happen if you agree to be in this study?” If the patient answers incorrectly, the staff member will provide correct information and allow the patient to try again. If the patient is unable to answer questions correctly after three attempts, we will conclude that they do not have capacity to consent. The staff member will then attempt to identify the patient’s Legally Authorized Representative (LAR). Next, a research team member will contact the LAR to review the study, answer their questions and request their verbal consent for the patient to participate in the study. (At the end of this section, we describe processes for patients who do not have capacity and do not have an LAR.) For patients who lack capacity, participation will require both verbal assent from the patient (indicating interest in/willingness to participate) and verbal consent from the LAR.

Patients who provide verbal consent and appear to have capacity at this stage, and those for whom an LAR has consented, will be scheduled for a brain health assessment visit. As part of the scheduling process, we will encourage patients to identify a care partner to join them for the visit. We do this because having an informant/proxy present is considered “best practice” when conducting a cognitive assessment. That person may provide key insight and information about the patient’s functioning, which some patients who lack insight are not able to accurately provide.

We recognize that there could be some patients who appear to have capacity during this initial call but later are found not to have capacity. At the start of the brain health assessment visit, the Research Interventionist will review key elements of the study, such as that this is a research study, all assessments are optional, and the patient may end the visit at any time. S/he will confirm consent/assent by asking patients if they wish to proceed. If patients appear confused or to not understand the purpose of the visit, s/he will reassess capacity following the same process as above for handling incorrect answers and seeking consent from an LAR if needed. If the patient does not have capacity and does not have an LAR, or the LAR is not available during the visit, the patient will not be able to proceed with their brain health assessment visit. We will recommend that they schedule a visit with their PCP .

Patients who do not have capacity to consent and who do not have an LAR (or who have an LAR we are unable to reach) reflect an ethical challenge. The fact that they are found to lack capacity to consent for the study strongly suggests that they have impairment, most likely cognitive impairment. This puts them at risk for harm. We believe that there is a “duty to care” for these vulnerable patients and that we are ethically required to communicate about this impairment with their PCP. First, we will send a Staff Message to their PCP in Epic communicating that the patient appeared confused and lacked capacity to consent, and that this suggests impairment and needs further evaluation. Second, we will send a follow up letter to the patient’s home summarizing our findings. The hope is that this letter will remind the patient about our recommendation that they schedule an appointment with their PCP. It is also possible that a person involved in their life, such as someone who lives with them and/or cares for them and may be reviewing their mail, will receive the letter and can help them arrange a visit with their PCP for more evaluation.

We also have carefully considered how to respond if a research study participant requests to withdraw after their brain health assessment visit, particularly if they have screened positive for dementia. If they were found to have capacity to consent for research and request that the results of the brain health visit not be entered into their medical record and not be shared with their physician, we will honor their request. If they did not have capacity to consent, we will send a Staff Message to their PCP in Epic communicating the results of the brain health assessment, but will not put them into the medical record. To clarify, Staff Messages are not part of the permanent medical record in Epic as a clinical note would be. If the participant seems angry or upset by the visit, we will document the event as a reportable incident and will notify their PCP.

11.3 Consent Strategy for Other Study Procedures

Below, we describe the process for reaching out to inform primary care providers about the project. We also describe consent processes for the following activities: 1) observation and/or recording of assessment visits; 2) semi-structured interviews with patients and care partners to learn about their experience with the intervention; and 3) semi-structured interviews with primary care providers and other clinical team members to learn about their experience and satisfaction with the intervention. This research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context. Therefore, we will obtain verbal consent/assent using an information sheet for the groups below. The process of obtaining verbal consent from these groups will include:

1. Providing a copy of the information sheet.

2. Discussing the information sheet with the participants and providing them with the opportunity to ask questions about the study.
3. Participants giving their verbal consent/assent to participate or not participate in the study.
4. Documenting the consent process of each participant in a study database or study binder.

For patients who were previously identified as lacking capacity to consent, we will involve the LAR in these discussions and seek both verbal assent from the patient and verbal consent from their LAR.

We do not plan to repeat the process of ascertaining capacity to consent for these activities because they will occur fairly soon after we have assessed capacity as part of initial recruitment, within about 4 months. Because so little time has elapsed, it is unlikely their capacity to consent will have changed between the initial assessment and the time we obtain verbal consent for these activities.

11.3.1 Provider (PCP) Opt-Out Process

Clinic chiefs will have the opportunity to specify in advance certain providers who they do not want to include (e.g., physicians who are newly hired, in the process of retiring, locum tenens providers, etc.). In addition, providers will be given an opportunity to opt out, as follows. Before randomization occurs at each site, Study Investigators will give presentations about the eRADAR study at clinic meetings to ensure that PCPs and other staff members are aware of the study and their anticipated role. PCPs will be encouraged to inform the research team in advance if they do not want to participate. In addition, eligible PCPs will be emailed study information detailing the study and their anticipated study activities. This email will request PCPs who wish to opt out to send an email to the PI indicating their preference. PCPs who do not send an email opting out within one week of receiving the email will be randomized. PCPs who wish to opt out of the study may do so at any point.

11.3.2 Patients & Care Partners: Observation and Recording of Assessment Visits

For the subgroup of patients who are selected to have their brain health assessment visits observed and/or recorded, we will include in the initial mailing a separate information sheet that specifically describes this component of the study. After they have agreed to participate in the main study and scheduled their brain health assessment visit, we will review the information sheet and ask if they are willing to have the visit observed and recorded. If a care partner will be joining the patient for the visit, both will need to consent in order for the visit to be observed/recorded. The research interventionist conducting the assessment visit will be alerted that the visit should be recorded and will confirm consent/assent before beginning the recording.

As part of the recruitment process, we also will ask permission to contact the patient and care partner later to invite them to participate in longer interviews.

11.3.3 Patients & Care Partners: Semi-Structured Interviews

For patients and care partners who are selected for semi-structured interviews, we will send a separate invitation letter and information sheet after they have completed their brain health assessment visit. We will then follow up with a phone call to review the information sheet, answer any questions they have about the interview, and determine whether they are willing to take part in the interview and, if so, to schedule the interview. At the start of the interview, we will review the information sheet and confirm their verbal consent/assent to participation. Both the mailed information sheet and the verbal review of the information sheet will convey to the participant that the interview is optional and that they can stop the interview at any time.

It is particularly important for us to interview participants found to be cognitively impaired and their care partners, because they are likely to have been impacted the most by the study intervention. We recognize that some of these participants may lack capacity to consent. We will rely on the capacity assessments conducted at the initial stages of the study (recruitment call and brain health assessment visit). For patients who lacked capacity to consent at these stages, we will seek verbal assent from the participant and verbal consent from their LAR.

11.3.4 Clinicians: Semi-Structured Interviews

A subgroup of participating PCPs and clinical staff (n=20) who care for one or more patients who participated in an eRADAR brain health assessment visit will be invited for semi-structured interviews. Before conducting these interviews, the research team will obtain their verbal consent using an information sheet that provides summary information on the study.

11.4 Decisionally Impaired Patients

This study, which seeks to increase recognition and detection of Alzheimer's disease or dementia, will include adults who are decisionally impaired or lack capacity to consent to participation in research. Excluding participants who are unable to consent for themselves would lead to the recruitment of a selected group of patients and make results of the trial less valid and, therefore, less useful. Furthermore, the patients most likely to be excluded are those whom this trial is directed at helping. Thus, we have sought to develop procedures that are respectful, seek to protect these patients, and also allow them to participate as far as possible.

To sum up, we will assess capacity at 2 steps in the study: the initial recruitment call and the brain health assessment visit. For patients who lack capacity to consent, we will seek to obtain consent from an LAR. We will strive to include the LAR as the "care partner" in the brain health assessment visit to the extent that this is consistent with patient preferences and desires.

We also seek to protect vulnerable individuals who are found not to have capacity and who lack an LAR by informing people who care for them about their lack of capacity to consent through approaches outlined above, including notification of their PCP, a letter sent to the patient's home, and notification of a close family member or friend chosen by the patient, where appropriate.

The table below is an overview of the proposed processes for patient consent/assent and waiver of informed consent for this study.

Study Activity (Group Included)	Informed Consent			HIPAA Authorization	
	Informed Consent	Waiver of documentation of informed consent/assent	Waiver of informed consent/assent for research	HIPAA authorization	Waiver of HIPAA authorization
Identification of eligible patients and calculation of eRADAR scores using EHR data (all patients)			X		X
Brain health assessment visits (intervention group)		X		X (included in information sheet)	
Observation/recording of study visits (patients & care partners)		X			X
Semi-structured interviews (patients, care partners, clinicians and clinical team members)		X			X
Assessment of study outcomes from EHR (all patients)			X		X
Monitoring safety outcomes from EHR data (all patients)			X		X

11.5 Participant Confidentiality

Well-developed internal policies and procedures will be put in place to maintain confidentiality of participant records. Research procedures will be conducted in accordance with the Health Insurance Portability and Accountability Act of 1996. Participant identification numbers (PIDNs) will be assigned to all study participants. Study team members will only have access to

participants' identifiers as required for the completion of their assigned study activities (e.g., programmer to pull participant data, research specialist for scheduling activities, research interventionist for assessment visits). Identifiers other than dates and ages will not be shared outside the research team. Results of the intervention visit will be recorded in the medical record for the PCP to use in evaluating the patient. Data collected on paper forms (e.g., notes from semi-structured interviews, evaluation surveys) will use PIDNs and will be filed separately from the list linking participant identifiers (e.g., medical record numbers) with their PIDNs. 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. Electronic data will be maintained in files located in a secure server with access restricted to only the project team working on this study. These servers are accessed through KPWA and UCSF networks, which in turn require a valid user ID and password for access. Paper forms will be stored in locked file cabinets.

11.6 Study Discontinuation

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

12 ETHICAL CONSIDERATIONS

Risks/Benefit Ratio: The study team places a high priority on minimizing harms or potential harms to study participants. For this reason, we have planned formative evaluations early in the study to identify potential harms or discomfort that participants may have experienced with respect to the assessment visit, and we will modify scripting and study procedures if needed to reduce distress or harm.

We have thought carefully about whether and how to disclose to participants why they were chosen for the study. In our judgement, it could cause psychological distress if we were to disclose that a computerized algorithm identified them as having an elevated risk of undiagnosed dementia. Since the algorithm is not perfectly accurate, we expect to identify many people who in fact do not have dementia. Telling them they appear to be at high risk for dementia could cause unnecessary anxiety and suffering, and so we elected not to disclose this aspect of the recruitment process. If participants specifically ask study team members why they were chosen (for example, during a recruitment phone call), the team member will provide a scripted and generic response stating that we have chosen people who have some risk factors for cognitive impairment such as older age and certain health conditions.

Autonomy: we recognize the right of participants to decide whether they want to participate in study activities, and so at many points in the study, we remind them that procedures are voluntary and they may discontinue at any time. We seek verbal consent (or assent, for patients who lack capacity) for their participation in the main study activity, the brain health assessment visit. On a broader level, providing patients with an earlier dementia diagnosis may give them more autonomy in their lives by allowing them to express preferences and make choices about their future while they are still able. They can make decisions about their desired living environment and/or caregiver(s) and designate people to have power of attorney if they become

incapacitated. Delayed diagnosis of dementia often robs people of the opportunity to participate in these decisions about their future.

Risks and harms of study activities are comparable to those experienced in daily life. If our intervention increases the recognition and diagnosis of dementia, this means that some participants may experience grief and loss related to life changes. Some patients and/or their families may determine that it is time for the patient to stop living independently and move into a more structured living environment. Patients may have to stop driving or become more dependent on others for their daily activities. All of these changes, which are experienced as losses, occur during the natural progression of dementia – they are not caused by the study but rather by the underlying disease that the study is designed to bring into the open.

13 COMMITTEES

We have formed a Patient Advisory Committee consisting of patient representatives from both participating healthcare systems. Currently none of our patient advisors are people living with dementia, but many have experience with family members including close family members who have developed dementia. The Patient Advisors will provide feedback on study materials including outreach letters, telephone scripts and the process for follow-up support after a new dementia diagnosis. They will also provide perspectives to inform the choice of a cut-point to define “high-risk” eRADAR scores, including how much value they place on avoiding false positives (prioritizing a higher PPV) vs. avoiding missed cases of dementia (prioritizing high sensitivity). We will meet with them regularly throughout the study to solicit input and guidance and problem-solve any challenges that arise.

14 PUBLICATION OF RESEARCH FINDINGS

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

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