PROTOCOL TITLE: *Models of Primary Osteoporosis Screening in Male Veterans*

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VERSION NUMBER AND DATE: *Version 1, November 6, 2018*

SPONSOR/FUNDING SOURCE*: VA Health Services Research and Development*

Purpose

The purpose of this study is to test 2 new models of osteoporosis screening and treatment adherence on fracture risk in older men using a group randomized trial compared to no additional screening support (control). Randomization and intervention will occur at the Patient Aligned Care Team (PACT) level; therefore, the PACT providers will complete the informed consent process, agreeing that their team will utilize the randomly assigned care model. Because many PACT teams are located off site, we request a waiver of documentation of informed consent.

All care models deliver VA guideline-recommended osteoporosis screening and treatment to high-risk Veterans by DVAHS credentialed clinical staff, which represents usual clinical care. Patient-level measures are all routine clinical ultilization and outcomes collected soley from the electronic medical record. Therefore, a waiver of informed consent and HIPAA authorization for the patient-level data collection procedures is requested as the study presents minimal risk beyond routine clinical care to Veterans.

Specific aims:

1. Compare the impact of PACT practice management and BHS primary osteoporosis screening models on **patient level outcomes** strongly associated with fractures as measured by the EHR at 2 years; 1) eligible proportion screened; 2) medication adherence (initiation; implementation, and discontinuation). PACT fracture rates (fractures/patient years) are exploratory.

2. Determine the impact of PACT practice management and BHS primary osteoporosis screening models on **provider and facility level outcomes** including change in DXA volume, change in metabolic bone disease clinic volume (assessed by EHR), and PACT provider time and satisfaction (assessed by Nominal Group Technique).

3. Determine the impact of PACT practice management and BHS primary osteoporosis screening programs on **health system and policy level outcomes** using Markov models of screening program cost per quality adjusted life year. Model inputs are based on VA national fracture data from our prior work, aggregated results from aims 1 and 2, and published quality of life estimates.

Background and Significance

Osteoporosis is under-recognized in older men. At age 50 years, 1 in 5 men can expect to suffer a major osteoporotic fracture in their remaining lifetime, comparable to the risk of prostate cancer.[1] Men are more than twice as likely as women to experience complications after a fracture,[2] and have greater excess mortality after hip fracture.[3] Because risk factors are common in Veterans, osteoporosis is particularly prevalent in the Veterans Health

Administration (VA) system. More than half of male Veterans over age 50 years have osteopenia or osteoporosis, a rate nearly double the non-Veteran population.[4]

Fractures resulting from osteoporosis have negative consequences on functional status, mortality, and quality of life, with high rates of pain, depression, and loss of independence.[2] After a hip fracture, nearly 75% of patients spend time in a nursing facility, and only 20% regain their prior level of ambulation. Many fractures are associated with substantial excess mortality; men with a hip fracture have excess annual mortality of 20% that persists up to 10 years.[3] Osteoporotic fractures also have an important economic impact. It is estimated that hip fractures result in 43 million dollars of excess cost to the VHA annually.[5]

Fortunately, osteoporotic fractures are preventable. The generic bisphosphonate alendronate (annual VA cost VA $20) reduces the risk of vertebral, hip and other non-vertebral fractures by 45%, 40%, and 16% respectively.[6] Although fewer studies in men are available, fracture risk reduction has been similar.[7-9] Importantly, our work shows that bisphosphonates also reduce mortality in men and women.[10,11] Medication adherence is critical, but has been documented to be poor within VA and community settings.[14-16]

Osteoporosis screening is simple and inexpensive. Patients without a prior fracture are selected for treatment based on the results of a non-invasive Dual Energy X-ray Absoptiometry (DXA) measurement of bone mineral density (BMD). Current U.S. guidelines suggest that it is cost-effective to treat patients with BMD T-score of $\leq$ -2.5 (osteoporosis), and those with T score between -1.5 and -2.5 (osteopenia) who have additional risk factors resulting in a 10 year fracture risk of over 3% for hip fracture, or 20% for major osteoporotic fracture.[18-20]

Despite the high burden and preventability of osteoporotic fractures, men are rarely diagnosed or treated for osteoporosis before a fracture has occurred. Economic models based on large cohort studies have suggested that screening is likely to be highly cost-effective.[27-30] Furthermore, our national VA cohort study (see preliminary studies) demonstrates screening effectiveness in high risk subgroups. Professional groups including the American College of Physicians, Endocrine Society, National Osteoporosis Foundation, the Canadian Medical Association, the U.K. Health System, and the VA Undersecretary for Health all advocate for primary osteoporosis screening in men.

Osteoporosis screening and treatment services within VA are ineffective overall. Our national study of primary osteoporosis screening in male Veterans (preliminary studies) showed wide variation in patient selection. Overall, screening rates were 8% for men over age 65; far lower than expected based on the prevalence of osteoporosis risk factors in the population. Moreover, even among men in whom screening was completed, it was not associated with lower overall fracture rates because osteoporosis treatment and adherence following screening were extremely low. The result is an **ineffective and wasteful primary osteoporosis screening program across VA** that does not identify appropriate men for screening, nor facilitate treatment adherence for those found to be at high fracture risk. Notably, we found that screening was associated with clinically important reductions in fractures for high-risk men in pre-specified subgroup analyses.

Attempts to improve osteoporosis screening using traditional quality improvement programs have been minimally effective.[34-36] EHR alerts alone do not improve osteoporosis screening rates[37] and do nothing to address adherence. However, two distinct osteoporosis screening paradigms have been suggested, and form the scientific premise for the models proposed in this application. A practice manager approach in which a non-physician staff member is responsible for organizing osteoporosis screening led to a doubling in osteoporosis screening in a single academic medical center, but its impact on medication adherence is unknown.[37] In this paradigm, responsibility remains at the individual practice level (or in VA, PACT). In contrast, a Fracture Liaison Service (referred to here as “Bone Health Service”, BHS) represents a

centralized model that has been successful in improving *secondary* osteoporosis screening and treatment adherence after a fracture has already occurred.[38,39] In this model, a team of nurses led by a bone specialist identify patients with fracture within the entire health system, and arrange for evaluation and treatment. Such models have reduced 2-year fracture rates by 56%[40] and are cost saving or highly cost-effective.[41,42] The National Bone Health Alliance and others recommend expansion of BHS models to address primary fracture prevention, however its impact on osteoporosis screening and treatment rates in this context are unknown.

Based on this body of evidence, we conclude that the VA urgently needs data on the impact of primary osteoporosis screening and adherence models to inform the adoption of rational clinical programs.

Design

Pragmatic group randomized trial of PACT teams (n=39 teams recruited, estimated 24 at DVAHS and 15 at Richmond VAMC) will be randomized into 3 groups: a control group (no additional support); a PACT practice management model; or a centralized Bone Health Service (BHS) model. Outcomes for all patients eligible for osteoporosis screening within the randomized PACTs will be assessed by investigators masked to group assignment via EHR at baseline and 2 years**.** Outcomes for PACT providers will be assessed using qualitative methods (nominal group technique).

Outcome measures are listed in the table 1 below.

Table 1. Outcome measures by Aim. RDW=Regional Data Warehouse; MPR=Medication Possession Ratio; FRAX=Fracture Risk Assessment Tool.

Outcome	**Definition/Measure**	**Data Source/Timing**	**Important Difference**
Patient (Panel) Level (Aim 1)			
Screening Rates	Proportion of eligible men screened in last 12 months	RDW at baseline, year 1 and year 2	25% increase from 6% Control
Medication Initiation	Proportion of screened men meeting treatment threshold (T score ≤-2.5 or FRAX score high-risk) who receive at least 1 prescription	RDW, intervention period year 1 and year 2, non-VA medication lists by chart abstraction.	30% increase from 55% Control
Medication Implementation	Days of medication dispensed divided by follow-up days	Pharmacy dispensing records, for patients started within prior year at baseline, year 1 and 2. Non-VA medication lists by chart abstraction.	20% increase in MPR≥80%[14] from 30% Control
Medication Discontinuation	Time between first prescription dispensing date and the date of first medication possession gap of ≥3 months		20% difference
Harms	Proportion of men started on oral medication for new GI distress in 3 months Subtrochanteric fractures or	RDW ICD10 codes, new prescription for proton pump inhibitor or H2 blocker.	15% increase from 30% Control >expected 1/50,000 patient years

	Osteonecrosis of the jaw	RDW ICD10 codes	treatment
Fractures (exploratory)	All clinical fractures excluding facial, digital	RDW, confirmed by chart abstraction	10% decrease from 2.5/100 person years Control
Provider/Facility Level (Aim 2)			
DXA volume	DXA orders/ 1000 patients/year, by intervention group	EMR data, calculated at 2 years	
Bone Disease clinic volume	Consults/ 1000 patients/year, by intervention group	EMR data, calculated at 2 years	
PACT satisfaction, time	Nominal Group Technique at Routine Staff meeting	Measured at 2 years	
Health System/Policy Level (Aim 3)			
Program Cost Effectiveness	Cost/quality adjusted life years (QALY) of the screening models compared to control	Markov model with above outcomes, fracture rates, cost and quality of life from VA and medical literature	Probability of cost/QALY >80% at thresholds of $50,000, $100,000, $200,000[71]

Provider-level Covariates will be collected from the PACT providers at the time of randomization, including medical provider type (Advanced Practice Provider vs. MD), medical provider and RN years in practice, years in VA, and practice site (rural CBOC, urban CBOC, VAMC).

Patient-level Covariates will be extracted from the Regional Data Warehouse and CPRS. Demographics include age, self-reported race, body mass index, and rural zip code as classified by Rural-Urban Commuting Area. Because medication co-pays may be a barrier to adherence, co-pay status will be collected. Co-morbidities related to fracture risk include chronic lung disease, diabetes, endocrine disorder (hyperthyroidism, hyperparathyroidism, Cushing's, hypogonadism), prostate cancer, rheumatoid arthritis, Parkinson's disease, stroke, gastrectomy/malabsorption, smoking, alcohol abuse, chronic kidney disease, chronic liver disease, dementia. Medications include calcium, vitamin D, glucocorticoids, androgen deprivation therapy, traditional anti-epileptic drugs, proton pump inhibitors, selective serotonin reuptake inhibitors, and psychoactive medications.

Risk/Benefit Assessment

Protection against Risk:

1) **Disclosure of protected health information**. All human subjects' data will be stored in a restricted access folder behind the VA firewall on a server meeting Federal Research Data Security requirements. Only study stuff listed on the IRB staff listing will have access to the folder, and all computer access requires a PIV card and password. Data will not be transferred outside of this environment.
2) **Nominal Group Technique**. An experienced qualitative researcher will conduct the nominal group sessions with PACT providers. Participation in the sessions is voluntary, and

steps will be taken to reduce social desirability and psychological discomfort during the session including using anonymous responses on index cards and anonymous ranking sheets.

Potential Benefits of the Proposed Research to Human Subjects and Others:

1) **Benefits to PACT providers**. All PACT providers will be provided with educational materials to improve their knowledge of osteoporosis screening guidelines. Those in the practice management and bone health service groups will have additional tools and support to assist them in providing guideline-recommended care for their patients.
2) **Benefits to Veterans**. If the new screening models are effective, Veterans will benefit from improved fracture prevention services, with fewer expected to suffer painful and debilitating low-trauma fractures.

Selection of Subjects

PACT Providers (n=78, estimated 48 at DVAHS and 30 at RVAMC) include the medical provider (MD or advanced practice provider, APP) and registered nurse (RN) who provide primary care to a panel of 800-1000 patients. Providers will be identified by the ACOS and ACNS for Ambulatory Care at each site. Eligible PACT medical and RN providers must be:

- At least 0.75 FTE
- Completed training (i.e., PACT teams led by residents and fellows are excluded)
- Care for male Veterans ≥65 years (i.e., Women's Health PACTs are excluded)

Patients (estimated n at both sites = 2376; 1462 at DVAHS) include men aged 65-85 years eligible for primary osteoporosis screening within enrolled PACT teams. Patients will be identified using Corporate Data Warehouse queries. Inclusion criteria:

- No prior fracture or osteoporosis diagnosis
- At least 1 VA Undersecretary Guideline risk factor (weight loss >20% in 5 years; BMI <25 kg/m^2; diabetes; pernicious anemia; gastrectomy; anticonvulsants; glucocorticoids; androgen deprivation therapy; hyperthyroidism; hyperparathyroidism; rheumatoid arthritis; alcohol dependence; chronic lung disease; chronic liver disease; stroke; Parkinsonism; prostate cancer; and current smoking).[63]

Exclusion criteria:

- Active non-skin cancer diagnosis
- Enrollment in hospice or palliative care

Subject Recruitment

The intervention is focused on the PACT medical and RN providers; therefore, both will be asked to provide verbal informed consent for participation in all training and data collection activities. Study procedures will be described to PACT providers during a monthly Ambulatory Care meeting, with written materials distributed via VA Outlook email. Study personnel will follow-up individually with each provider to answer questions and complete the informed consent process. Both the PACT provider and RN must agree to participate. As PACT providers turn-over in our health system, patient panels are left intact and a new provider assigned; study team members will therefore approach the new provider to request continued participation in the group randomized.

In year 3, a sub-sample of medical providers and RNs whose PACTs have participated in the care models will be recruited for a 1-hour Nominal Group session to collect qualitative data about their experience with the care model. Study stuff will send out an informational Outlook email to the work address of all participating PACT providers. Those expressing interest will be contacted individually to provide more

information and schedule their participation in the session. Written informed consent will be complete at the beginning of the session, as described below.

Consent Process

If a PACT provider expresses interest in participation, a study staff member will arrange a time for them to meet to further describe study procedures, risks, and benefits. When possible, this meeting will occur in-person in the PACT staff workroom or other quiet workplace location; however, providers in Community Based Outpatient Clinics may choose to have VA Skype for Business or telephone meetings to accommodate their schedules. Study staff will distribute copies of the Participant Consent Handout to each provider prior to the meeting so they are available for review during the meeting.

Once the informational meeting has been completed and PACT team members have had a chance to ask any questions, the study staff will encourage them to discuss privately whether or not they wish to participate. This may occur immediately after the meeting, or they may choose to take several days to consider. If both choose to participate, they will be asked to provide verbal informed consent to 2 study staff members; a waiver of documentation of informed consent is requested for this process.

In year 3, a subset of PACT medical providers and RNs will be recruited for the Nominal Group sessions as above. Each will be sent an electronic copy of the informed consent document via VA Outlook email prior to the session to review individually. As each staff member arrives, a study staff member will review the procedures, risks, and benefits with each individual or small group. They will have the opportunity to ask any questions, and will be informed that they can leave now or at any time during the session. If they wish to participate, they will be asked to sign 2 copies of the informed consent, HIPAA authorization, and notice of privacy practices, keeping 1 set for themselves and giving the other set to the study staff.

A waiver of patient informed consent and HIPAA authorization is requested for patient outcomes assessment via the EMR because this is a low risk study implementing routine clinical care as currently recommended by the VA Undersecretary.

Study Interventions

Randomization. Stratified, block randomization will be used after all provider recruitment is complete. Randomization will occur at the level of PACT team. PACT teams will be stratified by

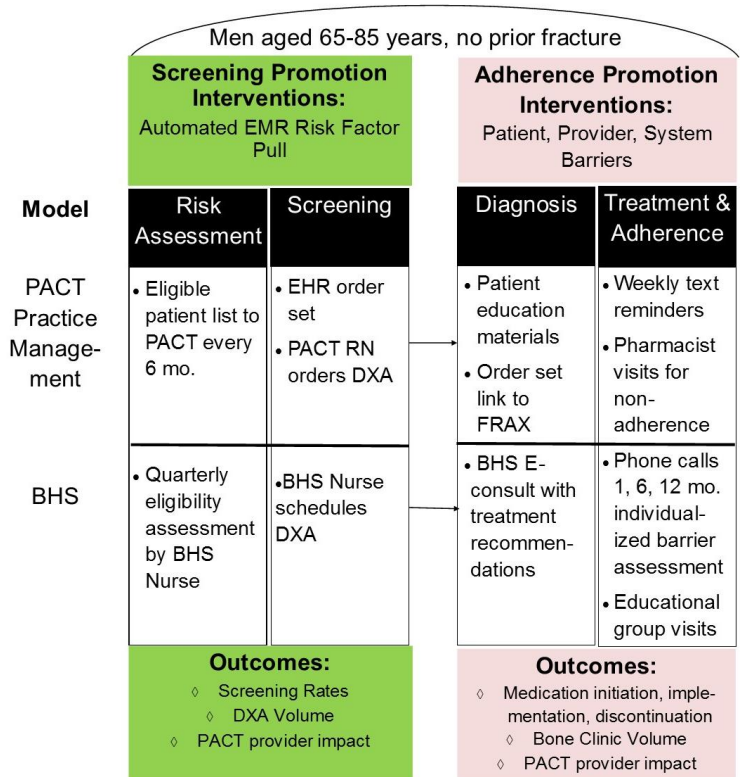


Figure 2. Main model components and outcomes by PROSPR model step and screening model.

medical provider type and blocked by site (e.g., specific CBOC/VAMC). A statistician unaware of team identity will randomize PACTs in blocks of 3 within strata to ensure similar distributions. If insufficient numbers of PACTs are recruited within small CBOCs, they will be combined with other similar CBOCs (rural vs. urban) for randomization.

Interventions. Two screening models will be compared to control. Each includes *2* main categories; 1) osteoporosis screening promotion, and 2) medication adherence promotion. Figure 6 depicts the main intervention components and outcome measures as they relate to the PROSPR conceptual model.[48]

Note that Veterans in all enrolled PACTs receive guideline-recommended "usual clinical care" for osteoporosis screening delivered by a VA clinical provider and endorsed by their primary care provider. In this situation, the "intervention" is how the model organizes responsibility and support for this care. Table 2 describes how the steps differ between the screening models and which providers are responsible for them.

Control– PACT providers in the control group will be given the VA Undersecretary Guidelines for primary osteoporosis screening and standard patient education materials for adherence support without additional support. This arm represents a "no practice management support" control group.

PACT Practice Management Model. This model represents a robust practice management support model, with multiple tools and processes to facilitate osteoporosis care. In addition, it adds an adherence support component. All components are implemented by PACT providers, who will receive 1 hour of individualized instruction by study staff in their clinics at the beginning of the study period.

PACT Screening Promotion includes 3 tools to assist the PACT team with selecting patients and ordering screening. This "panel management" component has been shown in community settings to improve osteoporosis screening from 18 to 35%.[37]

1. The study team will provide a list of all PACT panel patients who are currently eligible for primary osteoporosis screening via encrypted email to the PACT medical provider and RN every 6 months. Our group has developed a Regional Data Warehouse report using ICD codes, pharmacy records, and DXA orders to identify eligible patients. This process avoids the concern for "alert fatigue" that has been documented for EHR alerts with other screening and health maintenance activities, and is consistent with a 2017 VA Directive to reduce the number of provider alerts.[64]
2. We will activate an osteoporosis order-set for PACTs randomized to this group (see preliminary studies). This allows rapid ordering of DXA and osteoporosis medications with fewer clicks. Consistent with the PACT philosophy of all providers working to the top of their license, we will utilize the RN for much of the process; the Chief of Staff has agreed to a standing order that will allow RNs to enter DXA orders for eligible patients (see letter of support).
3. We will provide these PACT teams with patient educational materials from the National Osteoporosis Foundation about osteoporosis screening and treatment for use at their discretion.

PACT Adherence Promotion. Because our approach is pragmatic and capitalizes on tools available in usual clinical practice, this component will utilize adherence promotion-strategies that are broadly available in ambulatory care, and address patient and health care system barriers to adherence specific to osteoporosis medications. These strategies are compatible with a practice management model.

1. A commonly cited barrier is the intermittent dosing schedule and complex administration requirements for osteoporosis medications;[50] for example, the first-

line drug alendronate is taken weekly while fasting, and patients must remain upright for 30 minutes. Alternative medications are self-administered every 6 months subcutaneously, or yearly intravenously. To address barriers related to the complexity of the regimen, patients who agree will receive automated SMS text message reminders from a VA approved messaging application corresponding to their dosing schedule. The text will include safe administration directions, and is sent automatically through the VA-approved "script your future" website.[65] Electronic reminders have shown promise for promoting adherence,[46] but have not been well-studied beyond 1 year.

2. The study team will generate a biannual list of PACT panel patients who have missed 1 or more refills for ordered osteoporosis medications within the last 6 months using RDW data. The list will be provided to the team, and patients will be scheduled for a follow-up telephone or in-person visit to address adherence. PACT Pharmacists will receive 60 minutes of training from the study team on common reasons for osteoporosis medication non-adherence, and alternative formulations.

Bone Health Service Model – Patients in PACTs randomized to the BHS model will have osteoporosis screening, education, and follow-up handled centrally by the bone health team. PACT providers can opt out of the service for patients in whom they believe it is not appropriate, and approve all orders, but are not responsible for most activities.

BHS Screening Promotion

1. The Bone Health Nurse (BHS RN) will identify eligible patients quarterly as described previously. Patients will be contacted via letter and telephone, and if they agree will be scheduled for DXA.
2. The BHS RN obtains DXA results, calculates Fracture Risk Assessment Tool (FRAX) score[33], and those meeting treatment thresholds are referred to the Bone Health MD for e-consult.
3. The Bone Health MD reviews additional clinical information in the EHR and generates an e-consult containing recommendations for additional laboratory evaluation (if needed) and treatment; this note is co-signed by the PACT provider. The BHS RN then contacts the patient to provide education and shared decision making, and places orders for PACT provider co-signature.

BHS Adherence Promotion

1. All patients initiating bisphosphonates will be called by the BHS RN at 1, 6, and 12 months to identify adherence barriers using a validated tool modified for osteoporosis therapy.[47] Algorithms for overcoming patient and health-care system adherence barriers to osteoporosis medications will be used in these calls (appendix 1).[51,52,66] For example, patients reporting gastrointestinal distress will be offered annual intravenous therapy; patients with difficulty ordering refills will be assisted to enroll in *myhealthevet*. The 12-month call will ensure that the medication has been re-ordered. Subsequently, patients not refilling medications will be identified from RDW every 6 months as described for the PACT practice management group, with telephone follow-up as indicated.
2. Patients with medication nonadherence identified during these calls will be offered an additional educational visit, based on the content of a prior successful osteoporosis adherence promotion program.[45] The educational program will be delivered by the BHS RN during a group visit, Virtual Medical Room visit, or telephone visit at the Veteran's choice.

Table 2. Model components by step in the Screen and Treat Process. *All steps represent usual clinical care for the Veteran.*

Step in Process	Control	PACT Practice Management	Bone Health Service (BHS)
Screening Promotion			
Selection for screening	Discretion of provider	List of eligible patients provided to PACT RN biannually	BHS RN queries RDW quarterly
Scheduling screening	Provider orders; MSA or Veteran phone call to radiology	PACT RN orders; MSA or Veteran phone call to radiology	BHS RN orders and coordinates scheduling with Veteran
Quantify risk from DXA results, determine if they meet treatment threshold	Discretion of provider	Provider accesses FRAX link on Osteoporosis order set	BHS RN and BHS MD based on FRAX risk
Shared decision-making with Veteran	Provider by phone or at next primary care visit	Provider by telephone or at next primary care visit, patient education materials available	E-consult to provider, BHS phone call with Veteran, decision- tool sent to patient
Adherence Promotion			
Ordering treatment	Provider	Provider on Osteoporosis Order Set	BHS RN with provider co-signature
Adherence monitoring	Discretion of provider	List of non-adhering patients provided to PACT Pharmacist quarterly	BHS RN telephone follow-up and personalized barrier assessment
Intervening when non-adherence detected	Discretion of provider	PACT Pharmacist phone call or visit	BHS RN uses adherence algorithm, educational visit

Adverse Events

Potential risks to PACT providers include disclosure of confidential demographic information, disruption or change of usual workflow, and emotional discomfort sharing information in a nominal group technique session. Potential risks to the Veterans (included in medical record review only) include disclosure of protected health information.

All adverse events will be reported per Durham VAMC requirements. All Serious, Unanticipated and Related adverse events will be reported to IRB within 5 business days of hearing of the event. All other adverse events will be reported at continuing review.

Costs and/or Payments to Subjects
There are no costs or payments to subjects.

Data and Safety Monitoring

Although this is a low-risk study that is promoting guideline-recommended care, a data safety monitoring board will be recruited to include at least 1 ambulatory care clinician and 2 additional members from the Durham HSR&D COIN. The DSMB will meet biannually to review subject recruitment, data collection and management procedures, and safety outcomes. Screening rates at the PACT level will be measured at baseline and 2 years after implementation. Adverse drug effects related to osteoporosis medications will be evaluated by the DSMB every 6 months. Inadvertent data disclosures will be reported to the DSMB, IRB and VA ORD as soon as discovered, and immediate steps to minimize sharing will be taken.

Withdrawal of Participants

PACT Providers may choose to withdraw their team at any time with no consequence to them or their patients. No further data collection will be completed on their PACT team, and there will be no end-of-study visit. Study staff will request an in-person or phone meeting with the provider to assess reasons for withdrawal.

There are no anticipated circumstances under which subjects will be withdrawn without their consent.

Data Collection, Flow and Management

Provider-level data is limited to demographic information, and is collected on a paper form at the time of informed consent and entered into the study database. Paper forms are stored in the Durham GRECC as above.

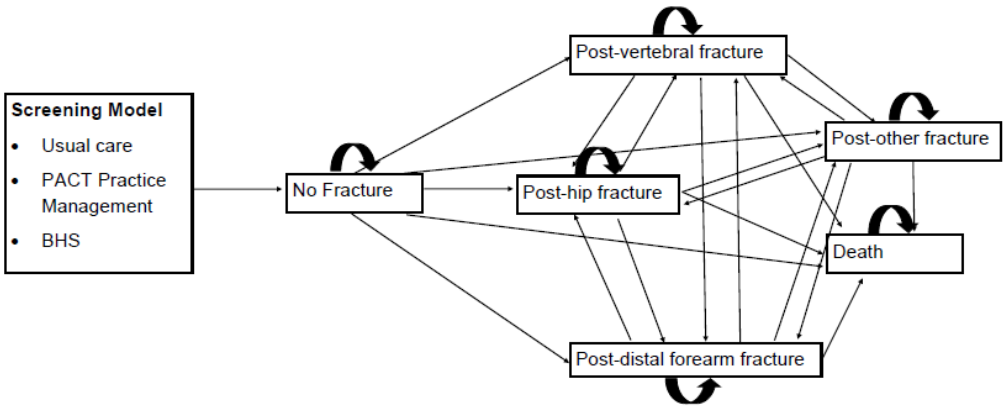
Patient-level data from both Durham and Richmond VAMCs is downloaded directly from the Regional Data Warehouse on an excel spreadsheet, and uploaded into the study database behind the VA firewall. Additional data fields are abstracted by study staff from CPRS directly into the study database. The study database is maintained in a secure HSR&D drive folder \\vhadurhsmcifs01.v06.med.va.gov\DURHAM_HSRD_P\MOPS. Data will not be transferred to outside entities.

Data Analysis and Statistical Considerations

Data for Aims 1 and 2 will be analyzed by the study statisticians (Mr. Sloane, Dr. Pieper) on the HSR&D server using the most currently available version of SAS. Nominal Group Technique data will be analyzed using qualitative methods by the PI (Colón-Emeric) and other relevant study staff on the HSR&D server. Aggregated, population-level data for aim 3 economic analyses will be provided to the study economist (Dr. Nelson) at the Salt Lake City VAMC using TreeAGE software.

Aims 1 and 2. Mixed-model ANOVA/ANCOVA will be employed. This extension of the ANOVA/ANCOVA based on the General Linear Model is preferred for group randomized trials with 1 or 2 follow-up time points.[85] We will use the General Linear Mixed Model or the Generalized Linear Mixed Model to account for clustering of patients within providers; this approach accommodates regression adjustment for covariates and has the advantage of both allowing for correlation between subjects within cluster, and within subjects over time. Simulations have shown these methods have the nominal Type I error rate across a wide range of conditions common in group randomized trials.[86] Our general strategy is to follow an "analyze as you randomize" strategy, comparing PACT level parameters between randomization groups. PACTs and individuals will be entered into the model as random effects, while group and time will be tested as fixed effects. We note, however, that if there are minimal differences between PACTs, we will be able to merely control for PACT in the analysis. Further, unlike a longitudinal panel study, subjects will enter and leave the PACT over time. For events that should occur only once (e.g. screening), we will censor the subject at the point of the event. Further, entry into some analyses are conditional on prior events (e.g. medication adherence will occur only among those who are screened and who have a low DXA value and are subsequently prescribed). And, these conditional probabilities may differ by group. We will be careful to control (by weighting or propensity score matching) to make the groups conditionally equal. The parameter of interest will be the Group mean (and standard error) over time, and measured by the 'average' PACT value at each time point. Finally, we note that the estimation models above can be adapted to outcomes distributed other than normal, including Poisson (for number of events/time) and binary (for events).

This is a 3 group by 3 yearly time point design. To control the overall Type-I error level, we will use the baseline time point as a baseline covariate, and assess group differences at the following time points controlling for baseline. Level of statistical significance will be set at 0.05 (two-tailed) for all tests. Initially, we will assess a Time by Group interaction (on 2 degrees of freedom). If that effect is declared statistically significant, we will perform follow-up tests to determine where the group differences exist at each follow-up time point. Two orthogonal tests will be assessed – usual care vs. PACT practice management and BHS groups, and difference between the PACT and BHS groups. If the Group by Time interaction is not significant, then the main effects of Group and Time will be tested. If the group effects are declared significant, the same



follow-up group contrasts listed above will be assessed, across the follow-up time points.

Aim 3. Prior Markov models of osteoporosis screening have been adapted for this study (Figure 6).[28,29,87,88] A Markov cost-utility model with 6 health states will be constructed comparing 3 different strategies of DXA screening, followed by 5 years of treatment with alendronate (the most commonly prescribed medication) for those with a femoral neck T-score of ≤−2.5 or FRAX 10 year fracture risk above current treatment thresholds (3% hip, 20% major osteoporotic fracture). For the base-case analyses, the model will be run for five different starting ages (65, 70, 75, 80, and 85) using Monte Carlo simulations with 40,000 trials each. Running the models for 5-year increments allows us to adjust the transition probabilities for observed differences over time (e.g., higher fracture rates or different adherence rates with older age). The health states in the model are no fracture, post distal forearm fracture, post clinical vertebral fracture, post hip fracture, post other fractures (humerus, scapula, ribs, pelvis, distal femur, pelvis, patella, tibia, or proximal fibula), and death. Following the recommendations of the 2nd Panel on Cost-Effectiveness in Health and Medicine,[89] we will analyze our model from both the VA and societal perspectives and present our results as an impact inventory.

Figure 6. Markov model for Aim 3 analyses of economic impact of 3 screening models.

The direct and indirect costs of that fracture will be assigned as a transition cost. The disutility associated with these fractures will be modeled as a QALY decrement associated with that fracture state based on a published systematic review of fracture disutility rates[90] and is assigned for 6 months upon which they return to baseline state, except for hip and vertebral fractures for which permanent disutility is the norm. If an individual suffers an additional fracture, the costs of that fracture are assigned, but the person remains in the post vertebral or post hip fracture state because the long-term disutility associated with prior vertebral and hip fractures is greater. Long-term care costs beyond the first year after hip fracture are assigned as a cost per year. Individuals in the model will be eligible (at risk) of transition to a different state once every 3 months, and a maximum of 2 fracture types is assumed. We will parameterize our model using inputs derived from Aims 1 and 2 of the current grant and from the published literature. A discount rate of 3% will be assumed for costs and health benefits.

Table 5. Data Sources for Aim 3 (see also Health Systems Policy Outcomes Section)

Data Category	**Source(s)**
Proportion screened and treated	Aggregated aim 1 results
Medication adherence, persistence	Aggregated aim 1 results
Treatment efficacy	Published efficacy for bisphosphonates by medication adherence and persistence rates
Fracture rates	National VA data (preliminary results)
Fracture costs	National VA and CMS data including Fee Basis and CHOICE costs (preliminary results)
Screening and Treatment costs	Aim 2 results, current VA/CMS DXA cost, rare serious harm estimates from population data
Fracture disutility	Systematic review of disutility by fracture type

Treeage software will be used for analyses. One-way sensitivity analyses will be performed varying discount rates, fracture rates, fracture costs, fracture disutility, costs of DXA, the onset and offset of fracture reduction benefit following initiation and cessation of drug therapy, medication adherence, the relative risks of fractures attributable to osteoporosis or prior clinical fracture, cost of screening and yearly bisphosphonate. Because of uncertainty regarding the nonvertebral fracture reduction efficacy of oral bisphosphonates for men, 2-way sensitivity analyses will be performed assuming reduced fracture efficacy. Probabilistic sensitivity analyses will be performed using 2nd order Monte Carlo simulations in which each parameter value will be drawn from a distribution with characteristics specific to that parameter. For example, log-normal distributions of fracture direct costs and normal distributions of fracture rates and long-term care costs following hip fracture. The distributions of the relative risks of incident fractures associated with osteoporosis, prior fracture, and oral bisphosphonate therapy are assumed to be log-normal. Uniform distributions will be used to model variability in fracture disutility and indirect fracture costs. Results from the PSA will be presented as scatterplots on the cost-effectiveness plane and as cost effectiveness acceptability curves.

Table 6. Power calculation assumptions for Aim 1 analyses.

Outcome	**Assumptions**	**PACTs or Patients needed for 80% power**	**Power for 36 PACTS and 2376 patients**
Screening Rates (PACT level)	6% Usual Care, 70% new models	18 PACTS (6/arm)	>0.99
Osteoporosis Treatment	25% of screened meet treatment thresholds. 30% increase from 55% Usual Care	306 patients (102/arm)	>0.99
Medication Adherence	Usual Care MPR 0.60 (SD 0.35). 20% increase new models	1680 patients (560/arm)	0.85
Fractures (exploratory)	Usual Care 2.5 fractures/100 patient yrs (SD 0.2), 10% decreased hazard with new models	78,297 2175/arm	0.32

Nominal Group Analysis. During structured group discussion and voting, each nominal group generates a list of statements in response to each question, and rank orders them on order of importance. To analyze the resulting data, we will first generate a spreadsheet for each question listing the group-generated statements, scores, and average score (total score/number of group members) by group. The statements from each group will be entered into Atlas.ti, and content analysis used to generate themes recurring across groups. Themes will be generated independently by the PI who has extensive experience in qualitative analysis[72-74,91-94] and the Project Director who will engage in additional qualitative training for this project (see budget justification). A code book will be developed in an iterative manner, and confirmatory content analysis completed independently by co-investigator Lee to enhance reliability. All statements will then be coded by at least 2 independent investigators.

Once the data is coded, final analysis will proceed in 2 steps. **1) Generation of top 7 themes for each question**. Although each group responds to the same questions, because they work independently the number, wording and order of the statements will be different. Larger groups also have a wider score range than smaller groups. To address this issue we will use procedures described by van Breda[95] to analyze data across groups. Using the coded data described above, we will calculate average scores for each theme by summing the total of statement scores for the theme divided by the number of statements in the theme. The top 7 themes will be listed for each question, along with exemplar statements. **2) Assessment of Implementation Variation**. We will examine variation in implementation by site and provider type in order to better inform dissemination. Co-occurrence tables and matrices of the themes identified through content analysis as described above will be generated by site characteristics (urban/rural, academic/community) and provider type (medical/RN). We will identify similarities and differences in the frequency of the themes, the ordering of the statements, and the discussion around the statements.

Power. We estimate power using aim 1 (patient level) outcomes. Because the study will operate under a waiver of informed consent, we do not account for refusal to participate; however, the expected Veteran refusal of screening and treatment rates are reflected in our assumptions (table 6). We expect a low ICC for patients within PACTs as patients are randomly assigned PACT provider, and based on prior studies of patient behavior change within primary care providers ICC<0.1.[96] We conservatively estimate 66 eligible patients/panel (panel size 1200 MD and 1000 NP/PA, 15% of panel aged 65-85, 40% of these with 1 or more risk factors). We do not expect attrition as new patients are added as others leave with relatively constant panel size. Finally, we determine power for the single degree of freedom contrast of import – Usual Care vs. PACT Practice Management and BHS groups across the follow-up time points. For each of the individual outcomes, assumptions and power requirements are listed in Table 6. A sample size of 36 PACTs (12/group) provides over 85% power for all our primary patient-level outcomes, except fracture rates which are exploratory in this analysis. We will recruit 15 PACTs/group conservatively estimating attrition of 3 PACTs over 2 years.

Missing data Strategies. As is standard in administrative databases, the absence of a diagnosis code (e.g., fracture) will be assumed to indicate that the event did not occur, and coded by default as 'not present'. For continuous measures where zero is illogical, we will impute a value, simulate and use bootstrapping to derive estimates of effect with appropriate standard errors. To implement the multiple imputation techniques for primary analyses, we will use preliminary analyses of such associations, including graphical displays, to investigate the plausibility of the assumptions underlying the imputation model employed.[97] Further, we will use 25 or more imputed data sets, with FU bootstrapped estimates in order to reduce the impact of the random sampling.

Privacy, Confidentiality, and Information Security

1. Lists of Data Reviewed and/or Collected for Screening/Recruitment and Conduction of Study:

The Personal Health Information that will be obtained, used, and/or shared for this study includes:

Identifier(s)	Source(s) of Health Information
☒ Names	☒ Medical history & physical exam information
☒ All geographic subdivisions smaller than	☐ Photographs, videotapes, audiotapes,

Identifier(s)	Source(s) of Health Information
a State, including street address, city, county, precinct, and zip code. Describe: VAMC/CBOC location	or digital or other images
☒ All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, visit or treatment dates, etc.; and all ages over 89, Describe: fracture date, prescription fill dates, birth date, DXA testing date, death date	☐ Biologic specimens (e.g., blood, tissue, urine, saliva). Describe:
☐ Telephone numbers	☒ Progress notes
☐ Fax numbers	☒ Diagnostic / Laboratory test results
☒ Electronic mail addresses (staff only)	☐ Operative reports
☒ Social Security Numbers	☒ Imaging (x-ray, CT, MRI, etc.)
☒ Medical record numbers	☐ Discharge summaries
☐ Health plan beneficiary numbers	☐ Survey / Questionnaire responses
☐ Account numbers	☐ Billing records
☐ Certificate and/or license numbers	☐ HIV testing or infection records
☐ Vehicle identifiers and serial numbers, including license plate numbers	☐ Sickle cell anemia information
☐ Device identifiers and serial numbers	☒ Alcoholism or alcohol use information
☐ Web Universal Resource Locators (URLs)	☐ Drug abuse information
☐ Internet Protocol (IP) address numbers	☐ Mental health (not psychotherapy) notes
☐ Biometric identifiers, including finger & voice prints	☐ Psychological test results
☐ Full-face photographic images and any comparable images	☐ Genetic testing
☒ Any other unique identifying number, linked study ID, characteristic, or code, describe: A unique study ID to link patient direct identifiers, maintained in a separate file, to the other study data.	☐ Other, describe:

2. Data and/or Specimen Acquisition:

Data for this study will be collected through:

☒ Prospective data and/or specimen collection obtained from participants. Provide description of processes:

Prospective data collection is ***for consented staff only***. The Nominal Group Technique combines quantitative and qualitative data collected from small groups of 8–20 people to rapidly generate a prioritized list of responses to specific questions during a 45–60 minute facilitated meeting. Purposive sampling will be used to include at least 2

representatives from different PACTs assigned to each of the 3 interventions for an estimated 10 sessions including at least 1 provider from all 36 PACTs. The nominal group technique will include four steps: (1) each participant writes responses to specific questions posed by the facilitator; (2) responses are anonymously recorded in a round-robin fashion, with brief discussion for clarification if needed; (3) similar responses are grouped into themes through group discussion; (4) each person records the 5 most important themes identified in step 3, in order of importance to that individual. Questions will elicit providers' perceived barriers and facilitators to osteoporosis care, experience with their assigned model, and estimated time spent per month. See grant Appendix 2 for the nominal group protocol.

☒ Retrospective data collection and/or specimens obtained from medical chart review/data access. Describe how data will be obtained (e.g., fileman, CDW, etc.): ***For Veterans within enrolled PACT teams only***. Data is obtained through CDW queries (SQL) and manual abstraction from CPRS. At the completion of data collection, a limited dataset with direct identifiers removed will be created, and a cross-walk file maintained in a separate location. Data will not be fully de-identified.

☐ Retrospective data collection and/or specimens obtained from an IRB-approved data and/or specimen repository. Indicate the repository source including name, VA location, and IRB number: .

3. Level of Data:

The following level(s) of data will be acquired/maintained for this study (*check all that apply*):

☒ Identified (e.g., names, addresses or other identifiers included)
☐ Coded (direct and/or all identifiers removed, but study code/ID included)
☐ De-Identified (all HIPAA 18 and study ID/code removed):
- ☐ Verified Statistically

OR

- ☐ Verified by Absence or Removal of HIPAA 18 and study ID

☐ Limited Data Set
☐ Other: Describe:

4. Location of Data and/or Specimens, and Data Retention Plan:

A. Data and/or Specimen Location:

Data will be stored electronically in \\vhadurhsmcifs01.v06.med.va.gov\DURHAM_HSRD_P\MOPS. Data that will be stored electronically are listed in the "Outcome Measures" and "Covariates" sections, and summary results from provider nominal group techniques.

Paper records of data include staff demographic surveys. They will be stored in a locked cabinet in the DVAHS Geriatrics Research Education and Clinical Center (GRECC) room N3006, Durham VA Hospital.

There are no biological specimens.

☐ Data will be also be placed at the VA Informatics and Computing Interface (VINCI; http://vaww.vinci.med.va.gov/vincicentral/VINCIWorkspace.aspx). The VA Informatics and Computing Infrastructure is a partnership between the VA Office of Information Technology and the Veterans' Health Administration Office of Research and Development. Researchers and operations staff can use VINCI to access data and statistical analysis tools in a virtual working environment through a certified VHA network computer using the VA Intranet or Virtual Private Network (VPN).

B. Data Retention Plan

☒ Research records will be maintained and destroyed according to the National Archives and Records Administration, Records Schedule Number: DAA-0015-2015-0004. Records destruction, when authorized, will be accomplished using the then current requirements for the secure disposal of paper and electronic records. Currently, destruction of research records (see DAA-0015-2015-0004, section 7.6 "Research Investigator Files" for materials included in research records) is scheduled for 6 years after the cut-off (the cut-off is the completion of the research project) and may be retained longer if required by other federal agencies. Records will not be destroyed without pre-notification to the facility records manager.

☐ Other data retention plan, describe:

5. Data Access and Data Recipients:

Only members of our DVAMC research team will have access to identifiers and coded data.

All VA research personnel who have access to VHA records are instructed, in accordance with VA policy, on the requirements of Federal privacy and information laws and regulations, VA regulations and policies, and VHA policy. All study personnel who are VA employees working within the VA system have fulfilled all required HIPAA and other VA security and privacy policy training requirements and have agreed to follow guidelines pertaining to the protection of patient data. All research staff sign VA Rules of Behavior, and all study staff are up-to-date with VHA Privacy Policy Training and the VA Office of Cyber and Information Security Awareness Training Course. The data security and privacy procedures summarized in that course include logging off or locking the computer when walking away from it; no sharing of access codes, verify codes or passwords; not allowing anyone else to use the computer under one's password; and disposing of sensitive information using VA-approved methods (e.g., shredder bins).

Access to study data will be removed for all study personnel when they are no longer part of the research team.

6. Data and/or Specimen Transportation and/or Transmission for all data and/or specimens involved in the study:

I. ☐ Data and/or specimens will not be transported or transmitted outside of Durham VAMC environment.

II. ☒ Data and/or specimens will be transported BETWEEN sites that are under the auspices of the Durham VA Medical Center. Study staff may transport paper staff demographic information forms back to the DVAMC GRECC from Community Based Outpatient Clinics. Forms will be kept in an envelope in the staff's briefcase at all times during transport. Forms may also be sent via VA intra-office mail in sealed envelopes marked "confidential".

III. ☐ Data and/or specimens will be transmitted to other VA sites using the following method(s):

A. Data

☐ Data are de-identified and thus will be sent via unencrypted e-mail or unencrypted disk (encryption is optional).

☐ Data are coded or contain identifiers and thus will be sent

☐ Other, describe:

B. Specimens

☐ Specimens are de-identified and thus will be sent via standard carrier (tracking is optional).

☐ Specimens are coded or contain identifiers and thus will be sent via VA-authorized carrier with tracking.

☐ Other, describe:

IV. ☐ Data and/or specimens will be transported to non-VA/VHA sites (e.g., academic affiliates, laboratories, etc.) using the following method(s):

A. Data

☐ Data are de-identified and thus will be sent via unencrypted e-mail or unencrypted CD.

☐ Data are coded or contain identifiers and thus will be sent via using VA—approved carrier with tracking.

☐ Data are coded or identified and will be sent via the Safe Access File Exchange (SAFE) at https://safe.amrdec.army.mil/safe/. SAFE is a secure

method of exchanging files <2GB to and from individuals with a valid .gov, .mil, .com, or .edu email address.

☐ Data are coded or identified and will be uploaded to sponsor website using electronic case report form (eCRF) ☐ Other, describe:

B. Specimens

☐ Specimens are de-identified and thus will be sent via standard carrier (tracking is optional) or will be hand-delivered by research study personnel. Specify method of delivery:

☐ Specimens are coded and thus will be sent via VA-approved carrier with tracking or will be hand-delivered by research study personnel. Specify method of delivery:

In accordance with the HIPAA and the Privacy Act, for any coded or identifiable data or specimens released from the Durham VAMC (with the exception of Limited Data Sets), an Accounting of Disclosure (AOD) will be maintained (e.g., in a database or spreadsheet) that includes the participant's name, date of the disclosure, description of the nature of the Individually Identifiable Information (III) disclosed, purpose of each disclosure, and the name and address of the person/agency to whom the disclosure was made.

C. ☐ Local DVAMC memorandum "Authorization to Use, Process, Store, or Transmit VA Sensitive Information Outside VA Owned or Managed Facilities" has been pre-filled out for each study team member who may transport the data and/or specimens off-site. This (these) forms are included with the IRB materials.

D. ☐ Containers (e.g., briefcase, bin) are labeled with the following notice (label placed on the outside of container) in accordance with VHA Directive 6609:

NOTICE!!!

Access to these records is limited to: AUTHORIZED PERSONS ONLY. Information may not be disclosed from this file unless permitted by all applicable legal authorities, which may include the Privacy Act; 38 U.S.C. §§ 5701, 5705, 7332; the Health Insurance Portability and Accountability Act; and regulations implementing those provisions, at 38 C.F.R. §§ 1.460 – 1.599 and 45 C.F.R. Parts 160 and 164. Anyone who discloses information in violation of the above provisions may subject to civil and criminal penalties.

V. ☐ We will communicate with veterans enrolled as participants in this research study through MyHealtheVet.

7. Risk Mitigation Strategies:

The PI, statisticians, and study coordinator bear primary responsibility for overseeing privacy and security of research data. Risk mitigation strategies include: 1) developing a limited dataset with direct identifiers maintained separately in a cross-walk file as soon as data collection is completed; 2) restricting access to folders containing research data to approved Durham VA personnel only; 3) individual research data will be used only by VA entities for analyses to complete study aims; 4) not transmitting individual data outside VA protected environment; 5) never storing research data on a computer hard drive or mobile device.

☐ Data are fully de-identified (stripped of HIPAA 18 and study ID/code) before being shared outside of Durham VAMC.

☐ Specimens are fully de-identified (stripped of HIPAA 18 and study ID/code before being shared outside of Durham VAMC.

☒ Direct identifiers will be maintained separately from data and or specimens by using a code to "identify" subjects. In a separate database (i.e., a "linking" or "cross-walk" database) this code will be linked to identifying subject information.

☐ Other, specify:

8. Suspected Loss of VA Information:

Should any incident such as theft or loss of data, unauthorized access of sensitive data or non-compliance with security controls occur it will be immediately reported according to VA policy. All incidents regarding information security/privacy incidents will be reported to the ISO and PO within 1 hour of acknowledgement of issue and done so using the VHADUR Research Events Report e-mail group (VHADURResearchEventReport@va.gov).

9. Reporting of Results:

☒ Reporting of results, such as in scientific papers and presentations, will never identify individual subjects. Data will be presented in aggregate and individual-level data will not be published.

☐ Other results reporting plan, describe:

10. Future Use of Data:

☐ Data will be retained for future use. This is described elsewhere in the protocol and is noted in the HIPAA authorization.

☐ Future Use of data is optional (i.e., not required by the research subject).

☐ Future Use of data is required for participation in the study.

☒ No future use of data is currently planned.

11. Use of Mail Merge Technology

☐ Mail merge programs will be used to generate letters and/or address labels for mailings to potential or already enrolled research subjects. The study team is aware that to reduce risk of mail merge related privacy incidents, use of mail merge programs requires a 25% accuracy check to verify that (potential) research subject name and mailing address are properly "matched". If discrepancies are found, a 100% accuracy check is required before letters may be mailed.

12. Use of Non-Standard Software

☒ I do NOT intend to use any new specialized software (i.e. Software that's not already approved OR installed) in this study.

☐ I intend to use specialized software that has not already been installed and it has been approved for use by the VA Technical Reference Model (TRM) Group.
(Note: All new software must be approved by TRM before it can be installed on VA systems.)

☐ I intend to use previously installed software on my VA computer.

13. Use of Cloud Computing Services

☒ Cloud computing services will NOT be used in this study.

☐ Cloud computing services WILL be used in this study as described below and have been approved nationally by the VA Chief Information Officer (CIO). (Note: ONLY cloud computing services that have been approved nationally may be used.)

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Revised Specific Aims

1. Compare the impact of BHS primary osteoporosis screening models on **patient level outcomes** strongly associated with fractures as measured by the EHR at 2 years; 1) eligible proportion screened; 2) medication adherence (initiation; implementation, and discontinuation); 3) bone mineral density at the femoral neck in a random sample of high risk patients. Fracture rates (fractures/patient years) are exploratory.
   H1a: PACT teams randomized to BHS will have better patient level outcomes compared to usual care at pre-specified clinically important levels, adjusting for baseline levels.
2. Determine the impact of BHS primary osteoporosis screening models on **provider and facility level outcomes** including change in DXA volume, change in metabolic bone disease clinic volume (assessed by EHR), and PACT provider time and satisfaction (assessed by Nominal Group Technique).

   H2a: DXA and metabolic bone disease clinic volumes will increase during the intervention, with a higher proportion of referrals coming from PACTs randomized to BHS.
   H2b: Provider satisfaction with osteoporosis screening systems will be higher for PACTs randomized to BHS management compared to usual care.
3. Determine the impact of BHS primary osteoporosis screening programs on **health system and policy level outcomes** using Markov models of screening program cost per quality adjusted life year. Model inputs are based on VA national fracture data from our prior work, results from aims 1 and 2, and published quality of life estimates.

Revised Analysis Plan

Mixed-model ANOVA/ANCOVA will be employed. This extension of the ANOVA/ANCOVA based on the General Linear Model is preferred for group randomized trials with 1 or 2 follow-up time points.[85] We will use the General Linear Mixed Model or the Generalized Linear Mixed Model to account for clustering of patients within providers; this approach accommodates regression adjustment for covariates and has the advantage of both allowing for correlation between subjects within cluster, and within subjects over time. Simulations have shown these methods have the nominal Type I error rate across a wide range of conditions common in group randomized trials.[86] Our general strategy is to follow an “analyze as you randomize” strategy, comparing PACT level parameters between randomization groups. PACTs and individuals will be entered into the model as random effects, while group and time will be tested as fixed effects. We note, however, that if there are minimal differences between PACTs, we will be able to merely control for PACT in the analysis. Further, unlike a longitudinal panel study, subjects will enter and leave the PACT over time. For events that should occur only once (e.g. screening), we will censor the subject at the point of the event. Further, entry into some analyses are conditional on prior events (e.g. medication adherence will occur only among those who are screened and who have a low DXA value and are subsequently prescribed). And, these conditional probabilities may differ by group. In order to get into a groups (example, the osteoporosis treatment group, you must have been diagnosed as having osteoporosis, and, for medication treatment adherence, you must be on treatment. Thus, each group is determined, conditional on having the factor or event that gets them into the group. We will assess if the groups differ on either the rates or demographic/clinical characteristics, and, if necessary, we will employ ‘causal models’(1,2) to derive estimates of effect. If differential dissolution of PACTs is observed we will consider the negative binomial model in addition to the Poisson for the generalized linear and generalized linear mixed models analyses. We will be careful to control (by covariate control, weighting or propensity score matching) to make the groups conditionally equal. The parameter of interest will be the Group mean (and standard error) over time, and measured by the ‘average’ PACT value at each time point. Finally, we note that the estimation models above can be adapted to outcomes distributed other than normal, including Poisson (for number of events/time) and binary (for binary events). This is a 2 group by 3

yearly time point design. To control the overall Type-I error level, we will use the baseline time point as a baseline covariate, and assess group differences at the following time points controlling for baseline. Level of statistical significance will be set at 0.05 (two-tailed) for all tests. In this work, we proposed a GroupxTime interaction, using the time effects as classes/factors. Depending on the significance of this omnibus test, we can assess tests of individual differences (say, group differences at a specific point) by gate-keeping strategy. In the case where the omnibus group by time interaction is significant, then, these will be done without a Type-I error penalty. Initially, we will assess a Time by Group interaction (on 1 degree of freedom). If that effect is declared statistically significant, we will perform follow-up tests to determine where the group differences exist at each follow-up time point, using the gate-keeping strategy listed above. If the Group by Time interaction is not significant, then the main effects of Group and Time will be tested.

Power. We estimate power using aim 1 (patient level) outcomes. The power-limiting endpoint of interest is BMD. We can feasibly invite 100 patients for primary screening in each BHS team given DXA capacity and staff limitations. To achieve 90% power for our minimally clinically significant change in BMD, we will randomly select 25 (25%) from these patients and the top 100 highest risk patients in the Usual Care teams. Recruitment of 712 patients (19/team) will still provide 80% power to detect this difference. Power for the feasibility and acceptability endpoints exceeds 85% with this sample size.

Outcome	**Assumptions, Minimal Clinically Significant Difference**	**Power for 39 PACTS and 3900 patients**
Screening Rates (PACT level)	6% Usual Care, 40% new models	>0.99
Osteoporosis Treatment	Assume 25% of screened meet treatment thresholds. 30% increase from 55% Usual Care	>0.99
Medication Adherence	Usual Care MPR 0.60 (SD 0.35). 20% increase	0.85
Bone Mineral Density (BMD) Femoral Neck in random sample of high-risk patients	0.939 g/cm^2 in BHS group vs. 0.967 Usual Care with SD_{pooled}=0.133	0.90 for random sample of 952 patients (25/team); 0.80 for 712 (19/team)

We expect a low ICC for patients within PACTs as patients are randomly assigned PACT provider, and based on prior studies of patient behavior change within primary care providers ICC<0.1.[96] Our enrolled PACT teams all have >100 patients/panel eligible for osteoporosis screening, and we will select the 100 with highest risk based on the Osteoporosis Screening Tool calculation. We do not expect attrition as new patients are added as others leave with relatively constant panel size. Finally, we determine power for the single degree of freedom contrast of import – Usual Care vs. BHS groups across the follow-up time points. For each of the individual outcomes, assumptions and power requirements are listed in the Table. A sample size of 39 PACTs (19 BHS vs. 20 Usual Care) with an average 100 patients / PACT provides over 85% power for all our primary patient-level outcomes, except fracture rates - an exploratory analysis.

Table 1. Revised Timeline

2020											
1	2	3	4	5	6	7	8	9	10	11	12
January	February	March	April	May	June	July	August	September	October	November	December
								Invite top 50 pts/team			
								BHS 1-4	BHS 5-8	BHS 9-12	BHS 13-16
2021											
1	2	3	4	5	6	7	8	9	10	11	12
January	February	March	April	May	June	July	August	September	October	November	December
	Invite pts 51-100 on each team					Re-invite top 50 pts/team; newly on list or unscreened					
BHS 17-19	BHS 1-4	BHS 5-8	BHS 9-12	BHS 13-16	BHS 17-19	BHS 1-4	BHS 5-8	BHS 9-12	BHS 13-16	BHS 17-19	BHS 1-4
2022											
1	2	3	4	5	6	7	8	9	10	11	12
January	Februar	March	April	May	June	July	August	Septembe	October	November	December
Re-invite pts 51-100 on each team								2 years after 1st invite top 50 patients			
BHS 5-8	BHS 9-12	BHS 13-16	BHS 17-19								
2023											
1	2	3	4	5	6	7	8	9	10	11	12
January	February	March	April	May	June	July	August	September	October	November	December
	2 years after 1st invite pts 51-100					2 years after 2nd invite of top 50					
						DXA - select random sample from top 50 of n=13/team					DXA -select ra
											Team outcom
						BHS 1-4	BHS 5-8	BHS 9-12	BHS 13-16	BHS 17-19	BHS 1-4
						UC 20-23	UC 24-27	UC 28-31	UC 32-35	UC 36-39	UC 20-23
2024											
1	2	3	4	5	6	7	8	9	10	11	12
January	February	March	April	May	June	July	August	September	October	November	December
2 years after second invite pts 51-100				Data cleaning and analysis, Aims 1-2, DXA							
DXA - select random sample from 51-100				of n=12/te	Economic modeling, Aim 3						
Team level outcomes								Write manuscripts, dissemination			
BHS 5-8	BHS 9-12	BHS 13-16	BHS 17-19								
UC 24-27	UC 28-31	UC 32-35	UC 36-39								

Department of Veterans Affairs

Office of Research and Development (ORD)

Request for Administrative Project Modification			
Project is funded by:		Health Services R&D (HSRD)	

Instructions: *The VA principal investigator (PI) should complete this form, sign it electronically, obtain the electronic signatures of site investigators, if required, and email it to the local Research Office. If the ACOS/R supports this request, he/she should sign it electronically, and submit it to the appropriate ORD Service by clicking on the button at the end of the form.*

Check appropriate box(es) on left and follow instructions on right for all the changes that you are requesting. Note: additional documentation may be required per the Criteria and Instructions for Requesting an Administrative Project Modification document.

☑ No-Cost Extension ☐ Cost Extension ☐ Redistribute Funds	• Complete sections 1, 4, and 6 below. • Section 6 must clearly describe the justification for a project extension, additional funds, and/or redistribution of funds, if applicable (amount and timing), and details by site, if multi-site.
☑ Change in Aims, Methods, Key Personnel/Effort, and/or Budget	• Complete sections 1 and 6 below. • Section 6 must clearly describe the proposed change from the approved design, its rationale, and implications for the project in sufficient detail to allow scientific review of the request.
☐ Add/Replace Study Site ☐ Change Site-PI	• Complete sections 1, 2, 3, and 6 below. • Section 6 must clearly explain why an additional or replacement study site is being requested and/or why a change in Site-PI is being requested and how the change will benefit the project.
☐ Change in PI	• Complete sections 1, 2, and 6 below. • Section 6 must clearly explain why a change in PI is being requested. Include a detailed explanation of the new PI's current and proposed involvement in the project, VA eligibility, qualifications to complete the work, and whether the current PI will have any continued role.
☐ PI Station Transfer	• The receiving station completes sections 1, 3, and 6 below. • Section 6 must clearly explain what the PI's role and VA appointment (8ths) will be at the new Medical Center. Provide information that demonstrates resources (e.g. required specialized equipment, animal models, access to relevant patient population, etc.) and personnel at the new station will permit the work to be conducted.
☐ Change in Eighths of PI	• Complete sections 1, 5, and 6 below. • Section 6 must clearly explain why the PI is requesting a change in eighths and implications for the project.

1. VA PI (complete for all types of requests)

Last Name, First Name, Middle Initial, Degree(s)
Colon-Emeric, Cathleen, S, MD, MHS

Telephone	VA email	
919 286-0411 x 176777	cathleen.colon-emeric@va.gov	
eRA Grant Number	Project Start Date	Project End Date
VA Project ID 1 I01 HX002512-01	08/31/2019	08/31/2024

Project Title
Models of Primary Osteoporosis Screening in Men

VAMC Name and Location (City, State)	Station No.
Durham VAHS, Durham, NC	558

Electronic signature of the PI	Date
Cathleen Colon-Emeric, MD, MHS Digitally signed by Cathleen Colon-Emeric, MD, MHS Date: 2020.07.31 11:25:57 -04'00'	07/22/2020

2. Proposed PI (if changing PI or adding study site)

Last Name, First Name, Middle Initial, Degree(s)

Telephone	VA email

Number of VA eighths to be held by PI during the award period

VAMC Name and Location (City, State)	Station No

Electronic signature of proposed PI/Site-PI	Date

3. New VAMC (if transfer of station or adding new study site)

VAMC Name and Location (City, State)	Station No.

Location of research space for this study at the new VAMC

ACOS/R Last name, First Name, Middle Initial, Degree(s)

Electronic Signature of the new VAMC ACOS/R (By signing this form, the ACOS is affirming that all VA requirements regarding the conduct of VA research for this study will be met (e.g. appropriate committee approvals).)	Date

4. Project Extension

New end date requested	Total amount, if additional funds are requested
12/31/2024	

5. Change in Eighths of PI

Current Eighths	Requested Eighths

6. Explanation or Justification (see page 1 for required information)

The overall objective of this application is to determine whether new models of primary osteoporosis screening reduce fracture risk factors in older male Veterans compared to usual care. We initially proposed a group randomized trial of n=39 Patient Aligned Care Teams (PACTs) to one of three groups: 1) usual care; 2) a PACT practice management model with tools and processes to facilitate screening and adherence activities by PACT providers; 3) a Bone Health Service (BHS) screening model in which screening and adherence activities are managed by a centralized expert team. We had fully recruited and begun the intervention for the first 9 teams when all osteoporosis screening (DXAs) were halted by the study sites due to COVID-19 in March, 2020. The screening DXA (the only face-to-face contact in the study) is considered standard clinical care by our IRB and we are operating under a waiver of informed consent, therefore our ACOS for Research has indicated that we can resume screening as per the facility timeline.

The study team has carefully considered what modifications to the study aims and timeline need to be made to optimize Veteran safety and to maintain sufficient power to meet study objectives in light of pandemic impacts. Specifically, the following factors need to be addressed.

1. DXA testing is resuming in July, 2020 but at 20-30% capacity. This will slow down our DXA screening rate.

2. We are recommending that Veterans schedule their DXA test on a day in which they have another clinical face-to-face visit in order to minimize their exposure and that of other patients in the health system. Because many clinics are still using telehealth as their primary modality, there will likely be substantial delays in screening for many Veterans and they may require a second screening invitation if they do not have upcoming appointments. This will further slow our DXA screening rate.

3. Several providers in the PACT practice management arm (the only arm in which PACT providers have study-related training requirements and workflow changes) have expressed concern about their ability to complete study activities in the challenging COVID environment. The Ambulatory Care Chief of Staff indicated that it would not be feasible for providers to participate in this arm for at least another 6 months. Further, we expect that there will be differential attrition with greater team drop-out in this arm.

In light of these factors we request an extension of the study timeline to account for slower than anticipated DXA screening rates. This is reflected in the revised study timeline, attached. In addition, we believe that it is no longer practicable to include the PACT practice management arm in the study as it would incur an additional 6 month or more delay, with likely differential drop-out and resulting lack of power. Therefore, we suggest re-randomizing the PACTs in this arm into Usual Care or BHS. This will allow us to minimize the delay and take

ACOS/R Last name, First Name, Middle Initial, Degree(s)

John D. Whited, MD, MHS

Electronic Signature of the current VAMC ACOS/R (By signing this form, the ACOS is affirming that all VA requirements regarding the conduct of VA research for this study will be met (e.g. appropriate committee approvals).)	Date
JOHN D. WHITED 399178 Digitally signed by JOHN D. WHITED 399178 Date: 2020.08.01 18:23:26 -04'00'	08/01/2020

7. ORD Decision (for Central Office use only)		
◯ Approved ◯ Disapproved ◯ Partial Approval		
Name	Title	
Electronic Signature		Date
Comments		

Electronic signatures are preferred, but a scanned copy will be accepted.

To attach the required documents, compile them into a single pdf and attach as follows:
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