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14. ABSTRACT

Despite the large burden of osteoporotic fractures, their associated complications, and costs to military personnel and veterans, there is considerable controversy about how to screen for and treat osteoporosis in men. The recommendations of clinical practice guidelines vary in how to select men to be screened, and the United States Preventive Services Task Force recently found insufficient evidence to recommend screening and treatment of osteoporosis in men at all, citing a lack of studies measuring fracture outcomes.

This project will develop a large database combining Veterans Affairs and Centers for Medicare and Medicaid Services (CMS) information on bone health risk factors and outcomes. We will use this database to determine the benefits of osteoporosis screening, including rates of fractures and mortality. We will quantify the harms of osteoporosis screening and treatment, including rare but important side effects such as heart disease, esophageal cancer, and atypical fractures. We will prospectively measure healthcare costs in the screened and unscreened individuals, and model the impact of different screening selection criteria on healthcare system costs. The goal is to develop evidence-based male osteoporosis screening recommendations that optimize benefits to patients, while minimizing harms and health system costs.

This study will establish the largest male osteoporosis database in the United States, including over 5.5 million screened and unscreened individuals followed for up to 10 years; prior studies have included fewer than 6000 screened men. Our study team includes representatives from important stakeholder groups including VA Patient Care Services, Pharmacy Benefits Management, the Agency for Healthcare Research and Quality (AHRQ), and professional societies. Therefore, the results of this study will have a high impact on osteoporosis care for male veterans, and will inform healthcare policy nationally.

15. SUBJECT TERMS
Osteoporosis, Males, Screening

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Introduction

Osteoporotic fractures are a major and under-recognized problem in older men.[1] Osteoporosis is particularly prevalent in the VA system; more than half of male veterans over age 50 years have osteopenia or osteoporosis, and nearly 12% of those over age 75 years have osteoporosis, a rate nearly double the non-veteran population.[6] Despite the widespread recognition that osteoporosis is an important disease in men, there is no clear consensus on the appropriate approach for the primary prevention of osteoporotic fractures. While clinical practice guidelines in women uniformly endorse osteoporosis screening beginning at age 65 years,[11] clinical practice guidelines for men vary substantially in the recommended selection of the screening population, and indeed, on whether or not sufficient evidence exists to support osteoporosis screening at all. Current recommendations include screening all men at a given age [National Osteoporosis Foundation (NOF), Canadian Medical Association (CMA)], or selecting men based on the presence of osteoporosis risk factors [VA HSR&D, American College of Physicians (ACP)].[12-15] In the U.K., clinical risk factor scoring systems such as the Fracture Risk Assessment Tool (FRAX) are used to stratify patients; high risk groups receive treatment without further screening, intermediate risk groups go on to Dual Energy X-ray Absorptiometry (DXA) screening, and low risk groups receive no further screening.[15] Most recently, the United States Preventive Services Task Force (USPSTF) completed a systematic review of osteoporosis screening and treatment in men, and concluded that there was insufficient evidence to recommend for or against screening.[16] This conclusion was also adopted by the VA National Center for Health Promotion and Disease Prevention. This project will develop a large database combining Veterans Affairs and Centers for Medicare and Medicaid Services (CMS) data to quantify the benefits, costs, and harms of osteoporosis screening among men. We will use this database to determine the benefits of osteoporosis screening, including rates of fractures and mortality. We will quantify the harms of osteoporosis screening and treatment, including rare but important side effects such as heart disease, esophageal cancer, and atypical fractures. We will prospectively measure healthcare costs in the screened and unscreened individuals, and model the impact of different screening selection criteria on healthcare system costs. The goal is to develop evidence-based male osteoporosis screening recommendations that optimize benefits to patients, while minimizing harms and health system costs

Body

I. Overview

Research accomplishments associated with each task in the approved statement of work are outlined in the table in section below. This first year of the award was dedicated to regulatory approval, data access and cleaning. This project requires the acquisition and cleaning of multiple datasets (VA Austin, CMS ViREC, pharmacy, DXA score natural language processing results, fracture risk score results), with merge and cleaning planned for months 18-21. Our findings to date, are therefore limited to cohort size and initial exclusions.

II. Summary of Specific Aims

1. Determine the benefits of a screen and treat strategy for the primary prevention of osteoporotic fractures in male veterans.
    a. To determine whether **receipt of DXA screening** is associated with a **lower risk of fracture**.
    b. To determine whether **receipt of bisphosphonates** is associated with a lower risk of fracture.
    c. To determine whether receipt of bisphosphonates is associated with a **lower risk of mortality**.
2. Determine the harms of screening and treatment strategies to prevent osteoporotic fractures in male veterans.
    a. To explore the impact of oral bisphosphonates on gastrointestinal events and other possible rare but important side effects including: osteonecrosis of the jaw, esophageal cancer, subtrochanteric fractures, and atrial fibrillation.
    b. To explore the impact of calcium prescriptions on cardiovascular events, adjusted for important covariates and vitamin D use.
3. Determine the costs of a screen and treat strategy to prevent osteoporotic fractures in male veterans.
    a. To determine the VA and Medicare cost implications of a strategy of "screen and treat" for osteoporosis in older men retrospectively through medical claims and prospectively using different screening eligibility criteria and treatment thresholds.
        i. Estimate the five-year cost implications of screen and treat for our study cohort based on observed screen and treat practices, fracture incidence, and VA and Medicare medical costs from 1999-2009.
        ii. Estimate prospective cost implications of different screening eligibility and treatment thresholds using baseline results and the following scenarios:
            I. Screening:
                a. All men over age 70 years
                b. Men over age 70 with risk factors for osteoporosis (current VA and ACP guidelines)
                c. Men with an intermediate FRAX 10-year fracture risk (current U.K. guidelines)
            II. Treatment thresholds:
                a. T score <= -2.5
                b. FRAX 10-year fracture risk for major osteoporotic fracture >20% or hip fracture >3% (current NOF guidelines)
    b. In the retrospective cost analysis, to determine the relative differences in osteoporosis DXA screening rates over time for special populations of older

veterans of interest, and then their costs, including: rural populations, veterans on high risk pharmacotherapies, and veterans with high risk conditions.

III. Barriers Encountered

Delays in data acquisition were encountered due to a new requirement to obtain real social security number data access prior to accessing Veteran radiology reports, and requirements for IRB approval at the clinical sites of all Co-Investigators, even those not directly accessing Veteran data. Data access has now been accomplished. Our programmers used an existing approved data set to develop and test the Natural Language Processing (NLP) code, so that the final data set merge should not be substantially affected by these delays.

IV. Performance Expectations

As stated in the approved Scope of Work, the Principal Investigator conducts weekly meetings with the data management staff, biostatistician, economist, and project director. The full team of co-investigators will has monthly teleconferences to review progress, make data definition and analysis decisions, and interpret findings. Study consultants are asked to join these meetings as appropriate to their expertise and role. Minutes of each call and a log of key decisions are kept by the Project Director and PI.

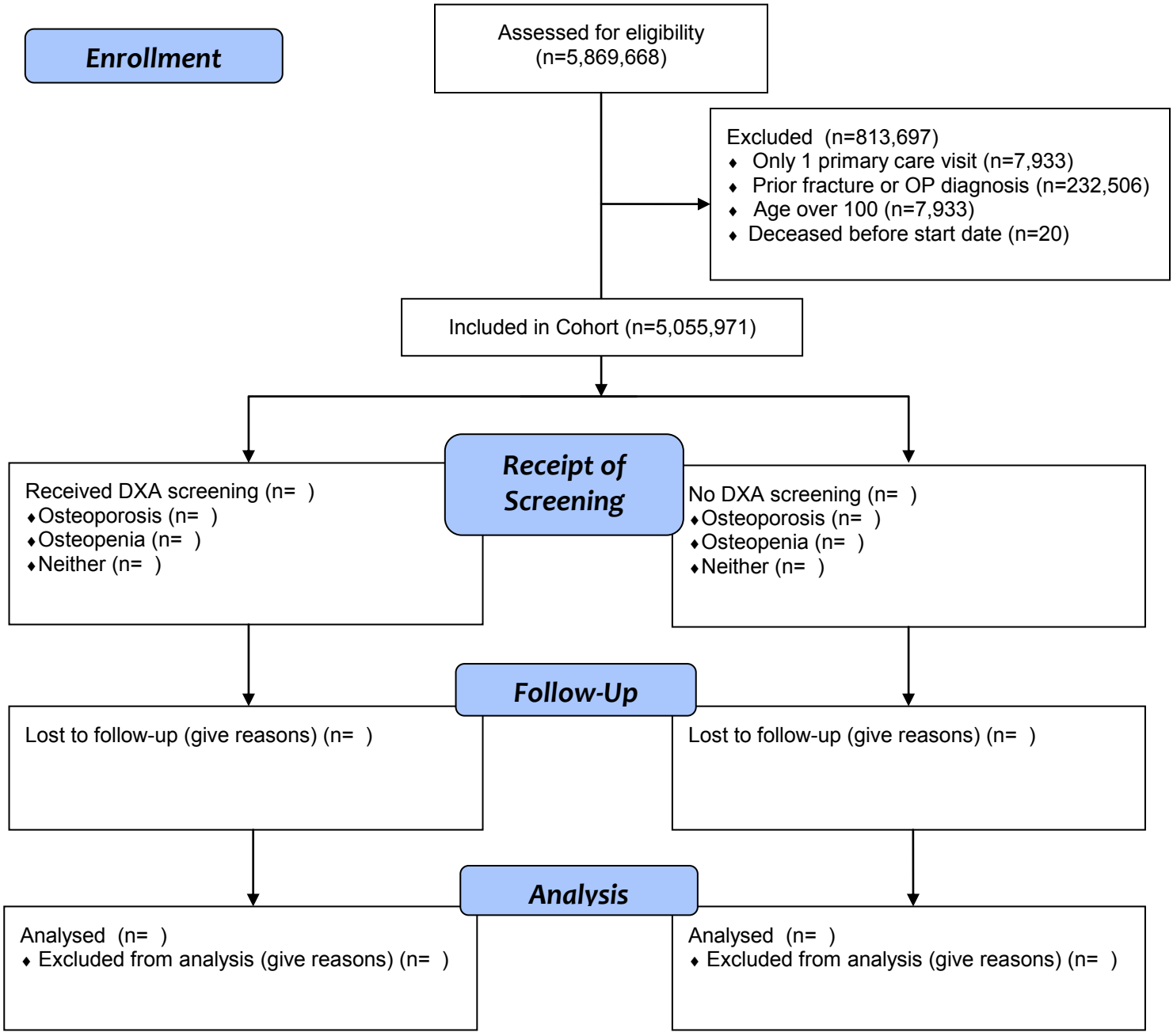
We have formed an Advisory Board comprised of an interdisciplinary group of experienced osteoporosis and VA researchers to assist with oversight and decision-making about data management and analysis. The Advisory Board is scheduled to meet October 3, 2013 in conjunction with the American Society of Bone and Mineral Research annual meeting.

The co-investigator team has established a formal, written process for determining analysis priority and authorship at the beginning of the study. We also established a mechanism for reviewing requests from outside investigators to use the data collected and cleaned for this study for additional clinical questions of interest to the DOD and VA.

V. Research Subjects

We estimated that approximately 1,400,000 subjects will be eligible for inclusion in the database, with some 28,000 screened individuals. In fact, we have identified 5.5 million Veterans meeting eligibility criteria, which will substantially improve the precision of our findings. The preliminary CONSORT diagram for study subjects is below. Note that identification of screened vs. unscreened status will not be completed until the NLP analysis is finalized.

CONSORT Flow Diagram



VI. Milestones, Tasks, Methods, and Outcomes

Task	Methods	Outcome/Deliverable/Product	Status
Milestone 1. Regulatory Approval, CMS and VA data requested and obtained. (months 1-6)			
Submit IRB and Human Subjects initial and continuing reviews at Durham VAMC and Salt Lake City VAMC (month 1-4)	Regulatory document completion, human subjects training	Maintenance of IRB approval at all sites engaged in research, study binder, personnel training up to date	Completed. In addition, approval was obtained from the Richmond VAMC for Dr. Adler
Request Corporate Data Warehouse (CDW), and 1994-1999 Austin data (month 1-3)	Data Access Request Tracker (DART) system	Finder file of all Veterans in study period meeting eligibility criteria developed	Completed
Request Medicare (CMS) data from VA Information Resource Center (VIReC) (month 4-6)	Per VIReC Medicare data request process, using finder file developed from Austin data	Medicare data on eligible subjects downloaded to Durham VA server	Completed
Develop data management and security standard operating procedures (SOPs) (month 1-6)	Modification of existing and creating new SOPs as needed to describe data management practices	• Secure server files created and maintained • Clear procedures for data cleaning and management tasks documented	Completed
Milestone 2. Dual Energy X-ray Absorptiometry (*DXA*) data extracted and cleaned, VA and CMS data cleaned and ready for merge with DXA data (months 1-12)			
Extract DXA data from eligible subjects (month 1-6)	Natural language processing used to extract DXA results from text notes in radiology and consultation records	Dataset containing DXA results from all eligible subjects assembled.	In progress – delay in obtaining text files due to new requirement for real SSN access. However, NLP programming is completed, validated, and ready to run on the dataset.
Clean and validate DXA data (month 6-12)	Random subset of records hand pulled to calculate validations statistics	• Accuracy, Precision, Recall, and F measure calculated for DXA dataset. • DXA dataset is cleaned a ready for merge with VA and CMS files	• Completed. Accuracy for T score and anatomic site is 90.4%. • In progress (see above)
VA database variables cleaned and validated (month 6-12)	Outlier variables are identified using graphical and numerical methods, and confirmed, replaced or deleted per the SOPs developed above. Missing variables are imputed if indicated.	Clean database of VA variables created and ready to merge with CMS and DXA files	• Variable definitions completed • Variable cleaning in progress

CMS database variables cleaned and validated (month 6-12)	Outlier variables are identified using graphical and numerical methods, and confirmed, replaced or deleted per the SOPs developed above. Missing variables are imputed if indicated.	Clean database of CMS variables created and ready to merge with CMS and DXA files	• Variable definitions completed • Variable cleaning in progress
Milestone 3: Utilization and cost measures constructed for both VA and CMS data, and VA and CMS data files merged. (months 9- 18)			
Construct utilization and cost measures for VA database. (months 9-15)	Fracture related costs will be summarized across VA and non-VA contracted care using ICD9 and CPT codes and aggregated across inpatient and outpatient fields annually for each subject	Fracture-related costs to VA calculated for eligible subjects	• Utilization and Cost Variable definitions completed
Construct utilization and cost measures for CMS database. (months 9-15)	Fracture-related costs to Medicare will be identified using ICD-9 codes and surgical procedure codes. Total costs to Medicare will be aggregated using the Beneficiary Annual Summary File, and aggregating the positive values from each of the following variables for the year.	Fracture related costs to CMA calculated for eligible subjects	• Utilization and Cost Variable definitions completed
VA and CMS data files merged (month 15-18)	Using unique subject identifiers, CMS and VA data files will be merged, and cleaned using SOPs.	Cleaned database containing relevant VA and CMS variables created for all eligible subjects	
Milestone 4: Final analytic file completed. (month 21)			
DXA data merged with combined VA and CMS files (month 18-19)	Using unique subject identifiers, DXA data files will be merged with the main analytic file, and cleaned using SOPs.	Database containing all VA, CMS, and DXA result variables ready for cleaning	
Merged file cleaned, data inconsistencies identified and cleaned using SOPs. (month 20-21)	Contradictory or multiple variables across files are identified using graphical and numerical methods, and confirmed, replaced or deleted per the SOPs developed above. Missing variables are imputed if indicated.	Cleaned database containing relevant VA and CMS variables and DXA results is ready for analysis	
Data de-identification of merged file completed according to SOPs (month 21)	Using current VA Information Security Officer guidance, merged datafile will be stripped of HIPAA key identifiers to create a limited data set	Cleaned dataset created with risk of subject identification and loss of privacy minimized	
Milestone 5: Analyses for specific aims completed. (month 30)			
Analyses for specific aims 1-2 (benefits and harms) completed. (months 21-30)	A "propensity to be screened" model will be developed for each VAMC (strata) based on their osteoporosis and fracture risk	• Hazard ratio reflecting risk of fracture and all-cause mortality (dependent	

	factors. This screening propensity score will be used as a further stratification variable in Cox Proportional Hazards models, with receipt of DXA as a time-varying covariate, to estimate the impact of osteoporosis screening and treatment on fracture rates, mortality rates, and treatment-related harm outcomes.	variables) in screened and unscreened individuals, adjusting for important covariates including bisphosphonate treatment • Hazard ratio reflecting risk of harm in treated vs. untreated individuals, adjusting for important covariates (dependent variables include cardiovascular events, esophageal cancer, atypical fractures)	
Analyses for specific aim 3 (costs) completed. (months 21-30)	We will calculate VA and Medicare fracture related resource utilization costs as well as total VA and Medicare resource utilization costs for subjects in five year increments. Costs to the VA and costs to Medicare will be modeled separately and also aggregated to understand overall costs across the two public insurers.	• Cost to VA, Medicare, and total costs of different strategies of osteoporosis screening in male veterans	
Milestone 6: Result dissemination, final report completed. (month 36)			
Summary results (technical reports) of specific aims 1-3 written. (month 30-33)		Executive summary and technical report created for presentation to relevant stakeholders	
Technical reports presented to key stakeholder groups identified by advisory board members. (months 33-36)		• Report presented to VA National Center for Health Promotion and Disease Prevention • Report presented to VA Pharmacy Benefits Management	
Scientific presentations and articles for peer review drafted on specific aims 1-3. (months 30-33)		• Results presented at American Society of Bone and Mineral Research, VA Health Services Research and Development, or other professional meetings	

Key Research Accomplishments

- Regulatory approval attained, data acquired from VA Austin, PBM, ViREC, and CDW.
- 114 variables defined using CPT, ICD9, and pharmacy codes (when applicable).
- Cost analysis variables and datasets have been identified.
- Propensity score analysis plan completed.
- Natural Language Processing coding completed. Validation on test data with excellent performance characteristics.

Reportable Outcomes

- Large database constructed with over 5.5 million male Veterans age 50 years and older who receive primary care in the VA system. The database includes clinical, laboratory, pharmacy, and CMS data.

Conclusion

This study will create the largest cohort of men screened for osteoporosis examined to date, and will allow us to quantify the benefits, harms, and costs of screening with excellent precision. This study will therefore inform screening guidelines within the VA and nationally. Despite delays in accessing the data for Natural Language Processing (required for determination of DXA results), we do not anticipate any overall impact on the study findings or timeline.

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Appendices

None