Aims Page

Osteoporosis has historically been viewed as a women's disease with the majority of evidence in risk factors, diagnosis, and management focused on postmenopausal women. Osteoporosis and related fractures is a significant clinical problem in men. Approximately two million American men already have osteoporosis and about 12 million more are at risk [1]. Over their lifetime, it is estimated that 1 in 12 men will sustain a hip fracture (20-25% of all hip fractures occur in men), and up to 37.8% of older men are expected to experience a hip fracture by the year 2030 in the United States. A major bone fracture is a devastating life event that leads to increased disability and premature death in older men [2]. Relative risk of death in men within a year after hip fracture is eight-fold greater than in men without fracture and almost 50% greater than 1-year mortality in women post-fracture at any given age [3].

Despite the clinical importance of the issue, little is known about standard of care for osteoporosis in men, including rates of diagnosis and relative importance of traditional risk factors in care planning and monitoring. Largely unknown or not systematically assessed in men are the proportion of primary and secondary osteoporosis in patents receiving care in primary care settings, the role of potentially modifiable risk factors in health care and preventative services, and current services utilization such as rates of screening, bone density assessments, post-assessment follow-up, diagnosis rates, and treatment patterns. Even though the general recognition that osteoporosis and related fractures are preventable, the quality of care for osteoporosis remains suboptimal even in women and more so in men [4]. Primary care plays an important role in osteoporosis prevention and management. Primary care providers will benefit from future clinical studies aimed at improved osteoporosis care informed by the data obtained in this observational study.

The goal of this cohort study is to characterize male osteoporosis in primary care patients who receive services and treatments as a part of their standard of care, including patient characteristics, prevalence and rates of diagnosis, treatment and prescribing patterns, and complications of treated and untreated osteoporosis by utilizing secondary data analysis of electronic health records from 209 primary care practices.

The **Specific Aims** of the project include the following:

Aim 1: to characterize primary care population of males with and at risk for osteoporosis who receive services and treatment as part of their standard of care. For this objective we will describe prevalence of diagnosed osteoporosis, risk factors and their relative importance, documented osteoporosis causes, and key socio-demographic characteristics of the persons in the total male registry population.

Aim 2: to characterize standard of care for male osteoporosis, including rates of clinical testing, treatment prescribing patterns, and monitoring patterns. For this objective we will describe osteoporosis related health care services utilization around male osteoporosis screening, diagnosis, treatment, and monitoring and concordance with guideline-based care for persons in the male registry population.

Aim 3: to characterize rates of complications and adverse events related to treated and untreated osteoporosis. For this exploratory objective we will focus on descriptive statistics of rates of documented complications related to osteoporosis and treatment-related adverse events based on the level of care, the presence of diagnosis, risk factors, and treatment type.

This study will address important gaps in specific knowledge about male osteoporosis including patient-related and care-related characteristics such as prevalence, rates of diagnosis, treatment patterns, prescribing patterns, and complications of treated and untreated osteoporosis. The data from this study will be used to inform development of clinical trials to improve uptake and implementation of effective prevention and treatment strategies for osteoporosis in men. The study will provide the standard of care data to be used as a historic control in future clinical trials, as well as in future initiatives to address gaps in care and to raise awareness about male osteoporosis and available preventative and therapeutic interventions.

Research Strategy

Significance

Burden of osteoporosis: Osteoporosis is a major public health issue that is commonly referred to as a "silent killer"[5]. While the disease progresses without any clinical manifestations, it often results in serious health consequences such as bone fractures. Osteoporosis-related fractures are among the major health and socioeconomic concerns in aging. In the USA, 1.5-2 million fractures, including 325,000 hip fractures, occur annually with an estimated direct cost of $20 billion/year. The number of hip fractures in the USA is predicted to double within 30 years. Hip fractures in older adults result in increased morbidity, disability, and premature death (18-33% of hip fracture patients die within a year).

Despite the general recognition that osteoporosis and related fractures are preventable, the quality of care for osteoporosis remains suboptimal. In postmenopausal women for example, although osteoporosis is well studied, methods to identify persons at risk are available, prevention and treatments guidelines are established, and effective pharmacological and non-pharmacological treatments exist, a plethora of clinical issues still remain. Among the gaps in clinical care identified in women are under-diagnosis, under-utilization of bone density testing, inadequate assessment of risk factors and secondary causes, especially in high risk patient populations. Even with a diagnosis of osteoporosis, treatment is often inadequate with insufficient follow-up [6]. The International Osteoporosis Foundation reports that these clinical gaps are even wider in care of male patients[7].

Current state of knowledge about male osteoporosis: Osteoporosis is a significant clinical problem in men. Approximately two million American men already have osteoporosis and about 12 million more are at risk[1]. Over their lifetime, it is estimated that 1 in 12 men will sustain a hip fracture (20-25% of all hip fractures occur in men), and up to 37.8% of older men are expected to experience a hip fracture by the year 2030 in the United States. A major bone fracture is a devastating life event that leads to increased disability and premature death in older men[2]. Relative risk of death in men within a year after hip fracture is eight-fold greater than in men without fracture and almost 50% greater than 1-year mortality in women post-fracture at any given age[3]. Osteoporosis, however, has historically been viewed as a women's disease with the majority of evidence in risk factors, diagnosis, and management focused on postmenopausal women. Several large observational studies provided initial evidence on prevalence and risk factors in male cohort of research participants[8] and reviews suggested risk factors for poor bone health in men that are available in primary care practice[9]. It is unknown however to what extent this evidence is utilized in actual clinical care. Additionally, the actual US prevalence of osteoporosis in general men population is unknown, and there is no comprehensive description of clinical practices for diagnosis and treatment of osteoporosis in men in the US. Despite the clinical importance of the issue, little is known about standard of care for osteoporosis in men, including rates of diagnosis, documentation and relative importance of traditional risk factors in care planning and monitoring. Largely unknown or not systematically assessed in men are the proportion of primary and secondary osteoporosis in patents receiving care in primary care settings, the role of potentially modifiable risk factors in

health care and preventative services, and current services utilization such as rates of screening, bone density assessments, post-assessment follow-up, diagnosis rates, and treatment patterns.

Necessity for future clinical trials: The evidence about awareness of male osteoporosis is alarming: there is almost nonexistent awareness among health care providers of the need to assess male patients for osteoporosis[10]. This is particularly challenging in primary care, where the majority of patients at risk or with osteoporosis go undetected and undiagnosed[11,12]. The male patients also have very poor understanding of the basics of osteoporosis, risk factors, and treatments[13]. There are limited recommendations for male osteoporosis prevention or management, even despite that studies suggest that osteoporosis in men is undetected, underdiagnosed, and under treated[14,15]. In 2010 the US Preventive Services Task Force published the review of the evidence on effectiveness and harms of services and treatment related to osteoporosis[16]. The summary indicated that despite the available screening and assessment methods and availability of effective treatments the trials are lacking in men. The trials of screening tests are limited in men and no trials are available on the screening intervals in males. Additionally, no trials of screening effectiveness or screening harms and benefits in either gender were identified. The review of treatment effectiveness or the primary prevention trials identified only one trail in men on effectiveness of parathyroid hormone therapy with a trend toward reduction in vertebral fractures. Despite availability of other therapeutic agents for male osteoporosis no other primary prevention trials were identified in men. The male osteoporosis is a significant issue in health care and as evident from the literature (and the Letters of Support) the need for evidence to inform clinical trials and clinical practice is strongly supported. While a number of other reviews and original research studies have been published on tested effective interventions and gaps in research related to male osteoporosis, the US Preventive Services Task Force recommendations is the primary source of evidence for many medical societies and advocacy groups including the American Academy of Family Physicians (AAFP) for making evidence-based recommendations about clinical preventive services such as screenings, counseling services, and preventive medications. Currently, it is evident that osteoporosis in males is under-detected and undertreated. The evidence from observational studies and clinical trials will contribute to better prevention and treatment, and ultimately lead to a decrease in fractures and associated morbidity, disability, and premature death. Additionally, clinical trial may prevent treatment failure in osteoporosis in men, which is an unmet clinical need due to relative lack of trials in men [17].

Significance: With the high burden of the disease, increased mortality and disability among men, and availability of bone sparing treatments and preventive strategies including lifestyle changes and effective bone modifying medications, it is important to understand the gaps in care for men with osteoporosis or at high risk for osteoporosis to inform and strengthen clinical practice.

This study has a potential to inform clinical trials, practice-based research and education interventions and other studies that aim to optimize prevention, detection and management for male patients with osteoporosis in primary care and other settings. Information obtained in this study has potential to inform the clinical decision tools such as toolkits, recommendations, guidelines and clinical decision support health IT on male osteoporosis. Many effectiveness and comparative effectiveness trials utilize “care as usual” as comparator to the investigational intervention, drug or device however the standard of care for male osteoporosis is not well-defined. By identifying and describing the current standard of care and patient characteristics of those who receive standard care (or “care as usual”), this study has a potential to inform the choice of “care as usual” by other investigators as a comparator in future clinical trials and studies. Research on the extent of guideline concordance/discordance would shed light on the magnitude of the issue and would inform potential trials and interventions aimed to address the practice gaps. These research studies will subsequently lead to evidence translation to practice and policy and improved evidence-based care for male osteoporosis. This study will

also contribute to knowledge regarding issues associated with use of clinical data to inform future research and quality improvement.

This study will address important gaps in specific knowledge about male osteoporosis including key socio-demographic and clinical characteristics of the persons with and at risk for male osteoporosis, rates of diagnosis, treatment patterns, prescribing patterns, and complications of treated and untreated osteoporosis. The data from this study will be used to inform development of primary care-focused interventions to improve uptake and implementation of effective prevention and treatment strategies for osteoporosis in men. The results of this study will be utilized to directly impact clinical care through provider and patient education strategies to raise awareness about male osteoporosis and available preventative and therapeutic interventions.

Innovation: To our knowledge, this would be the first study of this size to examine the value of EHR socio-demographic and clinical data in defining the standard of care for persons of male gender with or at risk for osteoporosis in primary care with potential preventive and therapeutic targeting. The novel aspect of the study is its focus on osteoporosis risk factors that would be readily available in the clinical data found in primary care practice. We propose using the risk assessment tool, The Male Osteoporosis Risk Estimation Score (MORES, see in detail below) to assess the male patients in the registry by applying scoring algorithm to the patient record. We hypothesize that since all the data elements necessary for risk assessment are readily available in the patient's heath record, the tool could be easily applied to the patient records eliminating the necessity for the patient to have a visit to be identified as being at risk.

The results of this study could potentially lead to a low-resource population-based prescreening method of systematic identification of men at risk that need to be referred to the DXA scan for diagnostic confirmation and subsequent quality improvement and to future research projects for osteoporosis detection, treatment administration and improved outcomes. Recent studies in Europe exploring costs of pre-screening using risk assessment tools found that the risk assessment tools are valuable, cost-effective, and potentially effective approach to reduce the economic burden of mass screening for osteoporosis[18,19]. This approach may also be useful for describing availability and identifying potential clinical trial participants among persons receiving care in primary care clinics. This study will also contribute to emerging knowledge regarding use of electronic health records data to inform future research and quality improvement related to osteoporosis.

At the successful completion of this study the data derived will be available and included in the future clinical trials developed by the investigators at the AAFP National Research Network including principal investigator (Loskutova) and will become available for other researchers and clinicians to use. The results obtained in this project will be used for further trial development for guiding primary care providers on identifying, assessing and managing individuals at risk for or with male osteoporosis. In addition, the results will be useful in operationalizing male osteoporosis risk assessment and evaluation of these individuals in a cost-effective and timely manner. In the long-term, we propose to develop novel practice-based clinical trials for timely identification of persons at risk and in need of assessment or periodic re-assessment for male osteoporosis as well as risk reduction and improved management of male osteoporosis.

Approach

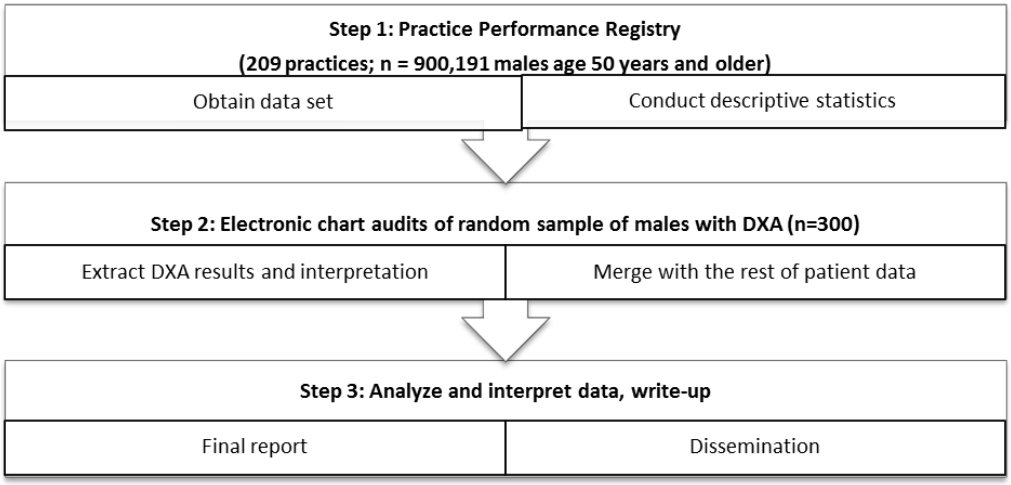
Study overview: This is an observational secondary data analysis study involving retrospective cohort study design. The study will consist of descriptive and analytic epidemiology data analyses applied to existing electronic medical record and administrative data from a sample of 209 primary care practices in the USA.

This will be a 18-month observational retrospective cohort study that will include Step 1: obtaining data according to study specifications and data pre-processing; Step 2: electronic chart audits; and Step 3: data analyses, interpretation and write up that includes a final report and at least one scientific manuscript for a peer-reviewed journal (Figure A.).

The secondary data analysis study design was chosen to characterize primary care population of males with and at risk for osteoporosis who receive services and treatment as part of their standard of care including prevalence, rates of diagnosis, and treatment and management patterns because 1. the primary data collection for the study of the equal size patient sample would be cost, resource and time prohibitive; 2. the database utilized in this study is of sufficient quality and quantity of data to conduct a high-impact study that addresses the stated objectives; and 3. it has significant advantages to assess a wide range of outcomes that are relevant to clinical care and have the greatest potential to be modified with future practice-based interventions.

Study population: Adult patients (50 years of age and older) of both genders will be included if they have a record in the database. Preliminary record count identified 1,245,109 women of 50 years and older and 900,191 men of the same ages in the database. The primary target population is adult males age 50 and older. For the purpose of complete audit, the relevant outcomes will be presented by gender whenever appropriate.

Figure A. Study Overview



Database overview: The clinical data set will be obtained through the DARTNet Institute (http://www.dartnet.info/). For this project we will utilize existing data from **the DARTNet Institute Practice Performance Registry database** that consists of previously extracted clinical data from patient health and claims primary care practice databases, up to 15 years in duration. This database includes over **4,725,103** individual patients 2,145,300 of whom are 50 and older, including **900,191 males age 50 years old** and older. Preliminary analyses identified **6,130 distinct male patients with a diagnosis of osteoporosis** (ICD-9-CM Codes 733.xx; ICD-10 Codes M81.0, M81.9, M85.2, M85.3, M85.4, M84.xx, M87.xx, M89.0, M89.3, M89.8X9, M94.0, M94.xx, S42.xx).

Electronic health records and administrative claims data are the major sources of data for clinical encounters and services; they have been used successfully to characterize various conditions and deliver interventions for health care quality improvement. While consistency in quality of administrative data overall still needs improvement, several studies have found the administrative health data to have a high degree of reliability and validity. Current evidence suggests that existing electronic medical records provide sufficient data about secondary causes of osteoporosis and risk factors[20,21]. Statistical remedies to address limitations of these data sets are available and will be used in this project as appropriate[22].

For this project we will be partnering with the DARTNet Institute for obtaining the set of data from the entire Practice Performance Registry as outlined in the Table 1 below. The DARTNet Institute is a not-for-profit research institute that coordinates and supports quality improvement activities through the reuse and improved collection of electronic health data. The DARTNet Institute has experience in extracting existing clinical data, in assisting in the discrete capture of new clinical data, and in linking and standardization of various data sources, such as multiple EHRs and claims data (see also the DARTNet Institute Letter of Support).

The AAFP NRN has sufficient experience with utilizing electronic health record data for research. We have conducted numerous studies examining pooled electronic health record data to assess clinical care. These studies used data from DARTNet Institute (the same organization that will provide data for this study). In one study, we investigated the effect of two professional development programs on the quality of care delivered by physicians to patients with diabetes mellitus.[23] In another study, our group used DARTNet data to conduct electronic chart audits followed by more in-depth manual audits to increase our understanding of community-acquired Methicillin-Resistant Staphylococcus Aureus diagnosis, treatments, and documentation.[24] Dr. Loskutova in collaboration with DARTNet recently conducted a study that evaluated dementia detection rates using secondary data analysis techniques[25]. We are currently conducting a retrospective- prospective study to optimize pharmacotherapy for patients with attention deficit hyperactivity disorder (ADHD) and promote safe and appropriate prescribing of stimulants and related medications in primary care. This study utilizes pooled electronic health record data to assess and improve clinical care (PI-Loskutova). Additionally, an ongoing clinical trial based on the electronic health records data (data analytics) and provider education to improve adult immunizations in primary care practices utilizes DARTNet electronic data for assessment of outcomes (Loskutova- PI).

The DARTNet Institute Practice Performance Registry has been endorsed by the American Academy of Family Physicians as a Quality Improvement Registry that also meets Stage 2 Meaningful Use Measure 6 requirements. The current Practice Performance Registry includes 209 primary care clinical sites, just over 1,000 clinicians, and about 5 million patient records.

Quality and quantity of data: The current database contains medical and administrative data for of 900,191 unique patients of male gender who are 50 or older years in age. Selected key data categories and elements related to the objectives of the study will be describes in the sections below.

The following data (Table 1) will be obtained for all patients in the data base for whom the data from the medical record are available:

Table 1 Data Variables to be Requested from the Practice Performance Registry for the Study

Domains	Data variables
Patient Characteristics	Age; gender; race; insurance status
Practice Characteristics	Practice location (state); size; type
Patient Diagnoses	ICD-9 codes; ICD-10 codes
Osteoporosis Risk Factors[9,26]	ICD-9 and ICD-10 codes (codes will be searched for CKD, COPD, diabetes, liver disease, hypogonadism, hyper- and hypothyroidism, rheumatoid arthritis, and dementia[27]); Smoking status; Height and weight; Vitamin D and calcium levels; Prescribed medications (the records will be searched for high dose of glucocorticoids for prolonged periods of time currently or in the near past and other identified bone-affecting medications; Immobilization records; Alcohol consumption
Bone fractures	History of fractures or objective evaluation

Investigation	Evidence of an assessment for osteoporosis: initial DXA orders (all patients) and results (sub-group, see below); Fall risk assessment
Management	Physical exam; Patient visits; Prescribed Medications (the records will be searched for treatments for osteoporosis); Insurance claims data (all CPT 2014 codes) Laboratory tests; Repeated DXA orders; Urinary bone turnover marker orders

CKD- Chronic kidney disease; COPD – Chronic obstructive pulmonary disease; CPT 2014 - Current Procedural Terminology 2014; DXA - Dual energy x-ray absorptiometry.

Patient characteristics: demographic and clinical data elements: The typical data elements available through this database include patient demographics (year of birth, gender, race-ethnicity); all diagnoses and medical problems that are documented in the patient's electronic medical record; all medical procedures associated with the patient's medical history (including dates and records of DXA scans ordered or performed as a part of typical medical care); laboratory work with results that is a part of a routine patient care, including level of vitamin D and calcium when indicated; all recommended preventative services such as screenings, risk factor assessments, vaccinations and required counseling; all prescribed medications, including medication name, dose, start and end dates and instructions (see in detail below).
A sample of an actual patient record that includes some selected information related to osteoporosis requested from the data base records for demonstration purposes is presented in Table 2 below.

Table 2 Example of an Actual Patient Record from the Dataset

Year of birth: 1939
Gender: Male
Race: White
Ethnicity: Non-Hispanic or Latino
Diagnosis: Osteoporosis (ICD-9_CM code 733.00)
Date of diagnosis: actual month/actual date/2012 (actual year)
Vitamin D, 25-Hydroxy: date of observation (actual date): level - 54.4 ng/mL
Calcium: date of observation (actual date); level - 8.9 mg/dL
Drug name: Fosamax; NQF code: 6003121; drug strength: 70mg; start date for drug exposure/end date for drug exposure (actual dates).

Note: the record includes only a few selected data elements from the dataset for demonstration purposes and actual dates and identifiable information are not included here; all patient-level data will be de-identified.

Prescribed medications data elements: For all prescribed medications, the following information at the prescriber (primary care provider) level whenever exists in the actual patient record will be available in the database:

- Drug name
- Drug exposure start date
- Drug exposure end date
- Drug type
- Stop reason
- Number of refills allowed
- Quantity
- Days of supply
- Prescribing provider
- Visit occurrence
- Relevant condition/indication

- Drug strength/dosing
- Directions (note: may involve free text analysis)

The dataset contains information on initially prescribed medications and prescription renewals for ongoing treatment and as exists, does not contain information about actual medication fulfillment, pharmacy refills and dispensing from pharmacies. This proposal will use existing EHR database to study prescribing patterns and prescriber behavior and will focus on which medications have been prescribed and the patterns and details of prescriptions for osteoporosis treatment. The records will be searched for high dose of glucocorticoids for prolonged periods of time currently or in the near past and other identified bone-affecting medications[8,27];

Bone density data elements (all patients): For DXA scans, all records of scans with dates when present or documented in the patient record will be available for the project. Preliminary data analysis indicates 78,112 distinct patients [Female: 72,617(93%) Male: 5,495(7%)] with at least one documented DXA scan in their record. Altogether these patients have 136,093 identified records of DXA that indicates that some proportion of the patients had more than one DXA scan.

It is currently unknown what percent of these DXA scans are baseline or follow-up DXA scans. The project will determine the percent of the baseline DXA scans and the flow-up rates. The objectives of the projects are to explore and describe the actual practice patterns related to DXA scan utilization in male patients as detailed further in the proposal. There has been very little evidence on DXA utilization in real-world primary care practice in male patients, thus this study will determine the rates of initial DXA assessment and repeated DXA in the total male registry population.

Confirmatory bone density assessment: Dual energy x-ray absorptiometry (DXA) is currently the "gold standard" for bone density assessment (bone densitometry) and for informing or confirming the diagnosis of osteoporosis. The World Health Organization defined diagnostic criteria for osteoporosis using bone mineral density (BMD) measurements reported in T-scores and z scores[28]. A T-score is the number of standard deviations above or below the mean BMD among young adults matched for sex and race (but not age). It classifies patients into three diagnostic categories: normal (T-score of -1.0 or higher), osteopenia (T-score between -1.0 and -2.5) and osteoporosis (T-score of -2.5 or lower). This definition is generally applicable to both genders, and it is commonly agreed that T-scores are useful for identifying men at higher risk of fractures.

The US Preventive Services Task Force concludes that the predictive performance of DXA is similar for men and women, though it does not make any specific recommendations on osteoporosis screening in men[16]. The American College of Physicians provides strong recommendation for obtaining DXA for men 65 and older who are at increased risk for osteoporosis and who are candidates for medical treatment[15]. The American Academy of Family Physicians Choosing Wisely® Campaign supports screening for osteoporosis with DXA for all men 70 and older[29]. For the purpose of this study we will focus on the evidence of a referral for bone densitometry (DXA) for the entire patient sample in the database. Additionally, we will obtain actual values for bone density or bone mineral content and T-scores, and the dates of DXA completion for a sub-group of patients via chart (electronic record) audit as described below.

Chart audits: In addition to existing data, we plan to conduct electronic medical record audits of a random sample of 300 men for whom the dual energy x-ray absorptiometry (DXA) scan was ordered. The following outcomes will be recorded from that sub-group of patients: actual values for bone density or bone mineral content and T-scores, and the dates of DXA completion. These will be used to analyze the rates of incomplete follow-up and missed diagnosis based on completed DXA scan results as well as the prevalence of osteoporosis and osteopenia among those men for whom a DXA scan was ordered.

All data will be obtained de-identified with the dates of service re-coded to preserve the chronological order of the events. The sequence of actual events from the medical records will be reconstructed to assess the concordance with the recommended clinical and treatment guidelines as presented in the Figure B and will be presented in a study concordance/discordance diagram according to the best practices in reporting secondary data analysis studies conducted on routinely collected data (RECORD - http://record-statement.org/).

Diagnosis: For the purpose of this study, clinically apparent osteoporosis will be defined by having a documented diagnostic code according to the International Classification of Diseases (ICD-9/10-CM).

Risk factors: For the purpose of this study we will focus on traditional risk factors for osteoporosis and osteoporotic fractures in men identified in several large prospective observation studies and other published literature: advanced age, selected chronic diseases and clinical syndromes (such as CKD; COPD; diabetes; liver disease, hypogonadism, hyper- and hypothyroidism; rheumatoid arthritis); low Vitamin D level; previous fragility fractures, white race, dementia, cigarette smoking, alcoholism, low weight and body mass index, history of falls, and immobilization [8,9,26,30].

MORES risk assessment: The Male Osteoporosis Risk Estimation Score (MORES) is a simple risk stratification tool that can be used at the point of care to identify men at increased risk for osteoporosis[31-33]. In contrast to other available risk assessment tools that were originally developed for women and later adapted for men, the MORES tool was developed specifically for men in 2007 and validated in several studies for identifying men at risk for osteoporosis including in lumbar region [32,34]. The scoring algorithm is presented in Table 3. Males with a score of ≥6 are considered at increased risk of osteoporosis and should be referred for confirmatory DXA.

Table 3 Male Osteoporosis Risk Estimation Score

Risk factors	*Points**
Age	
≤55 years	0
56 to 74 years	3
≥75 years	4
Presence of chronic obstructive pulmonary disease	3
Weight	
≤ 154 lb (70 kg)	6
155 to 176 lb (70 to 80 kg)	4
> 176 lb	0
* A total score of ≥6 points represents high risk [31,33]	

The tool is designed to be administered in a clinical office with the patient present and takes a few minutes to administer and score. We propose using the tool to assess the male patients in the registry by applying scoring algorithm to the patient record. We hypothesize that since all the data elements necessary for risk assessment are readily available in the patient's heath record, the tool could be easily applied to the patient records eliminating the necessity for the patient to have a visit to be identified as being at risk. We will be able to assess the proportion of patients in the registry who would qualify for being at high risk (score ≥6) according to the MORES risk assessment. Additionally, we will be able to compare risk assessment performance of the two methods: based on the presence of risk factors listed in the clinical recommendations and based on the structured risk stratification tool (MORES). The results of this study could potentially lead to a low-resource population-based prescreening method for systematic identification of men at risk that need to be referred to the DXA scan for diagnostic confirmation and subsequent quality improvement and research projects for osteoporosis detection, treatment administration and improved outcomes. Recent studies in Europe exploring costs of pre-screening using risk assessment tools found that the risk assessment tools are valuable, cost-effective, and potentially effective approach to reduce the economic burden of mass screening for osteoporosis[19].

Prescribed medications: Treatment patterns will be assessed using data on prescribed medications for osteoporosis. These medications will include medications currently approved for treatment of osteoporosis from all major classes (e.g., antiresorptive and anabolic). Additionally, certain prescription medications such as gonadotropin-releasing hormone agonists, aromatase inhibitors, antiepileptic drugs and several other medications have been associated with drug-induced osteoporosis, and these data will be collected for exploratory purposes and descriptive statistics [35].

Current practice standards for risk assessment, osteoporosis screening and management: As we mentioned earlier, the clinical recommendations for male osteoporosis detection and management in primary care are either absent (e.g. AAFP does not have an evidence-based guideline for male osteoporosis) or inconsistent or outdated. It is unknown to what extent the existing guidelines are followed by clinicians. For Aim 2 specifically, the clinical data will be compared against the current recommendations and best practices for osteoporosis assessment and management for pattern of care identification. We will test the clinical record data against the key recommendations from The Endocrine Society Clinical Practice Guidelines for Male Osteoporosis (presented in Figure B below). The current evidence-base care for male osteoporosis as described in the guidelines should include

- DXA assessment for all men age 70 and older and men ages 50-69 who have risk factors or a history of fragility fracture,
- laboratory testing to determine the cause of bone loss,
- treatment recommendations including pharmacological treatment,
- lifestyle modifications, and
- re-assessment with DXA every two years for men in treatment.

We will determine the proportion of patients who received guideline concordant or discordant care according to the outcomes for all clinical care relevant domains (Diagnosis through Management, Table 4). The guideline concordat care will be defined as compliance with The Endocrine Society Clinical Practice Guidelines for Male Osteoporosis recommendations (see Main Outcome Measures, Aim 2 for details).

The project team and Dr. Dickinson, an experienced biostatistician will conduct the analyses and interpret the results (see Budget Justification Document and Key Personnel Biosketches for details). Descriptive statistics of clinical factors and demographic characteristics of cases/participants selected for the study will be reported for continuous variables by the mean and standard deviations. Differences in mean values of continuous variables among the diagnosis groups will be tested using ANOVA methods adjusted for multiple pairwise comparisons using Tukey's HSD method. For categorical variables, counts (N) and percentages (%) will be reported. The association between the diagnosis status of osteoporosis and the clinical characteristics will be investigated using the $\chi 2$ tests for univariate associations. Univariate multinomial logistic regression will be used to investigate the intensity and direction of the association (odds ratios) between diagnosis status relative to the risk factors and demographic characteristics of cases/participants. The combined and integrated effect of the risk factors will be assessed in a multivariable multinomial logistic regression model.

The descriptive and analytic epidemiology methodology will be used for conducting the analyses on the prevalence of diagnosis and risk factors and assessment of treatment patterns in all patients in the dataset. The exploratory sub-group analysis will be conducted to assess and compare patient groups based on the level of care, the presence of diagnosis, risk factors and treatment type. All outcomes assessed in males will be compared to the age-matched female populations in reporting. All statistical analyses will be performed using SAS version 9.4 (SAS Institute Inc., Cary, N.C.).

Table 4 Main Outcome Measures (by gender whenever appropriate)

Domain	Main Outcomes
Patient Characteristics	• Descriptive statistics by gender
Practice Characteristics	• Descriptive statistics
Patient Diagnoses	• Prevalence of diagnosed osteoporosis in the total registry population; • Percent of patients with diagnosed osteoporosis who have evidence of current osteoporosis treatment in the last 6 months or specific osteoporosis assessment within the last 15 months; • Percent of patients on osteoporotic treatment who also have a recorded diagnosis of osteoporosis
Osteoporosis Risk Factors	• Percent of males aged 50+ years with recorded strong clinical risk factors for osteoporosis with evidence of either a referral for bone densitometry in the last three years or osteoporosis assessment in the last three years; • Percent of patients aged 50+ years with recorded strong clinical risk factors for osteoporosis and a diagnostic code for osteoporosis with evidence of a currently prescribed bone sparing agent; • Percent of patients who would qualify for being at high risk (score ≥6) according to the MORES risk assessment
Bone Fractures	• Percent of males aged 50 and older with a history of fragility fracture with evidence of referral for bone densitometry; • Percent of males aged 50+ years with a history of fragility fracture and a diagnostic code for osteoporosis (with and without referral for DXA); • Percent of males aged 50+ years with a history of fragility fracture and a diagnostic code for osteoporosis with evidence of currently prescribed osteoporosis treatment
Investigation	• Percent of patients aged 50+ years with osteoporosis or a history of a fragility fracture who have evidence of a falls assessment; • Percent of patients aged 50+ years at high risk of falls who have evidence of an assessment for osteoporosis in the last three years
Management	• Percent of patients on specific osteoporosis treatments and treatment combinations.

Main outcome measures:

Specific Outcomes of the study are listed in the Table 4 and grouped by the domain. Selected key outcomes are listed in relation to each of the study Aims below.

Aim 1: to characterize primary care population of males with and at risk for osteoporosis who receive services and treatment as part of their standard of care

The primary outcomes to be assessed for Aim 1 are:

- Prevalence of diagnosed osteoporosis in the total male registry population, assessed as the percentage of the total practice population by gender (denominator) with a diagnostic code (ICD9-733.xx and corresponding ICD-10 codes) for osteoporosis (numerator).
- Proportion of males at risk for osteoporosis (risk factor score computed using the MORES tool applied to the patient record) who could currently be identified as eligible for investigation or treatment according to The Endocrine Society Clinical Practice Guidelines for Male Osteoporosis[14]. This outcome will be assessed as the percentage of the total practice male population (denominator) with a MORES score of ≥6 (high risk for osteoporosis; numerator).

- Prevalence of primary and secondary osteoporosis (etiology) in the total registry population assessed as the percentage of the total practice population by gender (denominator) with a diagnostic code (ICD9-733.xx and corresponding ICD-10 codes) for osteoporosis and documented secondary cause of osteoporosis (numerator).
- The relative importance of traditional risk factors explored as combined and integrated effect of the risk factors on diagnosis status will be assessed in a multivariable multinomial logistic regression model. Exploratory Factor Analysis may be employed if appropriate.

Aim 2: to characterize standard of care for male osteoporosis, including rates of clinical testing, treatment prescribing patterns, and monitoring patterns.

We will identify individuals who have received osteoporosis related guideline concordant care and those eligible for care. For the purpose of this study we will follow the Endocrine Society Clinical Practice Guidelines for Male Osteoporosis with the expected concordant clinical algorithm shown in Figure B [14]. A descriptive summary of osteoporosis related care will include services utilization related to male osteoporosis screening, diagnosis, treatment, and monitoring. The rates of male osteoporosis related to care utilization will be defined as the percentage of the total practice male population (denominator) receiving services related to osteoporosis diagnosis and care/treatment (numerator). These exploratory outcomes will include descriptive statistics of those with information indicative of care related to suspected or confirmed osteoporosis or osteopenia and concordance with the osteoporosis assessment, diagnosis, and management guidelines extracted from administrative data or other records such as billing codes (CPT codes), pharmaceutical records (e.g., prescribed medications, dosage, and changes), record of repeated DXA scans once every two years for in-treatment patients, and any significant events (e.g., fall risk assessment) and changes over time related to care. Specifically we explore the following outcomes:

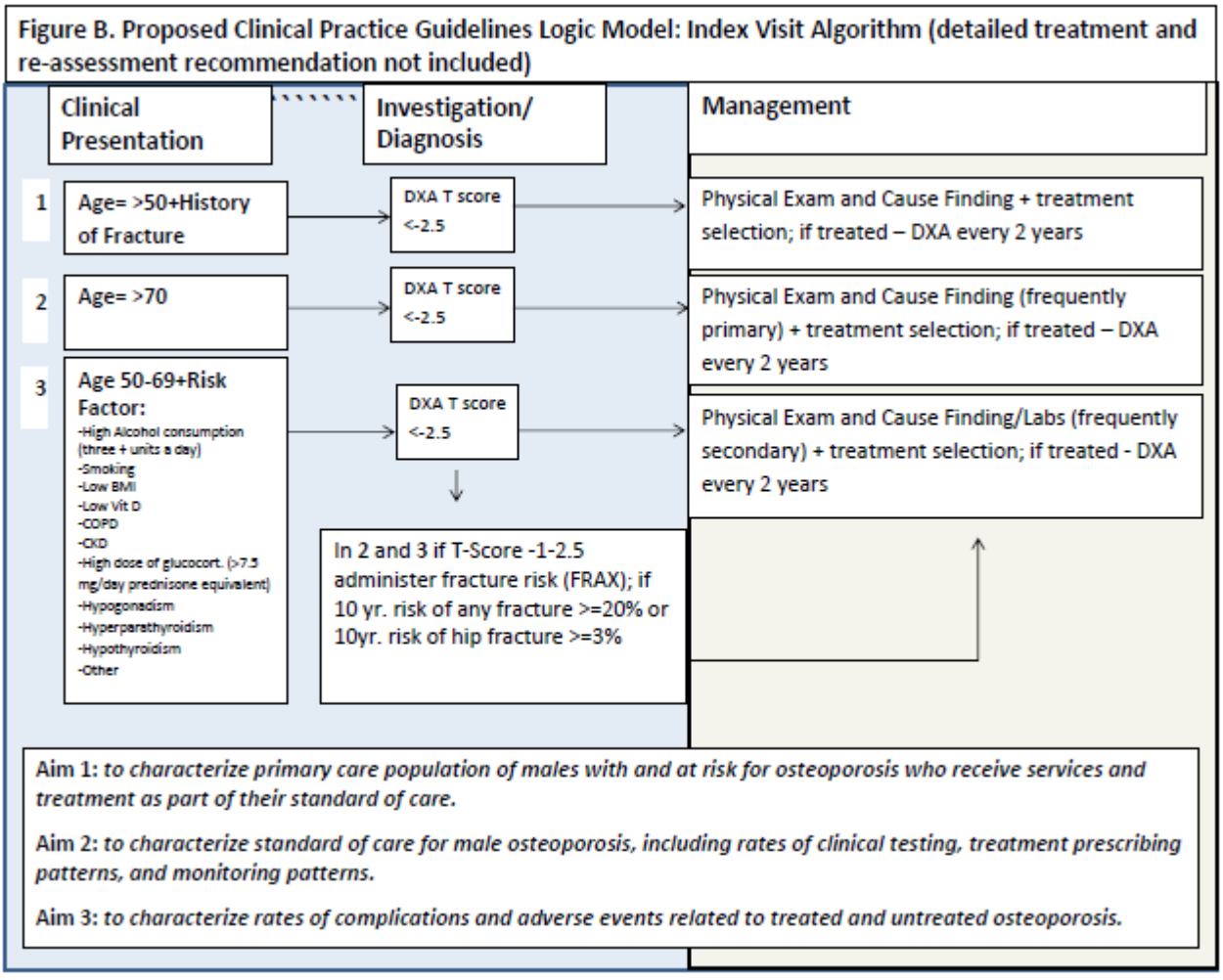
- Proportion of males aged 50+ years with recorded strong clinical risk factors for osteoporosis with evidence of either a referral for bone densitometry in the last three years or osteoporosis assessment in the last three years.
- Proportion of males aged 50+ years with a referral for bone densitometry and with the DXA result indicative of the osteoporosis or osteopenia and the rates of diagnosis and treatment after the referral in a sub-group analysis. This will allow us to explore the extent to which the care is concordant with the guidelines for initiating DXA referral and post-assessment diagnosis and treatment in nested case-cohort sub-study.

Additional outcome measures to be used in the guideline concordance/discordance assessment are:

- Proportion of patients aged 50+ years with osteoporosis or a history of a fragility fracture who have evidence of a falls assessment and/or assessment for osteoporosis in the last three years
- Proportion of patients aged 50+ years with recorded strong clinical risk factors for osteoporosis and/or a diagnostic code for osteoporosis with evidence of a currently prescribed osteoporosis treatment
- Proportion of patients on specific osteoporosis treatments and treatment combinations
- Proportion of patients with diagnosed osteoporosis who have evidence of current osteoporosis treatment with osteoporosis assessment (DXA) every 24 months
- Proportion of patients on osteoporotic treatment who also have recorded diagnosis of osteoporosis

Aim 3: to characterize rates of complications and adverse events related to treated and untreated osteoporosis. In this exploratory objective we will focus on descriptive statistics of rates of documented adverse events related to osteoporosis (e.g., fractures, disability) and treatment related complication categories (side effects and adverse event of various medications most commonly documented or cited in the literature) based on the level of care, the presence of diagnosis, risk factors, and treatment type. The proportion of events identified in the medical record following the documented prescribed treatment (listed below) will be summarized by the related treatment type. The most common adverse events included in the study will be obtained for all patients in the database for whom the data from the medical record are available:

- Osteoporosis related: Fragility fractures, disability after major and vertebral fractures (hospitalization, death, nursing home placement, pain and functional limitations)



- Treatment related: The bisphosphonate-induced hypocalcaemia and secondary hyperparathyroidism can be avoided or attenuated by the administration of adequate vitamin D and calcium supplements, starting about two weeks before the administration of the bisphosphonate; osteonecrosis of the jaw; femoral shaft fractures; stroke; hypocalcaemia; serious infections; upper gastrointestinal (GI) tract associated with bisphosphonate use such as nausea, vomiting, epigastric pain and dyspepsia; renal toxicity; newly diagnosed uveitis/scleritis following dispensing of bisphosphonates; deep vein thrombosis and pulmonary embolism; breast cancer; heart attacks; venous blood clots; and cognitive decline.

Dissemination and transition plans:

The results of the project will be disseminated by submitting manuscripts to peer-reviewed journals such as the *Annals of Family Medicine, Journal of Bone and Mineral Research,* or *Osteoporosis International,* and disseminating the results through AAFP physician-oriented publications, such as *Family Practice Management* and AAFP membership communication channels with the AAFP membership, and to the DARTNet learning community[36]. We plan to develop *at least one manuscript that outlines the methodology and results of the study* and submit it to appropriate peer-reviewed journal for publication within three months after completion of the project. Additionally, Dr. Loskutova's primary research focus is on the relation between osteoporosis and dementia [27,37,38]. Upon completion of this study, an additional secondary manuscript in that particular research area with submission to the *Journal of the American Geriatrics Society* is expected. Once the manuscripts are accepted for publication, we will work on community messages, press releases, and dissemination of study results with healthcare organizations, provider and patient group stakeholders. We plan to submit at least three abstracts with the results of the project for professional conference presentations including the North American Primary Care Research Group meeting, the Conference on Practice Improvement, the ASBMR Annual Meeting and other meetings of interest to the funder and key stakeholders.