Key abbreviations used in this application
BPs: bisphosponates
DPBRN: Dental Practice-Based Research Network
HP: HealthPartners
KPNW: Kaiser Permanente Northwest
HMO: health maintenance organization
ONJ: osteonecrosis of the jaws

A. SPECIFIC AIMS

Recent reports of osteonecrosis of the jaw (ONJ) have associated this otherwise rare, but potentially morbid, lesion to treatment with a relatively new class of drugs, the bisphosphonates (BPs). In the past two years, more than 200 cases have been described in patients treated with BPs for osseous cancer lesions or osteoporosis. Neither the true prevalence, nor the risk factors for development of these lesions have been clearly established. The number of indications for BP therapy (and the number of prescriptions written) has increased, raising legitimate concern. We propose to retrospectively study this topic in a cohort of patients from two large HMOs connected to the Dental Practice-Based Research Network (DPBRN).

The **Specific Aims** of this study are:

1. To quantify the prevalence of ONJ in a large cohort of patients enrolled in two HMOs.
   Rationale: The true prevalence of ONJ is currently unknown. Establishing the size of the problem will provide essential information for future study and help guide patients and practitioners. Given the large size and variety of the patient population in the electronic database of the two HMOs, we are in an ideal position to study this topic.

2. To test the hypothesis that BP treatment is a risk factor for ONJ.
   Rationale: The cases described in the literature have associated ONJ with BP therapy. However, as patients on these drugs already suffer from bone disease and may be taking many other medications, this connection needs to be confirmed.

3. To test the hypothesis that ONJ develops only in patients treated with BPs who have additional risk factors.
   Rationale: The estimated incidence of ONJ in BP-treated patients is relatively low. Additionally, BPs have been reported to be useful as treatment for other osteonecrotic lesions. Thus, we hypothesize that additional risk factors are necessary for ONJ to develop.

B. BACKGROUND AND SIGNIFICANCE

Jawbone necrosis is a relatively rare phenomenon and is typically encountered in severe disease or after iatrogenic intervention. In the past, this type of lesion has been associated with exposure to phosphorous. More recently, various infectious agents in the setting of malnutrition (e.g. noma oris) or immune suppression (e.g. necrotizing stomatitis, aspergilosis, mucormycosis, herpes zoster virus) have been associated with necrotizing jaw lesions. A more common etiology for modern osteonecrosis is ionizing radiation: mandibular exposure to more than 40 Gray results in high risk of vascular obliteration, subsequent bone ischemia, and death. Therapeutic advances have reduced the prevalence of these lesions.

An unusually large number of case reports and case series have recently described what appeared to be either spontaneous or (more commonly) idiopathic ONJ induced by dental treatment. These reports associated the lesions with a history of exposure to BPs, which are a relatively new class of drugs that inhibit osteoclast activity and may have anti-angiogenic properties. Their effects on bone make these drugs a prime suspect for the necrotizing processes; however, neither a causal relationship between BP use and ONJ nor a specific mechanism for the process have been established. Nevertheless, an increasing body of evidence suggests that BP therapy is a risk factor for ONJ. The following paragraphs discuss the current literature on this topic and review what questions remain unanswered.

B.1 Bisphosphonates

BPs became commonly used in this country in the early 1990's to treat osteolytic conditions associated with cancer (1-4). The number of therapeutic indications has since increased to include Paget's disease, heterotropic ossification, hypercalcemia, and osteoporosis (5,6). The efficacy of BPs for these diseases has been well established with studies that have shown significant decreases in cancer-induced skeletal morbidity (7,8) and significant increases in bone mineral density in osteopenic patients (6). Thus, BP administration has become standard care for solid tumor patients with bone metastases, and patients with multiple myeloma and osteoporosis. BPs also may be increasingly used by osteopenic patients to prevent osteoporosis.

Several agents of this class of drugs are available in the US, including alendronate, etidronate, pamidronate, risedronate, and zoledronic acid. Alendronate and risedronate alone accounted for more than three million prescriptions in 2003, and this number has been steadily increasing (6). An estimated 10 million people are afflicted by osteoporosis in this country and their number is expected to increase due to the general aging of the population.

Generally, BPs are relatively safe drugs with very tolerable side effects (2,9,10). Their main action is inhibition of osteoclast-induced bone resorption, which results in decreased osteolysis and increased bone mineral density (5,12). Both apoptosis and cell necrosis of osteoclasts have been observed in BP mechanism studies (13). Some reports have also suggested that BPs have anti-angiogenic and anti-tumor effects (14,15). However, the exact molecular mechanism of action for this class of medication remains unknown.

Theoretically, BPs could induce bone necrosis in various ways. First, inhibition of osteoclast remodeling may result in over-mineralization, which can strangle blood circulation to a specific area of the bone (16). Second, anti-angiogenic effects may directly impair blood circulation (14,15). Finally, direct toxicity of BPs may prevent or destroy vascular formation (17). However, none of these possible mechanisms has been scientifically proven.

B.2 Osteonecrosis

The skeletal system is metabolically active and requires consistent blood circulation (19). However, specific areas (the epiphysis of long bones, in particular), are poorly vascularized and consequently are more prone to necrosis (19,20). Nevertheless, osteonecrosis is a relatively rare phenomenon and typically occurs in disease (21,22,23) or due to iatrogenic factors (16,24,25,26). Most osteonecroses have a well-described cause or association, though a minority remain idiopathic (19).

The typical reported case of osteonecrosis involves the femoral head or other long bones in weight-bearing joints and is avascular in origin (27,24,25). The lack of circulation may be induced by infarction or destruction of endothelial cells in areas of bone with poor collateral blood supply. Most cases are symptomatic, involve high morbidity, and require surgical management (28).

Diseases commonly associated with bone necrosis include sickle cell anemia, AIDS, blood cancers and various states of hypercoagulation (31,27,30,29,23,24,25). Autoimmune diseases, such as lupus erythematosus and rheumatoid arthritis, and organ transplantation, have been associated with cases (32,33,34), but studies have consistently demonstrated that these necroses were related to corticosteroid treatment and not with the autoimmune disease itself. Other pharmacological agents associated with osteonecrosis include immune suppressants (25) and multimodal antiretroviral therapies (35). Note that we were unable to find any reports of corticosteroid- or immune-suppressing drug-induced osteonecrosis of the jaws. It appears that the maxilla and the mandible are relatively resistant to these deleterious effects.

Various infectious agents have been reported in necrotic bone, mostly in immunosuppressed patients. Invasive fungal organisms have been acknowledged to produce widespread destruction of bony tissues (36) and Gram-negative bacteria (37) have been associated with necrotizing disease. It remains unclear whether the pathogens caused necrosis or they simply colonized the already non-vital bone, but most authors accept the role of these microbes in the etiology of the disease; these lesions generally respond well to specific

antimicrobial therapy (37). Microorganisms like the varicella zoster virus have also induced osteonecrosis in immune-competent individuals (38,39), but these occurrences are rare, and their mechanisms remain obscure.

B.3 Osteonecrosis of the Jaws

By virtue of their location and function, the maxillary bones typically display an idiosyncratic physiopathology. These are neither long nor weight-bearing bones, but they support dentition, through which they are intimately related to the oral environment. The jawbones are prone to trauma, including the iatrogenic type, and commonly become infected by oral and periodontal pathogens. The upper and lower jaws are quite different from each other, with the mandible being denser and not as vascularized as the maxilla; these differences place the lower jaw at greater risk for osteonecrosis (24,40).

ONJ has been reported in the literature for more than a century. The first cases were associated with phosphorus exposure of industrial workers (41), which brought the lesions the name of "phossy jaw." With discontinuation of unsafe work practices, ONJ became a rare occurrence, which has been generally connected to severe disease, immune suppression, or medical intervention.

The most common association of necrotic lesions of the jawbones is with ionizing radiation. Data on the incidence of this complication are often conflicting and range from 0.4% to 56% of the patients exposed to cancer-curative doses (42). The mechanism of osteoradionecrosis consists of gradual vascular obliteration in the affected bone followed by avascular necrosis (43). If the dead bone becomes exposed to the oral microflora, suprainfection adds to the morbidity of the condition. Risks for osteoradionecrosis include treatment- and patient-related variables, such as dose and field of radiation, fraction size, presence of teeth, history of periodontitis, oral hygiene, and defective prostheses (43,42,44). Once established, osteoradionecrosis is a challenge to treat and typically requires prolonged and invasive therapy. With the advent of three-dimensional treatment planning and intensity-modulated radiation therapy, the incidence of osteoradionecrosis has decreased significantly (43,40).

Infectious agents have also been associated with ONJ, most often in the setting of immune suppression. Jaw necrosis was relatively common in AIDS patients prior to highly active antiretroviral therapy (HAART) (30). Conditions like Necrotizing Periodontitis or Necrotizing Stomatitis often produced large bony lesions associated with typical periodontal pathogens. Barasch and colleagues (37) reported jaw necrosis associated with *Pseudomonas aeruginosa* in immunosuppressed patients. Unlike osteoradionecrosis, these lesions responded well to appropriate antibiotic therapy. Similarly, Schwartz (24) described cases of ONJ in cancer patients treated with systemic chemotherapy. Finally, large areas of jaw osteonecrosis were described following varicella zoster virus reactivation (shingles) in the trigeminal nerve (38,39). The postulated mechanism for these lesions was local immune reaction, and they also may require comorbidity from other factors, as these lesions are very rare given the large number of varicella zoster virus carriers.

The first report of jaw osteonecrosis associated with BP treatment was published in 2003 (45) and was quickly followed by others. Wang and colleagues made the initial observations in cancer patients at the University of California at San Francisco. Within a few months, Rosenberg and Ruggiero (46), Marx (47), and Migliorati (48) published their respective case series in similar populations. These reports described patients with metastatic bone disease or multiple myeloma (MM) who had developed mostly dental treatment related, but also spontaneous, idiopathic necrotic lesions of their jawbones. The only common feature of their medical history was previous and/or current use of parenteral BPs. Specifically, all patients described in these initial papers had metastatic bone cancer and had been treated with either pamidronate or zoledronic acid, or both. However, in 2004 Ruggiero and colleagues (49) reported an additional 63 cases of ONJ, in which seven non-cancer patients had exposure to oral BPs (alendronate) for osteoporosis.

Following these initial articles, similar reports were published in quick succession, showing ONJ in BP-treated patients to be more common than anticipated (31,50-63). The vast majority of these publications were retrospective studies or case series, and few contained meaningful analyses. Nevertheless, a clearer picture of ONJ began to emerge.

Prevalence of ONJ in studied populations ranged from less than 1% (Van Poznak CH, abstract presentation) to over 20% (31). No sex differences have been noted and the average age for onset was in the 5th and 6th decade. Significantly higher frequency of lesions was seen in patients treated with zoledronic acid when compared to other BPs, while alendronate was associated with the fewest. Time from initiation of therapy to diagnosis of ONJ was also shortest in zoledronic acid-treated patients and longest in those on alendronate (31,51,60). Development of necrotic lesions was significantly associated with duration of treatment for all BP agents.

Clinically, these lesions appeared similar to osteoradionecrosis, presenting with non-healing ulcers, expanding osteonecrosis, and possible sequestration. The majority of lesions occurred in the posterior mandible, but location in the maxilla was also reported (52,47,48). Similarly, the response to therapy followed the osteoradionecrosis pattern: surgical debridement, primary closure, or antibiotics did not affect significantly the course of the disease and most lesions did not heal (52,56,58). Treatment with hyperbaric oxygen was also largely unsuccessful (31).

A histologic comparison of ONJ from eight BP-treated patients with specimens from ten patients diagnosed with osteoradionecrosis (54) yielded many similarities. However, ONJ was characterized by a multicentric, diffuse and patchy appearance, while the osteoradionecrosis was typically larger and uniformly distributed. Interestingly, this study also identified multiple osteoclasts adjacent to areas of bone resorption in both ONJ and osteoradionecrosis. This finding would appear to negate the role of osteoclast inhibition in the pathologic process. Further, the same study reported actinomyces colonization in all 18 studied cases, which prompted the authors to postulate a role for the bacteria in the necrotizing process.

Much larger numbers are needed to shed light on these issues. As BPs are almost exclusively used in patients with cancer or osteoporosis, it is difficult to assess whether or not these diseases by themselves represent risk factors for ONJ. In a published case series (58), one of four cancer patients with ONJ was not exposed to BPs. It also remains unclear why IV-administered BPs result in a higher rate of ONJ than their oral counterparts. One possible explanation is that compliance and persistence rates in patients on oral BPs are low: less than 50% adhere to their regimens and about 20% of the patients suspend their treatment before six months of therapy have passed (11,64).

Another interesting question is: why the jaws? A single article (31) reports concomitant necrosis in other bones in one third of the ONJ patients, while other authors (51) consider BP-associated necrosis to be unique to the maxillae. Another article (18) describes one case of BP-associated osteonecrosis of the auditory canal. Yet other studies (31,54) suggest that ONJ has an infectious etiology and the oral flora has a role. This theory remains speculative as bacteria could colonize the bone after exposure to the oral environment, and ONJ does not respond well to antibiotic therapy. To complicate the situation, BPs have been used successfully in osseointegration of prosthetic joints as well as in treatment of osteonecrosis of long bones (28,26). Consequently, efforts to improve the health of long bones may reduce the health of jaw bones. We expect this study will enable us to assess the extent of this problem.

B.4. Significance of the Proposed Study

In the years since the initial publication of BP-associated lesions, the number of reported ONJ cases has been increasing considerably. Coupled with the finding that cases were related to the duration of BP therapy, these cases raise the concern that the current literature has exposed only the tip of the iceberg. Are we indeed observing a new drug's late side effect? If so, how prevalent is it? Are other risk factors involved with the cases? Can ONJ be prevented? Given that about 3 million patients have been treated with BPs and another 7-8 million osteoporotic or cancer-afflicted Americans may take BPs in the near future, these questions must be answered.

To date, most publications on ONJ have presented case series or retrospective cohorts of BP-treated cancer patients. The literature has postulated some associations and risk factors; however, it has not described either a true prevalence or proven risk factors. In addition to having relatively few subjects, these publications also

suffer from inconsistent or incomplete sources of data and lack of control groups. We propose a study designed to overcome these limitations.

DPBRN is in an ideal position to investigate ONJ in a large group of patients. The two HMOs participating in this study have large populations that can be accessed efficiently through electronic medical/dental records. We will describe the prevalence and characteristics of the lesions and identify etiologic associations and risk factors. It is likely that our results will approximate the real size of the problem as well as the populations with the highest likelihood to develop this condition. More importantly, our results will open the door to prophylactic and interventional studies. In light of the high morbidity and cost associated with ONJ, this study will provide much needed information to make a significant difference.

C. PRELIMINARY STUDIES

DPBRN has a network of scientists who have a long history of successful collaboration. This network includes two large HMOs with access to electronic medical data of over one million current and former health plan members. Both plans also have extensive electronic records for dental plan members. The study team at Kaiser Permanente Northwest (KPNW) and HealthPartners (HP) has collaborated on numerous studies of medical and dental practice, and has extensive experience addressing health problems using data from the organizations' electronic medical and dental records. Examples are provided below that demonstrate the study investigators' history of collaboration and successful use of the electronic records. We also show preliminary data for osteonecrosis incidence and BP pharmacy dispenses. These data suggest ONJ prevalence and BP-related risks for ONJ can be assessed using historical data from KPNW and HP members.

C.1 Prevalence of Osteonecrosis and Bisphosphonate Dispensing in KPNW and HP

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For this application, we conducted a preliminary analysis of the electronic medical records of KPNW and HP members age ≥40 years. The purpose of the analysis was to obtain estimates of potential ONJ cases and BP dispensings from pharmacy records (oral and IV BPs) for medical and dental plan members from 2004 to the present. The proposed study cohort will be much larger, with data for members since 1994 in HP and 1998 for KP. At each HMO, a cohort medical plan members age ≥40 years was selected who had continuous membership from January 1, 2004–February 28, 2006 (the most recent month available). We collected incidence data for the same period for ICD-9 codes indicative for ONJ: 733.4, 733.40, 733.45, 733.99, 526.4, 526.5, 909.2, and 909.3. We also obtained BP dispensing data (oral and intravenous) for the cohort from 2000-2005 to assess the frequency of any dispensing among individuals with one of the potential ONJ diagnoses. We used the longer time period to capture potential long-term exposure in past years. The results are presented in Table C.1, and include separate estimates for individuals with medical plan membership only and the subset of members with both medical and dental plan membership. Upon study initiation, we will begin work to establish a much larger analysis cohort from 1994–mid-2005.

We found 468 individuals with one or more potential osteonecrosis cases since 2004 (191 in KPNW and 277 in HP). Many individuals had more than one diagnosis; thus, the total number of diagnoses (not shown) was about twice the number of individuals shown in Table C.1. The crude prevalence of these diagnoses was 0.18% over all medical plan members and 0.23% for members with both medical and dental coverage. We found that over 10,400 (4.1%) medical plan members had received oral or IV BPs in the last five years, while over 4,600 (4.1%) of medical plus dental plan members received BPs. When we looked at oral and IV dispenses separately, we found very few members (2004-present) with exposure to IV BPs. In KP and HP, 32 individuals had dispenses of IV BPs. While few individuals in our two-year sample were exposed to IV BPs, we expect our full study cohort will include substantially more individuals with IV BPs, though perhaps not enough to assess separately. Additional analyses of oral BP dispensings during 2000-2005 showed mean days supplies for BP recipients were well over 200 days. The data correspond with existing studies documenting the rarity of ONJ and the potential for BP to be a significant risk factor for ONJ. Although rare, ***our preliminary examination of only a fraction of the available data*** *strongly suggest we will be able to identify sufficient numbers of also indicate that the KPNW and HP medical and dental plan members data from 1994 (HP) and 1998 (KPNW) will provide us with sufficient ONJ cases to assess the risks of ONJ associated with BP exposure controlling for other hypothesized risk factors.*

Table C.1 Potential ONJ cases and bisphosphonate dispensing in KPNW and HP members age ≥40 years, 2004–present

	KPNW		HP*		Both	
	Medical only	**Medical + dental**	**Medical only**	**Medical + dental**	**Medical only**	**Medical + dental**
Age ≥40 years	N=178,509	N=57,665	N=75,384	N=56,433	N=253,893	N=114,098
Potential ONJ cases†						
Number	191	61	277	215	468	266
Percent	0.11%	0.11%	0.37%	0.38%	0.18%	0.23%
BP dispensing						
Number	7,049	1,992	3,389	2,687	10,438	4,679
Percent	3.95%	3.45%	4.50%	4.76%	4.11%	4.10%

*HP data for members receiving care in HP-owned facilities where medical charts are available for review. †The pool of potential ONJ cases includes osteonecrosis (ICD-9 codes: 733.4, 733.40, 733.45, 733.99), inflammatory conditions of the jaws (ICD-9 526.4, 526.5) and late effects of medical treatment (ICD-9 909.2, 909.3).

C.2 Research Collaboration Among KPNW and HP Researchers

The following studies are recent examples of collaborative research conducted by KPNW and HP staff.

C.2.1 A Multivariate Examination of Caries Risk Assessment (DORA). Drs. Rindal and Rush collaborated on this project with investigators at KPNW (R01 HS133339) to measure the predictive validity of dentists' caries risk assessments for future caries experience. For patients receiving caries risk classifications, we determined assessment accuracy using caries experience in a subsequent two-year period. Structural equation modeling was used to determine prognostic ability of the assessment with respect to subsequent caries while controlling for receipt of preventive treatment. The study also measured the congruence between patients' caries risk classifications and caries preventive treatment. We examined whether caries risk classification predicted future preventive treatment and the extent to which patients received caries preventive treatment appropriate for their levels of caries risk. We evaluated several aspects of caries risk assessment as applied in dental practice. The evaluation was performed retrospectively using data from routine caries risk assessment in the clinical examination protocols and "reference" risk classifications performed between 1997 and 1999. The analyses included data from one year prior to the risk assessment through two and half years after the risk assessment. The unit of observation and analysis was an eligible patient, defined as a dental HMO enrollee who had a caries risk assessment between 1997 and 1999, and who had continuous enrollment for one-year prior and two-and-one-half years after the risk assessment. The operational model in this study has many parallels to the model in the current proposal. This project has produced presentations at IADR and a publication (65).

C.2.2 Prescribing Practices of Dentists. With funding from the Centers for Disease Control and Prevention (Project # 200-95-0953-039), KPNW investigators and Drs. Rush and Rindal collaborated to describe dentists' antibiotic prescribing practices. These data are important because of new or increasing microbial resistance to antibiotics, which lead to significant morbidity and costs. Dispensing data from 1995–1999 at two health maintenance organizations were examined quantitatively and qualitatively to describe the percentage and categories of all antibiotic prescriptions by type of provider. Chart abstraction data were used to describe the reason for the prescription. Other data sources were used to explore factors that may influence prescribing

practices. Dentists accounted for 4% of the total antibiotics prescribed in the HMO A population and 7% in the HMO B population. Penicillins were the most commonly prescribed antibiotics, accounting for 77% of thedispenses. Collectively the penicillins, erythromycins, and cephalosporins accounted for 87% of the dispenses. These results suggest that antibiotic dispenses by dentists represent a small but significant contribution to the total number of antibiotics prescribed.

In addition, the authors compared fluoride prescriptions written by dentists, physicians, and other providers and to analyze factors that influence prescribing patterns, such as patient age and fluoridation of the community water supply. Descriptive statistics were used to analyze these data. Prescribing rates were: dentists 7%, physicians 78%, and other providers 15%. Overall rates of fluoride prescribing were much lower in the fluoridated communities of Minneapolis/St. Paul than the non-fluoridated community of Portland, Oregon. Age data show that physicians write the most prescriptions for children from birth through age two. Dentists write the most prescriptions for children ages 3–12.

C.2.3 Dental Performance Measurements. In an AHRQ-supported project (U18-HS09453), dental plan performance measures were developed and pilot tested at both HMOs. Effectiveness of care measures were specified through a modified Delphi process using two stakeholder panels consisting of senior managers of dental care plans, employee benefits managers, directors of state Medicaid and dental public health programs, and practicing dentists. Two versions of the measures were pilot tested, one based on electronic medical record systems used by KPNW and HP that incorporate diagnostic codes, and another driven by manual record audits without diagnostic information. The latter versions of the measures were also tested in public dental clinics and private dental offices that participated in a preferred provider network. Both HMOs had assessed a majority of their enrollees for caries risk, in contrast to both the public clinics and private practices. However, a minority of adult enrollees classified at high risk had received at least the appropriate minimum level of preventive treatment in the year subsequent to the classification. The HMO performance was similar to that of two of the three public clinics, and superior to that of the private practices examined.

C.2.4 Carious Effects of Drug Induced Xerostomia (CEDIX). This project was an investigation of the impact of xerogenic medications upon dental caries. The study used dental patients with medication coverage at HP and KPNW. Each subject was required to have continuous dental and pharmacy coverage for at least four years between 1990 and 2000. Dental restorations were used as a proxy for caries. In the sub-analysis of the association of xerogenic antidepressants and caries counts, we found that the subjects on antidepressants had significantly more caries when compared to a control on no xerogenic medications ($p<0.0001$) as well as a control with no prescription medication exposure ($p<0.0001$) (66,67).

C.3 Longitudinal Study Using KPNW Electronic Medical Records

C.3.1 Estimating the Return on Investment to Smoking Cessation. Dr. Fellows was PI of this Robert Wood Johnson Foundation-funded study, the aims of which were to: a) estimate annual predicted medical expenditures over time for a defined population of current, former, and never smokers; b) estimate average and incremental return on investment for low- and high-intensity smoking-cessation programs, including pharmacotherapy and counseling (in-person and telephonic quit lines) for each year over a 3-to-5-year period; c) estimate time thresholds for achieving cost neutrality for investments in cessation; and d) estimate separate return on investment figures for health plans and employers (in terms of averted medical expenditures and productivity losses). A longitudinal cohort model used electronic medical record data for 200,000 KPNW members from 1997–2002 to estimate mean annual medical expenditures for smokers and quitters controlling for smoking-related diseases, amount smoked, and plan disenrollment over the study period. We estimated the annual predicted probabilities (using multivariate logistic regression) of a new smoking-related disease diagnosis, for quitting and relapse given a smoking-related disease diagnosis or not, and for disenrollment given smoking and smoking-related disease status. In each subsequent year, we added covariates to the model to capture previous experience with smoking-related disease and quitting. We annualized expenditures for individuals who left during a given year and used separate models for individuals who began 1998 as current smokers, former smokers, and never smokers.

We used published data (68) to estimate the reach, efficacy, and costs of delivering alternative evidence-based smoking-cessation programs that included clinical counseling based on the 5 A's model (Ask, Advise, Assess, Assist, Arrange), medications, and a proactive telephone cessation quitline. For the population enrolled in the health plan during year one, we estimated the impact in year one on program participation and quitting separately for each intervention (including usual care). We then followed the cohort over five years to assess the impact of each intervention on their annual medical care expenditures and productivity (allowing for disenrollment). The results of the analysis suggested a one-year cessation program reaching 10% of smokers generated a positive net financial savings within three years. The results indicate investments of $.18-$.79 per member per month generate positive net savings of over $1.69-$2.24 per member per month after five years. This study documents our ability to use medical records to assess the health effects of risk exposure in a large defined population.

C.4 Other Dental Practice Research

C.4.1 Implementing Tobacco Control in Dental Practice. Dr. Fellows is co-investigator and project director of a large, ongoing NIDA-funded (R01-DA-17974) randomized trial evaluating system-level organizational change strategies for implementing tobacco control practices into the routine delivery of dental care within a random half of 14 large KPNW dental care plan facilities. The aim of this study is to change standard practice to include more extensive counseling beyond advice and to actively refer smokers interested in quitting to a centralized telephone tobacco counseling program. Dental facilities were matched on size, socioeconomic status, smoking rate, and periodontal specialty status, and then randomly assigned to intervention or usual care. Intervention dentists and hygienists were trained to ask about tobacco, deliver tailored advice and brief counseling, and encourage patients to call a tobacco counselor by phone before they leave the office. Counselors discussed pros and cons for quitting, barriers, and support resources. Patients could also request that the counselor call them back later. Dental staff documented asking, advising, counseling, clinic calls, and call-back requests in an electronic dental record. Patients were also interviewed by phone 1-4 weeks after the visit (N=2,472, 70% response rate) and 12 months after the visit. Dental staff receive monthly performance feedback reports documenting clinic-level smoking cessation delivery rates. The study includes encounter data for patients receiving counseling from a centralized Health Education Department and medical care providers. Dr. Fellows lead and developed the electronic data collection and tracking systems, and development of patient surveys and clinic performance feedback reports. Dr. Fellows is currently leading the analysis of the post-visit survey data. These activities demonstrate our ability to combine medical and dental plan data for analyses, and to work effectively with dental clinics to implement study protocols.

These prior collaborations demonstrate the ability of the investigators to work together and accomplish meaningful research with these data sets.

D. RESEARCH DESIGN AND METHODS

D.1. Overview

To assess the risks for ONJ associated with exposure to BPs and other factors, this study will use a retrospective cohort design and time-to-event modeling. The proposed study offers unique advantages in that the setting of two large HMOs provides the opportunity to reach thousands of patients through their electronic medical records and databases. First, we will use electronic medical and dental records in two large HMO dental plans to determine the prevalence of ONJ in a large cohort of adults 40 years of age and older (Specific Aim 1). The study period will begin on January 1, 1994 and end on December 31, 2005. The data analyzed for this project will be derived primarily from computer-generated administrative files for medical and dental plan members of KPNW and HP. The electronic data will identify a diagnosis of osteonecrosis and ONJ, which will be validated by examination of the medical record. We define ONJ as symptomatic or asymptomatic exposed jaw bone that does not heal within 4 weeks following the date of detection.

Our most important aim will be to test the hypothesis that BP treatment is a risk factor for ONJ (Specific Aim 2). We will quantify the impact of BP exposure on the risk of developing ONJ, relative to comparable patients not exposed to BP, using a time-to-event (survival) analysis. The level of BP use will be a function of days of exposure. Finally, we will test the hypothesis that ONJ develops only in patients treated with BPs who have additional risk factors (Specific Aim 3). We will also identify utilization of other medications of interest. For each

subject, we create a pharmaceutical use profile during the study period. Among those members with dental coverage, we will compare the number and types of dental services received. The survival analysis will allow us to assess the impact of BP exposure on ONJ within the context of varying natural histories for BP treatment and risk exposure among individuals, considerable censoring of follow-up data, and the hypothesized interaction between BP and other risks.

This study will be conducted under the auspices of the NIDCR-funded Dental Practice-Based Research Network centered at the University of Alabama at Birmingham. University of Alabama at Birmingham investigators will work with co-investigators from Kaiser Permanente's Center for Health Research and Permanente Dental Associates in Portland, Oregon, and HealthPartners Research Foundation of Minneapolis, Minnesota. Under the guidance of the Principal Investigator, Center for Health Research and HealthPartners Research Foundation study staff will collect data from their respective electronic medical and dental records system, conduct electronic and paper chart reviews as needed, and combine all relevant data into a single analysis dataset. The analysis dataset will be built and maintained by Center for Health Research staff in collaboration with University of Alabama at Birmingham and HealthPartners Research Foundation investigators.

D.2. Research Setting and Organizations

The University of Alabama at Birmingham has joined forces with scientific colleagues and dentists in Florida, Minnesota, Oregon, Washington, and Scandinavia to form the Dental Practice-Based Research Network (DPBRN). The DPBRN is a group of outpatient dental practices that, although primarily devoted to providing health care services, has affiliated with dental researchers at University of Alabama at Birmingham to investigate scientific questions and to share experiences and expertise. Researchers and practitioners at each location have extensive experience conducting cross-sectional and longitudinal practice-based studies. The network constitutes an organization that transcends any single research project, and offers opportunities to conduct research of high program relevance to NIDCR, using "real-life" settings with direct relevance to clinical care.

Network partners in Minnesota and Oregon include two large HMOs: Kaiser Permanente Northwest (KPNW) and HealthPartners (HP), in the two states, respectively. Both the KPNW and HP sites have a history of conducting practice-based research in their health care systems, both singly and in collaborative efforts. This history specifically includes several dental and oral health projects that involve practice-based research and dentists in these networks. Center for Health Research comprises a research infrastructure to facilitate and guide these studies, and the Permanente Dental Associates, through its Clinical Effectiveness Committee, facilitates the conduct of studies. Dr. Jeffrey Fellows, a Center for Health Research Investigator, is the site PI for the Dental PBRN and is a co-investigator and project director for a NIDA-funded trial assessing a dental system-level tobacco cessation intervention. Dr. Fellows also has extensive experience conducting longitudinal analyses using electronic medical records. HealthPartners Research Foundation is the formal mechanism that provides sustained infrastructure to support research conducted in the HP organization. As is evident from his attached Biographical Sketch, Dr. Brad Rindal, who devotes a 60% effort to providing clinical care for HP, has a history of leading dental practice-based research in the organization.

D.2.1 Kaiser Permanente Northwest (KPNW): Kaiser Permanente was the United States' first HMO and is currently the world's largest non-governmental supplier of health care services. Kaiser Permanente is a not-for-profit organization encompassing Kaiser Foundation Health Plan, Kaiser Foundation Hospitals, and the Permanente Medical Groups. Five basic principles shape this system's organization: voluntary enrollment; prepayment for comprehensive benefits on a service basis; preventive medical care; integrated, hospital-based health care facilities; and provision of physician services through group medical practice.

Kaiser Permanente Northwest is a federally qualified, not-for-profit HMO serving more than 470,000 members in northwest Oregon and southwest Washington. KPNW maintains one hospital and 26 outpatient medical offices. KPNW is an integrated, group-model health delivery system that provides and coordinates the entire scope of care for its members. Every health plan member is given a unique health record number upon enrollment, which remains with that patient even through gaps in membership. Every contact an individual makes with the medical care system and all referrals to outside services are recorded in a comprehensive

electronic medical record under the patient's health record number. This computerized patient care process, Health Connect, stores information, such as patient demographics, medical history, and visit summaries. The electronic medical record allows rapid clinician access to test results and medication and treatment history. KPNW's data systems are accessible by Center for Health Research staff for research purposes; all members are informed of this as part of their membership agreement, and members can elect to be excluded from all or some research studies.

D.2.2 Kaiser Permanente Dental Care Program: Kaiser Permanente Dental Care Program has a long history of conducting population-based, public domain research. The program has about 250,000 members and 16 dental clinics in the Portland, Oregon metropolitan area. Permanente Dental Associates is an independent professional corporation of dentists contracting exclusively with Kaiser Foundation Health Plan to provide professional dental services for members enrolled in the program. Permanente Dental Associates employ about 140 full-time equivalent (FTE) general dentists, five FTE pediatric dentists, two FTE oral surgeons, one FTE prosthodontist, and three FTE orthodontists. The dentist staff is supported by dental assistants, dental member assistants, and 110 FTEs of dental hygienists. Each office has a dental office manager and a professional director who are jointly responsible for clinical operations. The program also includes a Regional Support Services Center housing a complete prosthetic laboratory and a temporomandibular joint disorders center.

D.2.3 Kaiser Permanente Center for Health Research: Center for Health Research is a professionally independent research organization conducting academic quality, public domain research that is advancing knowledge to improve health care and inform health policy. Founded in 1964, Center for Health Research is a multidisciplinary institution that studies medical care organization, health care financing, health services delivery, epidemiology, health promotion, and disease prevention. Center for Health Research's research is conducted within the Kaiser Permanente health and dental care programs. Center for Health Research researchers have ready access to Kaiser Permanente's health care data systems, which provide each member's medical, pharmacy, and dental information.

The Center for Health Research is organized on an academic model and has relationships with academic researchers and institutions throughout the United States. Students from colleges and universities around the world come to Center for Health Research for training and education. Center for Health Research's 43 investigators are experts in their fields of study. The Center's clinical investigators help bridge research and clinical experience. Support staff are organized into centralized departments, including Data Technology, Computer Operations, Behavior Assessment and Change, Research Clinic Resources, Financial Management, Library Services, Editing, and Graphic Design. These centralized resources provide highly trained and experienced staff for Center projects. In addition, PhD and masters-level statisticians and analysts are available for Center projects.

D.2.4 HealthPartners: HealthPartners operates a mixed-model HMO-style medical plan serving almost 800,000 enrollees in the Minneapolis/St. Paul metropolitan area and is an integrated health care system focused on improving the health of its members and the community. HP provides medical and health services to members through a variety of professionals, programs and services, in coordination with health care plans and administrative services. A large network of owned and contracted clinics, medical offices, and dental centers is the foundation of the HP care delivery system.

HP is the parent company for a family of health care organizations that include Regions Hospital, Ramsey Clinic; Group Health, Inc.; HP Research Foundation; Regions Hospital Foundation; and Central Minnesota Group Health Plan, Minnesota's first Community Integrated Service Network. More than 7,800 employees staff the various HP divisions. HP was formed through the August, 1992 affiliation of Group Health, a staff model HMO founded in 1957, and MedCenters Health Plan, founded in 1972. HP merged with Ramsey Health Care, Inc. in 1993.

D.2.5 HealthPartners Dental Group: HP provides dental benefit plans and dental care through its dental division. The HP Dental Group is responsible for providing administration for a broad range of comprehensive dental plans that HealthPartners markets independently of its medical plans. HealthPartners dental benefit plans use a variety of funding mechanisms and dental network options. HP subsidiary corporations are utilized for dental products that are self-funded or those that include indemnity insurance options. The HP Dental

Group also administers a variety of dental benefits that are included in HealthPartners medical plans, such as TMD treatment.

The dental division owns and operates 18 staff-model clinics staffed by 58 dentists serving more than 80,000 comprehensive enrollees. The remainder of the enrollees are served in contracted, community clinics (about 58,000 enrollees), and the dental preferred provider organization. The owned clinics offer a complete range of services including periodontics, endodontics, orthodontics, prosthetics, oral surgery, temporomandibular joint treatment, and general dentistry. The dental division provides preventive dental benefits to an additional 144,000 individuals.

HP is a family of HMOs that offer a wide variety of health plans and broad delivery networks. These health plans offer flexible benefit packages and funding alternatives to meet the needs of individual and group purchasers. HP-Regions is the parent corporation of Regions Hospital, Ramsey Clinic, and the Regions Hospital Foundation. Together, the Regions organizations deliver medical and health services to the residents of the east Twin Cities metropolitan area and western Wisconsin.

D.2.6 HealthPartners Research Foundation was established in 1989 (as Group Health Foundation) to initiate and support research activities that contribute to the improvement of health care delivery to HealthPartners members and the community at large. In particular, research efforts focus on projects that enhance health care outcomes and/or the cost effectiveness of health care delivery. This mission is accomplished through the involvement of HealthPartners' medical, dental, and mental health professionals, who carry out research in their specific areas of interest and fields of expertise and through collaboration with other organizations whose resources and expertise contribute to the completion of high-quality research. Research activities conducted through the Foundation are intended to result in public domain and/or peer review publications.

HP Research Foundation serves as the fiscal agent for all grants and contracts in the HP foundations and institutes. HP Research Foundation receives about $7,500,000 in grants and contracts annually from corporations, foundations and the government. In addition, HP Research Foundation appropriates $360,000 annually to investigators for small research projects. These proposals are awarded competitively based on the scientific merit review by a committee of peers. HP Research Foundation has responsibilities for protection of human subjects and animal subjects in research and for ensuring adherence to all federal regulations.

The HP Research Foundation has a designated professional and support staff of over 90 members. Currently, HPRF is conducting more than 350 research projects encompassing preventive care, clinical care, health services, outcomes, guideline evaluation, epidemiology, and basic science. Capacities of HP Research Foundation include access to direct operations of 22 HP staff-model clinics to conduct research; 13 career research scientists and 45 clinician/researchers; programmer/analysts and PhD and masters-level statisticians; and access to 400 professional staff providers in multiple specialty areas.

D.3. Electronic Administrative Databases

This project uses multiple clinical, research and administrative databases at KPNW and HP (described below).

D.3.1 Kaiser Permanente Northwest Data Systems:

Both the KPNW dental and medical programs use fully electronic record systems to track covered members and document the care they receive. Data from these various systems may be linked using a common patient health record number and include the following:

Common Membership System. The Common Membership System contains administrative and financial data for all past and present KPNW members. Implemented in 2002, the Common Membership System maintains the base of membership data and employer group data to support member and patient identification, group contract and benefit administration, group and direct-pay billing, and membership and revenue reporting. The Common Membership System's data are transferred to a database with two major components—current eligibility, which has information on all persons currently eligible or who terminated within the past year, and historical eligibility, which has information on every person who has ever been a KPNW medical or dental plan member. This system serves as the single source of member information for all of KPNW's automated systems.

HealthConnect is the automated clinical information system used in all KPNW medical offices. This computerized medical record provides direct, immediate, and easily accessible information on patients' medical histories, procedures, diagnostic findings, and treatments. HealthConnect automatically links a patient's record with other databases, such as the Laboratory information system (divisional laboratory) and Inpatient and Outpatient Pharmacy databases to provide a more complete characterization of a patient's health and medical history. This system contains information on health problems, history and physical findings, tests ordered, medications prescribed, therapies ordered, and progress notes. Physicians interact with this system in their offices and examination rooms. HealthConnect includes a sophisticated graphical user interface with point-and-click functions, drop-down menus, auto coding, "smart sets" that permit physicians to order sequential testing strategies from the laboratory with a single click, and embedded practice guidelines. This system includes access to online bibliographic resources and numerous other reference resources, such as KPNW's Regional Formulary. All of Kaiser Permanente's eight regions use HealthConnect, creating a system that includes the health information of over eight million members. HealthConnect provides Center for Health Research researchers with an automated source of outpatient diagnoses and procedures from an internationally recognized health care model. HealthConnect includes a **Results Reporting System**, which is organized by individual patient in reverse chronological order. The system gives clinicians rapid access to all key events for the patient, including cytology reports, pathology reports, laboratory test results, imaging reports, dispenses, office visits, emergency room visits, hospital admissions, nursing home admissions, and surgeries.

Outpatient Pharmacy System. This automated system records all prescriptions dispensed by KPNW outpatient pharmacies. KPNW pharmacies dispense more than two million outpatient prescriptions annually. An estimated 90 percent of all prescriptions are filled at a program pharmacy, including those for members without a prepaid drug benefit. While KPNW has a formulary of recommended medications, physicians may prescribe any marketed drug. The outpatient pharmacy system tracks over-the-counter medications, such as insulin and niacin, to monitor adverse effects and record injection data. Community pharmacy prices for each prescription are also recorded. Data from this system are linked to administrative and research databases containing detailed information on the patient, clinician, and medication for each dispensed prescription.

Dental Administrative and Clinical Tracking System. The Dental Tracking System provides administrative and clinical data on all dental office visits in KPNW's Dental Care Program. This system captures data for the dental programs' 15 offices, representing over 100 dentists and dental specialists, as well as KPNW's Regional Support Services Center, which houses a complete prosthetic laboratory and a temporomandibular joint disorders center. This electronic record is updated at each patient visit to include demographic and benefit information, along with dental service provided and current and past treatment plans.

Outside Claims and Referral System. The Outside Claims and Referral Information System is an automated system that processes claims for covered services provided outside KPNW. This database also identifies covered expenses for outpatient drugs purchased at non-KPNW pharmacies. This database captures emergency out-of-area hospitalizations, ambulance usage, and out-of-area dental claims. Data include date and type of service, total charges, and reimbursement date. The Outside Claims and Referral Information System is a traditional claims processing system with inpatient (facility) claims in UB-92 standardized format and professional services claims in HCFA-1500 standardized format.

D.3.2 HealthPartners Data Systems:

Enterprise Wide Information Source. The Enterprise Wide Information System is a central repository of corporate data that serves as a resource for obtaining detailed, integrated historical data for analytical purposes. A wide variety of data is currently stored in the Enterprise Wide Information System, some of which are membership, medical encounters and claims, pharmacy utilization, and lab data. The data are stored in an Oracle relational database on an open VMS operating system and are updated with monthly snapshots of operational data from the claims processing, laboratory and pharmacy systems. Data are currently available from 1997 to the present. The Enterprise Wide Information System contains data on all members from both HP's owned and contracted networks. The data can be queried using SQL (Structured Query Language), SAS, Microsoft Access, SQL Plus, etc.

Research Data Mart. The Research Data Mart is a specially constructed data warehouse designed to support research. It contains a subset of the data found in Enterprise Wide Information System that is most clearly related to research. Data within the Research Data Mart also reaches back to earlier periods than that found in Enterprise Wide Information System, where it has been archived. The Research Data Mart also contains normalized dental data from the Dental Practice Systems. Research Data Mart is also on an Oracle system and can be queried using the same tools that are used for the Enterprise Wide Information System.

Electronic Medical Record. HealthPartners Medical Group has shifted from a paper charting system to an automated electronic medical record using the system produced by the vendor EPIC of Madison Wisconsin. This means that every examining room within each clinic has a terminal for the display and capture of patient encounter data on a real-time basis. Each evening encounter data from the previous days experience are loaded into an Oracle database (Clarity) designed specifically for reporting support. At the time of the introduction of the electronic medial record charting notes, diagnoses and procedures and laboratory results were back-loaded from the prior electronic system, making available a historical view of a patient treatment.

Dental Practice Systems). The Dental Practice Systems application, used until 2004 in HP Dental Group, supported the business functions performed by dental clinics and administrative offices, including patient scheduling, treatment planning, recording clinic services, patient and insurance billing, receipt processing and reporting. The Dental Practice Systems was a combination of purchased vendor software and DEC applications. Dental Practice Systems function which run as DEC applications include 1) Member Mini-Registration, 2) Membership Maintenance and Inquiry, 3) Dental Authorizations, 4) Clinic and Chart Assignment, and 5) End User/Data Reporting (FOCUS). Membership, benefit meters, dental claims and clinic service data interfaces allow for the sharing of information between the DEC and IBM systems.

Electronic Dental Record. The electronic dental records in use at HP Dental Group since 2004 is a product named 'Soel Focus', created by Software of Excellence (URL: www.soeidental.com). Besides providing charting, appointment and billing needs of a dental practice, it is designed to operate over a network system with a central data storage system. It also has the capability for local modification in the presentation and collection of data based on patient characteristics. The installation at HP Dental Group stores all its data in an Oracle relational database where they are readily available.

D.4. Analysis Plan

D.4.1 Study Cohort. To be included in the study, adult KPNW and HP members will be **≥40 years old**, have **both medical and pharmacy** coverage, and have been **continuously enrolled in the medical plan for at least two years** between 01/01/1994 and 12/31/2005; the last entry into the cohort will occur on 01/01/2004. We will **exclude** individuals with any **exposure to bisphosphonates** or **broken jaw** external injury codes during the first 90 days of enrollment. We will also exclude members with **sickle cell anemia,** which is a lifetime risk factor but also an extremely rare disorder in our population (likely <20 cases). If any individual has more than one period of two-year membership in the HMO interrupted by more than 90 days disenrollment, only the first period will be included.

HP has comprehensive electronic medical record data beginning in 1994, whereas KPNW data are comprehensive beginning in 1998. Potential differences between sites will be evaluated during the statistical analysis (see Section D.4.4).

D.4.2 Study Variables. Table D.1 lists the data we will collect for possible inclusion as dependent and independent variables for this study. Cell size considerations will limit the number of model covariates we can include in the analyses. These include features of osteonecrosis of the jaw, of exposure to bisphosphonates and of other hypothesized risk factors for ONJ, demographic data, and other information. About 50% of medical plan members also have dental coverage. For these cohort members, the dental procedure data in Table D.1 will support analyses of services that may precipitate ONJ (e.g., tooth extraction).

Table D.1 Variables collected for assessing ONJ risks

Description	Measures	Source	Role in analysis
Outcomes			

Table D.1 Variables collected for assessing ONJ risks			
Description	**Measures**	**Source**	**Role in analysis**
Osteonecrosis of the jaw	ICD-9 CM codes 526.4, 526.5, 733.4, 733.44, 733.45, 733.99	Medical	Primary outcome (0/1)
Osteonecrosis (other than ONJ)	ICD-9 CM codes 733.4, 733.44, 733.99; Osteoradionecrosis, jaw: 526.89	Medical	Secondary outcome (0/1)
Descriptive variables			
Demographics	Age, sex, plan type (e.g., commercial, Medicare, Medicaid)	KP/HP membership and other databases	Age (40-64/65+) Male (0/1); plan (private/public)
Socio-economic status	Median income geocoded using member's last known address	Membership and Census	Two level income (low/other)
Risk factors for ONJ			
Smoking status	Current, former, never smoker; heavy and light smoking	Medical	Risk factor (0/1)
Osteoporosis	ICD-9 codes 733.00–.09	Medical	Risk factor (0/1)
Radiation therapy to head and neck	CPT-4 codes 774xx for cancers in the head and neck region (ICD-9 codes 142.0–.9, 143.0–.9, 160.0–.9, 170.0–.9, 195.0)	Medical; cancer registry	Risk factor (0/1)
Chemotherapy	CPT-4 codes; NDC codes	Medical, pharmacy, cancer registry	Risk factor (0/1)
Cancers	Capture all ICD-9 cancer codes; focus on breast (174.0-.9), metastatic (199.0, 199.1), and bone (170.0-.9) cancers, and oral cancers (see radiation therapy above)	Medical	Risk factor (0/1)
Diabetes	ICD-9 CM codes 250.0-.9	Medical	Risk factor (0/1)
Immuno-suppressive conditions	ICD-9 CM codes 279.00-.9, Lupus-710.0), AIDS-042	Medical	Risk factor (0/1)
Bisphosphonate exposure (alendronate, etidronate, ibandronate, pamidronate, risedronate, tiludronate, zoledronate)	Oral or IV; dosage (mg); frequency; duration (days); NDC codes,	Pharmacy, Medical	Risk factors considered: BPs (0/1); days exposure (#); cumulative dose; Oral (0/1)
Steroid exposure (prednisone, dexamethasone, medrol, Sol-U-Cortef)	Dosage (mg); frequency; duration (days); NDC codes,	Pharmacy, Medical	Risk factor (0/1)
Dental Procedures*			
Tooth extraction	ADA codes 7110, 7120, 7130, 7210, 7220, 7230, 7240, 7241, 7250	Dental	Risk factor (0/1)
Periodontitis, periodontal surgery	ADA codes 4210, 4211, 4220, 4240, 4249, 4250, 4260	Dental	Risk factor (0/1)
Other dental surgical procedures	ADA codes including 7xxx.	Dental	Risk factor (0/1)

Table D.1 Variables collected for assessing ONJ risks			
Description	**Measures**	**Source**	**Role in analysis**
Removable Partial Denture	ADA codes 5xxx	Dental	Risk factor (0/1)
Removable Complete Denture	ADA codes 5xxx	Dental	Risk factor (0/1)
Denture Adjustment	ADA codes 5410, 5411, 5421, 5422	Dental	Risk factor (0/1)
*We will also capture any location-designed (non-ADA) codes for these procedures.			

Primary Outcome. The primary outcome variable is a confirmed incident onset of ONJ (defined below). For confirmed ONJ events, we will use the initial encounter date for the ONJ onset. In secondary analyses, we will examine predictors of all incident osteonecrosis episodes.

*An **ONJ event** will be defined as a non-healing exposed bone lesion of any size in the mandible or maxilla that persists for more than four weeks with or without treatment (which we define as an "active" lesion). The duration of four weeks has been selected based on previous reports of ONJ. In some BP manufacturer-sponsored studies, the defined time period for ONJ was three months or longer. The Special Subcommittee of American Association of Oral Maxillofacial Surgeons suggest a six-week time period. While we consider four weeks to be sufficiently conservative to avoid inclusion of non-ONJ lesions, we will conduct separate analyses using a six-week period in order to determine if the results are sensitive to this slight variation in our case definition. We emphasize that diagnosing ONJ is a purely clinical exercise, as no radiographic, laboratory or microscopic features are pathognomonic for this entity. Generally, necrotic bone lesions in the oral cavity are unmistakable to the keen observer and clinical examination is both reliable and reproducible for this disease.*

Events will be confirmed through electronic and manual chart review of the medical and dental records for cohort members with suspected events of ONJ. The ONJ case identification process is diagramed in Figure 1. For health plan members at least 40 years of age and with at least two years of continuous membership during 1994–2005 for HP and 1998–2005 for KPNW, "potential" ONJ cases will be identified by searching each plan's electronic medical records for osteonecrosis diagnoses using the International Classification of Diseases, Ninth Revision (ICD-9) codes for osteonecrosis (733.4, 733.40, 733.45, 733.99) selected diseases of the jaw (ICD-9 526.4, 526.5), selected late effects of radiation or other treatment (ICD-9 909.2, 909.3), and by searching for CPT codes for inflammatory lesions (21025, 21026, 41830, 41850) and CDT surgical procedure codes (7465, 7490, 7550). Other ICD-9 and CDT codes may be included if chart reviews indicate other codes are used to document ONJ cases. After identification of a possible ONJ event through identification of specific diagnosis codes, we will need to validate the presence of ONJ vs. other osteonecrotic event or possibly rule-out diagnosis. We will include CPT codes for malignancy treatment procedures (21015, 21034, 21040, 21045-47) as part of our effort to also identify false negatives.

***Validation of ONJ events.** We will use an existing natural language processing program, **Physicians Notes System**, to eliminate **"suspected" non-ONJ events** from the pool of suspected events among the list of "potential" cases identified using the above list of ICD-9 codes. Elimination will be based on evidence of the use of rule-out diagnoses, that the osteonecrotic lesion is located outside the jaw structure, or other obvious descriptors of a non-event. The intent of this process is to reduce the total number of charts reviewed manually to a reasonable number. We expect that the ICD-9 codes will identify more than 1,000 potential ONJ cases in each health plan. For **suspected ONJ non-cases**, we will review a small (n=100) random sample of the NLP-excluded events in order to validate the accuracy of the exclusion process. If we find any confirmable events that the natural language processing program flagged as non-events. If we find ≥10% false negatives among the ICD-9 coded suspected non-cases, we will adjust the natural language processing search criteria, and rerun with the whole data file. The search criteria will be revised based on univariate chi-square tests for predictors of false negative results.*

To expand our search for true ONJ events, we will use the natural language processing program to examine the above-listed CPT and CDT codes for potential false negative ONJ cases. For identified potential false

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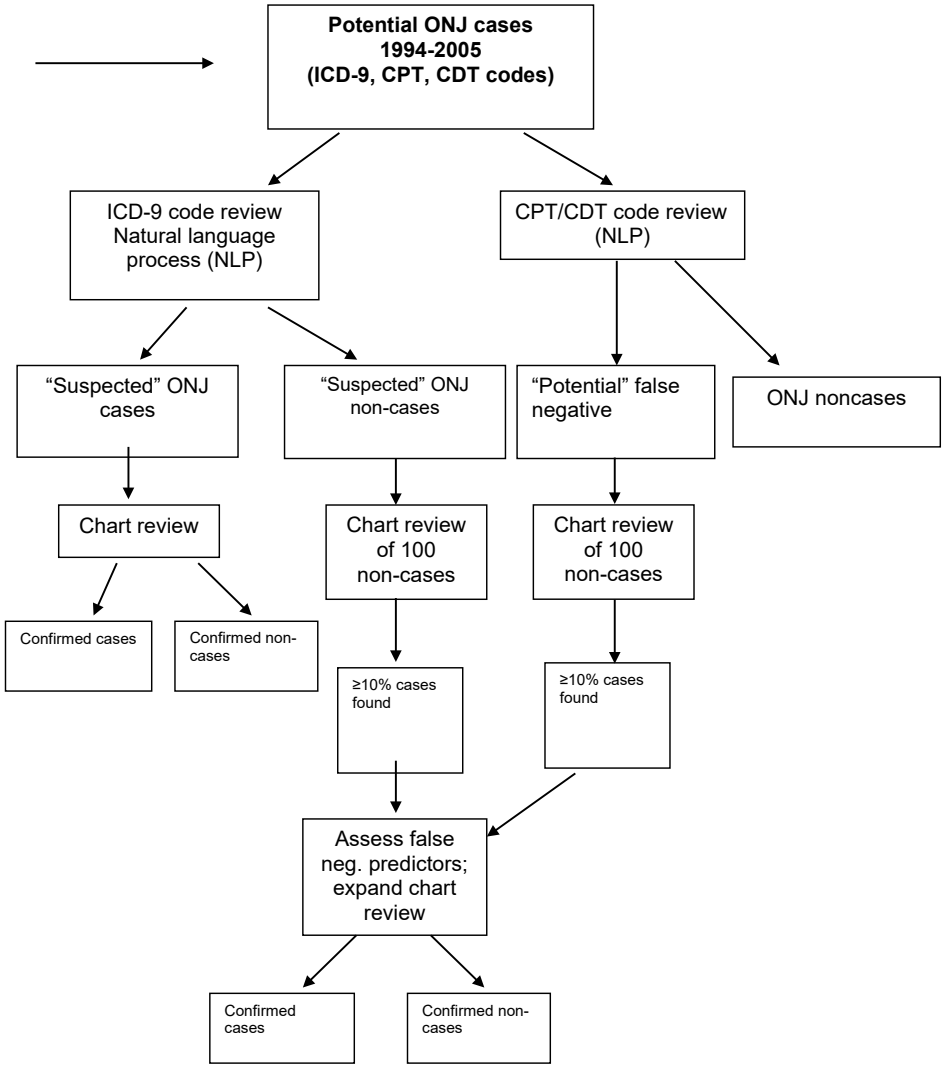
negative events, we will select a random sample of 100 cases and conduct a manual chart review. We will use the same predictors analysis described in the previous paragraph.

Figure 1. ONJ case identification flow diagram



To use the Physician Notes System, we first identify encounters containing target diagnoses or procedures, extract the associated notes from the electronic medical records system, and load the notes into the Physician Notes System. Once in the Physician Notes System, specific key words and/or phrases are used in searching the body of notes. If deemed appropriate to the purpose of the search the patient is flagged as having a

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suspected ONJ event. The system provides various supporting functions, such as the option of combining key words with boolean logic and the ability to do further searching within saved search results. The Physician Notes System also provides specific summary information relative to the numbers of keywords found and how many patients are represented. Dr. Rush at HP has used this tool successfully to identify patients with depression, cancer and measles (69).

Suspected ONJ events flagged by Physician Notes System will be confirmed through manual review of the physician notes. Experienced chart reviewers, under the guidance of study investigators, will review the database of provider notes for reference to the jaw, description of lesion, duration of lesion and possible explanations for onset.

The start and recovery dates for an active lesion will be determined by combining abstractors' codes based on provider notes and encounter dates where the lesion was noted in the charts. Existence of encounters four or more weeks apart that document the non-healing lesion will be evidence for a confirmed event. If the lesion has healed by a subsequent encounter with a date occurring more than four weeks after the initial ONJ visit, there is the possibility that the lesion could have been active for at least four weeks. In these instances, we will consider the event confirmed if the provider documented that the lesion was active for at least four weeks. The remaining events will be flagged for additional review by the review team.

The research team will finalize the precise decision rules that will define a confirmed ONJ case in the first month of the study. In addition, a process for adjudicating these events will be developed, which may include discussing the clinical evidence with outside experts and/or the provider of record.

Suspected ONJ events with an inconclusive chart review will not be coded as an event; however, the individual will continue to be followed. Excluding a potential ONJ event is conservative with respect to the hypotheses. The number of inconclusive suspected events will be reported. Given the relative rarity and significance of ONJ lesions, we expect the number of inconclusive events will be small.

Cohort members with no evidence of ONJ who leave the cohort before 12/31/2005 (death, loss of medical or dental coverage), who have a disqualifying event (broken jaw), or who are followed to 12/31/2005 will be coded as censored on incident ONJ at that time. Only the first ONJ episode for a given cohort member will be included in analysis; follow-up will cease with this event.

Finally, the date of onset of osteonecrosis events that are not ONJ will be noted, for use in secondary analyses. The same rules for censoring will apply.

Independent Variables. The independent variables that we will measure include selected features of **bisphosphonate exposure** and presence or absence of **selected risk factors** for ONJ (other than BP exposure). A complete list of FDA-approved bisphosphonates is provided in Appendix 1

Bisphosphonate Exposure. Seven bisphosphonates are FDA-approved in the US: zoledronate (Zometa) , pamidronate (Aredia), alendronate (Fosamax), risedronate (Actonel), tiludronate (Skelid), ibandronate (Boniva), and etidronate (Didronel). We will record route of administration, duration of exposure (start and stop dates) and quantity dispensed, and combine these to compute cumulative dose. Our experienced analysts have worked with similar pharmacy data in previous studies and are aware of the potential adjustments needed for administrative censoring (e.g., follow-up ends before medication runs out), sequential treatments with different bisphosphonates, and carryover for changes in risk status. We will express BP exposure as an equivalent dose per kilogram using estimates of preclinical anti-resorptive relative potency (39).
Known or Hypothesized Risk Factors. We will record exposure to risk factors other than bisphosphonates (see Table D.1). For cohort members whose medical and dental coverage begins during the observation period, we will use the entering history and physical (as recorded in the medical record) to identify existing risk factors. For already-enrolled members on 01/01/1994, we will identify individuals with preexisting chronic conditions hypothesized as a risk for ONJ, and we will examine notes in the patient history to determine disease onset dates, and chemotherapy treatment history and dates. Cancer registry data for KPNW members will also be available. These will be coded as present or absent at the beginning of the observation period; we will make every attempt to establish date of onset for these existing risk factors; since these may be approximate dates, this might introduce some imprecision to the time scale. The date of onset of any incident risk factors during the observation period will be noted and used to construct time-dependent covariates (see D.4.4). Additional

risk factors we will consider include: exposure to corticosteroids (using pharmacy data and NDC codes); radiation treatment to the head and neck (CPT-4 codes 774xx, precise codes to be determined); immunosupressed states (HIV/AIDS, curative cytoreductive cancer therapy); cancer diagnoses, particularly with chemotherapy; diseases commonly associated with bone necrosis include sickle cell anemia, blood cancers, and various states of hypercoagulation; and autoimmune diseases, such as lupus erythematosus, rheumatoid arthritis, and organ transplantation.

D.4.3 Data Management and Audit. Data will come primarily from the computerized medical record databases at the two performance sites. The Physician Notes System program will generate an electronic data file, and, in addition, manual chart review will generate data on a paper form. Data coordination staff at Center for Health Research using standard operating procedures including ongoing, random re-entry to monitor accuracy will enter data from paper forms. These data will be integrated, audited, and reconciled by the Center for Health Research analyst and statistician, in close communication with the site Principal Investigators and HP analysts. Finally, the time-to-event dataset with time-dependent exposure status variables will be constructed and carefully checked for accuracy. We will conduct data audits and analyses using the current version of SAS®.

Missing data. We do not expect to have missing data because of the nature of the data sources we will be using. The risk factors for ONJ are medical conditions or events that are a high priority for follow-up in the managed care environment, so it is unlikely that absence of evidence of such a factor would be a result of the factor being overlooked. Therefore, we will code no evidence of a risk factor as negative. The date of onset of a risk factor may not be known with precision. We will develop decision rules early in the study to use in assigning a plausible onset date (to the nearest year, say) for risk factors with onset before the beginning of our observation period. Because the time scale to development of ONJ appears to be years rather than months or weeks, we anticipated that this will be sufficiently precise. No other reasons for missing data are likely to occur.

D.4.4. Methods to Achieve Specific Aims

Aim 1: To quantify the prevalence of ONJ in a large cohort of patients enrolled in these HMOs.

Aim 1 is descriptive in intent. We will present summary statistics in each HMO population, and combined estimates for prevalence of ONJ in each HMO population over the entire observation time, expressed as annual prevalence per 100,000 members age ≥40 years, and in subsets defined by various risk factors, including type of BP exposure, specific types of cancer, exposure to radiation. In addition, we will compare the two HMO populations and subgroups on age, sex, and other demographics.

Aim 2: Test the hypothesis that bisphosphonate treatment is a risk factor for ONJ. Aim 2 is the most important aim of this study. We will quantify the impact of BP exposure on the hazard of developing ONJ, relative to comparable patients not exposed to BP, using a time-to-event (survival) analysis.

We will use the **counting process formulation** of the Cox proportional hazards model as the primary analysis (70). This generalization of the Cox model allows us to analyze varying risk profiles within cohort members over time. Let $\boldsymbol{X}_i(t)$ be a covariate matrix of order t x p observed on subject i at time t. If the covariates vary over time, $\boldsymbol{X}_i$ has multiple rows, each measured at time t_k (k=1,…,t). The number of rows in the matrix will depend on the number of times any value in $\boldsymbol{X}_i$ changes.

Under the ordinary Cox model, the instantaneous hazard for individual i is specified as $\lambda_i(t) = \lambda_0(t)exp(\boldsymbol{\beta X}_i)$, where the baseline hazard, λ_0 is an unspecified, nonnegative function of t, and $\boldsymbol{\beta}$ is the vector of k unknown coefficients relating $\boldsymbol{X}$ to $\lambda_i(t)$. In this model, the covariates are fixed and time t takes a single value, which denotes the lesser of time to event and censoring time.

In contrast, under the counting process formulation, t is replaced with the start and stop times for a given covariate (or risk) profile. This interval is open on the left and closed on the right—(t_1, t_2]--where the covariates and outcome are constant from the instant after t_1 to the instant of t_2. This approach permits us to partition the time-at-risk at instants when the risk profile changes for an individual, and in effect to reclassify a cohort member into a different risk group whenever the risk profile changes. Each change in risk profile generates a new record for that participant in the analysis dataset. Until an outcome event occurs, the outcome is censored at each time t_2, and the time of an outcome event defines the end of the last at-risk period for a participant.

This use of time-dependent covariates increases the sensitivity of the analysis by increasing the accuracy of risk assignment and by using all data in the estimates of relative hazards. To summarize, during the study period, individual members of the study cohort could contribute information to more than one risk group, depending on the timing of the onset of exposure to different risk factors and of the ONJ outcome.

The start time, t_1, of the first interval is initialized at 0 for cohort members who have no existing risk factors at baseline, and exposure time, T_E, starts accruing later, at onset of the first risk factor. However, when the onset of a risk factor occurs before the observation time starts accruing, a cohort member has accrued time, $T_E > 0$ at t_1. In this case, t_1 is initialized at the value of T_E at the start of observation. This is a case of *left truncation* (70). Using this approach, two individuals who experience the outcome event at the same length of time following onset of exposure contribute consistent time to event data regardless of when the exposure started relative to baseline.

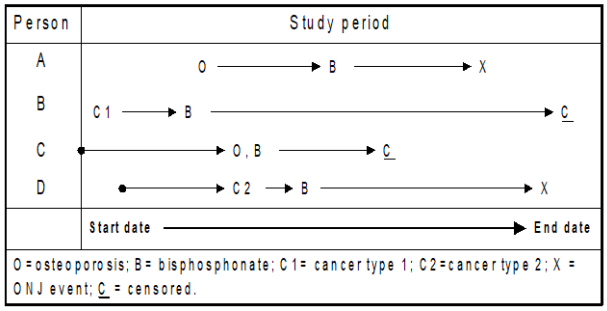
The time accrued by individuals with no bisphosphonate exposure will represent the control for time following bisphosphonate exposure. Similarly, the time individuals accrue while negative on a risk factor will serve as a control for that risk factor. This scheme will allow us to evaluate whether the combined impact of risk factors is additive or multiplicative. We expect that bisphosphonate exposure will invariably follow onset of another known or hypothesized risk factor, but the converse will not be true (i.e., individuals with the risk factor may have no bisphosphonate exposure).

The benefits of using a Cox proportional hazards model can be illustrated using the information in Figure 1, which shows a variety of disease and treatment histories that can be expected in the study cohort. For each person (A–D), we present a simplistic hypothetical timeline for exposure ~~experience~~ to bisphosphonates (B), other risk factors (O=osteoporosis, C1 and C2=cancer 1 and 2), censored follow-up (C), and onset of ONJ (X). The hypothetical examples show different time periods between BP exposure and ONJ diagnoses and censoring, and varying times between exposure to other risk factors and initiation of BP treatment. These variations will influence the number of days of exposure that the model will add for each exposure variable.

The primary model for Aim 2 will include the following *a priori* fixed predictors: age at entry, sex, and data collection site (KP vs. HP). In addition, the following time-varying covariates will be included in the initial model:

- Indicator for BP exposure (yes/no)
- Indicators for IV and PO bisphosphonate (vs. both) (binary, change in either signals start of new interval)
- Duration of BP exposure (continuous quantity, reset at end of each interval, t_2)
- Indicator for cancer (binary, change signals start of new interval)
- Indicator for osteoporosis (binary, change signals start of new interval)
- Indicator for diabetes (binary, change signals start of new interval)
- Indicator for dental work (extraction or periodontal surgery, binary, change signals start of new interval)

Figure 1. Selected examples of disease and treatment histories relevant to ONJ onset



The Wald X^2 statistic will be used to test the null hypothesis of no effect. We will use the likelihood ratio X^2 statistic as a global test the model's goodness of fit.

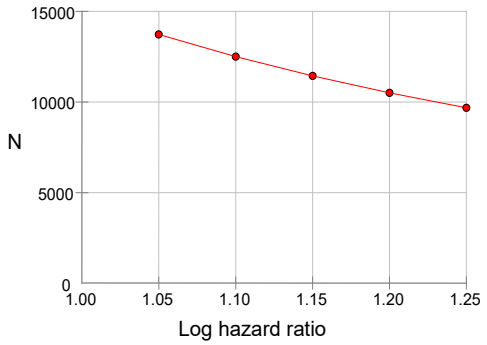
In follow-up analyses, we will examine the impact of increasing cumulative dose of BP, test whether different kinds of BP are associated with different hazard rates, and evaluate effects separately in the largest risk subgroups (e.g., breast cancer, osteoporosis).

Aim 3: Test the hypothesis that ONJ develops only in patients treated with BPs who have additional risk factors.

We will use the same dataset as was developed to address Aim 2, with a similar modeling approach.

The model specified for Aim 2 permits evaluation only of additive (on a log scale) effects of risk factors on the estimated hazard. However, if the effect of BPs is conditional on presence of additional risk factors, then we would expect to find significant interactions between BP and one or more other risk factors. These can be evaluated by examining the improvement in model fit that occurs when interaction terms are added to the model (by comparing the likelihood for the expanded model vs. the original model). In addition, the hypothesis suggests that a contrast conditioning on presence of a risk factor will demonstrate significantly higher hazard of ONJ when BP and the risk factor are present than when the risk factor is absent.

Figure 2. N vs log hazard ratio with event probability of 0.01, α=0.05, power=0.80



Secondary Analyses

In addition to the planned primary analyses, we believe that the large dataset constructed with such care and effort to answer our primary questions on the association of BP treatment and ONJ may also yield information regarding the prevalence and risk factors involved in development of osteonecrosis at other sites.

D.4.5. Sample Size and Statistical Power

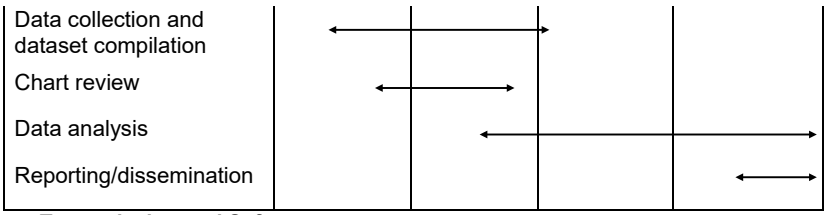
The power of the Cox regression model depends on the number of events observed as well as the relative hazards under the alternative hypothesis. We expect the number of confirmed ONJ events will be more than sufficient to detect statistically significant variations in mean survival times associated with exposure to bisphosphonates (our primary outcome). Preliminary data over a two-year period indicated there were over 450 individuals aged ≥40 years at KPNW and HP with suspected ONJ. In addition, we have identified over 10,000 individuals in the same two-year cohort who received at least one dispense of a bisphosphonate. Based on our two-year sample, which indicates a rough odds ratio of 3 to 3.5 (odds of suspected ONJ with BP dispense), and the reported survival rate of about 99% in individuals exposed to IV bisphosphonates, we estimate that we have sufficient power to evaluate the association of bisphosphonates with osteonecrosis in subsamples as small as 15,000, especially given that the total analyzable population exceeds 200,000 persons. The figure shows the 80% power curve over varied log hazard ratio. Based on the published research, we hypothesized that other risk factors may be important predictors of ONJ onset. However, the effect sizes for other hypothesized risks are not known and, thus, statistical power to detect such risks cannot be assured.

D.6. Work Plan and Timeline

A timetable for completion of study activities is shown in Figure 3. This schedule allows for finalization of the analysis plan, local IRB approval, data collection and processing, case verification, data analysis, and dissemination activities. The study investigators will also meet in Alabama in early October 2006.

Figure 3. Study timeline

	Sept-Dec 06	Jan-Mar 07	Apr-June 07	July-Sept 07
Analysis plan and IRB				



D.7. Data Transmission and Safety

Individual-level study data will be transmitted from HP to KPNW and merged with KPNW individual-level study data. The Center for Health Research team will merge the data into an analysis dataset. A data use agreement will be developed that governs the use and release of study data by KPNW Center for Health Research staff. We expect some suspected ONJ cases may require review by study investigators in order to determine if the individual is a case or non-case. Any case reviews will be conducted using de-identified information, and transmitted to study investigators via the secure web portal described below. During the analysis, any individual-level reviewed by study staff will be transmitted using the secure web portal. Below, we describe how the data will be transmitted and secured. Identifiable, individual-level data will not be included in study reports, presentations, or manuscripts.

D.7.1. Data Transmission

Secure, Study-Specific Web Portal. Center for Health Research will build a HIPAA-compliant, secure website for the study that will serve as a platform for study-wide data transfers and communications and documentation. Only select study staff will have access to the web portal. At the Center for Health Research, multi-center study teams rely heavily on websites for data collection and tracking. Thus, internal and external security is of prime concern; processes are continually upgraded as more secure technical tools become available.

Web Security. Internally, each website user will be assigned an individual security identification that allows access to only those parts of the study website to which that user is authorized. Thus, users will be given access to all documents, forms, committee information, and data matched to their individual security status, but will be restricted from accessing areas for which they have no security clearance.

Externally, Center for Health Research websites use Secure Sockets Layer (SSL) technology and the highest level of packet encryption currently supported by servers and browsers. This technology secures data from interception while in transmission between study sites. In addition, the Center for Health Research servers sit behind firewall hardware and software that dedicated staff members maintain and upgrade to the highest current standards in order to ensure the safety of all information from outside attack.

D.7.2. Data Safety.

Access to all project PCs, directories, and electronically stored data, will be restricted to authorized personnel and will be password protected. Furthermore, data safety will be enhanced by Web-based security steps that include a combination of certificate authentication for clinical center connection to the host server, custom programming to secure individual access to forms and other documents, and data packet encryption to ensure that confidential data cannot be revealed even if packets are intercepted in transmission. All Center for Health Research staff annually sign a confidentiality statement attesting to their understanding of the Center for Health Research's written policies on research ethics and confidentiality.

D.8. Potential Challenges and Limitations

As this is an epidemiologic study, it will be unable to confirm a cause-effect relationship between BP and ONJ. However, we will determine associations of interest and their strength based on relative risk ratios. This study is also retrospective and it carries all limitations associated with its type of research. While the Cox proportional hazards model allows us to control for censoring during follow-up, the experiences of those lost to follow-up may be quite different than those who have complete data. Also, our efforts to establish risk exposure prior to the index date, left truncated data may introduce some imprecision in the time to event scale.

Results here will also be subject to the limitations of the databases and our ability to abstract and interpret such results. For example, cancer index dates may not be clear-cut; patients' compliance with oral medication may be hard to determine; and past medical histories will be as good as the clinician taking the interview and the patient's memory. Significant information may be missing, including additional unknown risk factors for ONJ, which are not listed in the medical record. We will make every attempt to obtain complete and accurate information by using more than one source to establish an ONJ case. If necessary, we will interview clinicians.

In addition to the above limitations, we will encounter some specific challenges relating to merging data across health systems and identifying cases in the medical and dental records. Merging medical record data from two HMOs has the potential for unforeseen compatibility issues. Based on our experiences merging data as part of our own work, and as part of the Cancer Research Network and HMO Research Network, we do not expect significant problems with the data. These networks have facilitated the creation of a Virtual Data Warehouse that allows analysts from each organization to use single algorithms to extract common data elements across organizations. In the unlikely chance that a severe problem arises, the Virtual Data Warehouse can be used to find a common linkage between datasets. Identifying cases in the medical and dental records can be problematic, and depend on proper recording of diagnoses for a rare condition, clear information in the chart notes, and lack of data for dental members without medical care and vice versa. Lastly, while we will review a sample of suspected cases that were eliminated using the Natural Language Processing program, some actual cases may be missed.

Despite these inherent limitations and challenges, we are in an ideal position to study prevalence and risk factors for ONJ and shed significant light on these issues. The number and heterogeneity of the patient population we can access is unmatched and, as our previous collaborations have shown, we are typically successful at obtaining accurate and reliable information.

E. HUMAN SUBJECTS RESEARCH

E.1 Risks to the subjects and health care providers

E.1.2 Human subjects involvement and characteristics. This protocol is a retrospective data-only cohort study. It does not involve direct patient contact. The human subjects involved in this study are medical and/or dental plan members with at least two years of membership, and age 40 years and over, from HealthPartners (1994-2005) and KPNW (1998-2005). We will collect individual-level information from patients' electronic medical and dental records, and review paper dental charts for individuals with suspected ONJ diagnoses.

E.1.3 Sources of materials. We will collect individual-level information from KPNW and HP patients' electronic medical and dental records, and review paper dental charts for individuals with suspected ONJ diagnoses. Medical chart review will be conducted using electronic records. We will collect medical and dental care data for inpatient and outpatient encounters, out-of plan claims, diagnoses, procedures, pharmacy dispenses, and membership data (demographics) that will allow us to estimate the prevalence and risks for ONJ. These data are available in existing administrative databases.

E.1.4 Potential risks. The only risk to the participating subjects will be the highly unlikely accidental disclosure of health care provider information. However, every precaution will be taken to prevent this and the DPBRN has an unblemished track record in this regard. No additional exposure is expected from this protocol.

E.2 Adequacy of protection against risk

E.2.1 Recruitment and informed consent. Study participants will be identified from the electronic administrative databases. We will not have direct patient contact, and will seek a waver of informed consent that is typical for data-only studies. We will exclude plan members who have previously requested to be excluded from patient research. KPNW and HP maintain these lists.

E.2.3 Protection against risks. Records of participation will be kept confidential to the extent permitted by law. Only authorized personnel will have access to the data, and all information, whether electronic or in paper form, will be stored in a secure manner. This information will not be sold or used for any reason other than research. Results may be published for scientific purposes, but participant identities will not be revealed. A password-protected secure web portal will be used to transmit data from HP to KPNW. All study staff are required to complete annual IRB and HIPAA training. The UAB, KP, and HP IRBs will review and approve all study procedures.

E.3 Potential benefits of the proposed research to the subjects and others

Subjects may benefit from the research documenting potential risks for ONJ associated with the use of BPs independently, and in conjunction with other risks and co-morbidities. This knowledge may influence how and when BPs are used to prevent bone loss in at-risk patients. The potential benefits to the subjects and indirectly to their patients will far exceed the risk involved with the participation.

E.4 Importance of the knowledge to be gained

The knowledge to be gained from the current study will be to quantify the prevalence of ONJ in a large population and assess the risks of ONJ associated with BP use independently and in conjunction with other risk factors. ONJ incidence is increasing, but prevalence data are currently not available. The association between BPs and ONJ is suspected, but little is known whether this is a direct association, an indirect association given the presence of other hypothesized risks, or both. Determining these relationships will provide important guidance for delivering medical and dental care services to patients at-risk for ONJ.

E.5 Inclusion of women

Based on the population distribution of the health plans, we expect about half of the study subjects will be women.

E.6 Inclusion of minorities

Racial and ethnic minorities will be included in the study proportional to their composition in the medical community. The racial and ethnic distribution of dental practitioners expected to participate in the study is shown in the Targeted/Planned Enrollment table on the next page of this application. Historically, neither KPNW nor the Dental Plan collected or recorded race/ethnicity data on members or subscribers on the grounds that such information could be used for discriminatory practices. KPNW is currently reviewing this policy. HP recently began collecting race-ethnicity, but will not be usable for this study.

E.6.1 KPNW population Past studies of KPNW health plan members show their demographic characteristics closely match the local population. The Northwest's minority representation is lower than the national average, but growing rapidly, especially among Hispanics. The racial and ethnic distribution of the Oregon and KPNW populations are presented in Table E.1

Table E.1. Demographic Characteristics of KPNW Health Plan Members and Residents of the State of Oregon, 2000

	Residents of Oregon	KPNW Health Plan Members of
Male	49.0%	47.0%
Hispanic	8.0%	3.9%
White	86.6%	88.8%
Black	1.6%	2.6%
Native American	1.3%	1.1%
Asian/Pacific Islander	3.2%	4.1%
Other	4.2%	3.4%
Two or more	3.1%	-

Under 18 years of age	25.3%	21.4%
18 to 29 years of age	17.6%	12.5%
30 to 49 years of age	30.7%	30.7%
50 to 64 years of age	12.4%	16.9%
65 years of age and older	14.0%	18.5%

HealthPartners population

Race and ethnicity are not readily available on automated data systems at HealthPartners. The ethnicity data comes from census data of the population data served by HP and member surveys. The age/sex data comes from administrative data. This information is presented in Table E.2. While the HP member population has a similar race and ethnicity distribution compared to the general Minnesota resident population, HP does have a slightly higher proportion of minorities than Minnesota.

Table E.2.. Gender, racial/ethnic group, and age composition of HealthPartners membership.

	Residents of Minnesota	HealthPartners Health Plan
Male	49.3%	47.8%
Female	50.7%	52.2%
Hispanic	3.6%	6.0%
Non-Hispanic	98.1%	94.0%
White	89.5%	86.0%
Black	3.1%	4.5%
Native American	1.3%	2.0%
Asian	2.7%	4.0%
Other (includes multiracial)	NA	3.5%
<18	30.0%	25.0%
18-29	13.0%	16.0%
30-49	31.0%	32.0%
50-64	14.0%	18.0%
>64	12.0%	8.0%

E.7. Information to be provided for all clinical research studies

This study does not involve a clinical intervention. Subjects who participate in this data-only study will be adult medical plan members ages 40 years and over from each HMO. No gender or racial/ethnic group will be excluded.

E.8. Inclusion of children

This study includes health plan members age 40 years and over. Therefore, no children will be study participants.

Please see the following pages for Targeted/Planned Enrollment Tables.

KPNW table here

HP table here

F. VERTEBRATE ANIMALS

Not applicable.

G. LITERATURE CITED

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Appendix 1. FDA-Approved Bisphosphonates

Generic Name	Product Name	NDC NR number	Form	Route
ALENDRONATE SODIUM	FOSAMAX TAB 10MG #30	00006-0936-31	TABLET	ORAL
ALENDRONATE SODIUM	FOSAMAX TAB 10MG	00006-0936-58	TABLET	ORAL
ALENDRONATE SODIUM	FOSAMAX TAB 10MG UD	00006-0936-28	TABLET	ORAL
ALENDRONATE SODIUM	FOSAMAX TAB 40 MG	00006-0212-31	TABLET	ORAL
ALENDRONATE SODIUM	FOSAMAX TAB 5MG	00006-0925-31	TABLET	ORAL
ALENDRONATE SODIUM	FOSAMAX TAB 5MG	00006-0925-58	TABLET	ORAL
ALENDRONATE SODIUM	FOSAMAX TAB 70MG	00006-0031-44	TABLET	ORAL
ALENDRONATE SODIUM	FOSAMAX TAB 10MG	00006-0936-82	TABLET	ORAL
ALENDRONATE SODIUM	FOSAMAX TAB 35MG	00006-0077-44	TABLET	ORAL
ALENDRONATE SODIUM	FOSAMAX TAB 70MG UD	00006-0031-21	TABLET	ORAL
ALENDRONATE SODIUM	FOSAMAX SOL	00006-3833-34	SOLUTION	ORAL
ETIDRONATE DISODIUM	DIDRONEL 200MG TABLETS	00149-0405-60	TABLET	ORAL
ETIDRONATE DISODIUM	DIDRONEL 400MG TABLET	00149-0406-60	TABLET	ORAL
ETIDRONATE DISODIUM	DIDRONEL IV INJ 50MG/ML UD	58063-0457-01	SOLUTION	IV
IBANDRONATE SODIUM	BONIVA TAB 150MG UD	00004-0186-82	TABLET	ORAL
PAMIDRONATE DISODIUM	AREDIA 30MG VIAL	00083-2601-04	VIAL	INJ
PAMIDRONATE DISODIUM	AREDIA INJ 90MG UD	00083-2609-01	SOLUTION	IV
PAMIDRONATE DISODIUM	AREDIA INJ 60MG UD	00083-2606-01	SOLUTION	IV
PAMIDRONATE DISODIUM	PAMIDRONATE DISODIUM INJ 90MG	55390-0129-01	SOLUTION	IV
PAMIDRONATE DISODIUM	PAMIDRONATE DISODIUM INJ 30MG	55390-0127-01	SOLUTION	IV
PAMIDRONATE DISODIUM	PAMIDRONATE DISODIUM SOL 3MG/ML	63323-0734-10	SOLUTION	IV
RISEDRONATE SODIUM	ACTONEL TAB 30MG	00149-0470-01	TABLET	ORAL
RISEDRONATE SODIUM	ACTONEL TAB 5MG	00149-0471-01	TABLET	ORAL
RISEDRONATE SODIUM	ACTONEL TAB 35MG	00149-0472-01	TABLET	ORAL
RISEDRONATE SODIUM	ACTONEL TAB xxMG	00149-0475-01	TABLET	ORAL
TILUDRONATE DISODIUM	SKELID TAB 200MG	00024-1800-16	TABLET	ORAL
ZOLEDRONIC ACID	ZOMETA INJ 4MG/5ML	0078-0387-25	VIAL	INJ
ZOLEDRONIC ACID	ZOMETA SOL 4MG	00078-0350-84	SOLUTION	IV