A. SPECIFIC AIMS:

Osteonecrosis of the jaws (ONJ) is a morbid condition in which areas of bone in the maxilla or mandible are affected due to disruption of the resorption-remodeling cycle and inhibition of endothelial cell proliferation. Secondary infection of these lesions may lead to further complications, which may include non-healing extraction wounds, more necrosis and pain. ONJ has been considered similar to the condition known as 'phossy jaw' which was common from the1830s until the 1920s in workers who were making matches. Between 1920 and 2000 the condition was sporadic; however, both multiple case-reports and cohort studies have recently suggested an increased incidence of ONJ in relation to a relatively new class of drugs called bisphosphonates (BPs). In the past two years, more than 350 cases of ONJ have been described in patients treated with BPs for cancer metastatic to bone and/or osteoporosis. Neither the true prevalence, nor the risk factors for development of these lesions have been fully investigated. With the number of indications for BP therapy and the number of prescriptions written for BPs constantly increasing, ONJ has mobilized the attention of health care providers, drug manufacturers, general population, legal profession, and media, alike. We propose to study the risk factors for ONJ using the three Dental Practice-Based Research Networks (PEARL, DPBRN, PRECEDENT) and two large health maintenance organizations (Kaiser Permanente and Health Partners) associated with one of the Networks (DPBRN) using a large unmatched case-control study.

The first research goal of the proposed study is to investigate whether there is a greater exposure to BPs in subjects with ONJ compared to subjects without ONJ. The second goal is to determine whether dental disease and/or procedures have an etiologic role in the development of ONJ.

The study hypothesis upon which the sample size is calculated is that in comparison with individuals who do not have ONJ, individuals who develop ONJ will have had a history of greater exposure to BPs. This will be tested using an unmatched case-control study with a selection ratio of 1:3 (180 cases and 540 controls).

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

1. To test the hypothesis that BP treatment is a risk factor for ONJ.

   Rationale: The ONJ cases described in recent cohort studies (some published only as abstracts – see Background) suggest that potency and duration of BP are risk factors for ONJ. However, as most of the patients in these cohort studies were undergoing aggressive therapies for cancer, it is unclear to what extent ONJ is associated with the more aggressive use of BPs, or whether lower potency oral BPs are also a significant risk factor for ONJ in the general population.

2. To test the hypothesis that dental diseases (particularly periodontal disease), and invasive dental procedures such as dental extractions are true risk factors for ONJ.

   Rationale: Dental hygiene instructions and dental treatments have played an important role in the management of ONJ since the 1850s when the condition first occurred in relation to the industry of making matches. Whether or not these factors play any relevant role in the etiology of ONJ has not been established in controlled studies.

In addition to these two aims, on an exploratory basis, we will attempt to study 1) the possibility that ONJ subjects also have more clinically evident necrotic bone lesions in other parts of the

body (such as hip) compared to the controls, 2) the role of additional risk factors such as gender, age, and lifestyle factors (i.e., smoking), and 3) possible exposures such as external beam radiation therapy and chronic steroid therapy on the etiology of ONJ.

N.B.: We recognize that we may or may not have sufficient statistical power for the evaluation of some of these exploratory aims but generating at least preliminary data on these factors in this first trans-PBRN study will be valuable for future studies.

B. BACKGROUND AND SIGNIFICANCE

Jaw bone 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 phosphorus and nicknamed 'phossy jaw'. Currently, various infectious agents in the setting of malnutrition (e.g. noma oris) or immune suppression (e.g. necrotizing stomatitis, aspergilosis, mucormicosis, herpes zoster virus) have been associated with necrotizing oral lesions. A more common etiology for modern osteonecrosis is ionizing radiation: mandibular exposure to > 40 Gray results in high risk of vascular obliteration, subsequent bone ischemia, and death. Due to therapeutic and technological advances, the prevalence of these lesions has been declining.

Recently, an unusually large number of case reports and case series have been described in the literature that appeared to be either spontaneous or dental treatment-precipitated idiopathic ONJ. 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 antiangiogenic properties. It is their effects on bone that make these drugs a prime suspect for the necrotizing processes; however, neither a causal relationship between BP use and ONJ, nor specific mechanisms for the process has been established. In the following paragraphs we will discuss the current literature on BPs, ONJ, and the potential link between them.

B.1. Bisphosphonates

BPs became commonly used in the US in the early 1990's to treat osteolytic conditions associated with cancer (Berenson *et al.*, 1996; Berenson *et al.*, 2002; Body, 2003; Hillner *et al.*, 2003). The number of therapeutic indications has since increased to include Paget's disease, heterotropic ossification, hypercalcemia and osteoporosis (Devogelaer, 2000; Stafford *et al.*, 2004). The efficacy of BPs in treating these diseases has been well-established with studies that have shown significant decreases in cancer-induced skeletal morbidity (Hortobagyi *et al.*, 1996; Ross *et al.*, 2003), and significant increases in bone mineral density in osteopenic patients (Stafford *et al.*, 2004). Thus, the administration of BPs has become standard of care for solid tumor patients with bone metastases, patients suffering from multiple myeloma, and osteoporosis.

Several agents of this class of drugs are available in the US, including alendronate (Fosamax – Merck), etidronate (Didronel – Proctor & Gamble), pamidronate (Aredia/Pamisol - Novartis), risedronate (Actonel - Proctor & Gamble), and zoledronic acid (Zometa - Novartis), and ibandronate (Boniva – Roche). Alendronate and risedronate alone accounted for more than three million prescriptions in 2003, and this number has been steadily increasing (Stafford *et al.*, 2004). 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, the BPs are relatively safe drugs with a very tolerable side effect profile (Berenson *et al.*, 1996; Brumsen *et al.*, 1997; Cramer *et al.*, 2005). Their main action is inhibition of osteoclast-induced bone resorption, which results in decreased osteolysis and increased bone mineral density (Devogelaer, 2000; Rodan and Fleisch, 1996). Both apoptosis and cell necrosis

of osteoclasts have been observed in BP mechanism studies (Sahni *et al.*, 1993). Some reports have also suggested that BPs have antiangiogenic and antitumor effects (Fournier *et al.*, 2002; Santini *et al.*, 2003; Wood *et al.*, 2002). However, the exact molecular mechanism of action for this class drugs remains unclear.

Theoretically the BPs could induce bone necrosis by various pathways: first, inhibition of osteoclast remodeling may result in over-mineralization, which can strangle blood circulation to a specific area of the bone (Najm *et al.*, 2005). Second, antiangiogenic effects may directly impair blood circulation (Fournier *et al.*, 2002; Santini *et al.*, 2003). Finally, direct toxicity of BPs may prevent or destroy vascular formation (Moreira *et al.*, 2005). However, none of these possible mechanisms has been scientifically proven.

B.2. Osteonecrosis

The skeletal system is metabolically active and requires consistent blood circulation (Ardine *et al.*, 2006). However, specific areas, the epiphysis of long bones, in particular, are poorly vascularized and consequently are more prone to necrosis (Assouline-Dayan *et al.*, 2002; Vande Berg *et al.*, 2006). Nevertheless, osteonecrosis is a relatively rare phenomenon and typically occurs with other diseases (Enwonwu *et al.*, 2000; Robin *et al.*, 2005; Sun *et al.*, 2006) or due to iatrogenic factors (Najm *et al.*, 2005; Schwartz, 1982; Talamo *et al.*, 2005; Tarassoff and Csermak, 2003). Most osteonecroses have a well-described cause or association, though a minority remain idiopathic (Assouline-Dayan *et al.*, 2002).

The typical reported case of osteonecrosis involves the femoral head or other long bones in weight-bearing joints and is avascular in origin (Chollet *et al.*, 2005; Moon *et al.*, 2005; Talamo *et al.*, 2005; Vande Berg *et al.*, 2006). The lack of circulation may be induced by infarction or destruction of endothelial cells in areas of bone with no collateral blood supply. Most cases are symptomatic, involve high morbidity and require surgical management (Kim *et al.*, 2006). Recent literature has suggested that treatment with BPs may reduce morbidity and improve revascularization of the necrotic area (Kim *et al.*, 2006).

Diseases commonly associated with bone necrosis include sickle cell anemia, AIDS, blood cancers and various states of hypercoagulation (Badros *et al.*, 2006; Chollet *et al.*, 2005; Lima *et al.*, 2005; Moon *et al.*, 2005; Robin *et al.*, 2005; Sun *et al.*, 2006; Talamo *et al.*, 2005). Autoimmune diseases such as lupus erythematosus and rheumatoid arthritis as well as cases of organ transplantation have also been implicated (Calvo-Alen *et al.*, 2005; Celik *et al.*, 2006; Gebhard and Maibach, 2001), but studies have consistently demonstrated that these necroses were related to corticosteroid treatment and not with the disease itself. Other pharmacological agents associated with osteonecrosis include immune suppressants (Talamo *et al.*, 2005) and multimodal antiretroviral therapies (Reddy *et al.*, 2005). It is interesting to 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 (hence our inclusion of these factors as secondary exploratory aims).

Various infectious agents have been reported in necrotic bone, mostly in immunosuppressed patients. Invasive fungal organisms have been reported to produce wide-spread destruction of boney tissues (Huang *et al.*, 2005) and Gram-negative bacteria (Barasch *et al.*, 2003) have been associated with necrotizing disease. It remained unclear whether the pathogens caused necrosis or they simply colonized the non-vital bone, but most authors accept the role of these microbes in the etiology of the disease; these lesions generally respond well to antimicrobial therapy. Microorganisms like the varicella zoster virus have also induced osteonecrosis in immune competent individuals (Meer *et al.*, 2006; Mendieta *et al.*, 2005), but these are rare

occurrences, and their mechanisms remain obscure. In the proposed study, we will attempt to gather information related to the factors described above in relation to osteonecrosis.

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 jaws 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 (Schwartz, 1982; Studer *et al.*, 2004).

ONJ has been reported in the literature for more than a century. The first cases were associated with phosphorus exposure of industrial workers (Miles, 1972), 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 jaws is with ionizing radiation (Osteo Radio Necrosis – ORN). 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 (Jereczek-Fossa and Orecchia, 2002). The mechanism of ORN consists of gradual vascular obliteration in the affected bone followed by avascular necrosis (Assael, 2004). If the dead bone becomes exposed to the oral microflora, supra-infection adds to the morbidity of the condition. Risks for ORN 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 (Assael, 2004; Jereczek-Fossa and Orecchia, 2002; Niewald *et al.*, 1996). Once established, ORN 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 ORN has been decreasing significantly (Assael, 2004; Studer *et al.*, 2004).

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 (Lima *et al.*, 2005). Conditions like Necrotizing Periodontitis or Necrotizing Stomatitis often produced large boney lesions associated with typical periodontal pathogens. Barasch *et al*., (Barasch *et al.*, 2003) reported jaw necrosis associated with *Pseudomonas aeruginosa* in immunosuppressed patients. Unlike ORN, these lesions responded well to appropriate antibiotic therapy. Schwartz (Schwartz, 1982) described cases of ONJ in cancer patients treated with systemic chemotherapy. Finally, large areas of jaw osteonecrosis were described following VZV reactivation of shingles in the trigeminal nerve (Meer *et al.*, 2006; Mendieta *et al.*, 2005). The postulated mechanism for these lesions was local immune reaction. Co-morbidity from other factors may be required as these lesions are very rare given the large number of VZV carriers.

The first report of jaw osteonecrosis associated with BP treatment (Wang *et al.*, 2003) was published in 2003 and 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 (Rosenberg and Ruggiero, 2003), Marx (Marx, 2003), and Migliorati (Migliorati, 2003) published their respective case series in similar populations. These reports described cancer patients with metastatic bone disease or multiple myeloma who had developed mostly dental treatment-related, but also spontaneous, idiopathic necrotic lesions of their jaw bones. 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 cancer and had been treated with either pamidronate or zoledronic acid, or both. However, in 2004 Ruggiero et al (Ruggiero *et al.*, 2004) reported an additional 63 cases of ONJ, in which there were seven non-cancer patients who had exposure to oral BP alendronate given for osteoporosis.

N.B.: Barasch, Ruggiero and Migliorati are co-investigators of the proposed project.

Following these initial articles, similar reports were published in quick succession (Badros *et al.*, 2006; Bagan *et al.*, 2005; Bamias *et al.*, 2005; Farrugia *et al.*, 2006; Ficarra *et al.*, 2005; Hansen *et al.*, 2006; Hellstein and Marek, 2005; Hoff *et al.*, 2005; Katz, 2005; Lenz *et al.*, 2005; Lugassy *et al.*, 2004; Marx *et al.*, 2005; Melo and Obeid, 2005; Merigo *et al.*, 2005; Vannucchi *et al.*, 2005; Zarychanski *et al.*, 2006), showing ONJ in BP treated patients to be more common than anticipated. The vast majority of these publications were retrospective studies or case series, and few contained meaningful analyses.

Frequency of ONJ in studied populations ranged from less than 1% to over 20% (Badros *et al.*, 2006). No gender 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 patients and longest in those on alendronate (Badros *et al.*, 2006; Bamias *et al.*, 2005; Marx *et al.*, 2005). Development of necrotic lesions was significantly associated with duration of treatment for all BP agents.

Clinically, these lesions appeared similar to ORN, 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 (Farrugia *et al.*, 2006; Marx, 2003; Migliorati, 2003; Zarychanski *et al.*, 2006). Similarly, the response to therapy followed the ORN pattern: surgical debridement, primary closure or antibiotics did not affect significantly the course of the disease and most lesions did not heal (Farrugia *et al.*, 2006; Hoff *et al.*, 2005; Lenz *et al.*, 2005; Zarychanski *et al.*, 2006). Treatment with hyperbaric oxygen was also largely unsuccessful (Badros *et al.*, 2006).

Similarly, a histologic comparison of ONJ from 8 BP-treated patients with specimens from 10 patients diagnosed with ORN (Hansen *et al.*, 2006) yielded many similarities. However, ONJ was characterized by a multicentric, diffuse and patchy appearance, while the ORN was typically larger and uniformly distributed. Interestingly, this study also identified multiple osteoclasts adjacent to areas of bone resorption in both ONJ and ORN. 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.

Generally, the BPs are relatively safe drugs with a very tolerable side effect profile (Berenson *et al.*, 1996; Brumsen *et al.*, 1997; Cramer *et al.*, 2005). Their main action is inhibition of osteoclast-induced bone resorption, which results in decreased osteolysis and increased bone mineral density (Devogelaer, 2000; Rodan and Fleisch, 1996). Both apoptosis and cell necrosis of osteoclasts have been observed in BP mechanism studies (Sahni *et al.*, 1993). Some reports have also suggested that BPs have antiangiogenic and antitumor effects (Fournier *et al.*, 2002; Santini *et al.*, 2003; Wood *et al.*, 2002). However, the exact molecular mechanism of action for this class drugs remains unclear.

B.4. Role of Oral Health on Osteonecrosis: The infectious etiology and the role of oral flora in relation to ONJ suggested by some authors above raise the issue of the potential role of major oral diseases in relation to ONJ. Since the proposed study is conducted within three dental PBRNS using private dental practitioners, we have an ideal setting to gather information on oral health of ONJ cases and controls to carefully evaluate the role of caries, periodontal disease, and the associated risk factors such as smoking in the pathogenesis of ONJ.

B.5. Summary of Epidemiology of ONJ: What is known, uncertain, and unknown?

Descriptive epidemiology: Emerging evidence from 4 studies (Badros *et al.*, 2006; Durie, 2004; Hoff *et al.*, 2005; Van Poznak, 2006) suggests that the risk for ONJ for cancer patients on intravenous BPs is around 0.99 % (95% confidence interval: 0.75%-1.23% - see Figure 1 below). There is a more than 7-fold variability in reported ONJ-risk across the four studies with the industry-sponsored studies reporting a substantially lower risk than non-industry sponsored studies. Industry-sponsored studies currently provide over 95% of the known information on ONJ risk and the factors that may precipitate ONJ.

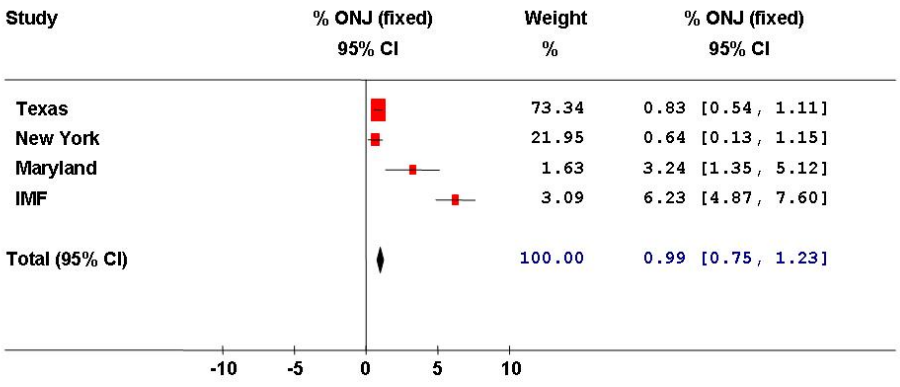
There is currently no similar cohort data available to estimate the ONJ risk for non-cancer patients on oral BPs. Clinicians with expertise in this area have suggested that no risk exists for patients who were on oral BPs for less than 6 months and that risks become measurable once when a patient has been on the medication for 7 years. The magnitude of the ONJ risk in these patients is unknown but has been estimated to be around 1/10,000.

Analytical Epidemiology: ONJ has been associated with the duration of BP treatment and the BP potency which can range from 1 (Etidronate) to 100,000 (zoledronate). The minimum duration subsequent to the start of BP treatments for ONJ to develop has been reported to be 6 months. On average, the mean duration on BP treatments ranged between 1.6 and 4.7 years depending on the BP type reported (zoledronate having a shorter induction time than alendronate).

The underlying disease condition of the BP-treated patient may influence the risk for ONJ development. Two studies reported that multiple myeloma patients have a higher risk for ONJ development than breast cancer patients. Osteoporosis has also been reported to increase ONJ risk.

A consistent finding in all four studies above is that dental problems were associated with ONJ. The most significant underlying disease that was predictive of ONJ is periodontitis. Three out of the four studies reported that dental extractions significantly increased the risk for ONJ. These findings are consistent with historical reports of ‘phossy jaw’ where it was long believed that dental disease was a pre-requisite for the development of necrosis. These beliefs led to the first public health laws where instructions on oral hygiene procedures and access to dental care became part of labor legislation. It has to be emphasized that it is unclear whether indeed dental conditions are a true risk factor for ONJ, or whether the dental diseases/procedures are markers of ONJ.

Fig. 1. ONJ Risk associated with IV-BIS



Weaknesses of current evidence:
The emerging data on ONJ risk are difficult to interpret for the following reasons: (i) most evidence is still only available in abstract form (i.e., no full reports), (ii) dental assessments in these studies were infrequent and of questionable reliability, (iii) the duration of follow-up for a substantial proportion of cohort members was less than the mean induction period, (iv) ONJ definitions have been vague and may only represent end-stage disease, and (v) miscellaneous reasons such as the potential conflict of interest of the authors. These different weaknesses are not explored in the published literature and below we attempt to expand on these.

(i) Most evidence is still only available in abstract form (i.e., no full reports): Currently, over 98% of the available evidence on the link between BPs and ONJ is given only in the form of abstracts or web-based reports. The extent to which the statistics reported in these abstracts will change as the final reports are published is unknown.

(ii) Dental assessments were infrequent and of questionable reliability: There seems to be uniform agreement across the 4 reports above that "dental problems" have the potential to play a significant role in the development of ONJ. Yet, the dental examinations in all studies were infrequent and the qualifications of the examiners were unreported. In two studies, only 7% and 26% of the known exposed patients received a dental exam. In the web-based survey, self-reports rather than examinations formed the basis for characterization of dental problems. Finally, in the largest cohort study, it was only specified that charts were reviewed and it was unclear whether these were dental or medical charts, whether examinations and diagnoses were performed by medical or dental personnel. Most importantly, none of the studies have attempted to establish a timeline of events to determine whether the "dental problems" are the early symptoms of ONJ or whether the "dental problems" truly reflect independent causal risk factors that precipitate the ONJ. In particular, information on the presence of periodontitis prior to the onset of BP therapy, the presence of possible osteonecrosis symptoms such as pain that caused a dentist to extract (rather than the opposite), remains elusive. In this trans-PBRN study, cases and controls are coming from the offices of the dental practitioners allowing us to recreate the dental history for each subject using the dental records within each practice.

N.B.: We admit that there is some degree of variability in the information recorded by different practices. However, this 'real world' situation still allows us to gather data on major factors such as what procedure was performed when and to obtain a general estimate of the amount of various dental diseases present at different time points.

(iii) The duration of follow-up for a substantial proportion of cohort members was less than the mean induction period: Since the risk for ONJ is a function of the duration of the BP treatment,

reports of the risk of ONJ without information on the duration of follow-up is of limited value. The one percent ONJ risk currently reported may only reflect the risk for early-onset disease.

(iv) ONJ definitions have been vague and may only reflect end-stage disease: It has been reported that ONJ is a disease with a complex natural history. The initial stages of ONJ may include symptoms such as tingling, a feeling of a heavy jaw, or pain. It has also been reported that the natural history of ONJ includes symptoms such as loose teeth, suppuration, and symptoms of periodontitis. Due to the low availability of dental examinations in these cohorts, the epidemiology of these ONJ symptoms is not known. A more comprehensive case-definition may lead to higher estimates of ONJ risk.

(v) Miscellaneous concerns: Over 95% of the current evidence is reported by Novartis-funded studies (manufacturer of two BPs). The extent to which this sponsorship, as well as the definitions used in these studies (ONJ defined as having > 3 months of exposed bone) influenced the results of the studies is unclear.

In summary, there is a critical need to evaluate the risk factors for ONJ using a well-designed, adequately powered, properly executed, epidemiological investigation. This trans-PBRN study is aimed at that need. The unique setting and the diverse expertise available in the 3 PBRNs will lead to a high quality study that will also be evaluated and interpreted in an unbiased manner without any 'conflicts of interest'.

C. PRELIMINARY STUDIES:

C.1. Prevalence of Osteonecrosis in the 3 dental PBRNs

The first step in assessing the feasibility of the proposed study was to obtain an estimate of the number of cases seen by members of the three NIDCR-funded dental PBRNs. Since cases are relatively rare and are typically quite memorable to practitioners, it was felt that this anonymous survey would provide an estimate, although not validated, on cases of osteonecrosis of the jaws seen by members of the three dental PBRNs.

Two questions were posed to practitioners, who were asked to respond anonymously and without obligations to participate in the future clinical investigation. The questions were:

1. How many cases of osteonecrosis of the jaw have you seen in your patients over the past two years?
   - A) None
   - B) One
   - C) Two
   - D) Three
   - E) Four
   - F) Five or more
2. If you have seen one or more cases, how many were associated with the following dental conditions?
   - A) Tooth extraction (0 to 5 or more)
   - B) Periodontal disease/treatment (0 to 5 or more)
   - C) Trauma (0 to 5 or more)
   - D) Mandibular exostosis (0 to 5 or more)
   - E) Denture trauma
   - F) Other (description _____)

Table 1 contains data from this survey.

Table 1. ONJ Responses from the three dental PBRNs

	PEARL[1]	NWPRECEDENT[2]	DPBRN[3]	Total

Responses	88	116	309	513
ONJ cases	**39**	**21**	**99**	**159**
				0
Extraction	16	11	58	85
Perio disease	3	4	9	16
Trauma	0	0	14	14
Exostosis	3	2	4	9
Denture	1	1	4	6
Other	16	8	10	34

[1]Practitioners Engaged in Applied Research & Learning
[2]Northwest Practice-based Research Collaborative in Evidence-based Dentistry
[3]Dental Practice-Based Research Network

As seen in the Table 1 above, as of April 26, 2006, we have potential access to 159 cases of ONJ among the three PBRNs. These numbers continue to go up as some PBRNs are still receiving responses from their members. The 21 cases identified by PRECEDENT come from 116 PRECEDENT practitioners who are considered active members (have undergone training and/or participated in the annual meeting). They plan to offer participation to an additional 85 practitioners who signed up on their web site, but who have not as yet gone through training. Applying similar percentages to those practitioners, PRECEDENT would expect to identify approximately 15 more cases (for budgetary and planning purposes PRECEDENT used 35 cases as the expected number to be enrolled).
Additional patients are available for entry into the study from large clinical practices. Dr. Sal Ruggiero (PEARL Network) independently reported another 152 cases of osteonecrosis due to BPs and radiotherapy that were seen in a multi-clinician practice (Long Island Jewish Medical Center). In addition, the two HMOs have also access to a large number of cases as described below.

C.2. Prevalence of Osteonecrosis and Bisphosphonate Dispensing in Kaiser Permanente Northwest (KPNW) and Health Partners (HP)

At each HMO, a cohort of 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 of osteonecrosis: 733.4, 733.40, 733.45, 733.99, 526.4, 526.5, 909.2, and 909.3. We also obtained outpatient 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 ON diagnoses. We used the longer time period to capture potential long-term exposure in past years. The results are presented in Table 2, and include separate estimates for individuals with medical plan membership only and the subset of members with both medical and dental plan membership.

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 2. 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 BPs in the last five years, while over 4,600 (4.1%) of medical plus dental plan members received BPs. Additional analyses of 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 suggests we will be able to identify sufficient numbers cases.

Table 2. 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 ON 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 ON 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).

We conducted a brief chart review (both dental and medical) for 20 members with at least one potential ON diagnosis and BP exposure. Nine of the 20 patients were medical and dental plan members. Medical charts were conducted online and we looked for references for the jaw or other osteonecrosis (ON) in a brief description field noting the reason for the visit. Three (3) ONJ cases (15% of 20 cases) were identified from the medical charts, yet a more thorough review may have found additional cases. All three, however, were also dental plan members. The dental charts were not readily available for the three cases (the charts were out at the clinics at the time of the review). For patients with both medical and dental coverage, and with both pharmacy data on BP and ICD-9 codes, chart reviews showed three of nine (33%) patients had confirmed ONJ. One additional case was indeterminate for ONJ and would be a candidate for wider research team review. These results understate the likely number of confirmed ONJ cases among KPNW dental patients, since we required two years of continuous membership and only included ONJ documented since 2004. We did not review charts for potential ONJ cases with no BP exposure.

N.B.: We will use these two HMOs to validate the BP exposure data using a method similar to the one described above. We are aware of the fact that the proposed validation will not be based on a random subset of the study subjects, rather, a group selected on the basis of having HMO records. This approach however is better than not validating the exposure data at all.

Based upon these preliminary data, if we assume KP and HP could identify 70 confirmed ONJ cases and recruit 54 (80%), together, the three PBRNs can expect to identify at least 221 cases of ONJ diagnosed within the past two years. Speculating that only 80% of available cases will provide consent or be alive, we will have over 176 available cases for the study. Given that this cautious estimate from preliminary attempts at case identification are within 90% of our goal, we fully expect that a systematic and exhaustive approach to identification and recruitment will result in more than 176 participating subjects with ONJ. In the unlikely event that there are still fewer than 176 cases, it would be a simple matter of relaxing the inclusion criteria by allowing

cases of ONJ diagnosed within the past 3 years. Because BPs have been in use for over 10 years and the diagnostic criteria for ONJ are stable, this would minimally impact characteristics of the patient data while significantly increasing the number of available cases. Relaxing this criterion for KP and HP alone would result in approximately 25 additional cases, easily raising the total above the 176 required for adequate statistical power.

D. RESEARCH DESIGN:

D.1. Overall Study Design: A case-control study is proposed to evaluate the risk factors for ONJ. The study flow is summarized in Figure 2 below. The first analytic aim is to identify the etiological risk factors for ONJ. These include BPs, dental, life style-related, and other factors such as radiation or steroid therapy. All the patients with ONJ identified from the PBRNs and HMOs (cases with a link to a PBRN office) will be recruited to identify risk factors. Cases will be 40 years and older, identified by a dentist of the PBRN, and have been diagnosed by the dentist or a specialist as having ONJ with an onset between January 2003 to present. Independent adjudicators from each PBRN will evaluate each reported case using prespecified criteria (Appendix 1) to minimize variability in case definition. Each case will have three controls from the same practice/dentist that generated the case (in other words, if the controls had developed ONJ, they would have navigated the pathway navigated by cases and end up in the same dental practice) . The dentist or a UAB research assistant will summarize the relevant dental treatment history and provide a dental disease diagnosis history from January 2000 until diagnosis of ONJ for cases and until recruitment for controls. The dentist or a UAB research assistant will sign the CRF document attesting to data abstraction validity. We expect to enroll 176 cases and 528 controls yielding adequate power to assess our major hypotheses.

D.2. Eligibility and Recruitment of Cases and Controls: Cases will be identified through the dentists that elected to participate in the ONJ study. An introductory postcard for the ONJ study will be sent to potential practitioner-investigators (Appendix 2). A letter will be sent to all PBRN dentists and dentists of subjects identified through the two HMOs inviting them to participate in the study (Appendix 3). The letter will also be sent to all other Alabama dentists, not yet enrolled in the DPBRN, whose specialty is not pediatrics, orthodontics and pathology. If these dentists have ONJ cases and would like to participate in the present study, they may choose to become DPBRN investigators if they are not already, or select option (b) below. This first letter will emphasize the need to identify potential ONJ cases in their practice and provide a description of what will be expected of them if they elect to participate. The letter will contain a detailed description of both the prodromal and clinical symptoms of ONJ. The letter will be mailed up to three times, three weeks apart, in order to maximize dentist recruitment in the study. If agreeing to participate, dentists will have two options:

Option a. The dentists could become DPBRN investigators if they are not already and participate in subsequent phases of the study, such as obtaining patient consent and data collection. The dentists' task will consist of the identification of potential cases of ONJ and, with the help of the coordinating center of the respective PBRN, identify a sample of their patients from which to select controls (individuals without ONJ).

Option b. The dentists will only contact the patient to ask that patient if he or she would allow further contact by a UAB investigator/research assistant. The UAB research assistant will then request the patient's consent to participate in the study. Following description of the project by telephone, the UAB research assistant will mail the potential participant an informed consent form and request that the participant sign this form and mail it back to the UAB research assistant. Following receipt of this signed informed consent, the UAB research assistant will abstract data from that patient's records.

For each case, three controls will be randomly sampled from the practice that generated the case. These will be patients of 40 years or older and will be matched with the case on their status in the practice as either *Active* or *Inactive*. For this purpose, an *Active* patient is one who is considered a "patient of record" at the practice and has a chart on file. If the practice

maintains a separate set of charts of inactive patients that have been purged from the regular files, then the patients with purged charts will not be considered *Active* patients for purposes of this study. It is understood that different practices use different criteria for selecting charts to be purged. The critical point is that the same definition of *Active* patient be used for both cases and controls within each practice. If the case is a patient of record, then the controls will be randomly sampled from the population of patients of record. If the case is not a patient of record, the controls will be sampled from appointments made by patients who are not patients of record. This procedure is designed to capture the population of persons who are not patients of record but would have been identified in the practice as an ONJ case if they had developed ONJ.

Sampling from Patients of Record. A systematic random sampling procedure will be applied. A staff member at the practice will identify the set of patients of record, which will be the sampling frame, and will report the number of these charts to the data coordinating center for their network. The coordinating center will then provide the practice or the PBRN staff (if the dentists chose not to become an investigator) with a random starting number (N) and a sampling interval (S), based on the number of charts. For example, if the practice reports that it has 1520 *Active* patient charts and the coordinating center provides a starting number of 890 and a sampling interval of 50. Then the patient charts selected would be numbers 890, 940, 990, etc. Initially, patients would be sampled in this order until 3 eligible patients are identified. These 3 patients would be mailed a study packet. If there is no response after one week, the patient will receive a phone call from the practice to ask if s/he is interested in participating. If there are negative responses, then additional patients will be sampled and mailed study packets until 3 controls are enrolled. If the end of the patient list is reached then the numbering would continue from the first chart (for example, in the above example, patient number 1490 would be followed by patient number 20, which is 1490 + 50 – 1520). If electronic records are used, then sampling may be performed from an electronic list of patients rather than paper charts. The ordering of the charts may be alphabetical, numerical by patient ID #, or by any other criterion.

Patient #	**1**	**2**	**3**	•	•	•	**890**	**891**	**892**	•	•	•	**940**	**941**	**942**	•	•	•	**990**	**991**	**992**	•	•	•
Order of Selection							**1**						**2**						**3**					

Sampling from Patient Visits by Inactive Patients. If the case is not a patient of record at the practice, then controls will be sampled using systematic random sampling applied to patient visits. The coordinating center will provide the practice with a randomly determined starting date and starting time. At the assigned time on the start date, the clinic staff would begin a log of patients seen in the clinic who are not patients of record at the practice. The patients would be entered into this log in the order they are identified by the staff. The first three of these patients who satisfy the criteria will be approached about participating in the study and will be given a study packet to take home. If there is no response from one of these patients after one week, the patient will receive a phone call from the practice to ask if s/he is interested in participating. If there are negative responses, then additional patients will be selected consecutively from the patient visit log until 3 controls are enrolled. The patient log will be used as in the illustration below to keep track of patients who have been selected, which have received study packets and the responses. If an error is discovered, such as a patient initially thought to be inactive being later determined to be a patient of record, then the entry for that patient would be corrected and that patient would not be enrolled in the study (but if the patient had already returned the signed consent form before the error is discovered, then it is necessary to keep them in the study).

Illustration of the Patient Log for Inactive Patients
(Start Date: 02/08/07, Start Time: 11:00 AM)

Patient #	Date of Visit	Time	Inactive Patient?	Age 40 years or greater?	Date patient given study packet	Date of follow-up phone call	Patient con-sented?	Notes
1	02/08/07	1:30	Yes	Yes	02/08/07	02/15/07	No	Declined on phone
2	02/08/07	3:15	Yes	Yes	02/08/07	NA	Yes	Returned form 02/17/07
3	02/09/07	9:00	Yes	Yes	02/09/07	02/16/07		No response
4	02/11/07	10:00	Yes	Yes	02/16/07	NA	Yes	Returned form 02/20/07
5	02/15/07	9:00	Yes	Yes	02/16/07	02/23/07	Yes	Returned form 02/24/07
6	02/18/07	8:30	Yes	Yes	02/18/07			

An important responsibility will be to help reconstruct the dental treatment history and dental disease history from the date of diagnosis of ONJ or the current date, for cases and controls, respectively, going a minimum of 3 years back. A clinical research coordinator from each PBRN will assist the dentist or his/her designated person with this activity using data collection forms. This will include contacting specialists whom the patient was referred to during the a minimum 3 years prior to the index date or dentists that provided care for the patient during this period. The dentists will be given the option to fill the data collection form themselves, delegate this task to an office administrator/hygienist, or grant access to the records to a PBRN researcher who will abstract the data. Either way, the dentist will be ultimately responsible for data accuracy and completeness and will sign the certification on the form.

The dentists who choose to participate in the ONJ study and their patients will form the sampling population on which the ONJ case-control study will be based. The dentist population will include both dentists from the PBRNs, dentists from the HMOs as well as dentists from Alabama and Mississippi who identified ONJ cases and chose to participate in the study under Option b. All dentists will receive a second letter (Appendix 4), by mail or delivered in person by the research assistant, instructing them how to identify subjects seen under their care after January 2003 that may have been a potential case of ONJ. Since dentists may refer potential ONJ cases to specialists, and since dentists may refer cases with unusual symptoms such as tingling of the jaw, they will be provided with a list of symptoms that may be prodromal to ONJ. Given the signature characteristics of ONJ and the substantial attention given by professional organizations to this condition, it is anticipated that memory recall by the dentists will be good. The extent to which the recall by dentists is accurate in identifying all cases, the sensitivity and the specificity of the recall will be assessed in the HMOs by comparing dentists' recall of cases with a computerized database of diagnoses at the HMOs.

Upon receiving the contact information of the cases and the location of the practices of the dental provider who identified the cases, the primary task of the PBRN is to start the process of control selection. The PBRN Coordinating Center (each PBRN has its own Coordinating Center) will subsequently contact the participating dental offices and make an appointment with a hygienist/office manager to provide instructions over the phone to randomly select control charts. Control selection will be done by the PBRN staff for those dentists who chose this option. The first three of these patients are provided the same letter as the ONJ cases and invited to participate in the study (Appendix 5). If the patient elects not to participate, the next potential control will be approached.

PBRNs will then contact the identified cases and controls in order to obtain permission to send the consent form by mail. The primary aim of the consent form will be to allow the PBRN to collect dental and medical information and conduct a telephone interview. Since the dentist is the primary dental care provider to the patient, s/he is allowed to contact previous dentists and specialists and the patient's permission will be obtained to transfer this information to the PBRNs. One week after the letter is sent to the patient; the dentist will call the patient and ask if s/he has any questions that the dentist can answer. We have no estimates available of the anticipated participation rates of cases.

Key Study Steps: December 2006- September 2007

Recruitment letter to 3 PBRN + HMO dentists; invitation to participate in ONJ Study

December 2006: Letter +email +phone contact with the following information to PBRN members:
Describe goal of study (risk factors for ONJ).
A detailed description of what a potential ONJ case may have looked like in their practice.
Brief description of what will be expected if they participate

- Contact patients with and without ONJ (typically 4-8 patients/dentist)
- Help reconstruct a dental treatment and disease history since 2000/contact specialists in care of patients.
- If dentist agrees to participate, he/she provides approximate number of patents under their care.

Instruction Letter for Case-identification and control selection to PBRN dentists who agree to participate in ONJ Study.

November 2006: Letter contains instructions for case identification.
Identify any POTENTIAL case in practice (exposed bone, paresthesias, unexplained pain, heavy Jaw) over the last 2 years.
If potential case was referred, contact specialist and determine outcome/diagnosis.
Determine how many potential cases satisfy entry study criteria: exposed bone after Jan. 2003 + age > 40
Select controls: Phone instructions to systematically sample control patients for dentists that generated cases.

Dental History and Patient Interview data collection for case/control.

January 2007- June 2007
Dentist contacts cases/controls by phone to obtain permission for study personnel to contact him/her.
After permission from patient is obtained, the dentist reconstructs a minimum of 3-year dental history and provides contact information to study personnel.

Data Analysis using Logistic Regression Models

August 2007- September 2007 (if behind schedule, no cost extension will be requested).
Estimate risk for ONJ associated with the exposures.
Estimate ONJ prevalence in HMO.
Report and manuscript writing.

Upon consent by the patient, the dentist, his/her designee or a PBRN researcher reconstructs the dental history since January 2000 on the provided form (Appendix 6). The dental history will focus on the following treatment procedures; extractions, delivery of partial or complete dentures, periodontal surgical procedures or scaling, implants, and root canal therapy. The following diagnoses will be abstracted from the chart as well; periodontitis (AAP Type I, II, III,

IV), occurrence of traumatic accidents (burns, soft tissue injury by patient), mandibular and maxillary exostoses, and level of oral hygiene by patients.

Due to the substantial geographical spread of subjects across the three networks, in-person interviews of cases and controls will not be possible. Instead, standardized phone interviews will be conducted by a research assistant at each office (see Appendix 7 patient ONJ interview document). These phone interviews will collect information on lifestyle factors, medication usage, and medical history using the methods described below.

D.3. Interview and Dental record review data: Chart abstraction and patient interviews [Appendices 5 and 6] will be performed by trained personnel. Collecting information from charts and patient interviews involves: 1) precise formulation of the questions to answer; 2) use of exact semantics in asking the question; 3) extensive clinical help and other documentation for the chart abstractors; 4) a software package that expedites data entry and editing and produces quality reports; 5) pilot tests with iterative cycles of improvement; 6) thorough abstractor and interviewer training; and 7) data quality monitoring throughout the process.

Variables captured in interviews and abstraction will include all data required to meet the study's specific aims. Our tools will be developed and pilot-tested prior to implementation in order to ensure high quality data collection. Abstractors will be trained and certified following standard protocols, and will travel to the site for on-site abstraction, if needed. There will be ongoing quality control via re-abstraction of at least 5% of charts, with measurement of inter- and intra-rater reliability, and retraining of abstractors, as necessary. After these data are transferred to the PBRN Coordinating Centers, additional editing checks will be done and analyses files created.

We will use a written case report form (CRF) developed to capture dental procedures and diagnoses during the 'induction period' prior to the diagnosis of ONJ (or within a comparable time period prior to the date of interview for controls) (Appendices 5 and 6).

N.B.: Upon NIH approval, these forms will be further refined and pilot tested prior to study initiation.

D.4. Research office audit visits: Consistent with Good Clinical Practice guidelines (GCPs), a proportion of research office sites will be visited by the Clinical Research Associate assigned to the study by each dental PBRN. During the year, approximately 10% of all offices will be visited and a comprehensive quality assurance audit will be performed on all study documents. An additional 10% study visits have been budgeted to account for sites that may recruit multiple cases and controls, and those sites for which further data verification is required.

D.5. Eligibility Criteria / Operational Definitions:

Cases: The following objective criteria will be used for the diagnosis of ONJ: Non-healing exposed bone lesion of any size in the mandible or maxilla that appears necrotic and is resistant to treatment. In order for a case to be eligible for the study, the onset of ONJ will have to have occurred after January, 2003. It is anticipated that this date of ONJ onset can be anywhere between January, 2003 and the day we contact the dental practice. The eligibility criteria for the selection of cases would be any case that is identified from the records of the dental offices of the participating dentists who are alive at the time of the case ascertainment. Those who are unable to provide prescription information due to cognitive impairment etc. will be excluded. This may bias the study estimates and the extent of this selection bias will be evaluated by comparing the available data from non-participating cases to participating cases.

Validation of Cases: Cases identified within each practice will be reviewed by an oral medicine/perio expert (adjudicators) within each PBRN (Ship for PEARL, Barasch for DPBRN and Hujoel for PRECEDENT) using the following pre-specified criteria. If there is a discrepancy between the dentist and patient self-report on *any* of these criteria, the case will be identified for review by the TRANS-PBRN network. Three clinicians (one from each network) will discuss the discrepancies over the telephone, consider the need for additional information, and come to a consensus decision whether the case qualifies for the study. Human subject approval and patient consent for re-contacting of patients will be requested. Decision for re-contacting of patient and/or clinicians for clarifying information will be decided at the time of this conference call. The panel will be blinded towards the history of bisphosphonates use, radiation exposures, or other hypothesized causes of ONJ. If the explanations provided by the patient and the clinician are consistent and explain the discrepancies observed, the case will be accepted. If no satisfactory explanation for the discrepancies can be identified, the case will be considered ineligible. Cases deemed ineligible by the TRANS-PBRN panel will be excluded from the study. Any cases identified by clinicians in the network that do not pass the entry criteria for this study will be similarly excluded from the study (ineligible as a control).

Controls: Subjects who do not have ONJ based on the above criteria, do not have suspicious ONJ and who are randomly selected from the practices that generated the cases as described earlier will be selected as controls. A patient will be eligible as a control if he/she presented for a visit to the office after January, 2003 and is older than 40 years. A log of the number of controls refusing participation into the study will be kept. For each confirmed control, a date will be randomly selected by the coordinating center between January, 2003 and the visit to the office. This will be the reference date for the controls, and the dentist will be asked to do a chart review for a minimum of 3 years prior to the reference date.

D6. Exposure Definitions: The primary exposure of interest is exposure to BPs, with secondary exposures being oral health and dental treatment, external beam radiation therapy to the head and neck region, and chronic steroid use. Duration, frequency, and dose and dose scheduling of each exposure and the specific details of the exposure (i.e., details of the condition it was used for, type of BP used, etc.,) will be collected using the telephone interview and validated using medical records and HMO reimbursement data.

D.7. Potential Confounding Factors or Co-Variates: As with any study of this type it is important to identify the important covariates and potential confounders to thoroughly explore the relationship between BP exposure and ONJ. Precisely because BPs are prescribed for relatively few indications, all of which are related to bone pathology it may prove difficult to separate the effect of BP exposure from the underlying medical condition. Furthermore, the covariates indicative of underlying disease may well contribute causally to ONJ, indicating that they are not, strictly speaking, confounders.

We have identified a list of what we predict to be the most important covariates which can be divided roughly into three categories. The first are general indicators of health and demographics. Age will be collected as standard demographic data along with gender. BMI will be collected as part of the standard medical data. Alcohol use will be defined as beverage equivalents consumed per day (BVE; 12 oz. of beer, 5-6 oz. of wine, 1.5 oz. hard liquor). Smoking exposure will be quantified by packs per day, current smoking status and when the patient began and stopped smoking.

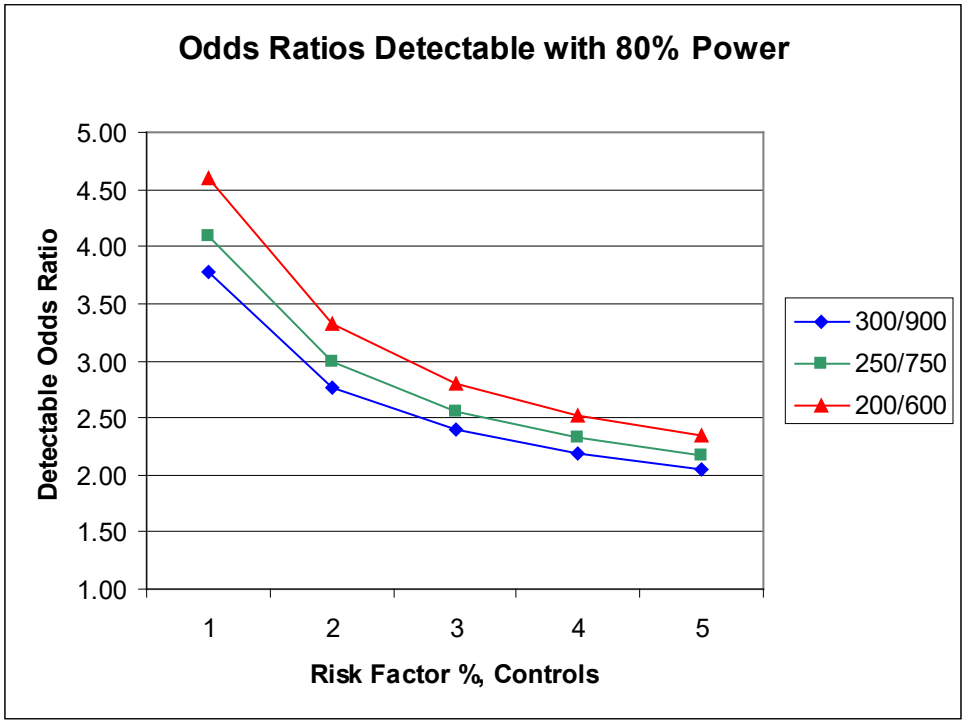
The second category consists of co-morbidities that may help predispose to ONJ in themselves and which may also be indications for BP therapy. These include cancers with propensities for bony metastases, osteopenia/ osteoporosis, sickle cell disease, blood dyscrasias,

coagulopathies, diabetes, hypertension, or immune suppression as indicated by infection with aspergillus, cryptococcus, pseudomonas, or clostridia species. The third category consists of specific treatments other than BPs which may also be risk factors for ONJ.

D.8. Sample Size and Power: We calculated power under different sample sizes and exposure frequencies, based on two-sided chi-square tests, at the 95% confidence level, using the nQuery Advisor version 6.0 software. This is a conservative analysis classifying subjects as to whether or not they were exposed to BP with no additional information about total exposure. This analysis assumes the use of 3 controls per case. The magnitude of the odds ratio that would be detectable with 80% power was calculated using sample sizes of 176 cases and 528 controls, which is the number of cases and controls that are expected based on preliminary investigation. Precision of the study was also estimated assuming 150 cases and 450 controls, and assuming 200 cases and 600 controls. Detectable odds ratios were calculated assuming exposure frequency of 1% to 5% among the controls. Note that power estimation for 1% is less reliable than for the higher exposure frequency due to questionable validity of the normal approximation for this exposure prevalence at this sample size.

With sample sizes of 176 cases and 528 controls, the study would provide approximately 80% power to detect odds ratios of 4.99, 3.52, 2.96, 2.67 and 2.47 for exposure frequencies of 1%, 2%, 3%, 4% and 5% among the controls, respectively. With 150 cases and 450 controls, the study would provide approximately 80% power to detect odds ratios of 5.43, 3.80, 3.16, 2.85 and 2.62 for exposure frequencies of 1%, 2%, 3%, 4% and 5% among the controls, respectively. With 200 cases and 600 controls, the study would provide approximately 80% power to detect odds ratios of 4.60, 3.32, 2.80, 2.52 and 2.35 for exposure frequencies of 1%, 2%, 3%, 4% and 5% among the controls, respectively. These values are illustrated in the Figure 4 below.

Figure 4



Based on our preliminary data, we are confident that this trans-PBRN study will have sufficient power with the available cases within the three PBRNs and their associated HMOs and specialized practices.

D.9. Data Validation: Data on case-control status, exposure information, and co-variates need to be validated. Case status will be validated using the adjudicators as described earlier. Exposure data will be validated by comparing the questionnaire data to the data abstracted from medical records and insurance claims data (only for the HMO participants). Another option is to obtain medical records of all subjects. If this proves to be a difficult task, we will resort to the HMO data using the methods described under preliminary studies. Secondary validation of data using the reimbursement claims will only also be restricted to the subjects coming from the two HMOs. Interviewers within each PBRN will be trained prior to the data collection with the help of the three coordinating centers. Draft data questionnaire is given in Appendix 7.

D.10. Data Coordination: Each of the NIDCR supported dental PBRNs has its own coordinating center and has developed its own protocols for the collection, tracking, and quality assurance of data from their own studies. Each system has been constructed tailored to the available resources of the participating institutions and the types of dental practices that will contribute to the studies. This trans-PBRN study will take advantage of these existing systems by requiring each PBRN, through its coordinating center, to be responsible for the collection and management of the data originating from practices within their respective networks.

Care will be taken to ensure that data gathered from the individual PBRNs can be merged for the final analysis. To this end data collection instruments and protocols will be developed in common across all three PBRNs with the expectation that minor modifications may have to be made to the common instruments and protocols to accommodate the networks' specific requirements. Each network's final data collection instruments will be subjected to the curation process to identify the common data elements thereby allowing the integration of data across networks (the three PBRNs have undergone training at NIH on data curation and common data elements).
Initial quality assurance and data analysis will be carried out within each network using its own data. The tasks of generating data reports and analysis using data from all the networks will be divided among the three coordinating centers of the PBRNs. The final analysis will be done using the integrated data sets from all networks and by using meta-analytic approaches which will combine the results from analysis done on each network's data. This will allow for informative comparisons of the overall results with those from each network.

D.11. Data analysis: This study will utilize a case-control design with three controls per case. These controls will be selected from the set of practices from which cases were identified. Univariate analysis will be used for the preparation of data summaries.

The primary analytic method that will be used to address the two specific aims of this study will be multiple logistic regression. The measure of association between the potential risk factors and ONJ will be the adjusted odds ratio. The odds ratios will be adjusted for potentially confounding demographic factors including age, race and gender, as well as other confounding variables that may be identified in preliminary analyses (we did not design a matched case-control study purposely in order to capture the maximum number of potential risk factors. Over matching could have masked some of the more subtle associations). 95% confidence intervals will be calculated for each reported odds ratio. Secondary analyses will be conducted to evaluate whether there are significant differences in the characteristics of the two groups of control subjects, and whether use of the different control subjects substantially alters the results of the analysis. Given the large number of potentially significant covariates, propensity scoring approaches may be pursued to control for the expected strong association between BP exposure and the conditions for which BPs are prescribed. This may depend both on how many cases are identified and how many covariates are ultimately found to be significant individual

predictors of ONJ. Recent literature suggests that propensity scoring reduces the bias when the number of cases per covariate is less than 7 (Calvo-Alen *et al.*, 2005).

For Specific Aim 1, the statistical test that will be of primary interest is the test for a main effect of BP, adjusted for potentially confounding variables. Model selection will be hierarchical proceeding by roughly three categories of covariates: 1) General indicators of health and demographics, 2) Co-morbidities possibly linked to BP use or ONJ, and 3) treatments other than BPs possibly linked to ONJ.

Specific Aim 2 will be addressed using multiple logistic models, in which ONJ risk factors other than BP use are added to a model including BP. These risk factors will include dental disease, dental procedures, radiation use, steroid use, systemic factors and presence of local infection. The statistical tests that will be of primary interest will be those for the main effects of the additional risk factors, adjusted for BP use. There will be several definitions of bisphosphonates use that will be employed in the analysis. The primary analysis will be based on a 3-level categorization of bisphosphonates use: (1) no reported utilization of bisphosphonates, (2) utilization of intravenous bisphosphonates and potential prior use of oral bisphosphonates), and (3) utilization of oral bisphosphonates only.

A secondary analysis will focus on both the duration of bisphosphonates usage and the potency of the bisphosphonates. The primary outcome variable in this analysis will be the summation of the product of the potency, the duration, and the dosage of the bisphosphonates a patient was exposed to. For instance, if a patient was on Clodronate for 2 years at 2400 mg per day, and was subsequently treated with 8 mg of zoldronate every 4 weeks for a period of 6 months, the exposure will be 2400 * 730 * 10 + 8 * 10000 * 6 or 18 million. This secondary analysis may be biased because one of the many assumptions it is based upon is that the risk for ONJ is linearly related to the multiplication of the dose*potency *duration (much like cigarette pack/years). Such approaches are known to lead potentially to biases since the relationship may be different from a multiplicative one. Therefore, the secondary analysis proposed here represents the initial exploration as to how dose, potency, and duration of bisphosphonates use influences the risk of ONJ development.

Potency

- **Non-nitrogenous** Non-*N*-containing bisphosphonates:
  - Etidronate (Didronel®) - 1 (potency relative to that of etidronate)
  - Clodronate (Bonefos®, Loron®) - 10
  - Tiludronate (Skelid®) - 10

- **Nitrogenous** *N*-containing bisphosphonates:
  - Pamidronate (APD, Aredia®) - 100
  - Neridronate - 100
  - Olpadronate - 500
  - Alendronate (Fosamax®) - 500
  - Ibandronate (Bondronat®) - 1000
  - Risedronate (Actonel®) - 2000
  - Zoldronate (Zometa®) - 10000

Alternative models and functional relationships will be explored and the model which fits best to the data will be selected. A most generic approach is to model the dose and the potency and the duration of use as three separate explanatory variables.

The data from the three PBRNs will be combined for the primary analysis and the primary structure for data analysis will be a conditional logistic regression model where cases and controls are matched on dental practices, and where each of the centers will be modeled as a fixed effect.

D.12. Missing Data: Missing data is a common problem to which careful thought must be given. The careful use of quality assurance procedures will minimize the quantity of missing data. Because data in this study will come from interviews and medical and dental record abstractions it is likely that some data will be missing despite extensive efforts and care. The most conservative approach would be to exclude subjects with incomplete data from the analysis. Depending on the prevalence of the missing data the resulting loss of information may not be tolerable. In any case, participants with missing data will be compared to those without to check for obvious differences in distributions then a number of techniques will be used. Analytic methods appropriate for the missing data mechanism (missing completely at random, missing at random, or missing not at random/non-ignorable) (Little, 1983a; Little, 1983b; Little, 1987; Vach, 1993) will be explored. Where appropriate multiple imputation techniques will be performed and sensitivity analyses conducted to assess robustness of results to different assumptions. All resulting datasets released will include both base and imputed data with clear documentation and suggestions of appropriate analytic methods for imputed data.

D.13. Timeline for the Proposed Study:

Study will be initiated in January 1, 2007 and expected to last 1 year. Key steps in the study and the proposed time frame for each step were given earlier in Fig 2. The following table summarizes these events.

	Month											
Activities	Dec 06	Jan 07	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov
Recruitment letter, email, call to PBRN members												
Instruction letter for case-identification/control selection												
Dental risk factor collection for case / controls												
Medical & Lifestyle risk factor collection												
Data Analysis using logistic regression models & Reporting												

*N.B.:In the likely event that the study activities will fall behind schedule due to the complex setting and the large numbers of practices involved in the study, we will request a no-cost extension for an additional year to complete the study as planned***.**

D.14. Limitations and Alternative Approaches:

There are certain limitations to the proposed approach. While recognizing these at the outset, we have attempted to develop alternative approaches. These limitations and alternative approaches are listed below:

1. Recall Bias: Case-control studies are notorious for recall bias as there is a possible differential misclassification of exposure data between cases and controls. In order to minimize this, we will obtain medical records and insurance data of at least a subset of subjects in addition to the interview used for data collection.
2. Variability in data collected from different practices: As this is a study conducted within a set of PBRNs using practice based records, the quality of historical data

obtained from dental records may be subjected to a certain degree of variability. In order to minimize this potential problem, we considered an oral examination for cases and controls using a standard protocol. However, it is not feasible to calibrate PBRN members in relation to the oral examination and as such; we will depend on the available records. We will use an electronic data abstraction system/form specially designed for this process and randomly visit a subset of practices to ensure data quality.

3. Obtaining Medical Records: We might encounter problems in gaining access to all medical records of cases and controls. We will consider using only a subset of the subjects (HMO) for medical data validation.

D.15. Potential Strengths of the Proposed Study:
The proposed approach has numerous strengths. These are:

1. Availability of sufficient cases: Our preliminary data indicate that we will have at least 176 cases of ONJ directly coming from the members of the three PBRNs and the two HMOs. Since all these cases may not enroll in the study, in order to reach the required sample size, we have also identified other sources of cases such as Dr. Ruggiero (PEARL Network). If that approach fails, we will relax the eligibility criteria by expanding the diagnostic period from 2 to 3 years.
2. Setting: This is the first trans-PBRN study that uses the three dental PBRNs and their coordinating centers all of which have remarkable track records. Expertise available to the study from the three PBRNs is greater than the 'sum of parts' and the populations covered by the three Networks are diverse.
3. Availability of the HMOs: It is not possible to validate the exposure data in case-control studies unless there is access to quality records. Having the two HMOs (KP and HP) as partners of one of the PBRNs (DPBRN), we have the opportunity to perform a two level validation, at least for a subset of the study subjects, using medical records and insurance claims data available through the HMOs.

D.16. Future Directions:
Once we uncover the potential dental and other risk factors for ONJ, the three PBRNs can develop educational programs for the benefit of private dental practitioners in the country. In subsequent studies, we will also be able to evaluate the quality of life of the ONJ subjects and the effectiveness of treatments and treatment outcomes related to various oral diseases among them.

E. HUMAN SUBJECTS:

E.1 Protection of Human Subjects.
Human subjects issues cover a wide array of topics including insuring compliance with applicable federal, state, and institutional regulations. Specifically it includes IRB approvals, Federal-wide Assurances, subject privacy issues (HIPAA), informed consent, OMB clearance (where appropriate), recruitment of women children and ethnic and racial minorities, serious adverse event monitoring and adverse events reporting, and data and safety monitoring. The three NIDCR-funded dental PBRNs are all experienced in providing the oversight activities associated with ensuring that appropriate policies and processes are in place to provide for protection of human subjects involved in research studies. Furthermore, each dental PBRN has Standard Operating Procedures in place for assuring the protection of human subjects in clinical investigations.

E.1.1 Risks to Subjects. There is minimal risk to research subjects involved in this investigation, and the risk will be similar to that which the subject would experience during a typical dental examination. Any potential risks will be disclosed to the subject in the informed consent form, which will be approved by each dental PBRN's Institutional Review Board (IRB).

E.1.2 Adequacy of Protection Against Risks. Each dental PBRN has SOPs for protection against risks for human study subjects, according to NIH and FDA rules and regulations. Further, each Practitioner-Investigator involved in the study has been certified by each dental PBRN on the responsibilities for protecting research subjects who are participating in PBRN studies. This certification required taking courses on Good Clinical Practice guidelines and Human Subject Research and passing tutorial-based examinations. Furthermore, Practitioner-Investigators have been trained on requisite procedures to protect the identity of research subjects and their research-associated data.

E.1.3 Potential Benefits of the Proposed Research to the Subjects and Others. This is the first trans-dental PBRN study designed for dental professionals and their patients, and provides a unique opportunity to create research data that will impact dentists and their patients in daily clinical dental practice. There are limited data on the prevalence of ONJ and its associated risk factors, and no data published from patients identified from dental practices. Accordingly, it is the intent of this investigation to impact positively the practice of dentistry and the care of patients.

E.1.4 Importance of the Knowledge to be Gained. This is the first study designed to identify the prevalence of cases of ONJ in dental practices and ascertain major risk factors for ONJ. Since data will be derived from oral health professionals from three different USA regions, and these practitioners have all been trained as clinical research investigators, this study provides a unique opportunity to gather data from a large geographical region and under carefully controlled protocols to ensure the safety and identify of human research subjects. Importantly, it is likely that the knowledge to be gained by the study will be directly applicable to the daily practice of dentistry and that the study's outcomes will generate important knowledge for the dental profession and its patients.

E.2 Inclusion of Women and Minorities in Clinical Research. Federal regulations require inclusion of participants including women and ethnic minorities in clinical research, so that research can benefit all persons at risk of the disease, disorder or condition under investigation (45 CFR 46). Inclusion of ethnic minorities, women, children (see E.3 below) and other potentially vulnerable populations increases the generalizability of study results, but also raises issues of recruitment and vulnerability that must be addressed by study policies and procedures. Each of the three dental PBRNs will track performance and provide reports on these issues throughout the conduct of this trans-PBRN study.

Table E.1: Demographics by Gender, Race/Ethnicity, and Age for the PEARL Network

	% among Practitioners	% among Patients
Females	15	60
Males	85	40
Whites	80	65

Blacks	5	15
Hispanics	3	10
Asians	12	10
Age 8-17	0	15
Age 18-64	90	60
Age 65+	10	25

Table E.2: Demographics by Gender, Race/Ethnicity, and Age for the PRECEDENT Network

% among Practitioners		% among Patients	
Females	17%		50%*
Males	83%		50%*
Whites	75%		90%*
Blacks	2%		1%*
Hispanics	15%		7%*
Asians	8%		2%*
Age 8-17	0	Age 0-5	7%
Age 18-61	97%	Age 6-17	18%
Age 61+	3%	Age 18-64	56%
		Age 65+	19%

Data from U.S. Census estimates

Table E.3: Demographics by Gender, Race/Ethnicity, and Age for the DPBRN Network

	% among Practitioners	% among Patients
Females	17	55
Males	83	45
Whites	93	70
Blacks	4	22
Hispanics	2	5
Asians	2	3
Age 1-18	0	24
Age 19-64	90	59
Age 65+	10	17

E.3 Inclusion of Children. Inclusion of children (individuals under the age of 21) in research is important to support treatment modalities for disorders and conditions that affect both children and adults. Children (individuals under the age of 21) must be included in all human subjects' research supported by the NIH, unless there are scientific and/or ethical reasons for exclusion. The proposed investigation addresses a condition, ONJ, that affects primarily middle-aged and older-aged adults. It is extremely unlikely that there are cases of ONJ in individuals aged less than 21 years. Excluding individuals under the age of 21 years is consistent with the biology

and pathophysiology of ONJ, and therefore would be consistent with the scientific purpose of the study.

E.4 Ethnic/Racial Planned Enrollment. A broad range of racial and ethnic minorities are anticipated to be enrolled in this investigation, according to Federal regulations (45 CFR 46). Data provided in Section E.2 (above) suggests that each of the three dental PBRNs is capable of accessing dental professionals and patients from a broad range of ethnic and racial minority groups. We believe this access will facilitate the appropriate representation of gender, ethnic and racial minority groups in this investigation.

E.5 Data and Safety Monitoring Plan (DSMP). The proposed investigation does not involve any investigational drugs, devices, biologics, or therapies, nor is it designed to be a clinical trial since there are no interventions planned. There are no known risks to subjects for enrolling in this study. Therefore, a DSMP is not required, nor the organization of a DSMB. However, SOPs have been established by each of the three dental PBRNs on the development of a DSMP. If a DSMB is required, it will operate in a manner consistent with the NIDCR guidelines for Data and Safety Monitoring of Clinical Trials.

Table E.4: Targeted/Planned Enrollment: Number of Subjects for PEARL

Ethnic Category	Sex/Gender		
	Females	Males	Total
Hispanic or Latino	16	11	27
Not Hispanic or Latino	145	96	241
Ethnic Category: Total of All Subjects *	161	107	268
Racial Categories			
American Indian/Alaska Native	0	0	0
Asian	16	11	27
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	24	16	40
White	104	70	174
Racial Categories: Total of All Subjects *	161	107	268

* The “Ethnic Category: Total of All Subjects” must be equal to the “Racial Categories: Total of All Subjects.”
[t]All data from U.S. Census estimates

Table E.5: Targeted/Planned Enrollment: Number of Subjects for PRECEDENT

Ethnic Category	Sex/Gender		
	Females	Males	Total
Hispanic or Latino	6	6	12
Not Hispanic or Latino	64	64	128
Ethnic Category: Total of All Subjects *	70	70	140

Racial Categories			
American Indian/Alaska Native	3	3	6
Asian	2	2	4
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	1	2
White	64	64	128
Racial Categories: Total of All Subjects *	70	70	140

* The “Ethnic Category: Total of All Subjects” must be equal to the “Racial Categories: Total of All Subjects.”
[t]All data from U.S. Census estimates

Table E.6: Targeted/Planned Enrollment: Number of Subjects for dPBRN

Ethnic Category	Sex/Gender		
	Females	**Males**	**Total**
Hispanic or Latino	8	4	12
Not Hispanic or Latino	184	100	284
Ethnic Category: Total of All Subjects *	192	104	296
Racial Categories			
American Indian/Alaska Native	1	0	1
Asian	6	3	9
Native Hawaiian or Other Pacific Islander	1	0	1
Black or African American	31	13	44
White	153	88	241
Racial Categories: Total of All Subjects *	192	104	296

* The “Ethnic Category: Total of All Subjects” must be equal to the “Racial Categories: Total of All Subjects.”
[t]All data from U.S. Census estimates

F. VERTEBRATE ANIMALS: None

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H. CONSORTIUM/CONTRACTUAL ARRANGEMENTS: None

I. CONSULTANTS:

Michael Siegel, DDS, MS (Consultant). Dr. Siegel is Professor and Chair, Department of Diagnostic Sciences at the Nova Southeastern University College of Dental Medicine. He is also Diplomate of the American Board of Oral Medicine, Fellow of the Royal College of Surgeons (Edinburgh), and President of the American Academy of Oral Medicine. He worked with the trans-PBRN ONJ working team in preparing the Osteonecrosis of the Jaws protocol which included advising the working team on critical aspects of the protocol and data collection devices. Dr. Siegel has worked extensively with Dr. Migliorati (Consultant) on Osteonecrosis of the Jaws research investigations and scholarly papers, and authored two critically important papers on the topic: “Managing the care of patients with bisphosphonate-associated osteonecrosis: an American Academy of Oral Medicine position paper”. J Am Dent Assoc 2005;136:1658-68 and “Oral osteonecrosis and other long-term complications of bisphosphonate therapy”. Lancet 2006; accepted for publication. Dr. Siegel will be a consultant for this trans-PBRN project and will assist on issues regarding development, implementation, completion, as well as interpretation of the results and preparation of manuscripts.

Cesar Migliorati, DDS, MS, PhD (Consultant). Dr. Migliorati is Professor, Department of Diagnostic Sciences at the Nova Southeastern University College of Dental Medicine. He is also Diplomate of the American Board of Oral Medicine. Dr. Migliorati worked with the trans-PBRN ONJ working team in preparing this proposal and providing expert clinical and scientific background for preparation of the protocol. Dr. Migliorati has worked extensively with Dr. Siegel (Consultant) on Osteonecrosis of the Jaws research investigations and scholarly papers. He is the author of five papers on the topic. Dr. Migliorati will be a consultant for this trans-PBRN project and will help guide the scientific design and clinical conduct of the investigation. He will also assist with interpretation of the results and preparation of manuscripts.