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National study on avascular necrosis of the jaws including bisphosphonate-related necrosis

A 2-year national new patient registration of patients with avascular necrosis of the jaws including bisphosphonate-related necrosis' (BRONJ) referred to Oral Surgery, Oral Medicine, Oral and Maxillofacial Departments and Dental Hospitals in England, Wales, Scotland and Northern Ireland

December 2012

Executive summary

Background

Bisphosphonate Related Osteonecrosis of the Jaw (BRONJ) is a rare condition and is considered as an adverse effect of taking bisphosphonate medication. Bisphosphonates are used for the management of osteoporosis (treatment and prevention) and in the treatment for some cancers. Bisphosphonate medications are effective and BRONJ is a well recognised adverse effect. To date there are no published studies that provide a reliable estimate of the incidence of avascular necrosis, specifically BRONJ, in a general population. Furthermore, although risk factors have been proposed, previous work has used cohort methodology that is inadequate to address this shortcoming. There is therefore a need for robust confirmatory studies and this national new case registration aimed to create a better understanding of incidence, case management and risk factors in relation to outcome for patient care management.

Methodology

This national study was based on patient case records and was a collaboration between the Faculty of General Dental Practice (UK) and the British Association of Oral and Maxillofacial Surgeons. The study was designed to capture all new patient referrals with avascular necrosis of the jaws including BRONJ to Oral Surgery, Oral Medicine, Oral and Maxillofacial Departments and Dental Hospitals in England, Wales, Scotland and Northern Ireland from 1st June 2009 to 31st May 2011. Clinicians and departments/units associated with the British Association of Oral and Maxillofacial Surgeons, British Society of Oral Medicine, the British Association of Oral Surgeons, and the Association of British Academic Oral and Maxillofacial Surgeons were all encouraged to register patients diagnosed with avascular necrosis of the jaw.

Key messages and recommendations

In terms of the original scope of the study (page 8) we have been able to estimate a population based national incidence of BRONJ and have been able to present data concerning bisphosphonate history, associated comorbidity, causation, and site. What remains to be investigated more fully is the 12 month outcome on all these referrals and an analysis of factors associated with outcome. The expectation is that further data will be reported in the future.

Despite every effort to encourage complete case registration and submission of patient details during and following the study period, the present study was reliant on the voluntary participation and efforts of busy clinicians. The response rate has shown variation between areas suggesting that there may be an underreporting of cases.

A total of 383 records were submitted. Accepting that there has been a degree of under-reporting of new cases nationally our best estimate of incidence is that BRONJ occurs in 10 patients per year per million population (95% confidence interval 8.2 to 12.8 per million per year). For females the estimated rate is 14 per million per year and for males 6 per million per year. In females aged 70-79 years the rate is in excess of 50 patients per million per year. As the elderly population and associated bisphosphonate prescribing increases it is expected that the number of BRONJ cases presenting each year will increase over time assuming that other risk factors remain constant. These estimates of incidence if applied to the current UK population of 62 million people would indicate a total of 620 (508-793) BRONJ cases a year.

We also estimated the incidence of BRONJ in a population of post-menopausal woman with osteoporosis and treated with an oral bisphosphonate developing BRONJ as being somewhere between 1 in 1,262 and 1 in 4,419 per year. Interpretation needs to be very cautious given the number of assumptions involved but if the logic is appropriate then this risk can therefore be

regarded at worst as 'rare' (occurring ≥ 1/10,000 to< 1/1,000). The risk of developing BRONJ has to be balanced against the risk and subsequent outcome following fracture neck of femur and vertebral fractures. The incidence of BRONJ for patients receiving bisphosphonates for cancer is likely to be higher but too few data are available to make an estimate.

Two-thirds of cases (69%) were female and the overall mean (SD) age was 69 (12) years. In 56% of cases the route of administration was oral, 34% IV, 7% both oral and IV and unknown for 2%. This high percentage of cases with oral administration probably reflects the predominance community prescribing of oral bisphosphonates. Denosumab, a non-bisphosphonate treatment for osteoporosis, was associated with 1 case. In cases who had received oral treatment the majority (71%) had taken alendronic acid. In cases who had received IV treatment the majority (61%) were given zoledronic acid. 46% of cases had been diagnosed with cancer, just under half with breast cancer, whilst for 50% of cases use was for primary or secondary prevention of osteoporosis, including corticosteroid induced osteoporosis. In terms of other medications taken it is notable that 50% were taking or had taken corticosteroids, 22% vitamin D, 20% cancer chemotherapy, 19% NSAIDs, and 10% methotrexate. In 73% of patients the precipitating event was a dental extraction. Pain (74%), discharge (46%), and swelling (43%) were the main symptoms stated. In 8% of cases the presentation was said to be asymptomatic.

The site of BRONJ was more often the mandible than the maxilla in a ratio of 2:1. Sites were predominantly in the molar region and evenly spread between left and right.

At the time of reporting, the 1 to 2 year outcome was available for only 22% of cases. It would appear from these data that the likelihood of healing is higher for those (predominantly non-cancer) patients only having taken oral bisphosphonates (35%) compared to those (mainly cancer patients) only having taken IV bisphosphonate (11%).

Actions/next steps

Wide dissemination is required to reassure both the dental profession and the general population that the incidence of BRONJ is low although it is probably higher than the often quoted rate of between 1 in 10,000 and 1 in 100,000 patients taking oral bisphosphonates.

Continued collection of outcome data on these patients (healing rates and time to heal) is required with analyses relating outcome to patient and clinical characteristics.

We also recommend that clinicians continue to complete the 'Yellow Card' for all cases of suspected BRONJ - http://yellowcard.mhra.gov.uk/

Limitations/future research

The main limitation has been the mixed level of engagement at a unit and regional level. This will be a challenge to future groups replicating similar studies. Although this was a national study it received little funding, limiting its ability to create a sufficient infrastructure compared to more prestigious and established national projects. We recognise the difficulties of obtaining accurate bisphosphonate drug histories and this highlights the importance of involving both primary and secondary sectors in projects like this. Another issue is that units had difficulty tracking back to individual patients they had registered in order to complete their initial registration data and to provide outcome follow-up data. This was due in part to the amount of patient identifiable information we collected on each patient centrally, because of ethical restrictions on patient confidentiality. The web-based entry tool had to be readjusted part way through the data collection phase which could have discouraged participation.

This study estimates BRONJ incidence in relation to general populations and in doing so it has been necessary to make various assumptions. One was that for a general population estimate, we only used two geographical areas that we felt had good engagement into this study. Another was that, in the same areas, we estimated BRONJ incidence in post-menopausal women with osteoporosis receiving bisphosphonate treatment. Future studies might use cohorts from primary care medical practice by using the national Clinical Practice Research Datalink (CPRD) and using this data to build up a cumulative history of drug exposure and of risk factors and then tracking these patients for BRONJ by linking with primary dental care and Oral Maxillofacial services. The cost and complexities of this approach were beyond the resources available for this project. The data we collected could be used to investigate risk factors as part of an expanded case-control study. This would assume that the cases we have collected are typical of all cases and that cases have enough identifying information to be traced. This project still highlights significant gaps in our knowledge base regarding BRONJ and there is further work around lifestyle and genetic factors that would be valuable as would a better understanding of treatment and outcome. The study provides a rough estimate of BRONJ incidence which future studies can use to predict viability and likely recruitment.

The number of BRONJ cases will increase in the years to come. A national register would be valuable to keep track of what is a rare condition and would facilitate further research into prevention, treatment of BRONJ and outcomes. An international register would help compare any different prescribing habit between countries. With such a register it might be possible to link in with other registers such as the National fracture databases to obtain better estimates of incidence in at-risk patients and to reflect on the balance between risks and benefits of bisphosphonate treatment. The lesson from our study is that any BRONJ register would require considerable amounts of energy and resourcing to be sustainable in the long-term.

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Mr Malcolm Lane, Patient Representative from Myeloma UK.

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Contents page

Introduction

Introduction and Importance of National study

Bisphosphonates are a class of agents used in the management of osteoporosis (treatment and prophylaxis), Paget's disease, malignancies involving bone (e.g. myeloma, breast cancer, prostate cancer) and tumour induced hypercalcaemia.[1] The efficacy of these agents in treating and preventing the significant skeletal complications associated with these conditions has had a major positive impact for patients and is responsible for their widespread use in medicine.

Bisphosphonate Related Osteonecrosis of the Jaw (BRONJ) has emerged as a significant complication in a subset of patients receiving these drugs, since the first cases were reported in 2003.[2]

Most cases of BRONJ have been reported in cancer patients receiving the intravenous aminobisphosphonates zoledronic acid and disodium pamidronate. [3-6] More recently there have been reported cases of BRONJ related to oral administration of bisphosphonates, used mainly in the treatment and prevention of post menopausal related osteoporosis.[7-9] Osteoporosis is estimated to affect around 3 million postmenopausal women in the UK, over one million of these have had a confirmed diagnosis of osteoporosis after a dual-energy x-ray absorptiometry (DXA) scan.[10] Prevalence increases markedly with age and after the menopause and approximately 30% of women in England and Wales aged 80years and older are estimated to have osteoporosis. It is estimated that 10-20% of women with osteoporosis receive drug treatment for the condition.[11] The total number of women receiving medication for osteoporosis is approximately 480,000. This equates to 23% of the female population who are expected to be suffering from osteoporosis.[3]

Events that appear to precipitate BRONJ include a history of trauma (extractions), dental surgery or dental infection. With intravenous bisphosphonate administration, the extent and duration of exposure to bisphosphonates seems to correlate with the risk.[12] The cumulative risk from long-term oral bisphosphonates is unknown. Other risk factors for developing BRONJ seem to be steroid treatment, immunosuppression (e.g. methotrexate), comorbidity such as rheumatoid arthritis, smoking, periodontal health. Guidelines for the management, by dentists, of patients on bisphosphonates are few and are based on expert opinion and clinician-based questionnaire surveys rather than scientific evidence. [14-17] Predicting those patients at risk and instituting preventive or prophylactic measures may minimise the likelihood of patients developing BRONJ.

To date there are no published studies that adequately report incidence of avascular necrosis specifically BRONJ in a general population. Also although risk factors have been proposed, previous work has been on selected cohorts. There is a need for robust confirmatory studies and this national new case registration allows for a better understanding of incidence, case management and risk factors in relation to outcome.

Scope of national study

1. To capture all new patient referrals (case-series) with avascular necrosis of the jaws including bisphosphonate-related necrosis' (BRONJ) to Oral Surgery, Oral Medicine, Oral and Maxillofacial Departments and Dental Hospitals in England, Wales, Scotland and Northern Ireland from 1st June 2009 to 31st May 2011.
2. To estimate national incidence using national estimates of population, overall and within age-sex and regional strata.
3. To collect data on medical and lifestyle history, medications history in particular the use of bisphosphonates (e.g. type of bisphosphonate, cumulative dose), other risk factors such as smoking, periodontal health, clinical presentation and causation e.g. recent dental extraction.
4. To collect 12 months outcome data on all these referrals
5. To investigate potential risk factors in relation to patient outcome

Abbreviation of bisphosphonate related osteonecrosis of the jaw (BRONJ)

The literature uses both BRONJ and BONJ as abbreviations for bisphosphonate related osteonecrosis of the jaw. Since 'BRONJ' has been used throughout this study this is the term used in this report, except for any verbatim extracts from published work that include the term 'BONJ'.

Methods

This was a longitudinal case-series study with prospective case-ascertainment over a two year period. Patient data was collected at a local level with data entry facilitated by a dedicated web-tool.

Target population

Definition of BRONJ - To distinguish avascular necrosis and BRONJ from other delayed healing conditions, the following working definition of BRONJ has been adapted from that used by the AAOMS [15]:

Patients may be considered to have avascular BONJ if the first two characteristics are present: 1) exposed or necrotic bone in the maxillofacial region that has persisted for more than 8 weeks; and 2) no history of radiation therapy to the jaws, and if there is 3) current or previous treatment with a bisphosphonate, then the patient is considered as having BONJ;

It is important to understand that patients at risk for avascular necrosis/BONJ or with established avascular necorosis/BONJ can also present with other common clinical conditions not to be confused as avascular necorosis/BONJ. Commonly misdiagnosed conditions may include, but are not limited to, alveolar osteitis (dry socket), sinusitis, gingivitis/periodontitis, caries, periapical pathology, and temporomandibular joint disorders.

For clarification: avascular necrosis/BRONJ can be asymptomatic, associated with pain, infection, extraoral fistula, jaw fracture. There will be radiographic changes on OPG for more established cases (ill-defined lytic lesions similar to osteomyelitis extending down from the surface to the ID canal in the mandible, and even the lower border in advanced cases). Radio-graphical assessment is not essential for the diagnosis although normally accompanies the assessment process. In its early stage the x-ray is normal. OPG is satisfactory although CT and MR can be used as an adjunct. Biopsy is not necessary to make the diagnosis.

Inclusion/exclusion criteria

Registration of cases to the study included any new case with 'avascular' jaw necrosis present for more than 8 weeks irrespective of whether or not the patient is on bisphosphonates. The diagnosis should not have included 'conventional' osteomyelitis or osteoradionecrosis. Although it is relatively

easy to exclude patients who have had radiotherapy to the jaws, it can be difficult to exclude patients who present with osteomyelitis as the primary pathology who also have a history of bisphosphonate use. However, usually from the history, examination and radiographs it is possible to clearly identify those patients with osteomyelitis not related to bisphosphonates.

Patients seen for the first time between 1 June 2009 and 31 May 2011 onwards were eligible. Patients were eligible irrespective of age, cause and comorbidity.

Patient consent was not necessary for case registration. Consent was required to enable future follow-up research such as pharmacogenetics studies.

Oral and Maxillofacial Departments were asked to link with university based Oral Medicine and Oral Surgery Departments for the purpose of case-finding. Awareness of the project was raised through BAOMS and FGDP, the Royal College of Surgeons of England, national meetings, local audits, journals and newsletters. Inclusion of the BRONJ project was suggested as part of the annual audit programmes. The named clinical leads were contacted by the project manager at regular intervals to encourage case registration. The 15 Regional BAOMS Clinical Effectiveness co-ordinators were also available to help promote registration in their regions.

Organisation – how the project was managed and conducted
Simon Rogers and Nikolaus Palmer were the main investigators, with Simon Rogers the project lead.

Mrs Amrita Narain (Research Officer, Faculty of General Dental Practice (UK), Royal College of Surgeons of England) as the project manager was the point of daily contact for sites. She linked directly with the main clinical lead for this project and with local site clinical leads, and was responsible for preparing newsletters and other circulars, materials for project group meetings, and for managing these meetings including formal minute taking. The project group met throughout the study by teleconference, about every 3 months. Project group members are listed on page 5.

Derek Lowe was the medical statistician to the project with responsibility for data analysis and drafting the report.

The data facilitator was responsible for liaising with unit and individual clinicians through emails, letters and telephone conversations regarding case registration, patient details, and data entry.

The project team worked in partnership with the Faculty of General Dental Practice (FGDP (UK)) of the Royal College of Surgeons of England, British Association of Oral and Maxillofacial Surgeons, British Society of Oral Medicine, Faculty of Dental Surgery, The British Association of Oral Surgeons, and The Association of British Academic Oral and Maxillofacial Surgeons.

Pilot
The national project followed a paper-based pilot conducted in the North West region of England from September 2008 and a technical pilot of web-based registration in May 2009.

Site recruitment
Clinicians and departments/units associated with the British Association of Oral and Maxillofacial Surgeons, British Society of Oral Medicine, the British Association of Oral Surgeons, and the Association of British Academic Oral and Maxillofacial Surgeons were all encouraged to participate. All Oral and Maxillofacial Surgery departments in England, Wales, Scotland and Northern Ireland were approached. A designated clinical lead was identified and a point of contact established at each department/unit. In order to be inclusive all other clinicians who are involved in the

management of avascular necrosis/BRONJ were encouraged to register their cases. At a local level we wrote to each hospital clinical audit lead. Trust chief executives were contacted at a later date by letter and newsletter.

Data collection/data management

The plan was to register patients and record their clinical details via a webpage designed for purpose. The project manager would have access to the web-tool and at regular time points would be able to interrogate this to see who had been entering cases and how complete any record was. In this way a continuous system of monitoring could be ensured throughout the progress of this study.

Though simple in concept the application of this was fraught with problems throughout this project. An initial web-based facility (SPSS (Statistical Package for the Social Sciences) Dimensions platform) was available on the Royal College of Surgeons (RCS) web site with password-protected access for uploading patient information. Units had issues with the length of the form and the website process, particularly gaining access and in the subsequent posting of details. Only 18 eligible cases were entered via this system and as IT support to the website was constrained to a minimum the project group agreed to move to another data entry system. This involved SNAP survey software and after the relevant SNAP form was designed (See appendix C) to accommodate less detail than before, the new data entry system was made available to units also via the RCS website. SNAP had the advantage that the access and data entry process were improved and looking ahead the data could also be exported directly into SPSS for data analysis.

In order to improve case registration a simple initial fax registration system requiring basic minimum case data (See appendix B) was introduced to flag up cases as they were being registered. Full details were required at a later date and local clinical leads were given a choice of either entering the remaining details themselves directly onto SNAP or sending the details on paper to the project manager for entry. Most units preferred the paper option. In the autumn of 2011 the SNAP data entry was closed and the contents exported to SPSS. A concerted effort was made to get any remaining baseline information submitted on paper by the end of 2011. Data updates in 2012, such as adding or amending case, were carried out using SPSS.

In April 2012 a simple one-year follow-up questionnaire requesting outcome data (Appendix G) was circulated. Data was used to update the SPSS dataset. Data collection continues, and final outcome data will be worked into the journal article that will be prepared at the end of 2012.

Limitations of information

Case finding and the quality of data relied on the voluntary participation and efforts of the local clinical leads. No formal quality checks on the data, in particular the consistency (reliability) of data received, have been undertaken. We have not had the opportunity to visit units to carry out any independent checks.

Ethics

Ethical approval was given via the National Research Ethics Service (Sefton Research Ethics Committee 08/H1001/179). The Ethics Committee confirmed that the case-registration study was an 'audit'. However, the Committee advised that patient consent be sought at registration to enable future contact to be made should the opportunity for further research occur in the future. See Appendix D for the patient consent form and Appendix E for the patient information sheet.

Background information on Community prescribing

We have included prescription data here as background information to give a feel for recent prescribing habits in the community. Similar details for hospital prescribing could not be found.

Community Prescription Cost Analysis (PCA) data for England is downloadable from the NHS Information Centre website. Data on the number of prescriptions dispensed between July and September 2011 are shown below. The table shows the number of prescription items dispensed within BNF chapter 6.6 'Drugs affecting bone metabolism' in England. From a total of 241.6 million items dispensed, 2.2 million items under the BNF section name of 'Drugs affecting Bone metabolism', and 2.2 million items under the BNF sub paragraph name of 'Biphosphonates and other drugs'. The most common items were Alendronic Acid Tab 70mg (1.74 million items) and Risedronate Sodium_Tab 35mg (0.19 million items).

BNF drugs affecting bone metabolism. Community prescribing for England July to September 2011

Drug name	Trade names	Items (thousands)
Alendronic acid	Fosamax	1771
Alendronic Acid & Colecalciferol	Fosavance	7
Risedronate Sodium	Actonel	208
Risedronate Sodium & Colecalciferol	Actonel Combi	0.4
Ibandronic Acid oral	Bonviva, Bondronat, Iasibon	69
Ibandronic Acid Inj	Bonviva	0.1
Sodium Clodronate	Bonefos, Loron, Clasteon	11
Disodium Etidronate	Didronel	10
Zoledronic Acid	Aclasta, Zometa	0.08
Disodium Pamidronate	Aredia	0.02
Tiludronic Acid	Skelid	0.01
Non-bisphosphonates		
Strontium Ranelate	Protelos	84
Calcitonin (salmon)	Miacalcic	1.8
Denosumab	Prolia	0.3
Parathyroid Hormone	Preotact	0.001

SOURCE: http://www.ic.nhs.uk/statistics-and-data-collections)

These prescription data do not include hospital prescribing and a similar breakdown is not available for hospitals. Limited data on Hospital prescribing for England are available via the NHS Information Centre. In 2010 prescribing costs for England were £12.9 billion of which hospitals accounted for 31.7%. Comparison of 2010 primary and secondary care prescribing for medicines approved by NICE includes data on alendronate and risedronate; alendronate £650,100 secondary care, £13,551,400 primary care and risedronate £616,000 secondary care, £22,865,900 primary care. For both drugs over 95% of the total cost was in primary care.

From the NHS Information Centre bulletin 'Prescriptions Dispensed in the Community: England, Statistics for 2001 to 2011', which highlights changes and trends in prescribing between 2011 and 2010 by British National Formulary (BNF) classifications the section on "Drugs affecting bone metabolism" states:

- The number of items dispensed has increased (since 2010) by 0.2m items (2.5 per cent),
- Use of a*lendronic acid* has increased by 5.5 per cent. 'Use of the once weekly tablets has fallen by 34.2 per cent',
- Use of r*isedronate sodium* has fallen by 15.0 per cent. Generic 5mg, 30mg and 35mg tablets are now available and use of the branded products has fallen.
- Use of *strontium ranelate* use has increased by 12.7 per cent, Use of the new drug *Denosumab* has increased by over 1000 per cent. This drug has been recently recommended by NICE for the prevention of osteoporotic fractures in postmenopausal women.

RESULTS

The results are broken down into six sections:

1. Participation by BAOMS-listed consultants and Oral & Maxillofacial Units.
2. Population based incidence of BRONJ.
3. Prescriptions data.
4. Case characteristics minimum dataset.
5. Further detailed case analyses.
6. Provisional analysis of outcome data within 1-2 years.

RESULTS: 1. Participation by BAOMS-listed consultants and Oral and Maxillofacial Units

Participation rate was estimated using two methods:

1. At consultant level for consultants listed by BAOMS (http://www2.baoms.org.uk/downloaddoc.asp?id=530);
2. At unit level by involvement of Oral and Maxillofacial units also as listed by BAOMS.

Details are given below, but in brief at least 45% of BAOMS consultants were engaged in some way with the study and about 60% of BAOMS units. All estimates of participation should be considered as 'ball park' figures.

CONSULTANTS

Of 363 consultants listed by BAOMS in May 2011 109 submitted cases to the study under their name (Study Question 4 – "name of consultant whose clinic it is"). A further 5 were listed by BAOMS in their 2008 list and 1 was on the associate specialist grades list for 2011. This leaves 26 names that cannot be matched to a BAOMS list and who probably submitted on behalf of their (unnamed) consultant. Another 24 consultants indicated in a separate survey (Appendix F) that they had no cases or that cases were submitted via colleagues. Therefore at least 45% (165/363) of BAOMS consultants were engaged in some way in the study. This ballpark figure may be higher if the denominator of 363 includes consultants not considered eligible for the study. Other sources of information have not been considered in arriving at this estimate.

UNITS

The BAOMS May 2011 list of 154 oral and maxillofacial units was used as the basis for estimating unit participation. Earlier BAOMS lists differ slightly and it is difficult to be precise about the most appropriate denominator, but this has been taken as 155. 80 units had consultants who submitted cases to the study, a further 11 units shared consultants with one of the 80 units, and 5 units stated that they had no cases to submit. It is difficult to be precise about the overall participation rate for units as the emphasis in recruitment was on the individual consultant to participate, but somewhere in the region of 55% (85/155) to 62% (96/155) of units is a reasonable estimate.

Thus just over half of BAOMS units are known to have participated in the study to some extent. What we don't know is to what extent all relevant consultants within a unit participated, and to what lengths each participating consultant went to, to be exhaustive of all possible eligible cases. Conversely there may be some units, particularly smaller units, who have been classed as non-participants that had no cases to submit.

A breakdown showing unit participation by region is given below.

Unit participation

	UNIT PARTICIPATION					% Participation	
	(1) Yes, cases in dataset	(2) Yes maybe with overlap of consultants participating elsewhere, BUT no cases submitted	(3) Yes, no cases for unit stated	(4) NO PARTICIPATION	Total UNITS	(1) or (3)	(1), (2) or (3)
East Midlands SHA	6	0	1	3	10	70%	70%
East of England SHA	7	2	0	5	14	50%	64%
London SHA	5	1	1	16	23	26%	30%
North East SHA	3	0	0	1	4	75%	75%
North West SHA	13	0	1	3	17	82%	82%
South Central SHA	7	2	0	3	12	58%	75%
South East Coast SHA	6	0	0	3	9	67%	67%
South West SHA	7	0	1	6	14	57%	57%
West Midlands SHA	7	0	1	6	14	57%	57%
Yorkshire & The Humber SHA	6	6	0	2	14	43%	86%
England	67	11	5	48	131	55%	63%
Wales	1	0	0	5	6	17%	17%
Northern Ireland	3	0	0	0	3	100%	100%
Scotland	9	0	0	5	14	64%	64%
Jersey	0	0	0	1	1	0%	0%
Total	80	11	5	59	155	55%	62%

There was a low unit participation in London; one unit (Homerton University Hospital) submitted 75% of the 49 cases for London.

Northern Ireland has only three units listed by BAOMS – Belfast, Ulster and Londonderry, with overlap of consultants between the first two – and all three units participated. The participation rate was also high for the North-West, boosted by efforts of the study clinical lead to ensure capture of all possible cases for the Merseyside area.

RESULTS: 2. Population based Incidence of BRONJ

In summary, the analyses below reveal a 10-fold variation by geographical location for estimates of BRONJ incidence. There is no logical reason for supposing such geographic variation. Variation in participation and engagement is a more likely explanation than true geographical variation. The two areas with the highest rates of involvement were Merseyside (base of the study clinical lead) and Northern Ireland where all three BAOMS listed units participated. These two areas had similar incidence rates of about 10 cases per year per million population. As it is unlikely that the population that lives in Merseyside and Ireland is inherently different, it suggests that the levels of commitment to the study have not been as intensive elsewhere. We must exercise caution in our interpretation of these data.

Final number of cases first seen, between 1 June 2009 and 31 May 2011

The final dataset, after data checking and cleaning and the elimination of duplicate submissions, included 383 records for analysis. Of these, 5 were described as being avascular necrosis and 369 described as BRONJ, with 9 not known. Of the 369 described as BRONJ 69 records had only minimum clinical data as per the fax registration form (Appendix B) whilst 300 had longer records which, though longer, were not always complete. The 9 unknowns had less than the minimum amount of data. Four of the 5 described as being avascular necrosis were from Scotland which is likely to indicate an under-reporting of avascular necrosis cases within other UK units.

Analysis proceeded with the 378 that were either BRONJ related (369) or not known to be BRONJ related (9). None of theses 9 cases were from Merseyside or N Ireland.

Cases in relation to general population

Two sources of population estimates for 2009 were used to calculate population incidence:

1. Based on catchment to Strategic Health Authorities (SHAs) in England (http://www.erpho.org.uk/viewResource.aspx?id=21919). These were based on all admissions, elective admission only and emergency admissions and were calculated withthe proportional flow method, using admissions from 2006/07 to 2008/09 and using 2009 ONS mid-year population estimates for LSOAs.
2. Based on residents within local government boundaries of the UK (http://www.erpho.org.uk/viewResource.aspx?id=21229) These mid-year population estimates for 2009 were available at smaller local authority level and the resident population for the 'Merseyside' patch was compiled in this way.

These methods yield wide variation between areas from 1 case per million per year to 11 cases per million per year. See the table below.

Cases in relation to 2009 populations

English SHA	Cases over two years	Catchment population estimate (thousands)	Cases per year per million population
North East	13	2755.9	2.36
North West	67	6963.9	4.81
Yorkshire & Humber	48	5335.7	4.50
East Midlands	17	3833.4	2.22
West Midlands	11	5470.6	1.01
East of England	15	5420.8	1.38
London	49	8782.4	2.79
South East Coast	29	4081.0	3.55
South Central	21	3856.1	2.72
South West	22	5309.8	2.07
Country	Cases over two years	Resident population estimate (thousands)	Cases per year per million population
England	292	51809.8	2.82
Wales	10	2999.3	1.67
Scotland	37	5194.0	3.56
N. Ireland	39	1788.9	10.90
UK	378	61792	3.06
Merseyside	41	2112.0*	9.71

*comprises Merseyside Met County (1350.6), Cheshire West and Chester UA (326.6), Warrington UA (197.8), Halton UA (118.7), Cheshire East UA – Crewe & Nantwich district only (118.3).

The next two tables below show incidence rates in relation to age and gender, first all the UK data and then for Merseyside and Northern Ireland combined. Merseyside and Northern Ireland data are presented separately as these two regions reflect greater levels of participation in this study. Comparison of rates between these two tables for ages <65, 65-74 and 75+ and by gender consistently suggest a 3 to 4 fold shortfall in the number of cases actually submitted to this study.

Both tables indicate an increasing incidence for men and women by age, notably higher in females in the 70-79 year age group.

BRONJ-related incidence: All 378 cases reported to the National study

	Cases over two years			2009 UK population estimate (thousands) rounded			Cases per year per million population		
AGE (years)	Female	Male	NK	Female	Male	Total	Female	Male	Total
<55	39	8	0	22004.8	22366.2	44371.1	0.89	0.18	0.53
55-59	16	12	0	1,828.7	1767.3	3596.0	4.37	3.40	3.89
60-64	34	14	1	1,901.2	1818.0	3719.1	8.94	3.85	6.59
65-69	39	21	0	1,472.6	1364.5	2837.1	13.24	7.70	10.57
70-74	37	22	0	1,295.0	1146.6	2441.6	14.29	9.59	12.08
75-79	40	18	0	1,108.5	880.8	1989.3	18.04	10.22	14.58
80-84	28	13	0	877.2	591.3	1468.5	15.96	10.99	13.96
85+	24	3	1	930.1	439.2	1369.3	12.90	3.42	10.22
NK	4	4	0						
Total	261	115	2	31418.1	30373.9	61792.0	4.15	1.89	3.06
<65	89	34	1	25734.7	25951.5	51686.2	1.73	0.66	1.20
65-74	76	43	0	2767.6	2511.1	5278.7	13.73	8.56	11.27
75+	92	34	1	2915.8	1911.3	4827.1	15.78	8.89	13.15

Note: Population Figures may not add due to rounding

BRONJ-related incidence: Merseyside region and N Ireland combined (80 cases over two years)

	Cases over two years		2009 UK population estimate (thousands)rounded			Cases per year per million population		
AGE	Female	Male	Female	Male	Total	Female	Male	Total
<55	10	1	1418.0	1421.0	2839.0	3.53	0.35	1.94
55-59	5	2	114.8	111.5	227.3	21.78	8.97	15.40
60-64	5	5	113.4	107.7	222.1	22.05	23.21	22.51
65-69	5	4	93.1	84.6	176.7	26.85	23.64	25.47
70-74	10	3	82.8	71	152.8	60.39	21.13	42.54
75-79	13	5	69.7	53.3	123.1	93.26	46.90	73.11
80-84	4	2	54.7	34.5	88.2	36.56	28.99	34.01
85+	4	2	50.0	22.7	71.7	40.00	44.05	41.84
Total	56	24	1996.3	1904.6	3900.9	14.03	6.30	10.25
<65	20	8	1646.2	1640.2	3288.4	6.07	2.44	4.26
65-74	15	7	175.9	155.6	329.5	42.64	22.49	33.38
75+	21	9	174.4	110.5	283	60.21	40.72	53.00

Note: Population Figures may not add due to rounding.

If we apply the rate of 10 cases per year per million population seen for Merseyside and Northern Ireland to the rest of the UK we would then expect around 620 cases per year for the UK as a whole, and 1240 over two years which is just over three times the number of cases actually submitted to this study. For 80 cases seen over two years in a population of 3.9 million there is a 95% (Exact

Poisson) confidence interval for the incidence from 8.2 to 12.8 per million per year which would imply a total of 620 (508-793) BRONJ from a UK population of 62 million people. The 95% confidence interval for females is 10.6 to 18.2 per million per year; for males 4.0 to 9.4 per million per year. For females aged 70-79 years the rate is in excess of 50 patients per million per year.

The results of cross-sectional surveys of consultants in 2008, 2009 and 2010 (see next section) suggest at least 600 new cases per year for the UK and possibly as many as 1000 per year, depending on how well the half that responded in each survey represented those that did not respond. These survey results further indicate a shortfall in case submission to this study.

Surveys in 2008, 2009, 2010, 2011 of BAOMS consultants regarding BRONJ cases seen

There have been four BAOMS consultant surveys in 2008, 2009, 2010, and 2011. Results of these surveys are consistent in suggesting that during a year most BAOMS consultants might expect to see at least one new case, and typically on average three to four. Response to these surveys was 40-50% and if responders were representative of non-responders then nationally more than 1000 new cases per year is suggested. At the other extreme if the non-responders hadn't seen any new cases then consultants might on average expect to see at most two new cases per year which would imply 600-700 new cases per year nationally. This matches the general population incidence of 10 per million per year calculated for Merseyside and Northern Ireland in the previous section. It is possible in cross-sectional surveys such as these that responders might over-estimate the numbers seen within any given time period or even that there is double counting of the same cases amongst colleagues. But one inescapable conclusion is that these survey results further indicate a shortfall in case submission to this current study.

Results of the specific surveys are summarised below:

(1) June 2008, a 55% (177/322) response. Within "the last year", 74% (124/168) had seen at least one new case of BRONJ from oral bisphosphonates, and 64% (103/162) from IV bisphosphonates, with 88% (142/162) seeing at least one new case irrespective of route and 65% (106/162) seeing at least three cases. 690 new cases were seen within the previous year (399 oral, 291 IV), equivalent to a mean of 4.3 per consultant.

(2) December 2009, a 44% (106/240) response, with 60% (64/106) seeing at least one new case since 1st June 2009 in a time period averaging about 7 months, with 31% (33/106) seeing three or more. Half (55%, 58/106) had a local audit supporting the National BRONJ study. It is harder to project annual figures from this survey as the exact time period since 1st June was unknown for many and the upper option for case numbers was "5 or more". For the 106 responders there were at least 182 new patients seen, equivalent to at least a mean of 2.9 per consultant per year.

(3) October-November 2010, the survey run on behalf of the Clinical Effectiveness Committee of BAOMS was designed specifically to complement the on-going National Avascular and Bisphosphonate Related Osteonecrosis of the Jaw National project (BRONJ). The survey asked how many new cases of BRONJ had been seen since the 1st June 2010 (last 4 months), whether this was an exact figure or an estimation, and whether there was a local audit in place to support the National Clinical Audit of BRONJ. The response from BAOMS consultants was 49% (129/264). Half (51%, 66/129) had seen at least one new case of BRONJ in the 4 months since 1st June 2010, with 14% (18/129) seeing three or more. Most responders (83%, 107/129) stated an "exact" number of new cases while the rest gave "estimates". A total of 169 new cases were seen in 4 months, equivalent to a mean of 3.9 per consultant per year. Half (55%, 71/129) had a local audit in place supporting the National Clinical Audit of BRONJ.

(4) November/December 2011 (Appendix F) the survey asked whether members had submitted cases to the national study and to ask what numbers of new cases they had seen in the two year period. Responses were received from 126 and the information was used to chase up any outstanding cases, as 31 indicated they had cases that had not been submitted, possibly over 200 cases, only a minority of which it is fair to say were submitted. Some of the responses to this survey were difficult to interpret because of the variation in the details, but an estimated 25 from the 126, or about 20% indicated they had seen no new cases during the two year study period. If this is typical of all BAOMS members then this result is consistent with the vast majority of members having seen at least one new case.

RESULTS: 3. Prescriptions data

Most bisphosphonates (~95%, see prescribing background information) are prescribed in the community. In light of the geographical variation seen in the previous section we have included community prescription data below to explore geographical variations in prescribing. We have done this in two ways:

1. By downloading data on prescription items dispensed in community pharmacies for one quarter (July-September 2011) at PCT level and then aggregating to SHA level and relating prescriptions to SHA catchment populations.
2. By relating community pharmacy prescriptions at a national level from 2008 to 2010 to resident national populations.

1. The July-Sept 2011 data on prescription items dispensed in community pharmacies indicates that the number of items dispensed per thousand population during July to Sept 2011 varied from 31 per 1000 in London to 55 per thousand in the North East. Overall the variation in prescriptions between SHAs does not resemble the regional variation in BRONJ submissions to the national study.

Drug items affecting bone metabolism prescribed per thousand SHA estimated population (July to September 2011).

Drugs Affecting Bone Metabolism	Total Items	GP list populations	Items per thousand population
Yorks & Humber	211199	5289015	*39.93*
W Midlands	210470	5445991	38.65
South West	263046	5221896	50.37
South East Coast	196172	4347587	45.12
South Central	140875	4112460	34.26
North West	315925	6962848	45.37
North East	144949	2600233	55.74
London	245513	7832487	31.35
E of England	252071	5787144	43.56
E Midlands	178008	4410612	40.36
ENGLAND	2158228	52010273	41.50

Source for prescribing data: http://www.ic.nhs.uk/statistics-and-data-collections/primary-care/prescriptions/primary-care-trust-prescribing-data--july-to-september-2011

Drug item data: Primary care trust prescribing data July to September 2011 with the number of items pertaining to 'Drugs affecting Bone metabolism' being aggregated to Strategic Health Authority Level (SHA).

Population data: populations registered with GP practices at Strategic Health Authority (SHA) and Primary Care Organisation (PCO) level. The data was collected in April 2011 for GP relevant populations and constrained to the Office for National Statistics 2010 mid-year population estimates - based on the 2001 Census, excluding some special populations. This reconciliation is carried out as the number of patient registrations is greater than the number of people living in England and Wales according to population estimates from the ONS. There may be a number of reasons for this, e.g. people leaving the country and not notifying their GP.

2. Overall community prescription rates were similar for England and Northern Ireland, higher in Wales and lower in Scotland; rates for all 4 countries increased from 2008 to 2009 and from 2009 and 2010. Alendronic Acid dominated the prescribing in England, Scotland and Wales whilst in Northern Ireland it was dominated by an even split between Alendronic Acid and Risedronate Sodium. Northern Ireland issued more than three times as many prescriptions of Risedronate Sodium per head of population than England, Wales and Scotland. Overall the variation in prescribing between countries shows little resemblance to the variation seen in BRONJ rates from the national study.

Prescription items dispensed by community pharmacies by Country

	2008	2009	2010	2011
Items prescribed (thousands)				
England	6786.2	7434.6	7949.4	8118.4
Wales	549.38	586.03	620.1	613.3
Scotland	622.21	655.21	697.3	685.1
N Ireland	233.77	251.21	273.0	284.4
UK	8191.56	8927.1	9539.8	9701.2
Items per thousand population				
England	132	143	152	na
Wales	184	195	206	na
Scotland	120	126	134	na
N Ireland	132	133	152	na
UK	133	144	153	na

Bisphosphonate prescription items dispensed by community pharmacies per thousand population

	2008	2009	2010
Alendronic Acid			
England	97	113	125
Wales	143	159	171
Scotland	91	99	110
N Ireland	54	60	71
UK	98	112	125
Risedronate Sodium			
England	26	22	19
Wales	28	23	20
Scotland	24	22	18
N Ireland	66	69	70
UK	27	24	20
Ibandronic Acid			
England	5	5	5
Wales	9	10	10
Scotland	3	3	3
N Ireland	8	9	9
UK	5	6	6

Sources for prescribing data:
England http://www.ic.nhs.uk/statistics-and-data-collections/primary-care/prescriptions
Northern Ireland http://www.hscbusiness.hscni.net/services/1806.htm
Scotland http://www.isdscotland.org/Health-Topics/Prescribing-and-Medicines/Community-Dispensing/Prescription-Cost-Analysis/
Wales http://wales.gov.uk/topics/statistics/theme/health/primary-care/prescribing/?lang=en

Risk of developing bisphosphonate related osteonecrosis of the jaw

The previously calculated population risk of BRONJ of 10 cases per million population per year is not the same as the risk of developing BRONJ for patients taking bisphosphonates. Below, we have estimated the one–year risk of developing BRONJ in a target population of post-menopausal women treated with oral bisphosphonates for osteoporosis. A number of assumptions have been made when calculating these risks which must be interpreted with caution. Calculations have been based on the data collected by Northern Ireland and Merseyside as we consider that these areas reflect more robust data collection and submission.

Background information: The following data on the prevalence of osteoporosis and its treatment are derived from the NICE costing template for osteoporosis (TA161) for England http://guidance.nice.org.uk/TA161/CostingTemplate/xls/English . The mid-2006 England estimate of the number of post-menopausal women (taken as age 50 and over) was 9,165,130. Of these the total cases of osteoporosis without prior fracture was 1,098,852 and the total cases of osteoporosis with a clinically apparent osteoporotic fragility fracture was 1,030,928, a combined total of 2,129,780 osteoporosis cases, 23% of all those women aged 50 and over. In terms of primary prevention of osteoporotic fragility fractures the total number of post-menopausal women with osteoporosis receiving bisphosphonate medication was 156,587. In terms of secondary prevention of osteoporotic fragility fractures the total number of post-menopausal women with osteoporosis and a clinically apparent osteoporotic fragility fracture receiving bisphosphonate medication was 195,877. The combined total of 352,464 currently receiving bisphosphonates was 17% of the 2,129,780 postmenopausal women with osteoporosis. The source also contained future projections for bisphosphonate usage, up from 352,464 to 550,002, from 17% to 26**%** of postmenopausal women with osteoporosis.

The calculations below are based on the assumption that 23% of post-menopausal women have osteoporosis, of whom 17-26% will be taking bisphosphonates.

Northern Ireland and Merseyside

The 2010 combined NI & Merseyside ONS population estimate for women aged 50 and over is 715,400 (NI 302,000, Merseyside 413,400). In our study there were 80 BRONJ cases, 56 women and 24 men, for these areas. Forty-eight of the cases were in women aged 50 and over; for 37 of these cases the diagnosis was known and was osteoporosis in 26 of the 37 .We have assumed that the same proportion of cases with an unknown diagnosis will be osteoporosis, a further eight cases have been added. Thus we take 34 as number of BRONJ cases in post-menopausal women in the two year study period following osteoporosis/use of steroids, 17 per year.

Combined NI & Merseyside women aged 50 and over: number at risk

% of women aged 50 and over with osteoporosis	% of women aged 50 and over with osteoporosis that were treated with bisphosphonates				
	15%	20%	25%	30%	35%
20%	21462	28616	35770	42924	50078
25%	26828	35770	44713	53655	62598
30%	32193	42924	53655	64386	75117

Combined NI & Merseyside women aged 50 and over: number treated per BRONJ case

% of women aged 50 and over with osteoporosis	% of women aged 50 and over with osteoporosis that were treated with bisphosphonates				
	15%	20%	25%	30%	35%
20%	1262	1683	2104	2525	2946
25%	1578	2104	2630	3156	3682
30%	1894	2525	3156	3787	4419

In summary, these analyses suggest that the risk in one calendar year of a post-menopausal woman with osteoporosis and treated with an oral bisphosphonate becoming a BRONJ case is 'rare' (≥ 1/10,000, < 1/1,000) according to EU convention for classifying risk.

Ideally we should want to know the number of patients who are taking bisphosphonates as well as those who have stopped taking bisphosphonates. This is then the at-risk group and we then calculate the percentage that in one calendar year will become a BRONJ case. It is not a one-year incidence risk from treatment as it is not timed from the onset of treatment. It is more akin to a general population risk but confined to a subgroup (at the start of the year) that have had bisphosphonates. In our BRONJ data below later we find a median of 3-4 years for those who had stopped oral treatment and at least one-third who had stopped. Our estimates of a bisphosphonate population exclude any who would have stopped and if we able to factor in those having taken bisphosphonates and stopped, this would increase the population at risk and reduce the risk of developing BRONJ. Our estimates must be treated with extreme caution.

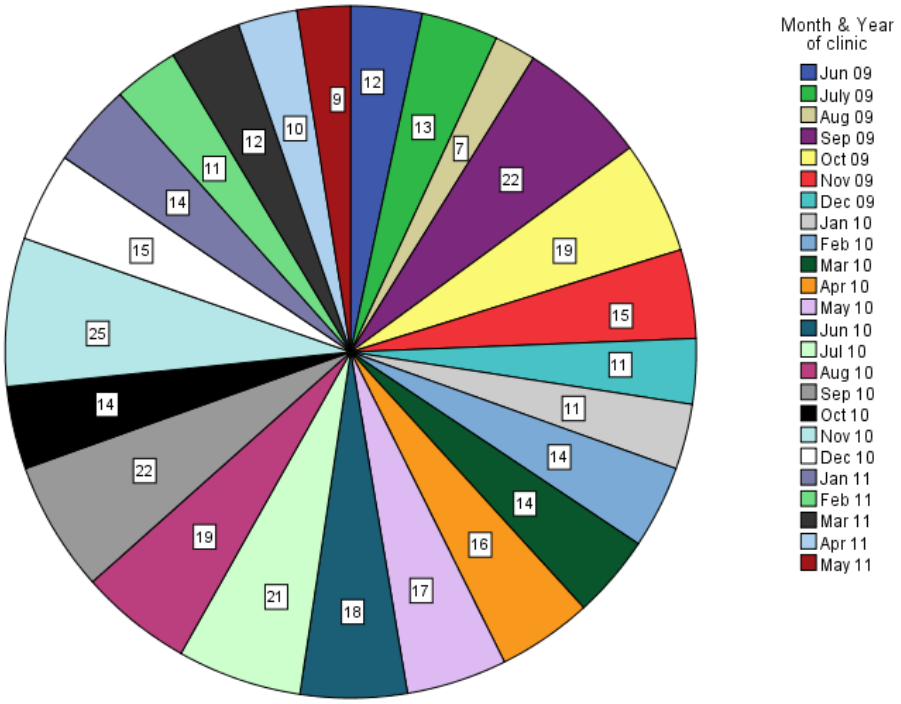
Furthermore, any risk projections stratifying by age group are problematic due to the few numerator cases available for stratification and the lack of age-related reference data. We did however look to repeat the calculations for women aged 70 years and over. The NICE costing template indicated a mid-2006 England population of 3,435,032 and a combined total of 1,533,459 with osteoporosis, i.e. 45% of all women aged 70+. We could not find any age breakdown (other than 50+) for the number of post-menopausal women receiving bisphosphonates, and thus were not able to estimate the percentage of women aged 70+ with osteoporosis receiving bisphosphonates. In the two regions the combined population estimate aged 70+ was 257,200 and in our study there were 29 women aged 70+ with BRONJ; for 22 the diagnosis was known and was osteoporosis in 17. Assuming the same proportion applies to the unknown a further 5 were added thus taking 22 as the number of BRONJ cases in the two year period, 11 per year. Assuming 40-50% of all women aged 70+ had osteoporosis and assuming between 15-50% of women aged 70+ with osteoporosis were treated with bisphosphonates then estimates of risk are also 'rare' (≥ 1/10,000, < 1/1,000).

RESULTS: 4. Case characteristics minimum dataset

This section presents the clinical data for the cases submitted to the study, and interpretation of these results makes the assumption that these cases are typical of all eligible cases, i.e. that there is no selection bias.

To recap, there were 369 cases described as BRONJ related and 9 cases for whom it was not known (but assumed) to be BRONJ related for the analysis of incidence (see previous section). These 9 were excluded from further analysis, because there were no further details to be analysed.

Question 1 of the study asked for the date of clinic at which the patient was first seen for BRONJ, and from these dates we can see from the pie chart below that month by month there was a fairly even spread of cases recruited over the 24 month period. The monthly variation was consistent with random variation (Goodness of fit test, Chi-squared =31.84, df=23, P=0.10, n=361) and thus there was no evidence of bias by clinic month in the submission of cases.



Two-thirds of cases (69%, 256) were female, 30% (111) were male, not known for 2 cases. Mean (SD) age was 68.5 (12.3) years, Median (IQR) 70 (61-77) years, range 18-96, with age being computed as year of clinic minus year of birth, unknown for 8 cases. Median (IQR) age for females was 70 (60-77) and for males was 69 (62-76). The route of administration was oral for 56% (207), IV for 34% (125), both oral and IV for 7% (27), the new drug Denosumab for 1 case, and unknown for 2% (9).

Further breakdown by age and gender is given in the next table. The oral-only route was seen in 74% (119/161) of women with BRONJ aged 65 years or older as compared with 49% (42/86) for women under 65 years (Fishers exact test, P<0.001), and 41% (44/108) for men. Females made up 79% (162/206) of those only having taken oral bisphosphonates, and 58% (88/151) of those having taken IV bisphosphonates (Fishers exact test, P<0.001). The median (IQR) age at first clinic seen was 72 (63-79) years for those on oral bisphosphonates alone, compared with 67 (59-75) years for those having had IV bisphosphonates (Mann-Whitney test, P<0.001); Median (IQR) for females were 71 (63-80) and 64 (54-75) respectively, and for males were 73 (62-77) and 68 (62-75).

Route of administration by age and sex

		Route of bisphosphonate administration						
		Oral only		IV only	BOTH Oral & IV	Denosumab	NK	Total
Female	<55	15	(39%)	21	2	-	1	39
	55-59	9	(56%)	5	2	-	-	16
	60-64	18	(56%)	9	5	-	-	32
	65-69	32	(84%)	6	-	-	-	38
	70-74	21	(58%)	10	4	-	1	36
	75-79	25	(63%)	13	1	-	1	40
	80-84	25	(89%)	2	-	-	1	28
	85+	16	(70%)	4	2	-	1	23
	NK	1	(25%)	1	1	-	1	4
	Total	162	(63%)	71 (20%)	17 (8%)	-	6 (2%)	256
Male	<55	5	(63%)	1	2	-	-	8
	55-59	4	(36%)	7	-	-	-	11
	60-64	3	(21%)	9	-	1	1	14
	65-69	6	(29%)	11	4	-	-	21
	70-74	9	(43%)	11	1	-	-	21
	75-79	8	(50%)	6	2	-	-	16
	80-84	7	(54%)	5	1	-	-	13
	85+	2	(67%)	1	-	-	-	3
	NK	0	(0%)	2	-	-	2	4
	Total	44	(40%)	53 (48%)	10 (9%)	1	3(3%)	111
NK	Total	1	(50%)	1 (50%)	-	-	-	2
Total	Total	207	(56%)	125 (34%)	27 (7%)	1	9(2%)	369

Name of IV

	Route of bisphosphonate administration		
	IV (125)	BOTH IV & Oral (27)	Total (152)
Disodium pamidronate (Aredia)	19	10	29
Zoledronic acid (Aclasta, Zometa)	78	15	93
Ibandronic acid (Bondronat, Bonviva)	6	3	9
Other	-	-	-
Not known	25	3	28

Multiples: Disodium pamidronate & Zoledronic acid (5), Disodium pamidronate & Ibandronic acid (1), Zoledronic acid & Ibandronic acid (1).

Name of Oral

	Route of bisphosphonate administration		
	Oral (207)	BOTH IV & Oral(27)	Total (234)
Ibandronic acid (Bondronat, Bonviva)	20	8	28
Sodium Clodronate (Bonefos, Loron/Clasteon)	5	4	9
Alendronic acid (Fosamax/Fosavance)	157	9	166
Disodium Etidronate (Didronel)	2	3	5
Risedronate sodium (Actonel)	24	3	27
Tiludronic acid (Skelid)	-	-	-
Other	-	-	-
Not known	7	1	8

Multiples: Alendronic acid & Risedronate sodium (4), Alendronic acid & Disodium Etidronate (2), Ibandronic acid & Alendronic acid (2), Sodium Clodronate & Alendronic acid (1)

RESULTS: 5. Further detailed case analyses

At this point in the analysis 69 cases are lost with only minimal data submitted, including the case taking Denosumab. Before progressing to analyse the 300 with more information, an exploratory analysis of the data was undertaken to see if any factors related to the degree of completion. There was little difference in cases having more complete data by sex of patient (80% female, 85% male), by route of administration (81% Oral only, IV or both 85%) or by age group (85% <65, 77% 65-74, 85% 75+). Greater variation (Chi-Squared test, P<0.001) was seen between regions (53-100%) which ultimately reflects on individual unit and consultant engagement in the study.

The results for the 300 with more information are presented in the results section to highlight the range of the data received.

The route of administration was oral for 56% (168), IV for 35% (104), both oral and IV for 8% (25), and was unknown for 1% (3).

Diagnosis for which a bisphosphonate was taken

This was known for 282 of the 300 cases. For 46% (131/282) the diagnosis was cancer, for 50% (141/282) it was osteoporosis, both diagnoses were mentioned for 2% (6) and for 2% other reasons were stated (3 with Paget's disease and 1 Thalassemia). The types of cancer stated (sometimes multiple) were breast (64), myeloma (37), prostate (26), and others (16, comprising a mix of primary or metastatic tumours – bone, cervical, colorectal, endometrial, liver, lung, renal spinal).

The vast majority of patients with cancer received IV bisphosphonates (84%, 108/129), the most common was Zoledronic acid. 94% (131/140) of patients with osteoporosis received oral treatment predominantly with Alendronic acid. It is recognised that there was considerable difficulty for the doctors involved in this study to elicit an accurate drug history from the patients. Patients can be vague regarding dose, frequency and even route of administration. For example some cancer patients are identified as having received oral bisphosphonates, which is unlikely and to have checked this would have required considerable extra effort. Further details are below:

	Diagnosis for which patient taking bisphosphonate				
	Cancer (131)	Osteoporosis / use of steroids (141)	Both (6)	Other (4)	Total (282)
Oral route only	21	131	4	-	156
IV route only	92	5	1	1	99
Both routes	16	4	1	3	24
Route NK	2	1	-	-	3

	Diagnosis for which patient taking bisphosphonate				
	Cancer (108)	Osteoporosis / use of steroids (9)	Both (2)	Other (4)	Total (123)
Disodium pamidronate (Aredia)	22	2	-	3	27
Zoledronic acid (Aclasta, Zometa)	65	4	2	-	71
Ibandronic acid (Bondronat, Bonviva)	3	3	-	-	6
Other	-	-	-	-	-
Not known	24	-	-	1	25

Multiples: Disodium pamidronate & Zoledronic acid (5), Disodium pamidronate & Ibandronic acid (1)

	Diagnosis for which patient taking bisphosphonate				
	Cancer (37)	Osteoporosis / use of steroids (135)	Both (5)	Other (3)	Total (180)
Ibandronic acid (Bondronat, Bonviva)	15	8	-	1	24
Sodium Clodronate (Bonefos, Loron/Clasteon)	7	-	-	-	7
Alendronic acid (Fosamax/Fosavance)	10	110	4	-	124
Disodium Etidronate (Didronel)	2	2	-	1	5
Risedronate sodium (Actonel)	2	18	1	1	22
Tiludronic acid (Skelid)	-	-	-	-	-
Other	-	-	-	-	-
Not known	2	4	-	-	6

Multiples: Alendronic acid & Risedronate sodium (4), Alendronic acid & Disodium Etidronate (2), Ibandronic acid & Alendronic acid (2).

Past medical history / comorbidity

The study proforma specifically listed certain conditions, and besides the conditions requiring the use of bisphosphonates (cancer, osteoarthritis or Pagets) patients had a wide range and mix of other problems, notably hypertension, respiratory disease and rheumatoid arthritis.

	Route of bisphosphonate administration				
	Oral (168)	IV (104)	BOTH (25)	NK (3)	Total (300)
Angina	24	2	1	-	27
Cancer	28	93	17	2	140
Diabetes (insulin)	8	4	1	-	13
Diabetes (oral control)	19	10	-	-	29
Chronic GI disease	9	4	5	1	19
COAD / Asthma	36	10	3	-	49
Hypertension	54	23	4	-	81
Liver disease	4	-	-	-	4
Malabsorption	-	-	-	-	-
Osteoporosis	115	7	5	1	128
Pagets	-	-	4	-	4
Primary Hyperparathyroidism	1	2	-	-	3
Renal failure	13	6	2	-	21
Rheumatoid arthritis	36	4	1	-	41
Other	30*[1]	3*[2]	4*[3]	-	37
Not known	12	4	1	-	17

*[1] Polymyalgia (10), Osteoarthritis (9), Pulmonary fibrosis (2), Sarcoid (2), Cervical spondylitis, MS, Nephrotic syndrome, Osteopenia, Scleroderma, Systemic lupus erythematosus & osteoarthritis, Wegener vasculitis & lung fibrosis.

*[2] Sjogrens syndrome (2), Osteoarthritis.

*[3] Osteoarthritis (2), Ankylosing spondylitis, Myasthenia Gravis.

	Diagnosis for which patient taking bisphosphonate				
	Cancer (131)	Osteoporosis / use of steroids (141)	Both (6)	Other (4)	Total (282)
Angina	2	22	-	1	25
Cancer	131	3	6	-	140
Diabetes (insulin)	4	6	1	1	12
Diabetes (oral control)	11	16	1	-	28
Chronic GI disease	8	9	1	-	18
COAD / Asthma	13	32	-	2	47
Hypertension	25	51	2	-	78
Liver disease	-	4	-	-	4
Malabsorption	-	-	-	-	-
Osteoporosis	3	118	6	1	128
Pagets	1	-	-	3	4
Primary Hyperparathyroidism	2	1	-	-	3
Renal failure	7	10	2	-	19
Rheumatoid arthritis	6	33	-	-	39
Other	4*[1]	31*[2]	-	2	37
Not known	-	5	-	-	5

*[1] Osteoarthritis (2), Ankylosing spondylitis, Sjogrens syndrome

*[2] Polymyalgia (10), Osteoarthritis (9), Pulmonary fibrosis (2), Sarcoid (2), Cervical spondylitis, MS, Nephrotic syndrome, Osteopenia, Scleroderma, Sjogrens syndrome, Systemic lupus erythematosus & osteoarthritis, Wegener vasculitis & lung fibrosis.

*[3] Osteoarthitis, Mysthnia Grasvis

Smoking status

Smoking status was stated for 69% (206) and of these 53% (109) had never smoked, 22% (46) was quit the habit and 25% (51) were current smokers.

	Route of bisphosphonate administration				
	Oral (168)	IV (104)	BOTH (25)	NK (3)	Total (300)
Never	67	34	8	-	109
Quit /Ex-smoker	27	13	6	-	46
Current	28	14	8	1	51
Not known	46	43	3	2	94

	Diagnosis for which patient taking bisphosphonate				
	Cancer (131)	Osteoporosis / use of steroids (141)	Both (6)	Other (4)	Total (282)
Never	45	55	3	1	104
Quit /Ex-smoker	17	24	2	-	43
Current	21	23	1	3	48
Not known	48	39	-	-	87

Questions 14 (How many years has the patients smoked), 15 (How many cigarettes per day – current situation) and 16 (Ex-smoker – how many years since quit) were poorly answered and have been omitted from the analyses.

Alcohol status (usual alcohol consumption)

Alcohol consumption status was stated for 64% (193) and of these 48% (92) were non-alcoholic drinkers, 48% (92) consumed less than 20 units a week and 5% (9) more than 20 units a week.

	Route of bisphosphonate administration				
	Oral (168)	IV (104)	BOTH (25)	NK (3)	Total (300)
Nil	57	25	9	1	92
Mild (less than 20 units a week)	49	34	9	-	92
Medium (21 to 40 units per week)	4	-	1	-	5
Heavy (more than 40 units per week)	3	-	1	-	4
Not known	55	45	5	2	107

	Diagnosis for which patient taking bisphosphonate				
	Cancer (131)	Osteoporosis / use of steroids (141)	Both (6)	Other (4)	Total (282)
Nil	28	54	4	3	89
Mild (less than 20 units a week)	49	36	2	-	87
Medium (21 to 40 units per week)	3	2	-	-	5
Heavy (more than 40 units per week)	-	4	-	-	4
Not known	51	45	-	1	97

Year of diagnosis of condition for which bisphosphonates taken

This was known for 62% (186/300) and the median year of diagnosis for which the patient was taking bisphosphonates was 2005, IQR 2002 to 2008. For those having taking medication only via the oral route only the median was 2007 IQR 2004-2009 whilst for those having taken IV or both routes the median was 2004 IQR 2001 to 2007.

	Route of bisphosphonate administration				
	Oral	IV	BOTH	NK	Total
1980	-	-	1	-	1
1989	-	-	1	-	1
1991	1	-	1	-	2
1992	-	-	1	-	1
1993	1	1	-	-	2
1994	1	1	-	-	2
1995	-	-	1	-	1
1996	1	-	-	-	1
1997	2	1	1	-	4
1998	1	-	1	-	2
1999	1	3	1	-	5
2000	5	3	2	-	10
2001	4	2	2	-	8
2002	1	4	1	-	6
2003	6	7	-	1	14
2004	6	7	3	-	16
2005	14	3	3	-	20
2006	5	6	2	-	13
2007	14	7	1	-	22
2008	10	5	-	-	15
2009	10	8	1	1	20
2010	16	2	1	-	19
2011	1	-	-	-	1
Total	100	60	24	2	186
Not known	68	44	1	1	114

Bisphosphonate drug history

Collection of accurate details of bisphosphonate prescription dose and frequency proved to be very difficult and consequently these have been omitted from the analyses.

Year IV started

The year IV treatment started was known for 59% (76/129) of those taking IV bisphosphonates. Median (IQR) years from start of IV to BRONJ clinic was 3 (1-6) years, n=75; for IV route only 3 (1-5) years n=55; for both oral & IV route 3 (2-8) years, n=20.

	Route of bisphosphonate administration		
	IV	BOTH oral & IV	Total
1989	-	1	1
1994	1	-	1
2000	3	2	5
2001	-	1	1
2002	2	2	4
2003	4	-	4
2004	4	2	6
2005	2	2	4
2006	8	-	8
2007	9	3	12
2008	7	3	10
2009	11	4	15
2010	4	1	5
Total	55	21	76
Not known	49	4	53

Years from IV started to	Route of bisphosphonate administration		
BRONJ clinic	IV	BOTH oral and IV	Total
0	4	2	6
1	11	2	13
2	12	5	17
3	5	2	7
4	7	1	8
5	3	2	5
6	5	1	6
7	2	-	2
8	2	1	3
9	1	2	3
10	2	1	3
15	1	-	1
21	-	1	1
Total	55	20	75
Not known	49	5	54

Patient still on IV

Whether the patient was still on IV treatment at the time of the BRONJ clinic was known for 64% (82/129). Of these 41% (34) were still taking IV and 59% (48) had stopped.

	Route of bisphosphonate administration		
	IV (104)	BOTH (25)	Total (129)
YES	29	5	34
NO	31	17	48
Not known	44	3	47

Year IV finished

Start and finish dates for IV was known for 43 cases.
Median (IQR) duration on IV for those who finished IV: 3 (1-5) years, n=43 of 48.
Median (IQR) duration on IV for those on IV alone and who finished IV: 3 (2-5) years, n=28 of 31.
Median (IQR) duration on IV for those having IV & oral and who finished IV: 2 (0-5) years, n=15 of 17.
Median (IQR) duration on IV for those still on IV drugs at BRONJ clinic: 2 (1-6) years, n=28 of 34.

			Year IV finished								Total
			1993	2000	2004	2005	2007	2008	2009	2010	2011	
IV	Year started	2000			1			1				2
		2002								1		1
		2003							2	1		3
		2004					2					2
		2006							2	2	2	6
		2007						1	3	2		6
		2008								2		2
		2009								5	1	6
	Total				1		2	2	7	13	3	28
BOTH	Year started	1989	1									1
		2000		1		1						2
		2001						1				1
		2002					1	1				2
		2004			1							1
		2005					1		1			2
		2007					1	1		1		3
		2008						1	1			2
		2009								1		1
	Total		1	1	1	1	3	4	2	2		15

Year Oral started

The year oral treatment started was known for 63% (122/193) of those taking oral bisphosphonates. Median (IQR) years from start of oral treatment to BRONJ clinic was 4 (2-6) years, n=120; for Oral route only 4 (2-5) years n=100; for both oral & IV route 4 (2-11) years, n=20.

	Route of bisphosphonate administration		
	Oral	BOTH	Total
1992	-	1	1
1993	-	1	1
1995	2	1	3
1998	-	2	2
2000	5	-	5
2001	6	1	7
2002	2	1	3
2003	4	-	4
2004	8	3	11
2005	14	2	16
2006	13	1	14
2007	13	1	14
2008	17	5	22
2009	12	3	15
2010	3	-	3
2011	1		1
Total	100	22	122
Not known	68	3	71

Years from oral started to BRONJ clinic	Route of bisphosphonate administration		
	Oral	BOTH	Total
0	7	1	8
1	12	2	14
2	16	4	20
3	11	1	12
4	16	3	19
5	9	1	10
6	13	2	15
7	1	-	1
8	3	-	3
9	5	-	5
10	5	1	6
11	-	1	1
13	-	1	1
14	1	1	2
15	1	-	1
17	-	1	1
19	-	1	1
Total	100	20	120
Not known	68	5	73

Patient still on Oral

Whether the patient was still on oral treatment at the time of the BRONJ clinic was known for 81% (157/193). Of these 61% (96) were still taking oral bisphosphonates and 39% (61) had stopped.

	Route of bisphosphonate administration		
	Oral (168)	BOTH (25)	Total (193)
YES	91	5	96
NO	44	17	61
Not known	33	3	36

Year Oral finished

Start and finish dates were known for 46 cases.
Median (IQR) duration on Oral for those who finished Oral: 3 (2-6) years, n=46 of 61.
Median (IQR) duration on Oral alone and who finished Oral: 4 (2-6) years, n=31 of 44.
Median (IQR) duration on Oral for those on Oral & IV who finished Oral: 2 (1-11) years, n=15 of 17.
Median (IQR) duration on Oral for those still on Oral at BRONJ clinic: 3 (1-6) years, n=69 of 96.

			Year oral finished									
			1999	2002	2004	2005	2007	2008	2009	2010	2011	Total
Oral	Year oral started	1995							1			1
		2000			1				1			2
		2001							2	1		3
		2002								1		1
		2003					1		1			2
		2004								1		1
		2005							1	3		4
		2006						1	2	1		4
		2007							1	2	1	4
		2008							2	2	1	5
		2009								1	3	4
	Total				1		1	1	11	12	5	31
BOTH	Year oral started	1992							1			1
		1993									1	1
		1995						1				1
		1998	1						1			2
		2002		1								1
		2004				1			2			3
		2005				1		1				2
		2006					1					1
		2008						1		1		2
		2009								1		1
	Total		1	1		2	1	3	4	2	1	15

Patients on both IV and Oral Bisphosphonates

Of the 25 on both IV and oral bisphosphonates the information about start and end dates indicate that 6 were started on IV first, 9 were started on oral first and for 10 the temporal situation is unclear due to the paucity of information. For the 15 with more complete information the median (IQR) time on bisphosphonates was 5 (3-11) years and the time from first starting to the BRONJ clinic was 5 (4-13) years.

Other medications patient taking or had taken

These items below were specifically asked about on the study proforma and data were known for 75% (225/300). Of these 50% (112) were taking or had taken corticosteroids, 22% (50) vitamin D, 20% (44) chemotherapy, 19% (43) NSAIDs, 10% (22) methotrexate, 4% (10) calcitonin, 4% (10) thalidomide, whilst 24% (55) had taken none on this list. Further details as below:

	Route of bisphosphonate administration				
	Oral (168)	IV (104)	BOTH (25)	NK (3)	Total (300)
Calcitonin	4	4	2	-	10
Chemotherapy	11	25	8	-	44
Corticosteroids	75	28	9	-	112
Methotrexate	19	1	2	-	22
NSAID	29	8	6	-	43
Thalidomide	2	5	3	-	10
Vitamin D	36	8	6	-	50
None of the above	31	20	4	-	55
Not known	32	37	3	3	75

	Diagnosis for which patient taking bisphosphonate				
	Cancer (131)	Osteoporosis / use of steroids (141)	Both (6)	Other (4)	Total (282)
Calcitonin	5	4	-	1	10
Chemotherapy	37	3	3	-	43
Corticosteroids	34	67	1	3	105
Methotrexate	3	16	-	-	19
NSAID	17	23	2	1	43
Thalidomide	8	-	-	-	8
Vitamin D	10	34	-	2	46
None of the above	20	28	2	1	51
Not known	45	25	-	-	70

Other medication

This was an open-ended free-text question and many patients were taking many medications. Particular note was made of the mention of statins for 1 in 5 of the patients overall (22%, 65/300) and of azathioprine in 4 cases.

Did a dental or other event initiate/uncover/expose BRONJ – Likely cause of BRONJ

The question about initiating event had these response options listed and responses were available for 79% (237). Multiple responses were possible. Extractions were mentioned for 73% (174), dental trauma for 7% (16), dental infection for 5% (13) and spontaneous for 17% (41).

	Route of bisphosphonate administration				
	Oral (168)	IV (104)	BOTH (25)	NK (3)	Total (300)
Extraction	109	49	16	-	174
Denture trauma	11	5	-	-	16
Dental infection	8	5	-	-	13
Spontaneous	20	15	6	-	41
Other*	3	-	-	-	3
Not known	21	35	4	3	63

*Removal of osteoma (1), Pressure Induced due to Severe Cervical Kyphoscoliosis (1), Fell at home and hit chin: trauma (1).

	Diagnosis for which patient taking bisphosphonate				
	Cancer (131)	Osteoporosis / use of steroids (141)	Both (6)	Other (4)	Total (282)
Extraction	63	91	5	3	162
Denture trauma	5	8	1	-	14
Dental infection	4	8	-	-	12
Spontaneous	19	18	-	2	39
Other*	-	3	-	-	3
Not known	44	17	-	-	61

*Removal of osteoma (1), Pressure Induced due to Severe Cervical Kyphoscoliosis (1), Fell at home and hit chin: trauma (1).

Symptoms of BRONJ

The question about symptoms had these options listed and responses were available for 81% (244). Multiple responses were possible. Pain was mentioned for 74% (181), discharge for 46% (112), swelling for 43% (104), sinus for 19% (47), fistula for 9% (21) and spontaneous exfoliation for 13% (31). Various other categories were created from the free-text received, notably asymptomatic (8%, 20) and numbness (5%, 13).

	Route of bisphosphonate administration				
	Oral (168)	IV (104)	BOTH (25)	NK (3)	Total (300)
Discharge	73	33	6	-	112
Pain	108	57	16	-	181
Swelling	68	29	7	-	104
Sinus	29	16	2	-	47
Fistula	14	3	4	-	21
Spontaneous exfoliation	18	7	6	-	31
Others*	27	14	8	-	49
• *Asymptomatic*	*10*	*6*	*4*	-	*20*
• *Bleeding*	*3*	-	-	-	*3*
• *Jaw fracture*	*1*	-	-	-	*1*
• *Numbness*	*8*	*3*	*2*	-	*13*
• *Soft tissue trauma*	*2*	*1*	*1*	-	*4*
• *Ulcer*	*3*	*4*	*1*	-	*8*
Not known	19	32	2	3	56

*these 'other' categories were created from the free-text responses received.

	Diagnosis for which patient taking bisphosphonate				
	Cancer (131)	Osteoporosis / use of steroids (141)	Both (6)	Other (4)	Total (282)
Discharge	39	62	4	1	106
Pain	70	92	4	3	169
Swelling	36	60	3	2	101
Sinus	16	28	1	-	45
Fistula	6	13	1	1	21
Spontaneous exfoliation	11	14	1	3	29
Others*	19	26	1	1	47
• *Asymptomatic*	*9*	*10*	*-*	*-*	*19*
• *Bleeding*	*-*	*3*	*-*	*-*	*3*
• *Jaw fracture*	*-*	*1*	*-*	*-*	*1*
• *Numbness*	*3*	*8*	*1*	*-*	*12*
• *Soft tissue trauma*	*2*	*2*	*-*	*-*	*4*
• *Ulcer*	*5*	*2*	*-*	*1*	*8*
Not known	38	14	1	-	53

*these 'other' categories were created from the free-text responses received.

Site or sites of BRONJ

The question asking about the site of BRONJ was open-ended and the detail received was mixed. From this free-text dental sextant categories were created. Enough information to do this was available for 62% (186/300) with various degrees of incompleteness also categorised. Excluding the multiple sites and complete unknowns the BRONJ site was situated in the lower dental region for 131 and the upper dental region for 70 i.e. almost a 2 to 1 ratio. BRONJ sites were predominantly molar and evenly spread to left or right.

	Route of bisphosphonate administration				
	Oral (168)	IV (104)	BOTH (25)	NK (3)	Total (300)
UR48	14	8	1	-	23
UR3-UL3	1	2	1	-	4
UL48	11	5	4	-	20
LR48	30	14	6	-	50
LR3-LL3	12	10	-	-	22
LL48	33	16	4	-	53
Not known but upper	20	2	1	-	23
Not known but lower	2	2	2	-	6
Not Known	39	38	5	3	85
More than one site	6	7	1	-	14

	Diagnosis for which patient taking bisphosphonate				
	Cancer (131)	Osteoporosis / use of steroids (141)	Both (6)	Other (4)	Total (282)
UR48	7	11	2	-	20
UR3-UL3	2	1	-	1	4
UL48	8	10	1	-	19
LR48	18	28	-	1	47
LR3-LL3	11	9	-	-	20
LL48	21	31	-	-	52
Not known but upper	1	17	1	1	20
Not known but lower	3	2	1	-	6
Not Known	50	29	1	-	80
More than one site	10	3	-	1	14

Length & Width of exposed bone in mm

Length (L) and width (W) of exposed bone were recorded for 52% (157/300) of cases, whilst in another 10 cases it was stated there was no exposed bone. Median (IQR) length was 8 (5-14) mm, median (IQR) width was 5 (4-10) mm and median area (LxW) was 48 (25-100) mm^2.

For those taking oral bisphosphonates only: Median (IQR) length was 6 (5-13) mm, median (IQR) width was 5 (4-8) mm and median area (LxW) was 25 (21-100) mm^2, n=89 of 168.

For those taking IV bisphosphonates only: Median (IQR) length was 10 (5-10) mm, median (IQR) width was 6 (4-10) mm and median area (LxW) was 55 (25-100) mm^2, n=52 of 104.

For those taking IV and oral bisphosphonates: Median (IQR) length was 10 (6-20) mm, median (IQR) width was 7 (5-10) mm and median area (LxW) was 60 (26-200) mm^2, n=16 of 25.

Kruskal-Wallis test of area between the three groups (oral, IV, both), P=0.07. It is not unreasonable to suggest that patients taking IV have a great severity of BRONJ in term of bone exposure.

			Width in mm													
			1	2	3	4	5	6	7	8	10	15	17	18	20	
Oral	Length in mm	1	2	1												3
		2		1	4		2									7
		3		2	4											6
		4				2										2
		5		1			19			1	1					22
		6			1	3		2								6
		7					1									1
		8		2	1		1			3						7
		10				1	3	2	1	1	4					12
		12					1									1
		14						1								1
		15					1				4	1				6
		20					2			1	3	1			1	8
		22												1		1
		25								1						1
		30				1	1								1	3
		35									1					1
		40													1	1
	Total		2	7	10	7	31	5	1	7	13	2		1	3	89
IV	Length in mm	1	1													1
		2		1			1									2
		3			1	1										2
		4		1												1
		5			2		4		1							7
		6			1			1		1						3
		7		1		1	2									4
		8				1	1			2						4
		10			1		3	1			11					16
		12							1							1
		15									1				1	2
		18					1									1
		20									2				1	3
		25													1	1
		30										1				1
		40				1					2					3
	Total		1	3	5	4	12	2	2	3	16	1			3	52
BOTH	Length in mm	2	1													1
		5					2									2
		6					1									1
		7							1							1
		8		1												1
		10					2		1							3
		15									1					1
		17											1			1
		20									2					2
		24								1						1
		30										1				1
		35								1						1
	Total		1	1			5		2	2	3	1	1			16

Maxillary dentition and denture

Maxillary dentition status was known for 74% (221) and of these 84% (186) were dentate. Denture status was known for 64% (193), with 63% (121) not wearing dentures, 23% (44) partial dentures and 15% (28) full dentures.

			Maxilla - denture				
			No	Partial	Full	Not known	Total
Oral	Maxillary dentition	Dentate	65	31	-	11	107
		Edentulous	-	2	18	1	21
		Not known	1	-	-	39	40
		Total	66	33	18	51	168
IV	Maxillary dentition	Dentate	41	5	-	14	60
		Edentulous	1	-	8	3	12
		Not known	-	-	-	32	32
		Total	42	5	8	49	104
BOTH	Maxillary dentition	Dentate	12	6	-	1	19
		Edentulous	-	-	2	-	2
		Not known	1	-	-	3	4
		Total	13	6	2	4	25
NK	Maxillary dentition	Not known				3	3
Total	Maxillary dentition	Dentate	118	42	-	26	186
		Edentulous	1	2	28	4	35
		Not known	2	-	-	77	79
		Total	121	44	28	107	300

			Maxilla - denture				
			No	Partial	Full	Not known	Total
Cancer	Maxillary dentition	Dentate	54	10	-	16	80
		Edentulous	1	-	8	3	12
		Not known	-	-	-	39	39
		Total	55	10	8	58	131
Osteoporosis / use of steroids	Maxillary dentition	Dentate	52	28	-	9	89
		Edentulous	-	1	17	1	19
		Not known	2	-	-	31	33
		Total	54	29	17	41	141
Both cancer and Osteoporosis	Maxillary dentition	Dentate	3	3	-	-	6
	Total		3	3	-	-	6
Other	Maxillary dentition	Dentate	3	1	-	-	4
		Total	3	1	-	-	4
Total	Maxillary dentition	Dentate	112	42	-	25	179
		Edentulous	1	1	25	4	31
		Not known	2	-	-	70	72
		Total	115	43	25	99	282

Mandibular dentition and denture

Mandibular dentition status was known for 73% (219) and of these 90% (198) were dentate. Denture status was known for 60% (181) with 73% (133) not wearing dentures, 18% (32) partial dentures and 9% (16) full dentures.

			Mandibular - denture				
			No	Partial	Full	Not known	Total
Oral	Mandibular dentition	Dentate	64	24	1	25	114
		Edentulous	1	-	12	1	14
		Not known	2	-	-	38	40
		Total	67	24	13	64	168
IV	Mandibular dentition	Dentate	44	6	-	13	63
		Edentulous	2	-	3	2	7
		Not known	1	-	-	33	34
		Total	47	6	3	48	104
BOTH	Mandibular dentition	Dentate	18	2	-	1	21
		Not known	1	-	-	3	4
		Total	19	2	-	4	25
NK	Mandibular dentition	Not known	-	-	-	3	3
Total	Mandibular dentition	Dentate	126	32	1	39	198
		Edentulous	3	-	15	3	21
		Not known	4	-	-	77	81
		Total	133	32	16	119	300

			Mandibular - denture				
			No	Partial	Full	Not known	Total
Cancer	Mandibular dentition	Dentate	62	6	-	16	84
		Edentulous	2	-	3	2	7
		Not known	1	-	-	39	40
		Total	65	6	3	57	131
Osteoporosis / use of steroids	Mandibular dentition	Dentate	53	24	1	18	96
		Edentulous	1	-	10	1	12
		Not known	3	-	-	30	33
		Total	57	24	11	49	141
Both cancer and Osteoporosis	Mandibular dentition	Dentate	2	2		2	6
Other	Mandibular dentition	Dentate	2			2	4
Total	Mandibular dentition	Dentate	119	32	1	38	190
		Edentulous	3	-	13	3	19
		Not known	4	-	-	69	73
		Total	126	32	14	110	282

OPG taken

Whether an OPG was taken was known for 74% (223) and of these an OPG was taken for 89% (199). Further details as below:

	Route of bisphosphonate administration				
	Oral (168)	IV (104)	BOTH (25)	NK (3)	Total (300)
Yes	112	66	21	-	199
No	20	3	1	-	24
Not known	36	35	3	3	77

	Diagnosis for which patient taking bisphosphonate				
	Cancer (131)	Osteoporosis / use of steroids (141)	Both (6)	Other (4)	Total (282)
Yes	85	94	4	4	187
No	4	17	2	-	23
Not known	42	30	-	-	72

If MAXILLA known to be dentate (Q37), n=186, OPG done for 159, not done for 18, not known for 9.

	% Bone loss on OPG				
	<25%	25-50%	50-75%	>75%	Total
Upper left molars	38	26	22	-	86
Upper canines / incisors	41	41	18	-	100
Upper right molars	37	26	23	3	89

Relating Site of BRONJ sextant code to the OPG, if MAXILLA dentate:

		Upper left molars %BONE LOSS ON OPG			
		<25%	25-50%	50-75%	Total
Site of BRONJ	UR48	6	1	3	10
	UR3-UL3	1	1	-	2
	UL48	2	-	4	6
	LR48	10	4	6	20
	LR3-LL3	-	1	1	2
	LL48	7	10	5	22
	NK BUT LOWER	3	2	-	5
	NK BUT UPPER	1	1	-	2
	NK	3	5	2	10
	MORE THAN ONE SITE	5	1	1	7
	Total	38	26	22	86

		Upper canines / incisors %BONE LOSS ON OPG			
		<25%	25-50%	50-75%	Total
Site of BRONJ	UR48	9	3	3	15
	UL48	3	3	3	9
	LR48	9	8	4	21
	LR3-LL3	2	-	3	5
	LL48	9	14	2	25
	NK BUT LOWER	2	3	-	5
	NK BUT UPPER	-	1	-	1
	NK	2	8	2	12
	MORE THAN ONE SITE	5	1	1	7
	Total	41	41	18	100

		Upper right molars %BONE LOSS ON OPG				
		<25%	25-50%	50-75%	>75%	Total
Site of BRONJ	UR48	8	1	3	-	12
	UR3-UL3	-	1	-	-	1
	UL48	3	1	4	-	8
	LR48	10	6	4	1	21
	LR3-LL3	-	1	2	2	5
	LL48	6	8	4	-	18
	NK BUT LOWER	3	2	-	-	5
	NK BUT UPPER	-	-	1	-	1
	NK	1	6	3	-	10
	MORE THAN ONE SITE	6	-	2	-	8
	Total	37	26	23	3	89

If MANDIBLE known to be dentate (Q43), n=198, OPG done for 170, not done for 19, not known for 9.

	% Bone loss on OPG				
	<25%	25-50%	50-75%	>75%	Total
Lower left molars	41	29	20	2	92
Lower canines / incisors	45	48	17	1	111
Lower right molars	41	29	15	3	88

Relating Site of BRONJ sextant code to the OPG, if MANDIBLE dentate:

		Lower left molars %BONE LOSS ON OPG				
		<25%	25-50%	50-75%	>75%	Total
Site of BRONJ	UR48	6	2	2	-	10
	UR3-UL3	-	1	-	-	1
	UL48	4	1	2	1	8
	LR48	11	5	2	1	19
	LR3-LL3	-	2	2	-	4
	LL48	9	10	5	-	24
	NK BUT LOWER	2	2	-	-	4
	NK BUT UPPER	-	-	1	-	1
	NK	4	5	5	-	14
	MORE THAN ONE SITE	5	1	1	-	7
	Total	41	29	20	2	92

		Lower canines / incisors %BONE LOSS ON OPG				
		<25%	25-50%	50-75%	>75%	Total
Site of BRONJ	UR48	8	5	1	-	14
	UR3-UL3	-	1	-	-	1
	UL48	4	2	3	-	9
	LR48	12	9	1	-	22
	LR3-LL3	2	2	3	1	8
	LL48	8	15	2	-	25
	NK BUT LOWER	3	3	-	-	6
	NK BUT UPPER	-	1	2	-	3
	NK	3	9	4	-	16
	MORE THAN ONE SITE	5	1	1	-	7
	Total	45	48	17	1	111

		Lower right molars %BONE LOSS ON OPG				
		<25%	25-50%	50-75%	>75%	Total
Site of BRONJ	UR48	7	3	1	-	11
	UR3-UL3	-	-	-	-	-
	UL48	3	1	1	-	5
	LR48	9	8	4	1	22
	LR3-LL3	-	1	1	-	2
	LL48	10	7	3	1	21
	NK BUT LOWER	3	1	-	-	4
	NK BUT UPPER	-	1	1	-	2
	NK	5	6	3	1	15
	MORE THAN ONE SITE	4	1	1	-	6
	Total	41	29	15	3	88

Peridontal Examination (BPE) assessment

Whether a BPE assessment was performed was known for 59% (176) and of these a BPE assessment was done in 19% (34). Further details as below:

	Route of bisphosphonate administration				
	Oral (168)	IV (104)	BOTH (25)	NK (3)	Total (300)
Yes	15	16	3	-	34
No	87	40	15	-	142
Not sure	66	48	7	3	124

	Diagnosis for which patient taking bisphosphonate				
	Cancer (131)	Osteoporosis / use of steroids (141)	Both (6)	Other (4)	Total (282)
Yes	16	14	1	-	31
No	57	73	2	4	136
Not sure	58	54	3	-	115

BPE assessment details

	BPE scoring code					
N=34 with BPE data	0	1	2	3	4	Total
Upper left sextant	6	4	8	11	1	30
Upper anterior sextant	6	5	12	7	2	32
Upper right sextant	6	5	8	8	4	31
Lower left sextant	5	2	8	10	1	26
Lower anterior sextant	4	5	13	8	1	31
Lower right sextant	5	3	9	8	5	30

BPE **Scoring codes**

0	No pockets >3.5 mm, no calculus/overhangs, no bleeding after probing *(black band completely visible)*
1	No pockets >3.5 mm, no calculus/overhangs, but bleeding after probing *(black band completely visible)*
2	No pockets >3.5 mm, but supra- or subgingival calculus/overhangs *(black band completely visible)*
3	Probing depth 3.5-5.5 mm *(black band partially visible, indicating pocket of 4-5 mm)*
4	Probing depth >5.5 mm *(black band entirely within the pocket, indicating pocket of 6 mm or more)*

Results: Provisional analysis of outcome data within 1-2 years

Because of the lack of patient identification in the registration and in baseline dataset for cases, it seems very difficult for some units to trace their patients for outcome data. Only 19 patient consents to allow approach in the future were submitted to us.

At the time of this report outcome status data (see Appendix G) were available for only 22% (83/369) of BRONJ cases, nearly half of which were from the North West (28) or Yorkshire & Humber (11) regions. Outcome was known for 93% (77). Of these 78% (60) were alive. In 25% (19/77) the patient was alive and the BRONJ had healed, in 44% (34/77) the patient was alive and the BRONJ was stable and on-going, in 9% (7/77) the patient was alive but the BRONJ had progressed/got worse, in 21% (16/77) the patient had died with BRONJ still present and in 1% (1/77) the patient had died after the BRONJ had healed. It would appear from these data that the likelihood of healing is higher for those (predominantly non-cancer) patients only having taken oral bisphosphonates (35%, 14/40) compared to those (mainly cancer patients) only having taken IV bisphosphonate (11%, 3/27). Further details as below:

OUTCOME closest to 12 months after the above clinic date, within 1-2 years	Route of bisphosphonate administration				
	Oral	IV	BOTH	NK	Total
1 Patient alive and BRONJ has healed	14	3	2	0	19
2 Patient alive and BRONJ is stable and on-going	20	11	3	0	34
3 Patient alive and BRONJ has progressed / got worse	3	3	1	0	7
4 Patient died with BRONJ still present	3	9	3	1	16
5 Patient died and BRONJ healed	0	1	0	0	1
6 Unable to trace patient / lost to follow up outcome NK	2	3	1	0	6
Total	42	30	10	1	83

OUTCOME closest to 12 months after the above clinic date, within 1-2 years	Diagnosis for which patient taking bisphosphonate				
	Cancer	Osteoporosis / use of steroids	Both cancer and Osteoporosis	Other	Total
1 Patient alive and BRONJ has healed	2	14	0	2	18
2 Patient alive and BRONJ is stable and on-going	9	20	1	0	30
3 Patient alive and BRONJ has progressed / got worse	4	2	0	0	6
4 Patient died with BRONJ still present	9	3	0	0	12
6 Unable to trace patient / lost to follow up outcome NK	2	2	0	0	4
Total	26	41	1	2	70

Appendix A: References

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Appendix B: Fax registration form

Faculty of General Dental Practice (UK)
The Royal College of Surgeons of England

National Audit on Avascular Necrosis of the Jaws including Bisphosphonate-related Osteonecrosis (BRONJ)

REGISTRATION FORM

Please complete this form once for every new patient with avascular necrosis / BRONJ of the jaws that you have seen for the first time from 1st June 2009 onwards and fax or email it to the Project Manager

We are simplifying the audit and one step in this process is this faxed registration form. Please also use this form as a record within your own unit's notes of the patient. The team will be back in touch with you to confirm some more information regarding the patient's history and presentation and how this can be submitted as part of the National Audit.

1. Date of Clinic_____

2. Time of Clinic *(please tick)* **Morning** ☐ **Afternoon** ☐

3. Name of Hospital_____

4. Name of Consultant whose clinic it is: _____

5. Patient's Year of Birth_____

6. Gender: *(please tick)* **Male** ☐ **Female** ☐

7. Is it Avascular necrosis ☐ **or BRONJ** ☐ **If BRONJ please answer Q 8 and 9**

8. Name of bisphosphonate _____

9. Route of administration Oral ☐ **IV** ☐ **Both** ☐

THANK YOU

Please fax this form to the Audit Project Manager, Amrita Narain on 020 7869 6765. Or email it to broni@rcseng.ac.uk

For any further information call 020 7869 6750

Appendix C: Final SNAP web data entry proforma

Faculty of General Dental Practice (UK)
The Royal College of Surgeons of England

NATIONAL AVASCULAR OSTEONECROSIS OF THE JAWS NEW CASE REGISTRATION

Please use this proforma for newly diagnosed patients presenting with avascular necrosis of the jaw / BRONJ from 1st June 2009

The first 9 questions are the same as those on the faxed registration form if you used this to register the patient

1. **Date of clinic at which the patient was first seen (dd/mm/yyyy)**

_____

2. **Time of clinic**

- ☐ *Morning*
- ☐ *Afternoon*

3. **Name of hospital**

_____

4. **Name of Consultant whose clinic it is**

_____

5. **Year of birth of patient (yyyy)**

_____

6. **Gender**

- ☐ *Female*
- ☐ *Male*

7. **Do you suspect that the avascular necrosis is related to bisphosphonates (BRONJ)**

- ☐ *Yes - BRONJ*
- ☐ *No avascular necrosis of other cause - if not you have now finished this questionnaire*

8. **Name of bisphosphonate**

9. **Route of bisphosphonate administration**

- ☐ *Oral*
- ☐ *IV (Intravenous)*
- ☐ *Both oral and IV*

Further details about the patient

10. **What is the diagnosis for which the patient is taking bisphosphonates?**

- ☐ *Breast cancer*
- ☐ *Myeloma cancer*
- ☐ *Prostate cancer*
- ☐ *Other cancer*
- ☐ *Osteoporosis*
- ☐ *Other cause*

Please specify other cancer or cause

_____

11. **Year of diagnosis e.g 2000**

_____

12. **Past Medical History / Comorbidity**

- ☐ *None*
- ☐ *Angina*
- ☐ *Cancer (please specify below)*
- ☐ *Diabetetes (insulin)*
- ☐ *Diabetes (oral control)*
- ☐ *Chronic GI disease*
- ☐ *COAD /Asthma*
- ☐ *Hypertension*
- ☐ *Liver disease*
- ☐ *Malabsortion*
- ☐ *Osteoporosis*
- ☐ *Pagets*
- ☐ *Primary Hyperparathyroidism*
- ☐ *Renal failure*
- ☐ *Rheumatoid arthritis*
- ☐ *Other (please specify below)*

Please specify type of cancer and other comorbidity

_____

13. **Smoking status**

- *Never*
- *Quit / ex-smoker*
- *Current*
- *Not known*

14. **How many cigarettes per day (current situation)**

- *0*
- *1-9*
- *10-19*
- *20-39*
- *40+*

15. **How many years has the patient smoked**

- *0*
- *1-9*
- *10-19*
- *20-39*
- *40+*

16. **Ex-smoker: How many years since the patient last smoked**

- *1*
- *2*
- *3*
- *4*
- *5-9*
- *10-19*
- *20+*

17. **Alcohol status (usual alcohol consumption)**

- *Nil*
- *Mild (less than 20 units a week)*
- *Medium (21 to 40 units per week)*
- *Heavy (more than 40 units per week)*
- *Not known*

Bisphosphonate drug history

18. **Route of bisphosphonate administration (although this question has been asked before please answer it again as it helps the flow of the next series of questions)**

- *Oral*
- *IV*
- *Both*

19. **Name of IV**

- *Disodium pamidronate (Aredia)*
- *Zoledronic acid (Aclasta, Zometa)*
- *Ibandronic acid (Bondronat, Bonviva)*
- *Not known*
- *Other*

Please specify Other

_____

20. **Dose of IV (mg) and frequency (e.g. weekly, monthly, yearly)**

_____

21. **Year IV started**

_____

22. **Is the patient still on IV**

- ☐ *Yes*
- ☐ *No*

23. **Year IV finished**

_____

24. **Name of Oral**

- ☐ *Ibandronic acid (Bondronat, Bonviva)*
- ☐ *Sodium Clodronate (Bonefos, Loron/Clasteon)*
- ☐ *Alendronic acid (Fosamax/Fosavance)*
- ☐ *Disodium Etidronate (Didronel)*
- ☐ *Risedronate sodium (Actonel)*
- ☐ *Tiludronic acid (Skelid)*
- ☐ *Other*

Please specify Other

_____

25. **Dose of Oral (mg) and frequency (e.g. weekly, monthly, yearly)**

_____

26. **Year oral started**

_____

27. **Is the patient still on oral**

- ☐ *Yes*
- ☐ *No*

28. **Year oral finished**

_____

29. **Please indicate if the patient is taking or has taken any of the following**

- ☐ *Calcitonin*
- ☐ *Chemotherapy*
- ☐ *Corticosteroids*
- ☐ *Methotrexate*
- ☐ *NSAID*
- ☐ *Thalidomide*
- ☐ *Vitamin D*
- ☐ *None of the above*
- ☐ *Not known*

30. **Other medication- please list any other medication the patient is currently taking**

_____

31. **Did a dental or other event initiate/uncover/expose BRONJ – Likely cause of BRONJ**

- ☐ *Extraction*
- ☐ *Denture trauma*
- ☐ *Dental infection*
- ☐ *Spontaneous*
- ☐ *Not known*
- ☐ *Other*

Please specify Other

_____

32. **Initiating event - please give details, for example date of extraction, age of dentures**

_____

33. **Symptoms of BRONJ**

- ☐ *Discharge*
- ☐ *Pain*
- ☐ *Swelling*
- ☐ *Sinus*
- ☐ *Fistula*
- ☐ *Sponateous exfoliation*
- ☐ *Other*

Please specify Other

_____

On Examination

34. **Site or sites of BRONJ - please describe the areas affected**

_____

35. **Length of exposed bone in mm**

_____

36. **Width of exposed bone in mm**

_____

37. **Maxillary dentition**

- ☐ *Dentate*
- ☐ *Edentulous*

38. **Maxillary teeth present**

	third molar	7	6	5	4	3	2	Central incisor
Right	☐	☐	☐	☐	☐	☐	☐	☐

39. **Maxillary teeth with severe caries or roots**

	third molar	7	6	5	4	3	2	Central incisor
Right	☐	☐	☐	☐	☐	☐	☐	☐

40. **Maxillary teeth present**

	Central incisor	2	3	4	5	6	7	third molar
Left	☐	☐	☐	☐	☐	☐	☐	☐

41. **Maxillary teeth with severe caries or roots**

	Central incisor	2	3	4	5	6	7	third molar
Left	☐	☐	☐	☐	☐	☐	☐	☐

42. **Maxilla - denture**

- ☐ *No*
- ☐ *Partial*
- ☐ *Full*

43. **Mandibular dentition**

- ☐ *Dentate*
- ☐ *Edentulous*

44. **Mandibular teeth present**

	third molar	7	6	5	4	3	2	Central incisor
Right	☐	☐	☐	☐	☐	☐	☐	☐

45. **Mandibular teeth with severe caries or roots**

	third molar	7	6	5	4	3	2	Central incisor
Right	☐	☐	☐	☐	☐	☐	☐	☐

46. **Mandibular teeth present**

	Central incisor	2	3	4	5	6	7	third molar
Left	☐	☐	☐	☐	☐	☐	☐	☐

47. **Mandibular teeth with severe caries or roots**

	Central incisor	2	3	4	5	6	7	third molar
Left	☐	☐	☐	☐	☐	☐	☐	☐

48. **Mandible - denture**

- ☐ *No*
- ☐ *Partial*
- ☐ *Full*

49. **OPG taken**

- ☐ *Yes*
- ☐ *No*
- ☐ *Not sure*

50. **Bone loss on OPG**

	<25%	*25-50%*	*50-75%*	*>75%*
Upper left molars	☐	☐	☐	☐
Upper canines / incisors	☐	☐	☐	☐
Upper right molars	☐	☐	☐	☐
Lower left molars	☐	☐	☐	☐
Lower canines /incisors	☐	☐	☐	☐
Lower right molars	☐	☐	☐	☐

51. **Has a Basic Peridontal Examination (BPE) assessment been performed**

- ☐ *Yes*
- ☐ *No*
- ☐ *Not sure*

52. **BPE assessment (please see website for details on how to code this if you are unsure)**

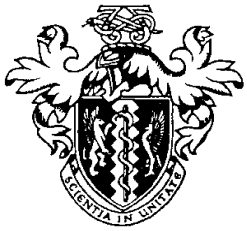
	0	*1*	*2*	*3*	*4*	*	*X*
Upper left sextant	☐	☐	☐	☐	☐	☐	☐
Upper anterior sextant	☐	☐	☐	☐	☐	☐	☐
Upper right sextant	☐	☐	☐	☐	☐	☐	☐
Lower left sextant	☐	☐	☐	☐	☐	☐	☐
Lower anterior sextant	☐	☐	☐	☐	☐	☐	☐
Lower right sextanr	☐	☐	☐	☐	☐	☐	☐

53. **Any other information concerning the patient's presentation that you feel may be relevant.**

Thank you. You will be contacted for one year treatment and outcome data in the future, so please keep an internal record of this patient for your own audit purposes

Appendix D – Patient Consent Form

Faculty of General Dental Practice (UK)
The Royal College of Surgeons of England



Study Number: 08/H1001/179

Patient Information Number for this trial: 01

Version 3: 1/10/2009

CONSENT FORM

Study Title: National study on avascular necrosis of the jaws including bisphosphonate-related osteonecrosis'**- new patient registration**

Name of Researchers: Professor Simon Rogers on behalf of the British Association of Oral and Maxillofacial Surgeons and Dr Nick Palmer on behalf of , The Faculty of General Dental Practice (UK) and all other stakeholders

[Please enter patient details in this box]

Please initial box

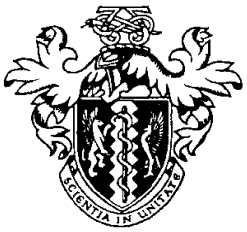
1.I confirm that I have read and understand the information sheet dated 1/10/2009 (version 3.) for the above study and have had the opportunity to ask questions	
2. I understand and consent to being approached and invited to participate in a further research project on Bisphosphonate Induced Jaw Necrosis	
3. I understand that my future participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected	

_____	_____	_____
Name of Patient	**Date**	**Signature**
_____	_____	_____
Clinician	**Date**	**Signature**

One copy of the signed consent form will be placed in the patients notes and the other returned to: Ms Amrita Narain, Research Officer, Faculty of General Dental Practice (UK), Royal College of Surgeons of England, 35/43 Lincoln's Inn Fields, London WC2A 3PE

Appendix E – Patient Information Sheet

Faculty of General Dental Practice (UK)
The Royal College of Surgeons of England



Patient Information Sheet **Version 2: 12/5/2009**

Research Study

***Study Title**: National study on avascular necrosis of the jaws including bisphosphonate-related osteonecrosis'*

*- **new patient registration***

We would like you to take part in our research study. Before you decide, it is important for you to understand why we are doing this research and what is involved. Please take time to read this information sheet carefully and discuss it with others if you wish. Please ask us if there is anything that is not clear to you or if you would like more information. Do take your time to decide whether or not you wish to take part in the study.

What is the purpose of the study?

Bisphosphonate related OsteoNecrosis of the Jaw (BRONJ) is a rare condition and is a side effect of taking bisphosphonate medication. Bisphosphonates are used for the management of osteoporosis (treatment and prevention) and in the treatment for some cancers. Bisphosphonate medications are effective but the side-effect of BRONJ only recently came to light, in around 2003. There are still some things we need to find out about BRONJ, for example how many patients have this side-effect, if there are any factors that put patients on bisphosphonate at more risk of developing BRONJ, and what is the best treatment if BRONJ develops. As BRONJ is a rare condition there are too few patients just in one hospital to answer these questions and therefore we are undertaking a national project. The project is a collaboration between the British Association of Oral and Maxillofacial Surgeons and The Faculty of General Dental Practice (UK).

What is involved if I decide to participate in the study?

You don't actually have to do anything extra at this time.

The first part of the study is the new patient registration. This will happen the first time the specialist doctor sees you about your diagnosis of BRONJ. He/she will take a full history and examine your mouth. This is standard practice though it might be slightly more detailed than usual. The clinical information will then be entered onto a

secure website at the Royal College of Surgeons of England but any details that could identify you as an individual will be removed. We hope that you will consent to this.

The second part of the study will require the study doctor to contact a group of patients for further information. Therefore, we might wish to contact you in the future. Because BRONJ is such a new condition we are not sure what form any possible further research would take. Although we will get ethical approval for any additional study but it is important that we seek your consent to allow us to contact you in the future if the need arises. We hope that you will consent to this.

Why have I been chosen?

The study will involve patients who are diagnosed with BRONJ over a two-year period starting on 1st January 2009 with full documentation from 1st April 2009 to 31st March 2011. Our aim is to register all new patients with BRONJ referred to Oral and Maxillofacial Departments and Dental Hospitals in England, Wales, Scotland and Northern Ireland.

Do I have to take part?

You can decide whether or not you want to take part in this study. The information we collect will be very valuable. We would like you participate in both the registration study and also to allow us to contact you in the future if necessary.

If you do decide to take part please keep this information sheet and please sign the consent form. If you do take part you can still withdraw at any time without giving us a reason. If you decide to withdraw or not take part this will not affect the quality of care you receive.

What will happen to me if I take part?

The anonymous clinical data will be collected at your normal hospital appointment.

If you consent to being contacted in the future for further research into BRONJ we will find out if you are alive using a link through your hospital records, your General Practitioner, and also the Office of National Statistics. We would only contact patients known to be alive as we would not want to cause any distress to your family. Any further research proposal will be explained to you and you will be asked for you consent at that time. By signing this current consent form it does not mean that you have given your consent to be part of a future study; you are consenting to us having the opportunity to contact you to discuss further studies.

What are the side effects and risks of taking part?

There is a very small risk that we might not have up to date details on your health status and in any follow-up study you might be contacted inappropriately. This might cause distress to your family.

What are the possible benefits of taking part?

By contributing to this study we will gain a better understanding of the risks of BRONJ. Your participation in this study will help future patients.

What if something goes wrong?

In the extremely unlikely event that you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanism is available to you.

What will happen to the results of the research study?

When we have finished this study we will disseminate our results and findings by publishing it in dental and medical journals. You will not be identified in any reports or publications resulting from this study. At your request we would be happy to send you a printed copy.

Who is organising and funding the research?

Professor Simon Rogers is organising this research on behalf of the British Association of Oral and Maxillofacial Surgeons and The Faculty of General Dental Practice (UK). Both national associations have helped fund the study.

Who has reviewed the study?

This study has been reviewed and approved by the Sefton Research Ethics Committee.

Contact for Further Information:

If you require further information about our study please contact the lead investigator:

Professor Simon Rogers
Regional Maxillofacial Unit
University Hospital Aintree Foundation Trust
Lower Lane
Liverpool
L9 1AE

Telephone: 0151 529 5287

We would like to thank you for taking the time to read this information and thinking about taking part in our study.

Appendix F – Final survey of BAOMS members November/December 2011

Subject: BAOMS 2nd National Audit in Support of Revalidation - Bisphosphonate related Osteonecrosis of the Jaw

British Association of Oral and Maxillofacial Surgeons

Clinical Effectiveness Subcommittee

National Audits in support of revalidation

November 2011

2nd National Audit in Support of Revalidation – Bisphosphonate Related Osteonecrosis of the Jaw

We are just in the process of wrapping up the national bisphosphonate osteonecrosis new patient registration project. Our records suggest that you have submitted no patients. It might be that you have submitted patients as a unit via another Consultant.

We are now trying to gauge the total number of cases nationally between 1st June 2009 and 31st May 2011. We would like to get an indication of how short we are in terms of all total new cases.

Please could you let me know:

1. How many new cases of BRONJ do you think there might have been seen in your clinics between 1st June 2009 and 31st May 2011?
2. It is still possible to register patients with final data collection ending 1st January 2012. Do you intend to submit any cases? YES NO

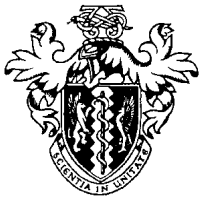
If you have answered NO please could you kindly state the reasons?

Please could you kindly complete this letter and return it in the pre paid envelope provided?
(If you are responding to an e-mail, please respond to leanne.gorvett@aintree.nhs.uk)

Thank you
With best wishes
Simon Rogers
snrogers@doctors.org.uk

Appendix G – 12 month patient outcome form

Faculty of General Dental Practice (UK)
The Royal College of Surgeons of England



National Audit Bisphosphonate-related Osteonecrosis of the Jaw
OUTCOME at last known MFU out-patient appointment after clinic date closest to 12 months

Dear Dr XXXXXX

Thank you for your contribution to this very important national audit. Below are the key summary fields for the patient(s) that you entered in the hope that it might be possible for you to tell us how the patient(s) got on. Because it is a national audit there are no patient identifiers so it is hoped that the details below are sufficient for your team to identify your patient(s) and the records pulled locally. In order for us to complete the final stages of the audit, we would be most grateful if you would kindly provide additional one to two year follow up information on the current status of the **patients identified** below who were registered on behalf of your clinic.

May I take this opportunity to thank you for supplying the information and for your continued support with the audit. This now brings the audit to a close and the report should be ready by the autumn. This form can be used as evidence of contribution to a national audit as part of your revalidation.

We would appreciate your returning the form at your earliest convenience by email to: **mealeyp@edgehill.ac.uk or alternatively by post marked for the attention of Pauline Mealey, Edge Hill University Faculty of Health, Western Campus, St Helens Road Ormskirk L39 4QP**

Yours sincerely
Pauline Mealey
Edge Hill University – Faculty of Health & Social Care
On Behalf Of Professor Simon Rogers

HOSPITAL	CONSULTANT	CLINIC DATE	CLINIC TIME AM/ PM	Gender	PATIENT YEAR OF BIRTH

Please tick one option (closest to 12 months after the above clinic date, within 1-2 years)

1. ☐ Patient alive and BRONJ has healed
2. ☐ Patient alive and BRONJ is stable and on-going
3. ☐ Patient alive and BRONJ has progressed / got worse
4. ☐ Patient died with BRONJ still present
5. ☐ Patient died and BRONJ healed
6. ☐ Unable to trace patient / lost to follow up outcome not known
7. ☐ Other please state……

Date of Outcome if Known……