1.0 Purpose

1.1 These guidelines are to enable staff members working within St Patrick's Hospital (Cork) Ltd. to make decisions regarding the administration of regular intravenous bisphosphonates.

2.0 Scope

2.1 Inpatients in Marymount Hospice, Cork, Ireland.
2.2 Patients attending Marymount Hospice Day Care.
2.3 Patients who are receiving regular intravenous bisphosphonates for any of the indications listed in 5.1.1. For emergency treatment of Hypercalcaemia these guidelines may be inappropriate given the need to correct the calcium level urgently. Adherence to the guidelines is at the discretion of the treating physician.

3.0 Definitions and Abbreviations

3.1 Bisphosphonates: A group of drugs which act principally by inhibiting osteoclastic bone resorption.[4]
3.2 Hypercalcaemia: Corrected serum calcium level of >2.6 mmol/l. (Appendix 1)
3.3 Osteonecrosis: Also called avascular necrosis or aseptic necrosis, a condition in which the death of bone cells due to decreased blood flow can lead to pain and collapse of areas of bone.

4.0 Responsibility

4.1 Initiation of bisphosphonate treatment – consultant physician.
4.2 Ongoing review and monitoring – prescribing medical officer.
4.3 Administration – registered staff nurse and medical officer.

5.0 Procedure

5.1 Indications for Regular Intravenous Bisphosphonate Use:

5.1.1 Tumour-induced Hypercalcaemia.[2,5]
5.1.2 Maintaining skeletal integrity in bone metastases.[2,3,4]
5.1.3 Bone pain in advanced malignancy.[3,4]

5.2 Which Bisphosphonate to Use:

5.2.1 The following bisphosphonates are licensed for use in tumour-induced Hypercalcaemia:[6]

Zoledronic Acid
Pamidronate

Ibandronic Acid
Clodronate

5.2.2 The following bisphosphonates are licensed for use in maintaining skeletal integrity in bone metastases:[6]

Zoledronic Acid
Ibandronic Acid

5.3.3 Bisphosphonates are currently not licensed for use in bone pain of malignancy. However, there has been some trial evidence supporting bisphosphonate use for this reason.[3,4] In this instance, choice of bisphosphonate is at the discretion of the treating physician.

5.3 Dental Review

5.3.1 Due to the risk of osteonecrosis of the jaw, all patients require a dental review prior to commencing regular planned intravenous bisphosphonate therapy [1] and every 4 months thereafter. This includes patients with dentures. This is necessary as ill-fitting dentures may traumatise the underlying mucosa.

5.3.2 Referral should be made to the oral surgery department in the University Dental School and Hospital, Wilton, Cork. (Appendix 2)

5.3.3 The oral surgery department should be contacted by telephone (021-4901127) and an appointment date and time obtained, as well as the name of the oral surgeon with whom the appointment has been made.

5.3.4 The dental referral proforma should be completed, faxed to the oral surgery department (Fax No: (021-4901179) and a copy given to the patient to bring to the oral surgery department on the day of their appointment. (Appendix 3)

5.3.5 The written report issued by the oral surgeon should be filed in the patient's medical records and any necessary interventions recorded in the modified care pathway.

5.3.6 Any interventions recommended by the oral surgeon should be carried out prior to commencement of intravenous bisphosphonate therapy. These may include any dental treatments and procedures which require bone healing.

5.4 Prior to Administration of Intravenous Bisphosphonate:

5.4.1 Each patient should be assessed on an individual basis, taking into consideration their underlying diagnosis, likely prognosis and overall performance status.

5.4.2 Bisphosphonate therapy is contraindicated in the following circumstances:

(i) A previous adverse reaction to bisphosphonates
(ii) Pregnancy
(iii) Breastfeeding

5.4.3 Serum urea and creatinine levels, as well as creatinine clearance should be checked within 1 week prior to each dose of intravenous bisphosphonate. (Appendix 4)

5.4.4 A baseline weight should be documented for each patient prior to commencing bisphosphonate therapy. This may be repeated during the treatment course at the discretion of the prescribing medical officer.

5.4.5 If renal function is abnormal based on the above measures, the following steps should be taken:

(i)The patients should be pre-hydrated with parenteral fluids, according to the patient's clinical condition, at the discretion of the prescribing medical officer.
(ii) The dose of intravenous bisphosphonate should be reduced. Manufacturer's guideline regarding dose reduction in renal impairment should be followed where possible. (Appendix 5)

5.4.6 In all cases the serum urea and creatinine values and creatinine clearance, along with any dose reduction made, should be documented on the modified care pathway. (Appendix 6)

5.4.7 (i) The patient should be asked about dental problems. In particular, the patient should be asked about tooth or jaw pain, jaw swelling, loosening of previously stable teeth, jaw "numbness" or abnormal sensation.[1] If the answers to these questions raises concern, urgent dental review should be sought and administration of bisphosphonate deferred.
(ii) It should be ensured that all patients have had a dental review for preventative dentistry and that all necessary dental interventions have been carried out prior to commencement of bisphosphonate therapy. It should also be ensured that a 4 month follow up dental appointment has been organised.
(iii) It should be ensured that the patient has a copy of the patient information leaflet, which includes a section regarding dental care.

5.4.8 (i) If serum calcium levels are below normal reference ranges, replacement therapy in the form of oral calcium supplements and Vitamin D supplements should be considered. (Appendix 7)

(ii) If serum calcium levels are below normal reference ranges following administration of bisphosphonates, renal function, serum magnesium and serum phosphate levels should also be monitored. The decision to prescribe short-term calcium replacement therapy should be made by the treating consultant on an individual, case by case basis.

5.4.9 The patient's drug history should be reviewed for interactions with bisphosphonates. This is the responsibility of the prescribing medical officer. (Appendix 8)

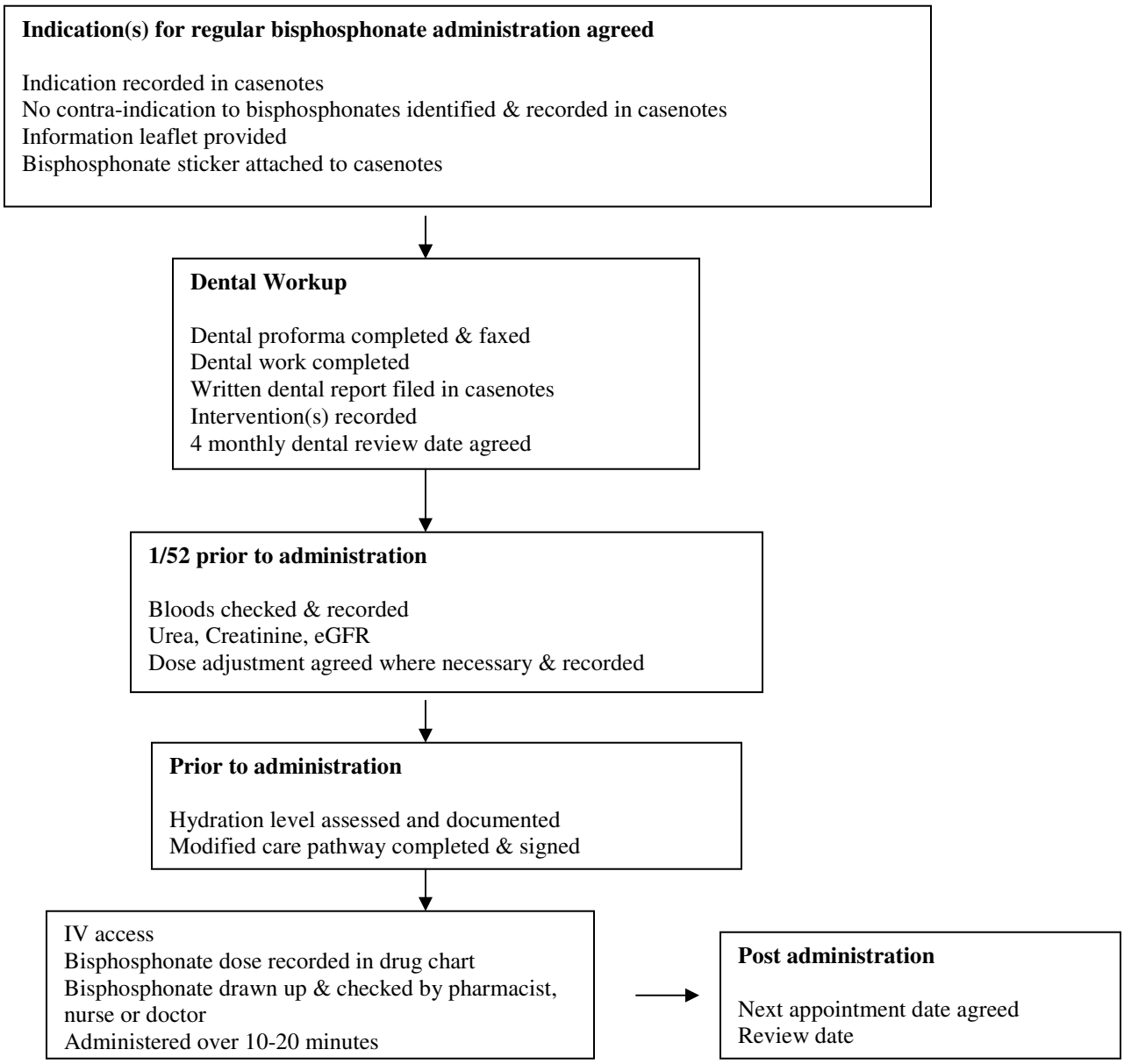
5.5 When to consider cessation of intravenous Bisphosphonates:

5.5.1 When osteonecrosis of the jaw is suspected, intravenous bisphosphonate therapy should be held pending urgent dental review. If osteonecrosis of the jaw is confirmed, then bisphosphonate therapy should be reviewed on a case by case basis.[(1)*]

5.5.2 After 6 months, the indication for treatment should be reviewed by the treating consultant. A treatment plan for the next 6 months should be put in place.

* In all cases it should be discussed with the treating consultant prior to suspension of regular intravenous bisphosphonate therapy.

5.6 The Process



6.0 Frequency of Review

6.1 6 months post implementation and every 2 years thereafter.

7.0 Methods Used to Review Guideline

7.1 Day-care or ward staff will undertake an audit of approximately 25% of patients medical notes who have received bisphosphonate treatment. The Audit tool (appendix 9) will be used to measure completion of documentation and highlight areas of difficulty in following the guidelines.

7.2 The bisphosphonate working group will review the audit results within one year and review the Guideline and Care Pathway accordingly.

8.0 References

1. Ruggiero S, Gralow J, Marx RE, Hoff AO, Schubert MM, Huryn JM, Toth B, Damato K, Valero V. Journal of Oncology Practice Jan 2006: 7-14. "Practical Guidelines for the Prevention, diagnosis and Treatment of Osteonecrosis of the Jaw in Patients with Cancer".

2. Ross JR, Saunders Y, Edmonds PM, Patel S, Broadley KE, and Johnston SRD Systematic review of role of bisphosphonates on skeletal morbidity in metastatic cancer BMJ Aug 2003**;** 327: 469.

3. Yuen KY Shelley M, Sze WM, Wilt T, Mason M. The Cochrane Library 2008, Issue 3. "Bisphosphonates for advanced prostate cancer (Review)".

4. Pavlakis N, Schmidt RL, Stockler MR. The Cochrane Library 2008, Issue 3. "Bisphosphonates for breast cancer (Review)".

5. Saunders Y, Ross JR, Broadley KE, Edmonds PM, and Patel S. Systematic review of bisphosphonates for hypercalcaemia of malignancy. Palliative Medicine, Jul 2004; vol. 18: pp. 418 - 431.

6. British National Formulary 55 March 2008. British Medical Association, Royal Pharmaceutical Society of Great Britain.

7. IPHA Electronic Medicines Compendium SPC Zometa Concentrate, Novartis Ireland Limited.

8. IPHA Electronic Medicines Compendium SPC Bondronat, Roche Products (Ireland) Ltd.

9. IPHA Electronic Medicines Compendium SPC Aredia Dry Powder, Novartis Ireland Limited.

10. Cockroft DW, Gault MH (1976). The estimation of creatinine clearance from serum creatinine concentration. Nephron, 16: 31-8.

9.0 Appendices

Appendix 1

Correcting serum Calcium

(40 – Albumin) x 0.02 = Corrected Calcium.

Appendix 2: Letter from Dental Hospital

Appendix 3: Proforma letter

Marymount Hospice/St. Patrick's Hospital (LTD).,
Wellington Road, Cork.
Tel: 021 4501201 Fax 021 4557404

To: Dr.
Oral Surgery Department
University Dental School and Hospital
Wilton
Cork.

Re: **Date:**_____

Dear Dr.

I would appreciate a dental review prior to commencing the above patient on regular Bisphosphonate therapy.

The details are as follows:
Name of Bisphosphonate:
Proposed date of commencement:
Indication for Bisphosphonate therapy:
Underlying diagnosis (including extent of malignancy where relevant):

_____

Cardiac valvular disease: **Yes** ☐ **No** ☐
If yes, give details: _____

Approximate date of most recent chemotherapy (where relevant):_____

Other relevant information: _____

I would appreciate if you could (Please tick)

☐ **(a) Give the patient a handwritten letter to bring back to Marymount Hospice for the attention of:**

_____

☐ **(b) Send a typed letter in the post addressed to:** _____

_____

If you require any further information at al please do not hesitate to contact Marymount Hospice on 021 4501201.

Yours sincerely,

Appendix 4

Calculating creatinine clearance

Cockroft & Gault Equation [10]

$$\text{Creatinine Clearance Rate (ml/min)} = \frac{F\,(140 - \text{age}) \times \text{Weight (kg)}}{\text{Serum Creatinine (micromol/L}}$$

Where F = 1.04 for females/F = 1.23 for males

Please note the Cockroft & Gault equation is not a good estimate of creatinine clearance in obese & fluid overloaded patients. In these cases, it may over- or under-estimate the creatinine clearance by up to 20%, and the ideal body weight should be used instead of actual body weight in the equation. In the case of pregnant women, children, patients with rapidly changing renal function or marked catabolism, the Cockroft & Gault equation may not give an accurate measure of creatinine clearance.

Appendix 5 Dose adjustment for patients with renal impairment

(i) Zoledronic Acid [7]

Baseline Creatinine Clearance (ml/min)	Zometa Recommended Dose
> 60	4.0mg
50-60	3.5mg
40-49	3.3mg
30-39	3.0mg

(ii) Ibandronic Acid [8]

Creatinine Clearance (ml/min)	Dosage / Infusion time	Infusion Volume
> 50	6mg / 15 minutes	1000ml
30 < Cr Cl < 50	6mg / 1 hour	500ml
< 30	2mg / 1 hour	500ml

(iii) Pamidronate

Aredia should not be administered to patients with severe renal impairment (creatinine clearance < 30 ml/min) unless in cases of life-threatening tumour-induced hypercalcaemia where the benefits outweigh the potential risk.

In patients receiving Aredia for bone metastases who show evidence of deterioration in renal function, Aredia treatment should be withheld until renal function returns to within 10% of the baseline value. This recommendation is based on a clinical study, in which renal deterioration was defined as follows:

For patients with normal baseline creatinine, increase of 0.5mg/dl.
For patients with abnormal baseline creatinine, increase of 1.0mg/dl.

A pharmacokinetic study conducted in patients with cancer and normal or impaired renal function indicates that the dose adjustment is not necessary in mild (creatinine clearance 61-90 ml/min) to moderate renal impairment (creatinine clearance 30-60 ml/min). In such patients the infusion rate should not exceed 90mg/4h (approximately 20-22 mg/h).[9]

Appendix 6: Bisphosphonate Care Pathway

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St Patrick's Hospital (Cork) Ltd

IV Bisphosphonate Care Pathway

Patients full name:		**Gender:**
Date of birth:		**MRN:**
Dental check **Yes** ☐ **No** ☐	**Indication for bisphosphonates:**	**Review date:** **Dental:** **Bisphosphonate:**

Renal function:
Date:

Urea:	
Creatinine:	
Creatinine Clearance:	

Renal function:
Date:

Urea:	
Creatinine:	
Creatinine Clearance:	

Renal function:
Date:

Urea:	
Creatinine:	
Creatinine Clearance:	

Renal function:
Date:

Urea:	
Creatinine:	
Creatinine Clearance:	

Renal function:
Date:

Urea:	
Creatinine:	
Creatinine Clearance:	

Renal function:
Date:

Urea:	
Creatinine:	
Creatinine Clearance:	

Prescription

Date	Pre Hydration IV Fluids	Bisphosphonate Dose and diluent	**Prescribers** signature, print and state designation	**Administrators** signature print and state designation Pre Hydration Fluid / Drug and Diluent
(1st cycle)				/
(2nd cycle)				/
(3rd cycle)				/
(4th cycle)				/
(5th cycle)				/
(6th cycle)				/

Sign each section as completed or indicate with a 'V' if variance from care pathway and document reasons on Variance Sheet (last page).

			Full name, signature designation and date
	Dental hygiene leaflet given to patient?	**Yes / No**	
	Blue Sticker attached to notes?	**Yes / No**	
	Referral for Dental review sent? (please circle) Dental interventions required prior to IV Bisphosphonate? If 'yes' please give details.....	**Yes / No** **Yes / No**	
	Patient's weight prior to first treatment .....Kgs		
1st cycle of bisphosphonate			Full name, signature designation and date
1	Is the patient experiencing any tooth/jaw pain/oral discomfort? If 'yes' please give details.....	**Yes / No**	
2	Renal function checked 1 week prior to treatment?	**Yes / No**	
3	Pre-Hydration assessed? Pre Hydration Fluids prescribed?	**Yes / No** **Yes / No**	
4	Has the patient had any adverse reactions to Bisphosphonates? (If 'yes' do not continue with treatment using bisphosphonates)	**Yes / No**	
5	Is the patient pregnant? (If 'yes' do not continue with treatment using bisphosphonates)	**Yes / No**	
6	Is the patient breast feeding? (If 'yes' do not continue with treatment using bisphosphonates)	**Yes / No**	
7	Has the patient's drug history been reviewed against contraindications with bisphosphonates?	**Yes / No**	
8	Has the patient been reminded about the importance of oral hygiene?	**Yes / No**	
2nd cycle of bisphosphonate			Full name, signature designation and date
1	Is the patient experiencing any tooth/jaw pain/oral discomfort? If 'yes' please give details.....	**Yes / No**	
2	Renal function checked 1 week prior to treatment?	**Yes / No**	
3	Pre-Hydration assessed? Pre Hydration Fluids prescribed?	**Yes / No** **Yes / No**	
4	Has the patient had any adverse reactions to Bisphosphonates? (If 'yes' do not continue with treatment using bisphosphonates)	**Yes / No**	
5	Is the patient pregnant? (If 'yes' do not continue with treatment using bisphosphonates)	**Yes / No**	
6	Is the patient breast feeding? (If 'yes' do not continue with treatment using bisphosphonates)	**Yes / No**	
7	Has the patient's drug history been reviewed against contraindications with bisphosphonates?	Yes / No	
8	Has the patient been reminded about the importance of oral hygiene?	**Yes / No**	

3rd cycle of bisphosphonate		Full name, signature designation and date
1	Is the patient experiencing any tooth/jaw pain/oral discomfort? **Yes / No** If 'yes' please give details.....	
2	Renal function checked 1 week prior to treatment? **Yes / No**	
3	Pre-Hydration assessed? **Yes / No** Pre Hydration Fluids prescribed? **Yes / No**	
4	Has the patient had any adverse reactions to Bisphosphonates? **Yes / No** (If 'yes' do not continue with treatment using bisphosphonates)	
5	Is the patient pregnant? **Yes / No** (If 'yes' do not continue with treatment using bisphosphonates)	
6	Is the patient breast feeding? **Yes / No** (If 'yes' do not continue with treatment using bisphosphonates)	
7	Has the patient's drug history been reviewed against contraindications with bisphosphonates? **Yes / No**	
8	Has the patient been reminded about the importance of oral hygiene? **Yes / No**	

4th cycle of bisphosphonate		Full name, signature designation and date
1	Is the patient experiencing any tooth/jaw pain/oral discomfort? **Yes / No** If 'yes' please give details.....	
2	Renal function checked 1 week prior to treatment? **Yes / No**	
3	Pre-Hydration assessed? **Yes / No** Pre Hydration Fluids prescribed? **Yes / No**	
4	Has the patient had any adverse reactions to Bisphosphonates? **Yes / No** (If 'yes' do not continue with treatment using bisphosphonates)	
5	Is the patient pregnant? **Yes / No** (If 'yes' do not continue with treatment using bisphosphonates)	
6	Is the patient breast feeding? **Yes / No** (If 'yes' do not continue with treatment using bisphosphonates)	
7	Has the patient's drug history been reviewed against contraindications with bisphosphonates? **Yes / No**	
8	Has the patient been reminded about the importance of oral hygiene? **Yes / No**	

5th cycle of bisphosphonate		Full name, signature designation and date
1	Is the patient experiencing any tooth/jaw pain/oral discomfort? **Yes / No** If 'yes' please give details.....	
2	Renal function checked 1 week prior to treatment? **Yes / No**	
3	Pre-Hydration assessed? **Yes / No** Pre Hydration Fluids prescribed? **Yes / No**	
4	Has the patient had any adverse reactions to Bisphosphonates? **Yes / No** (If 'yes' do not continue with treatment using bisphosphonates)	
5	Is the patient pregnant? **Yes / No** (If 'yes' do not continue with treatment using bisphosphonates)	
6	Is the patient breast feeding? **Yes / No** (If 'yes' do not continue with treatment using bisphosphonates)	
7	Has the patient's drug history been reviewed against contraindications with bisphosphonates? **Yes / No**	
8	Has the patient been reminded about the importance of oral hygiene? **Yes / No**	

6th cycle of bisphosphonate		Full name, signature designation and date
1	Is the patient experiencing any tooth/jaw pain/oral discomfort? **Yes / No** If 'yes' please give details.....	
2	Renal function checked 1 week prior to treatment? **Yes / No**	
3	Pre-Hydration assessed? **Yes / No** Pre Hydration Fluids prescribed? **Yes / No**	
4	Has the patient had any adverse reactions to Bisphosphonates? **Yes / No** (If 'yes' do not continue with treatment using bisphosphonates)	
5	Is the patient pregnant? **Yes / No** (If 'yes' do not continue with treatment using bisphosphonates)	
6	Is the patient breast feeding? **Yes / No** (If 'yes' do not continue with treatment using bisphosphonates)	
7	Has the patient's drug history been reviewed against contraindications with bisphosphonates? **Yes / No**	
8	Has the patient been reminded about the importance of oral hygiene? **Yes / No**	

Variance Sheet

(all staff to use this sheet if part of the prescribed care is not /cannot be followed and give reasons why)

Date	Variance	Signature, printed name and designation

(E. Willcock 2008)

Appendix 7

Calcium and Vitamin D supplementation
Information only available for Aredia (pamidronate)

In the absence of hypercalcaemia, patients with predominantly lytic bone metastases or multiple myeloma who are at risk of calcium or vitamin deficiency and patients with Paget's disease of the bone should take oral calcium and vitamin D supplements in order to minimise the risk of hypocalcaemia.[9]

Appendix 8

Bisphosphonate interactions with other medicinal products & other forms of interaction

(i) Zoledronic Acid (Zometa)

In clinical studies, Zometa has been administered concomitantly with commonly used anticancer agents, diuretics, antibiotics and analgesics without clinically apparent interactions occurring. Zoledronic acid shows no appreciable binding to plasma proteins and dos not inhibit human P450 enzymes in vitro but no formal clinical interaction studies have been performed. Caution is advised when bisphosphonates are administered with aminoglycosides, since both agents may have an additive effect, resulting in a lower serum calcium level for longer periods than required. Caution is also indicated when Zometa is used with other potentially nephrotoxic drugs. Attention should also be paid to the possibility of hypomagnesaemia developing during treatment.

In multiple myeloma patients, the risk of renal dysfunction may be increased when intravenous bisphosphonates are used in combination with thalidomide.[(7)]

(ii) Ibandronic Acid (Bondronat)

Bondronat should not be mixed with calcium containing solutions.
No interaction was observed when co-administered with melphalan/prednisolone in patients with multiple myeloma.

Other interaction studies in postmenopausal women have demonstrated the absence of any interaction potential with tamoxifen or hormone replacement therapy (oestrogen).
In relation to disposition, no drug interactions of clinical significance are likely. Ibandronic acid is eliminated by renal secretion only and does not undergo any biotransformation. The secretion pathway does not appear to include known acidic or basic transport systems involved in the excretion of other active substances. In addition, ibandronic acid does not inhibit the major human hepatic P450 isoenzymes and does not induce the hepatic cytochrome P450 in rats. Plasma protein binding is low at therapeutic concentrations and ibandronic acid is therefore unlikely to displace other active substances.

Caution is advised when bisphosphonates are administered with aminoglycosides, since both agents can lower serum calcium levels for prolonged periods. Attention should also be paid to the possible existence of simultaneous hypomagnesaemia.

In clinical studies, Bondronat has been administered concomitantly with commonly used anticancer agents, diuretics, antibiotics and analgesics without clinically apparent interactions occurring.

Interaction studies have only been performed in adults.[8]

(iii) Pamidronate (Aredia)

Aredia has been administered concomitantly with commonly used anticancer drugs without interaction occurring.
Aredia should not be co-administered with other bisphosphonates because their combined effects have not been investigated. Aredia has been used in combination with calcitonin in patients with severe hypercalcaemia, resulting in a synergistic effect producing a more rapid fall in serum calcium.
Since pamidronate binds to bone, it could in theory interfere with bone scintigraphy examinations.

Caution is warranted when Aredia is used with potentially nephrotoxic drugs.
In multiple myeloma patients, the risk of renal dysfunction may be increased when Aredia is used in combination with thalidomide.[9]

Appendix 9: Audit tool

Audit Number: Date: Name of Auditor:			
1.	Is the patient's first name written clearly?	Yes □	No □
2.	Is the patient's surname written clearly?	Yes □	No □
3.	Is the patient's date of birth written clearly?	Yes □	No □
4.	Is the patient's MRN written clearly?	Yes □	No □
5.	Is the gender clearly documented?	Yes □	No □
6.	Has a dental check taken place?	Yes □	No □
7.	Is a letter from the Dental Hospital filed in the notes?	Yes □	No □
8.	Is there evidence that the intervention/treatment required has been undertaken?	Yes □	No □
9.	Is the dental reviewed date completed with a date four months from commencement?	Yes □	No □
10.	Is there documentary evidence of a dental reviewed being undertaken four months from commencement of treatment? (ie Dental Hospital letter of review or entry on the variance sheet to support this)	Yes □	No □
11.	How long following any dental intervention/treatment was the bisphosphonate administered?	(days/weeks/months) or 'Not Applicable' □	
12	Has renal function been recorded prior to all treatments administered?	Yes □	No □
13.	Has the indication for bisphosphonate use been clearly documented?	Yes □	No □
14.	Is box '1' completed for all treatments given?	Yes □	No □
15.	Is box '1' signed, and dated legibly?	Yes □	No □
16.	Is box '2' completed for all treatments given?	Yes □	No □
17.	Is box '2' signed, and dated legibly?	Yes □	No □
18.	Is box '3' completed for all treatments given?	Yes □	No □
19.	Is box '3' signed, and dated legibly?	Yes □	No □
20.	If box 3 states 'yes' to 'Pre hydration fluids prescribed?', have they been prescribed correctly?	Yes □	No □
21.	Has the 'Administrator of the 'Pre Hydration Fluids' completed, signed and dated legibly?	Yes □	No □
22.	Is box '4' completed for all treatments given?	Yes □	No □
23.	Is box '4' signed, and dated legibly?	Yes □	No □
24.	Is box '5' completed for all treatments given?	Yes □	No □
25.	Is box '5' signed, and dated legibly?	Yes □	No □
26.	Is box '6' completed for all treatments given?	Yes □	No □
27.	Is box '6' signed, and dated legibly?	Yes □	No □
28.	Is box '7' completed for all treatments given?	Yes □	No □
29.	Is box '7' signed, and dated legibly?	Yes □	No □
30.	Is box '8' completed for all treatments given?	Yes □	No □
31.	Is box '8' signed, and dated legibly?	Yes □	No □
32.	Is each Bisphosphonate 'Dose and Diluent' prescribed correctly?	Yes □	No □
33.	Has the Prescriber completed, signed, printed, dated and stated their designation clearly?	Yes □	No □
34.	Has the Administrator of 'Drug and Diluent' completed, signed, printed dated and stated their designation legibly?	Yes □	No □
35.	Are all entries on the Variance sheet signed, dated and stated their designation legibly?	Yes □	No □

(E. Willcock 2008)