Oral Health Management of Patients at Risk of Medication-related Osteonecrosis of the Jaw

Guidance Development Methodology

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An accessible version of this document can be made available on request

Amendments

Date	Page	Comment
26/03/2108	6	Amended to accurately state that GRADE evidence ratings for the outcomes from each of the systematic reviews are recorded in the considered judgement forms in Appendix 3 and the respective evidence appraisal forms in Appendix 4. This previously incorrectly stated that GRADEPro software had been used to assign and record evidence quality levels. The GRADE process was used however the software was not used on this occasion.

Contents

1. Overview of the SDCEP Guidance Development Process

The *Oral Health Management of Patients at Risk of Medication-related Osteonecrosis of the Jaw* guidance is an update to the previously published *Oral Health Management of Patients Prescribed Bisphosphonates* guidance. Consequently, the guidance development followed an amended version of SDCEP's guidance development process as outlined below:

- GDG selection;
- Scoping including horizon scanning literature review and baseline research on stakeholder attitudes to the previously published guidance;
- Agreement on updated scope and key clinical questions;
- Preparation of draft guidance for consultation including:
    - Systematic literature review,
    - Evidence appraisal, synthesis and summary,
    - Considered judgements,
    - Formulating recommendations,
    - Grading recommendations;
- Open consultation and peer review;
- Review of consultation and peer review feedback and revision of the guidance and other related products;
- Final draft sign-off;
- Design for publication and print;
- Dissemination and implementation.

For further details of the standard process see the SDCEP Guidance Development Process Manual available at www.sdcep.org.uk/how-we-work/sdcep-guidance-development-process. Consistent with SDCEP's standard guidance development methodology, the development of *Oral Health Management of Patients at Risk of Medication-related Osteonecrosis of the Jaw* aimed to be transparent, systematic and to adhere as far as possible to international standards set out by the AGREE (Appraisal of Guidelines Research and Evaluation) Collaboration (www.agreetrust.org).

Specific details of the methodology used for the development of the *Oral Health Management of Patients at Risk of Medication-related Osteonecrosis of the Jaw* guidance are presented either in the full guidance or in the following sections of this methods document.

For further details, queries or requests for unpublished information, please contact SDCEP using the details provided on the front page of this document.

2. The Guidance Development Group

The following Guidance Development Group (GDG), comprising individuals from a range of branches of the dental and medical professions and two patient representatives, was convened to develop and write this guidance.

Michaelina Macluskey (Co-Chair)	Senior Lecturer/Honorary Consultant Oral Surgeon, Dundee Dental Hospital and School
Stephanie Sammut (Co-Chair)	Consultant in Oral Surgery, Dundee Dental Hospital and School
Alexander Crighton	Consultant in Oral Medicine, University of Glasgow Dental Hospital and School
Helen Devennie	Specialist Practitioner (Medically Compromised and Oral Surgery), Inverness Dental Centre
Elizabeth Foster	Patient Representative
Karen Gordon	Consultant in Special Care Dentistry, Edinburgh
Duncan Gowans	Consultant Haematologist, Ninewells Hospital, Dundee; Perth Royal Infirmary
Vicki Greig	Speciality Registrar in Oral Surgery, NHS Greater Glasgow and Clyde
Doris Hunter	Patient Representative
Douglas Kennedy	Consultant in Oral & Maxillofacial Surgery, NHS Tayside
Pamela Kidd	General Dental Practitioner, Glasgow
Penny Lockwood	General Medical Practitioner, Dundee; Honorary Senior Clinical Lecturer, University of Dundee
Nick Malden	Consultant in Oral Surgery, Edinburgh Dental Institute
Anna Macdonald	Senior Dental Officer, Specialist in Special Care Dentistry, Perth
Gillian Nevin	General Dental Practitioner, Coupar Angus; Assistant Director of Postgraduate GDP Education, Dundee Dental Education Centre
Terence O'Neill	Professor of Rheumatology and Clinical Epidemiology, University of Manchester; Member of Clinical & Scientific Committee, National Osteoporosis Society
David Reid	Emeritus Professor of Rheumatology, University of Aberdeen
Andrew Wight	General Dental Practitioner, Dundee

Scheduled meetings of the full GDG or of subgroups took place as part of the guidance development process. The minutes of these meetings are available from SDCEP on request.

3. Scoping Research

A preliminary evidence search was carried out to identify any policies, guidelines, systematic reviews and other material relevant to the topic published after the publication of the previous version of the guidance. This information was summarised in a provisional scope proposal which was considered by the GDG prior to agreeing on the general scope (Appendix 1).

Additional research to inform the scope and content of the updated guidance was carried out by SDCEP research collaborators TRiaDS (Translation Research in a Dental Setting), following their framework for translating guidance recommendations into practice.[1] The views of general dental practitioners on current practice, attitudes to the management of patients prescribed anti-resorptive or anti-angiogenic drugs and preferred content of this guidance were obtained via an online survey.

4. Key Clinical Questions

Key clinical questions relevant to the scope of the guidance were drafted by the SDCEP Programme Development Team (PDT) along with the GDG chair. These were further discussed and agreed by the wider GDG.

1. In patients prescribed anti-resorptive drugs for the management of osteoporosis, what is the incidence of medication-related osteonecrosis of the jaw?
2. In patients prescribed anti-resorptive or anti-angiogenic drugs for the management cancer, what is the incidence of medication-related osteonecrosis of the jaw?
3. In patients prescribed anti-resorptive or anti-angiogenic drugs are there any other factors which may increase the risk of medication-related osteonecrosis of the jaw?
4. In patients prescribed anti-resorptive or anti-angiogenic drugs, are there any interventions which have proved effective in the prevention of medication-related osteonecrosis of the jaw?

These key clinical questions informed the strategy for the systematic evidence searches.

5. Literature Search

The guiding principle for developing guidance within SDCEP is to first source existing guidelines, policy documents, legislation or other recommendations. Similarly, relevant systematic reviews are also initially identified. These documents are appraised for their quality of development, evidence base and applicability to the remit of the guidance under development. In the absence of these documents or when supplementary information is required, other published literature and unpublished work may be sought.

For this guidance, a comprehensive search of MEDLINE, EMBASE, CINAHL, AMED, CANCERLIT, Cochrane Database of Systematic Reviews (CDSR), Cochrane Database of Abstracts of Reviews of Effects (DARE) and Cochrane Central Register of Controlled Trials (CENTRAL) was conducted by the Trials Search Coordinator of the Cochrane Oral Health Group on the 1st June 2015. No date limits were applied. The details of the searches can be found in Appendix 2. Following de-duplication, a total of 1160 records were retrieved.

Potentially eligible articles were identified separately by two reviewers from the list of titles and abstracts retrieved by the dental specific search. An article was considered potentially eligible if it met all of the following criteria:

1. The article was a systematic review or a guideline. An article would be included as a systematic review, if it included a methods section, a search of 1 or more electronic databases and a table of included studies.
2. The article referred to (i) anti-resorptive or anti-angiogenic drugs and (ii) osteonecrosis of the jaw in the context of dental treatment.

Copies of all potentially eligible articles in full were retrieved. Additional manual searching of guideline repositories and other resources, and follow up of citations from relevant articles found through the systematic searching was also carried out. Other sources of evidence identified by GDG members were also considered, taking relevance and methodological quality into account. To ensure that the final version of the guidance included the most up-to-date evidence, the literature search was repeated during the consultation and peer review processes to identify any relevant articles published between June 2015 and August 2016. Following de-duplication, a total of 173 records were retrieved. Any relevant new evidence was considered by the Guidance Development Group prior to publication.

6. Evidence Appraisal and Synthesis

Eligible articles relevant for each of the key clinical questions were identified. Precedence was given to the most recent articles, where of suitable quality, published in English. A reviewer assessed the full text of each article and extracted the information applicable to the clinical question. The evidence appraisal form for each of the relevant articles can be found in Appendix 4.

For the development of this guidance SDCEP used the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach to assess and rate the quality of evidence (www.gradeworkinggroup.org). The GRADE framework is a widely accepted system for grading both the evidence and the recommendations, and is used internationally by other guideline producers.

After systematic consideration of several criteria, a GRADE 'quality of evidence' rating was assigned to the evidence relevant to each clinical question. GRADE evidence ratings are defined by the GRADE working group as:

High quality	*further research is unlikely to change our confidence in the estimate of the effect (e.g. risk of bleeding)*
Moderate quality	*further research is likely to have an important impact on our confidence in the estimate of effect and may change the effect*
Low quality	*further research is very likely to have an important impact on our confidence in the evidence and is likely to change the estimate of the effect.*
Very low quality	*any estimate of effect from the evidence is very uncertain*

The GRADE evidence ratings for the outcomes from each of the systematic reviews are recorded in the considered judgement forms in Appendix 3 and in the respective evidence appraisal forms (Appendix 4).

For guidelines, the AGREE II instrument was used in addition to GRADE to assess the methodological quality of the retrieved articles (www.agreetrust.org). The AGREE II instrument is a simple and validated assessment tool that provides an overall quality score for each guideline and an indication of how reliable the guideline might be. These assigned scores are recorded in the evidence appraisal forms in Appendix 4. The output forms produced by the AGREE II tool used for assessing guidelines are available on request.

7. Considered Judgements and Development of Recommendations

The synthesised evidence for each clinical question was summarised and used to inform and facilitate the development of the recommendations for the guidance. Where authoritative evidence was unavailable, the GDG was asked to make recommendations based on current best practice and expert opinion, reached by consensus.

The process for development of recommendations followed the GRADE approach, with considered judgements based on the quality of evidence, the balance of risks and benefits, the values and preferences of the patients, and the practicalities of the treatment. The relative importance of each of these criteria for a given recommendation was decided by the GDG.

According to GRADE the strength of recommendations should be defined as:

Strong for	*benefits outweigh risks of the intervention*
Strong against	*risks outweigh benefits of the intervention*
Weak for/or weak against	*most informed people would choose this recommendation but a substantial number would not (risks and benefits finely balanced)*

Note: It is possible to have a strong recommendation where the evidence is weak, but other considerations such as patient preference or cost make the decision to make a strong recommendation clear.

The evidence summaries, GDG consideration of the criteria and the resulting outcomes for each key recommendation are recorded in the Considered Judgement Forms (one for each key clinical question) which can be found in Appendix 3. Some of the recommendations were subject to further review and revisions by the group during the guidance development process.

The GRADE approach allows for different words, numbers or symbols to be used to express the strength of the recommendations. For clarity, the recommendation strength (strong or conditional) and the quality of evidence rating (high, moderate, low or very low quality) is directly stated along with each recommendation. This approach is preferred to avoid confusion over the meaning of symbols or numbers or misinterpretation of the wording used in the recommendations. Brief justifications for each recommendation are also included in the guidance text.

8. Consultation and Peer Review

A twelve-week external consultation process on the draft guidance was initiated on July 11th 2016. The consultation draft was made openly available through the SDCEP website and notification of this was sent to a wide range of individuals and organisations with a specific interest in this topic, in addition to professional bodies and charities representing patient groups. All dentists and pharmacists in Scotland were notified that the consultation draft was available for comment. To encourage feedback from the end-users of the guidance, 50 randomly selected dentists were contacted directly to evaluate the guidance. Additionally, interviews were arranged with dentists and pharmacists to further inform the guidance development.

A consultation feedback form was provided to facilitate the process. All comments received were compiled, considered carefully by the GDG and the guidance amended accordingly prior to publication. The compiled consultation comments and GDG responses are available on request.

Targeted external peer review was also conducted as a means of additional quality assurance. External experts, including experts in the field, representatives of professional bodies and those with a

background in the methodology of guidance development/evidence appraisal, were approached and asked to comment on the applicability and suitability of the guidance to the intended audience (predominantly primary dental care in Scotland) and to indicate whether they think the process used to develop the guidance was satisfactory. This process took place over a four-week period in August and September 2016 and all peer reviewers were asked to complete a Declaration of Interests form.

As with the feedback received during the open consultation, comments received during targeted external expert review were compiled and considered by the GDG to inform further development of the guidance. The compiled peer review comments and GDG responses are available on request.

9. Updating guidance

A review of the context of this guidance (e.g. regulations, legislation, trends in working practices, evidence) will take place three years after publication and, if this has changed significantly, the guidance will be updated accordingly.

10. Conflict of Interest

All contributors to SDCEP, including members of the GDG, are required to complete an SDCEP Declaration of Interests form to disclose relevant interests including financial conflicts of interest, such as receipt of fees for consulting with industry, and intellectual conflicts of interest, such as publication of original data bearing directly on a recommendation. These forms are held by SDCEP, updated yearly and are available on request. At the beginning of each group meeting during guidance development, participants are asked to confirm whether there are any changes to their Declaration of Interests.

Any declared interests which could constitute a conflict of interest are considered by the group to decide whether and how the extent of the individual's participation in the guidance development should be limited (e.g. exclusion from certain decisions or stages, or complete withdrawal).

For the *Oral Health Management of Patients at Risk of Medication-related Osteonecrosis of the Jaw* guidance project the following potential conflicts of interest and management decisions were recorded:

Guidance project	**Oral Health Management of Patients at Risk of Medication-related Osteonecrosis of the Jaw**
Summary of Disclosures	All of the GDG members completed and returned the Declaration of Interests form. The Clinical Co-Chairs of the group had no declared interests. Three of the 18 external group members disclosed interests relevant to the guidance which could potentially cause, or be perceived to cause, conflicts of interest.

GDG member – Duncan Gowans	
Details of interest(s) relevant to guidance	1. Local PI for Celgene-sponsored data collection study (PASS study) 2. Amgen sponsoring attendance at European meeting (June 2016)
Consideration of potential to cause conflict(s) of interest	*Are these interests likely in any way to affect the impartiality of the group member in his/her role in the guidance development e.g. in making recommendations?* 1. As Celgene do not market anti-resorptive or anti-angiogenic drugs, the declared interest would be unlikely to cause (or be perceived to cause) a conflict of interest. 2. Amgen do market drugs included in the guidance (denosumab). However, as

	the SDCEP guidance will not influence the prescribing of anti-resorptive or anti-angiogenic drugs, the declared interest would be unlikely to cause (or be perceived to cause) a conflict of interest.
Decision on the management of the conflict(s) of interest	*Should the group member be excluded from any stages of guidance development or decisions, or be asked to withdraw from the process?* Agreed that no action is required at this point. GDG member will be notified that if at any point in the guidance development they felt their impartiality could be affected, then they should contact SDCEP to advise of this.

GDG member – Terence O'Neill	
Details of interest(s) relevant to guidance	1. Amgen have agreed to provide denosumab and matched placebo for a RCT in knee osteoarthritis. The RCT is funded by a research charity.
Consideration of potential to cause conflict(s) of interest	*Are these interests likely in any way to affect the impartiality of the group member in his/her role in the guidance development e.g. in making recommendations?* 1. As the SDCEP guidance will not influence the prescribing of anti-resorptive or anti-angiogenic drugs, the declared interest would be unlikely to cause (or be perceived to cause) a conflict of interest.
Decision on the management of the conflict(s) of interest	*Should the group member be excluded from any stages of guidance development or decisions, or be asked to withdraw from the process?* Agreed that no action is required at this point. GDG member was notified that if at any point in the guidance development they felt their impartiality could be affected, then they should contact SDCEP to advise of this.

GDG member – David Reid	
Details of interest(s) relevant to guidance	1. Editor in Chief of *Therapeutic Advances in Musculoskeletal Disease* 2. Member of Vitamin D Consultancy Panel, Consilient Health 3. Shares in Astra Zeneca and GSK
Consideration of potential to cause conflict(s) of interest	*Are these interests likely in any way to affect the impartiality of the group member in his/her role in the guidance development e.g. in making recommendations?* 1. It is considered that this is unlikely to cause (or be perceived to cause) a conflict of interest. 2. As the SDCEP guidance will not influence the prescribing of Vitamin D, the declared interest would be unlikely to cause (or be perceived to cause) a conflict of interest. 3. As AZ and GSK do not market anti-resorptive or anti-angiogenic drugs, the declared interest would be unlikely to cause (or be perceived to cause) a conflict of interest.

Decision on the management of the conflict(s) of interest	*Should the group member be excluded from any stages of guidance development or decisions, or be asked to withdraw from the process?* Agreed that no action is required at this point. GDG member was notified that if at any point in the guidance development they felt their impartiality could be affected, then they should contact SDCEP to advise of this.

11. Equality Impact Assessment for the Guidance

The possibility of inequalities associated with the guidance was considered at various stages during guidance development. Guidance development group members were asked to identify any potential issues and the consultation feedback form included a specific question about the impact of the guidance on equality groups. Further feedback was sought through interviews with dentists, pharmacists and medics. Issues identified and actions taken were recorded in an EQIA checklist, which is available on request.

Appendix 1 – Scope

Oral Health Management of Patients at Risk of Medication-related Osteonecrosis of the Jaw

Why the guidance is needed

Bisphosphonate drugs are used to treat non-malignant conditions such as osteoporosis and Paget's disease and in patients who have some forms of cancer. Bisphosphonate treatment has been associated with the development of osteonecrosis of the jaw. In 2011, SDCEP produced national guidance on the *Oral Health Management of Patients Prescribed Bisphosphonates*, with the aim of raising awareness of the condition and the steps to be taken to prevent it, to encourage dental practitioners to manage such patients in primary care and to reduce inappropriate referrals to secondary care. Subsequently, there have been reports that other anti-resorptive or anti-angiogenic drugs are implicated in medication–related osteonecrosis of the jaw (MRONJ).

Post-publication research[2] carried out by SDCEP's partner programme TRiaDS (Translation Research in a Dental Setting) determined that at around 10 months after publication, all but one of the key behaviours were being performed more in line with guidance recommendations compared to self-reported practice in the pre-publication survey. However, a further survey performed at 22-months post-publication revealed that current practice had changed very little from that observed at 10-months post-publication.

In accordance with SDCEP's Guidance Development Methodology, all guidance publications are reviewed three years after publication to assess whether an update to the guidance is required. Based on a review of recent evidence, it was determined that a process to update to the *Oral Health Management of Patients Prescribed Bisphosphonates* guidance was appropriate.

What the guidance aims to do

The overall objective of the guidance is to promote a consistent and safe approach to the management of the oral health of patients taking anti-resorptive and anti-angiogenic drugs by raising awareness of the dental implications of treatment with these drugs, increasing knowledge of how to provide dental care to such patients, and providing information and reassurance to GDPs, GMPs and patients.

The specific aims of the guidance are to:

- raise awareness among GMPs of the possible dental implications of treatment with anti-resorptive or anti-angiogenic drugs;
- provide guidance to GMPs regarding the advice (with respect to dental care) to give to patients who are about to take anti-resorptive or anti-angiogenic drugs;
- raise awareness among GDPs of the possible dental implications of treatment with anti-resorptive or anti-angiogenic drugs;
- provide guidance to GDPs regarding how they should care for patients who are about to take anti-resorptive or anti-angiogenic drugs or who are already taking anti-resorptive or anti-angiogenic drugs;
- reassure GDPs that many patients taking anti-resorptive or anti-angiogenic drugs can be cared for within primary care;
- provide guidance on when it is appropriate to refer such patients from primary care dental practice and reduce the number of inappropriate referrals to secondary care;
- enable patients taking anti-resorptive or anti-angiogenic drugs to have access to safe dental care in the primary care setting (increase local care);
- reduce variation in practice across Scotland;
- raise awareness among patients of the rare but significant complication of treatment with anti-resorptive or anti-angiogenic drugs and the need to inform their dentist that they are taking or are about to take anti-resorptive or anti-angiogenic drugs;
- emphasise to patients the need to maintain good oral hygiene;
- reassure patients that their dentist and GMP will help to manage the risks associated with anti-resorptive or anti-angiogenic drug treatment.

What the guidance will include

- A brief description of anti-resorptive and anti-angiogenic drugs, including:
  - names (generic and trade) of drugs;
  - conditions used to treat;
  - mechanism of action.
- A brief description of MRONJ, including:
  - definition;
  - signs, symptoms, clinical and radiographic features
  - incidence;
  - risk factors e.g. concurrent medication, ill-fitting dentures etc.
- A summary of ongoing work, existing evidence and areas that require further research.
- A definition of which patients should be referred by their medical practitioner to a dentist for assessment and treatment, and when this should take place.
- Details of the advice that the GMP should give to a patient being prescribed anti-resorptive or anti-angiogenic drugs.
- Details of how the oral health of patients who are about to take anti-resorptive or anti-angiogenic drugs should be managed by a primary care dentist, and how this might differ for different categories of patient.
- Details of the treatment that can be carried out by primary care dentists for the different categories of patients taking anti-resorptive or anti-angiogenic drugs.
- Advice on treatment planning
- Details of the advice that the primary care dentist should give to a patient being prescribed anti-resorptive or anti-angiogenic drugs.
- Details of when patients prescribed anti-resorptive or anti-angiogenic drugs should be referred by a primary care dentist to a secondary care dentist.
- Details of what a primary care dentist should do if symptoms of MRONJ are observed.

What the guidance will not include

- Details of the clinical assessment of patients' oral health.
- Details of the clinical procedures used to treat patients taking anti-resorptive or anti-angiogenic drugs.
- Details of how a referred patient is managed in secondary dental care.
- Details of how to provide oral health care to a patient with ONJ.

What the guidance is based on

The guidance will be based on the existing SDCEP *Oral Health Management of Patients Prescribed Bisphosphonates* guidance plus any relevant guidelines, guidance and policy statements issued since 2010. To supplement this information, systematic reviews and primary research evidence published since 2010 will also be reviewed to inform recommendations. Where necessary, recommendations may be based on expert opinion, using consensus development techniques as appropriate.[3]

The questions that will be addressed through a systematic search of research evidence are:

i. What are the risk factors for developing MRONJ?
ii. What subset of patients are considered at higher risk of developing MRONJ?
iii. In patients treated for osteoporosis does the risk of MRONJ increase as the length of time taking anti-resorptive medication increases?
iv. For patients who have previously taken anti-resorptive or anti-angiogenic drugs, does the risk of developing MRONJ return to the same as those patients who have never taken the drugs and, if so, how long does this take?
v. How should patients who are considered to be at risk of developing MRONJ be managed in primary care?
vi. When is it appropriate to seek a second opinion/advice from secondary care and/or refer patients?

Target groups

- Patients who are prescribed an anti-resorptive or anti-angiogenic drug by a GP or other medical practitioner (those who are about to start taking the drug and those who are already taking the drug).
- Patients who have taken anti-resorptive drugs in the past and are no longer taking them.

Target users

- The guidance will primarily be directed at dentists in primary care dental practice, including the general dental service and public dental service.
- The guidance will also be of relevance to the secondary care dental service, those involved in dental education and undergraduate trainees.
- The guidance will contain specific patient information and advice for general medical practitioners and pharmacists dealing with patients taking anti-resorptive or anti-angiogenic drugs, relating to their dental care.

Format and usage

The format of the updated guidance will be similar to the present edition:

- A complete document with details of risk assessment, communication with patients, treatment planning and appropriate referral.
- A short summary of the main recommendations for regular use in the surgery (e.g. poster or a flowchart)
- Patient information, if appropriate, e.g. a patient information leaflet that GPs, pharmacists and dentists can distribute and/or a poster for display in surgery waiting rooms.

Appendix 2 – Evidence Searches

Summary of Searches: 2 June 2015 Searches carried out by Anne Littlewood, Trials Search Coordinator, Cochrane Oral Health Group			
Database	Version/issue	Date of search	Records retrieved
The Cochrane Library	**CDSR** – 2015, Issue 6 **DARE** – 2015, Issue 2 **CENTRAL** – 2015, Issue 5	01.06.15	CDSR: 6 DARE: 3 CENTRAL: 16
MEDLINE via OVID	1946 – 1 June 2015	01.06.15	634
EMBASE via OVID	1980 – 1 June 2015 (week 22)	01.06.15	689
CINAHL via EBSCO	1937 – 1 June 2015	01.06.15	1
AMED via Ovid	1985 – 1 June 2015	01.06.15	0
CANCERLIT via PubMed	1950 – 1 June 2015	01.06.15	620

Summary of Searches: 25 August 2016 Searches carried out by Anne Littlewood, Trials Search Coordinator, Cochrane Oral Health Group			
Database	Version/issue	Date of search	Records retrieved
The Cochrane Library	**CDSR** – 2015, Issue 6 to 2016, issue 8 **DARE** – 2015, Issue 2 to 2016, issue 8 **CENTRAL** – 2015, Issue 5 to 2016, Issue 7	25.08.16	CDSR:0 DARE:0 CENTRAL: 2
MEDLINE via OVID	1 June 2015 to 25 August 2016	25.08.16	97
EMBASE via OVID	1 June 2015 to 25 August 2016	25.08.16	111
CINAHL via EBSCO	1 June 2015 to 25 August 2016	25.08.16	0
AMED via Ovid	1 June 2015 to 25 August 2016	25.08.16	0
CANCERLIT via PubMed	1 June 2015 to 25 August 2016	25.08.16	88

THE COCHRANE LIBRARY SEARCH STRATEGY

#1 [mh Osteonecrosis]
#2 (osteonecro* or "bone necrosis")
#3 osteochemonecro*
#4 (BRONJ or BONJ):ti,ab
#5 [or #1-#4]
#6 [mh Jaw]
#7 [mh "Alveolar bone loss"]
#8 [mh ^"Jaw diseases"]
#9 (jaw or jawbone* or mandib* or maxill*)
#10 (alveolar near/4 bone*)
#11 [or #6-#10]
#12 [mh Diphosphonates]
#13 (diphosphonate* or bisphosphonate* or aminobisphosphonate* or alendronate or risedronate or pamidronate or "zoledronic acid" or ibandronate or "alendronic acid" or bevacizumab or denosumab or "etidronate disodium" or "ibandronic acid" or sirolimus or "sodium clodronate" or sorafenib or sunitinib or "tiludronic acid" or zoledronate or didronel or "clodronate disodium" or tiludronate or "risedronic acid" or "clodronic acid")
#14 (Fosamax or Fosavance or Actonel or Aclasta or Zometa or Reclast or Didronel or Skelid or Bondronat or Bonviva or Aredia or Bonefos or Nexavar or Avastin or Prolia or Xgeva or Boniva or Atelvia or Rapamune or Rapamycin or Sutent or Zometa)
#15 [or #12-#14]
#16 [mh Dentistry]
#17 [mh Tooth]
#18 (extract* or remov* or surgery)
#19 #17 and #18
#20 ((oral next (surgery or surgical)) or (((surgery or surgical*) near/3 (dental* near/3 surgery)) or (dental near/3 surgi*) or exodont*))
#21 ((osteotom* and mandib*) or apicoectom* or apicectom*)
#22 ((tooth or teeth or dental) near/4 (extract* or remov*))
#23 ((third molar* or wisdom tooth or wisdom teeth or 3rd molar*) near/6 (remov* or extract*))
#24 (dental implant* or oral implant* or (implant* near/4 mouth*) or (zygoma* near/4 implant*))
#25 ((orthognathic or maxillofacial or maxillo-facial) near/5 (surgery or surgical*))
#26 #16 or #19 or #20 or #21 or #22 or #23 or #24 or #25
#27 #5 and #11 and #15 and #26

MEDLINE via OVID SEARCH STRATEGY

1. Osteonecrosis/
2. (osteonecro$ or "bone necrosis").mp.
3. osteochemonecro$.mp.
4. (BRONJ or BONJ).ti,ab.
5. or/1-4
6. exp Jaw/
7. Alveolar bone loss/ci
8. Jaw diseases/ci
9. (jaw or jawbone$ or mandibl$ or maxill$ or (alveolar adj4 bone$)).mp.
10. or/6-9

11. exp Diphosphonates/
12. (diphosphonate$ or bisphosphonate$ or aminobisphosphonate$ or alendronate or risedronate or pamidronate or "zoledronic acid" or ibandronate or "alendronic acid" or bevacizumab or denosumab or "etidronate disodium" or "ibandronic acid" or sirolimus or "sodium clodronate" or sorafenib or sunitinib or "tiludronic acid" or zoledronate or didronel or "clodronate disodium" or tiludronate or "risedronic acid" or "clodronic acid").mp.
13. (Fosamax or Fosavance or Actonel or Aclasta or Zometa or Reclast or Didronel or Skelid or Bondronat or Bonviva or Aredia or Bonefos or Nexavar or Avastin or Prolia or Xgeva or Boniva or Atelvia or Rapamune or Rapamycin or Sutent or Zometa).mp.
14. or/11-13
15. exp Dentistry/
16. exp Tooth/
17. (extract$ or remov$ or surgery).ti,ab.
18. 16 and 17
19. ((oral adj (surgery or surgical)) or (((surgery or surgical$) adj3 (dental$ adj3 surgery)) or (dental adj3 surgi$) or exodont$)).ti,ab.
20. ((osteotom$ and mandib$) or apicoectom$ or apicectom$).ti,ab.
21. ((tooth or teeth or dental) adj4 (extract$ or remov$)).ti,ab.
22. ((third molar$ or wisdom tooth or wisdom teeth or 3rd molar$) adj6 (remov$ or extract$)).ti,ab.
23. (dental implant$ or oral implant$ or (implant$ adj4 mouth$) or (zygoma$ adj4 implant$)).ti,ab.
24. ((orthognathic or maxillofacial or maxillo-facial) adj5 (surgery or surgical$)).ti,ab.
25. 15 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26. 5 and 10 and 14 and 25

EMBASE via OVID SEARCH STRATEGY

1. Bone necrosis/
2. (osteonecro$ or "bone necrosis").mp.
3. osteochemonecro$.mp.
4. (BRONJ or BONJ).ti,ab.
5. or/1-4
6. exp Jaw/
7. Alveolar bone loss/
8. Jaw diseases/
9. (jaw or jawbone$ or mandibl$ or maxill$ or (alveolar adj4 bone$)).mp.
10. or/6-9
11. exp Bisphosphonic acid derivative/
12. (diphosphonate$ or bisphosphonate$ or aminobisphosphonate$ or alendronate or risedronate or pamidronate or "zoledronic acid" or ibandronate or "alendronic acid" or bevacizumab or denosumab or "etidronate disodium" or "ibandronic acid" or sirolimus or "sodium clodronate" or sorafenib or sunitinib or "tiludronic acid" or zoledronate or didronel or "clodronate disodium" or tiludronate or "risedronic acid" or "clodronic acid").mp.
13. (Fosamax or Fosavance or Actonel or Aclasta or Zometa or Reclast or Didronel or Skelid or Bondronat or Bonviva or Aredia or Bonefos or Nexavar or Avastin or Prolia or Xgeva or Boniva or Atelvia or Rapamune or Rapamycin or Sutent or Zometa).mp.
14. or/11-13
15. exp Dentistry/
16. exp Tooth/
17. (extract$ or remov$ or surgery).ti,ab.

18. 16 and 17
19. ((oral adj (surgery or surgical)) or (((surgery or surgical$) adj3 (dental$ adj3 surgery)) or (dental adj3 surgi$) or exodont$)).ti,ab.
20. ((osteotom$ and mandib$) or apicoectom$ or apicectom$).ti,ab.
21. ((tooth or teeth or dental) adj4 (extract$ or remov$)).ti,ab.
22. ((third molar$ or wisdom tooth or wisdom teeth or 3rd molar$) adj6 (remov$ or extract$)).ti,ab.
23. (dental implant$ or oral implant$ or (implant$ adj4 mouth$) or (zygoma$ adj4 implant$)).ti,ab.
24. ((orthognathic or maxillofacial or maxillo-facial) adj5 (surgery or surgical$)).ti,ab.
25. 15 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26. 5 and 10 and 14 and 25

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S27 S5 and S10 and S18 and S26
S26 S19 or S20 or S21 or S22 or S23 or S24 or S25
S25 ((orthognathic or maxillofacial or maxillo-facial) N5 (surgery or surgical*))
S24 (dental implant* or oral implant* or (implant* N4 mouth*) or (zygoma* N4 implant*))
S23 ((third molar* or wisdom tooth or wisdom teeth or 3rd molar*) N6 (remov* or extract*))
S22 ((tooth or teeth or dental) N4 (extract* or remov*))
S21 ((osteotom* and mandib*) or apicoectom* or apicectom*)
S20 ((surgery or surgical) N3 dental)
S19 ("oral surgery" or "oral surgical")
S18 S16 and S17
S17 (extract* or remov* or surgery)
S16 (MH Tooth)
S15 (MH Dentistry)
S14 S11 or S12 or S13
S13 (Fosamax or Fosavance or Actonel or Aclasta or Zometa or Reclast or Didronel or Skelid or Bondronat or Bonviva or Aredia or Bonefos or Nexavar or Avastin or Prolia or Xgeva or Boniva or Atelvia or Rapamune or Rapamycin or Sutent or Zometa)
S12 (diphosphonate* or bisphosphonate* or aminobisphosphonate* or alendronate or risedronate or pamidronate or "zoledronic acid" or ibandronate or "alendronic acid" or bevacizumab or denosumab or "etidronate disodium" or "ibandronic acid" or sirolimus or "sodium clodronate" or sorafenib or sunitinib or "tiludronic acid" or zoledronate or didronel or "clodronate disodium" or tiludronate or "risedronic acid" or "clodronic acid")
S11 (MH Diphosphonates)
S10 S6 or S7 or S8 or S9
S9 (alveolar N4 bone*)
S8 (jaw* or jawbone* or mandib* or maxill*)
S7 (MH "Jaw diseases")
S6 (MH Jaw+)
S5 S1 or S2 or S3 or S4
S4 (BRONJ or BONJ)
S3 osteochemonecro*
S2 (osteonecrosis* or "bone necrosis")
S1 (MH Osteonecrosis+)

AMED via OVID SEARCH STRATEGY

1. Osteonecrosis/
2. (osteonecro$ or "bone necrosis").mp.
3. osteochemonecro$.mp.
4. (BRONJ or BONJ).ti,ab.
5. or/1-4
6. exp Jaw/
7. (jaw or jawbone$ or mandibl$ or maxill$ or (alveolar adj4 bone$)).mp.
8. 6 or 7
9. (diphosphonate$ or bisphosphonate$ or aminobisphosphonate$ or alendronate or risedronate or pamidronate or "zoledronic acid" or ibandronate or "alendronic acid" or bevacizumab or denosumab or "etidronate disodium" or "ibandronic acid" or sirolimus or "sodium clodronate" or sorafenib or sunitinib or "tiludronic acid" or zoledronate or didronel or "clodronate disodium" or tiludronate or "risedronic acid" or "clodronic acid").mp.
10. (Fosamax or Fosavance or Actonel or Aclasta or Zometa or Reclast or Didronel or Skelid or Bondronat or Bonviva or Aredia or Bonefos or Nexavar or Avastin or Prolia or Xgeva or Boniva or Atelvia or Rapamune or Rapamycin or Sutent or Zometa).mp.
11. 9 or 10
12. exp Dentistry/
13. exp Tooth/
14. (extract$ or remov$ or surgery).ti,ab.
15. 13 and 14
16. ((oral adj (surgery or surgical)) or (((surgery or surgical$) adj3 (dental$ adj3 surgery)) or (dental adj3 surgi$) or exodont$)).ti,ab.
17. ((osteotom$ and mandib$) or apicoectom$ or apicectom$).ti,ab.
18. ((tooth or teeth or dental) adj4 (extract$ or remov$)).ti,ab.
19. ((third molar$ or wisdom tooth or wisdom teeth or 3rd molar$) adj6 (remov$ or extract$)).ti,ab.
20. (dental implant$ or oral implant$ or (implant$ adj4 mouth$) or (zygoma$ adj4 implant$)).ti,ab.
21. ((orthognathic or maxillofacial or maxillo-facial) adj5 (surgery or surgical$)).ti,ab.
22. 12 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23. 5 and 8 and 11 and 22

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#27 (#5 and #11 and #15 and #26)
#26 (#16 or #19 or #20 or #21 or #22 or #23 or #24 or #25)
#25 (((orthognathic or maxillofacial or maxillo-facial) and (surgery or surgical*)
#24 ((dental implant* or oral implant* or (implant* and mouth*) or (zygoma* and implant*)))
#23 (((third molar* or wisdom tooth or wisdom teeth or 3rd molar*) and (remov* or extract*)))
#22 (((tooth or teeth or dental) and (extract* or remov*)))
#21 (((osteotom* and mandib*) or apicoectom* or apicectom*))
#20 (("oral surgery" or "oral surgical" or (dental and surgi*) or (dental and surgery) or exodont*))
#19 (#17 and #18)
#18 ((extract* or remov* or surgery))
#17 tooth [mh:exp]
#16 dentistry [mh:exp]
#15 (#12 or #13 or #14)

#14 ((Fosamax or Fosavance or Actonel or Aclasta or Zometa or Reclast or Didronel or Skelid or Bondronat or Bonviva or Aredia or Bonefos or Nexavar or Avastin or Prolia or Xgeva or Boniva or Atelvia or Rapamune or Rapamycin or Sutent or Zometa))

#13 ((diphosphonate* or bisphosphonate* or aminobisphosphonate* or alendronate or risedronate or pamidronate or "zoledronic acid" or ibandronate or "alendronic acid" or bevacizumab or denosumab or "etidronate disodium" or "ibandronic acid" or sirolimus or "sodium clodronate" or sorafenib or sunitinib or "tiludronic acid" or zoledronate or didronel or "clodronate disodium" or tiludronate or "risedronic acid" or "clodronic acid"))

#12 Diphosphonates [mh:exp]

#11 (#6 or #7 or #8 or #9 or #10)

#10 "alveolar bone"

#9 ((jaw or jawbone* or mandib* or maxill*))

#8 Jaw diseases [mh:noexp]

#7 "Alveolar bone loss" [mh:noexp]

#6 Jaw [mh:exp]

#5 (#1 or #2 or #3 or #4)

#4 ((BRONJ or BONJ) [tiab])

#3 osteochemonecro*

#2 ((osteonecro* or "bone necrosis"))

#1 Osteonecrosis [mh:exp]

Appendix 3 – Considered Judgement Forms

1. Incidence of MRONJ in patients being treated for cancer

SDCEP	**Considered judgement on quality of evidence**

Key question:	**Evidence table ref:**
What is the incidence of MRONJ in patients being treated with anti-resorptive or anti-angiogenic drugs for cancer?	Incidence – cancer patients

1. Summary of evidence

Comment here on any issues concerning the quantity of evidence available on this topic and its methodological quality.

Systematic Reviews

Boquete-Castro et al. (2015)[4] investigated the relationship between treatment with denosumab and the incidence of osteonecrosis of the jaw (ONJ). The overall incidence of ONJ in patients with cancer receiving denosumab was **1.7%** [95% CI: 0.9-3.1%]. The use of denosumab was associated with a significantly increased risk of ONJ in comparison with bisphosphonates (BPs)/placebo treatment (**RR 1.61**, 95% CI: 1.05-2.48, P = 0.029). Subgroup analysis based on controlled therapies demonstrated an increased risk of ONJ in denosumab therapy, when compared with BPs (RR 1.48, 95% CI: 0.96-2.29, P = 0.078) or placebo (RR 16.28, 95% CI: 1.68-158.05, P = 0.017). Similar results were observed for prostate cancer (RR 3.358, 95% CI: 1.573-7.166, P = 0.002). There does not appear have been any evaluation of the quality of the included studies or any consideration of potential sources of bias. The results of this study are almost identical to the results from the Qi study (see below) which was published a year earlier. This would not be unusual if both were looking at the same studies but this does not appear to be the case. It is this reviewer's view that this study should be excluded as there are too many inconsistencies and questions over whether the data is accurate.

Qi et al. (2014)[5] investigated the incidence and risk of ONJ in cancer patients receiving denosumab. The incidence of ONJ among patients receiving denosumab is **1.7%** (95 % CI: 0.9–3.1 %) with subgroup analysis based on tumour type shows that the incidence in prostate cancer patients is higher than in non-prostate cancer patients. The use of denosumab significantly increases the risk of ONJ when compared with controls (**RR 1.613**, 95 % CI: 1.050–2.478, P = 0.029). Subgroup analysis found that there is an increased risk of developing ONJ in the denosumab group when compared with the BP group (**RR 1.481**, 95 % CI: 0.957–2.293, P = 0.078) or placebo (**RR 16.279**, 95 % CI: 1.677–158.050, P = 0.016). There is no information on the randomisation or blinding process for any of the included studies and the authors do not consider any other sources of bias that may be present. There are is unexplained patient attrition in three of the studies.

Lee et al. (2014)[6] investigated the use of bisphosphonates (BPs) and risk of osteonecrosis of the jaw (ONJ) among cancer patients. Use of BPs was associated with a significantly increased risk of ONJ (**odds ratio (OR) 4.25**; 95 % confidence interval (CI) 3.67-5.36; I (2) = 0 %). IV BPs were associated with higher risk (**OR 4.27**; 95 % CI 3.38-5.40; I (2) = 0 %) than oral BPs (**OR 1.18**; 95 % CI 0.89-1.56; I (2) = 0 %). Hospital-based studies were associated with higher risk estimates than population-based studies. Issues with this review include difficulty in ascertaining how many patients were actually analysed. There is no attempt to identify any sources of bias, other than possible misclassification of disease outcomes due to the way in which data for some of the studies was recorded and there was no attempt to find grey literature.

Kuhl et al. (2012)[7] evaluated the literature published about bisphosphonate-related osteonecrosis of the jaws (BRONJ). 47 studies gave details on the incidence of BONJ after IV application; mean incidence was **7%** but varied from **0% to 27.5%** across studies. It is not clear if the method used to calculate this mean value was correct and the average value is very probably skewed by small studies reporting large incidence values (e.g. 27.5% incidence was observed in study with only 80 participants). The largest study (~13000 participants) reported an incidence of 0.9%. There was also variance in the design and duration of the studies so it may not have been appropriate to combine the data.

Guidelines

Khan et al. (2105)[8] investigated the incidence, pathophysiology, diagnosis, and treatment of osteonecrosis of the jaw (ONJ), and to offer recommendations for its management based on multidisciplinary international consensus. The review found that the incidence of ONJ is greatest in the oncology patient population (abstract quotes **1% to 15%** while main text seems to suggest **0 to 12.2%**), where high doses of these medications are used at frequent intervals. Risk factors for ONJ include glucocorticoid use, maxillary or mandibular bone surgery, poor oral hygiene, chronic inflammation, diabetes mellitus, ill-fitting dentures, as well as other drugs, including antiangiogenic agents. There was no mention of grey/unpublished literature. The relevant studies were critically appraised and graded based on quality of evidence (this was done in duplicate, evidence appraisal does not seem to be particularly rigorous - based on study type rather than assessment of how well study was done. Also, potential sources of bias were not reported). The review itself does not appear to include any meta analysis and the evidence for each question is summarised in a literature review style, with subsequent recommendations proposed by the Task Force. The sections covering incidence and prevalence are not particularly easy to interpret and a letter from other researchers in the field highlight some of the shortcomings of this review, such as inadequate risk of bias assessment.

Ruggiero et al. (2014)[9] produced a position paper for the management of patients with, or at risk of, MRONJ. This does not appear to be based on a systematic review of the literature. They note that medication-related risk factors vary based on the therapeutic indication (osteoporosis/osteopaenia or malignancy) and type of medication (BP or non-BP). Patients with cancer treated with zoledronate or denosumab have 50-100 times higher risk of ONJ compared to those treated with placebo (incidence **1-2%**). The risk of ONJ in patients with cancer treated with bevacizumab is 0.2% and the risk may increase in patients concurrently treated with zoledronate. There is evidence that incidence/risk increases as duration of drug treatment increases.

The majority of studies covered in these reviews and guidelines are observational, where data has been collected either prospectively or retrospectively. This means that the evidence be associated with the results would be considered low quality. Observational studies are often more useful in finding data for incidence and prevalence, especially with rare conditions like MRONJ, however some of the primary studies included were smaller than would be considered prudent. As Ruggiero et al.[9] state, due to the low frequency of MRONJ, studies with small samples (<500 patients) need to be interpreted cautiously. They found that as the sample size of the studies they assessed increased, the MRONJ disease frequency estimates decreased. They suggested that studies with larger samples should be weighted more heavily than those with smaller sample sizes (i.e. disease estimates of a study with a sample size of 10,000 should be weighted more heavily than a study with 500 patients).

2. Volume of evidence

Comment here on any issues concerning the quantity of evidence available on this topic and its methodological quality.

The majority of systematic reviews that have been performed in the field of MRONJ cover the incidence and prevalence of the disease. There does appear to be a significant amount of data from primary studies from which to draw, however the quality of these studies varies based on issues such as study design, size and definitions of disease.

The body of synthesised evidence reported above also varies in robustness, based on both the data from the primary studies and the methodology of the reviews themselves. Risk of bias is very rarely addressed in the reviews and the methods by which some of the figures for incidence and prevalence have been calculated are not at all transparent and in some cases appears to be inappropriate. Some reviews include errors and inconsistencies between figures quoted in different parts of the articles.

These articles are useful as a guide but it is not possible to use this data as a basis for a definitive value for the risk of ONJ in cancer patients treated with anti-resorptive or anti-angiogenic drugs, other than reporting the range of values quoted in the articles above.

3. Subgroup considerations

Comment here on any subgroup considerations e.g. should recommendations for patients at high or low risk be considered separately?

Patients with cancer are considered a sub-group of the patient population to be covered by the guidance. However, patients with a particular medical condition (e.g. prostate cancer) or those taking other concurrent medications (e.g. steroids, combination therapy) may be considered a subgroup of this group; both are considered to be at increased risk of MRONJ, although the risk is still small.

There may also be a difference between groups who are receiving the drugs as primary treatment for their cancer and for those who are receiving secondary, adjuvant treatment as the drug dose in the first instance are likely to be higher than in the second instance. This may be more relevant with regards to determining a patient's level of risk.

4. Consistency

Comment here on the degree of consistency demonstrated by the available of evidence. Where there are conflicting results, indicate how the group formed a judgement as to the overall direction of the evidence

Although there appears to be a large underlying body of evidence, there is great variation in the estimates of ONJ incidence/prevalence. This may be due to heterogeneity in study design, size, reporting and disease classification. The group may have to make decision on how the evidence should be communicated to patients.

5. Balance of Effects

Comment here on the desirable and undesirable effects of the intervention and how substantial the effects are. Indicate whether the overall balance of effects favours the intervention or comparison.

Not relevant for this clinical question.

6. Generalisability and applicability

Comment here on how reasonable it is to generalise from the results of the studies used as evidence to the target population for this guideline.

The data in these studies are directly applicable to a Scottish population and it would be reasonable to generalise from the results if these were consistent.

7. Values and preferences

How much do people value the main outcomes? Uncertainty about how much those affected value the outcomes of interest can be a reason not to make a strong recommendation and might affect the direction of a recommendation. Variability in how much those affected value the main outcomes (to the extent that individuals with different values would make different decisions) is also a reason not to make a strong recommendation.

An accurate assessment of the risk of MRONJ in this patient group is important as this is what will be used by clinicians when discussing risk with the patient. While it is important that patients are discouraged from taking their anti-resorptive or anti-angiogenic medication or from undergoing dental treatment, it is also important that they can balance these against an accurate estimate of their individual MRONJ risk.

8. Acceptability

Is intervention acceptable to patients, caregivers and providers?

Not relevant for this clinical question.

9. Feasibility

Comment on cost effectiveness, resource implications and implementation considerations here, if applicable.

Not relevant for this clinical question.

10. Other factors

Indicate here any other factors that were taken into account when assessing the evidence base.

Clinical experience of those in the group and others suggests that patients being treated for cancer are more likely to develop MRONJ than those being treated for osteoporosis.

9. Evidence statement *Please summarise the development group's synthesis of the evidence relating to this key question, taking all the above factors into account, and indicate the evidence level which applies.*	**Evidence Level** Low quality evidence

The Group agree that the range of values obtained from the included studies make it difficult to determine an overall incidence for MRONJ in cancer patients. There is a wide range in values quoted, with smaller studies appearing to show greater incidence than larger studies. In some cases, it is not clear if it was appropriate to combine results of the primary studies included in the reviews, due to differences in cancer types and drug regimens as well as study design. Studies are mostly observational with the data collected either retrospectively or prospectively. This means that the quality of the evidence would be rated LOW based on the GRADE classification of quality. The quality of the reviews/ guidelines was also variable, with very few addressing risk of bias. There is also an issue with the definition of indices used (e.g. incidence, prevalence, occurrence and frequency) with incidence and prevalence sometimes used interchangeably. It is sometimes unclear what unit of measurement is being quoted. The Group accept that it is difficult to obtain an accurate incidence figure for such a rare condition and that although observational studies are not considered to be as rigorous as RCTs, these types of studies are appropriate to determine incidence and prevalence of a disease. The Group agree that the incidence of MRONJ in patients being treated for cancer is higher than the incidence in patients being treated for osteoporosis or other non-malignant diseases of bone.

10. Recommendation *What recommendation(s) does the guideline development group draw from this evidence? Please indicate the grade of recommendation(s) and any dissenting opinion within the group.*	**Grade of recommendation** **Strong** recommendation

The Group recommend that dentists should assign a level of risk to patients. Patients being treated with these drugs for cancer should be assigned to the higher risk group.

KEY RECOMMENDATION:

Assess whether a patient taking anti-resorptive or anti-angiogenic drugs is at low risk or higher risk of developing MRONJ based on their medical condition, type and duration of therapy and any other complicating factors and record this in the patient's clinical notes. (Strong recommendation; low quality evidence)

- Assign a level of risk based on an assessment of the medical condition that the patient is being treated for and any other complicating factors such as concurrent glucocorticoid medication and length of exposure to the drugs. Ensure that the assigned risk level is recorded in the patient's clinical record.

The Group recommend that dentists should discuss the level of risk with patients, but should ensure the patient appreciates that the risk is low and is not discouraged from taking their medication or undergoing dental treatment.

- Advise the patient(or carer, where appropriate) that, due to the medication they are taking, there may be a risk of developing MRONJ but ensure that they understand that the risk is small. It is very important that a patient is not discouraged from taking their anti-resorptive or anti-angiogenic medication or from undergoing dental treatment. Record that this advice has been given. A list of points to cover in such a discussion can be found in Appendix 4.

From Appendix 4:

- Discuss the overall risk of MRONJ with the patient, based on the medical condition for which they are being treated, using language that they are able to understand. Stress that the risk is small and that the disease is an adverse effect of the medication and is not caused by dental treatment.
    - For patients being treated with anti-resorptive or anti-angiogenic drugs for the management of cancer, the risk of MRONJ approximates 1%, (range 0 – 2.3%) which suggests that each patient has a 1 in 100 chance of developing the disease. However, the risk appears to vary based on cancer type and incidence in patients with prostate cancer or

multiple myeloma may be higher.

- Patients who take concurrent glucocorticoid medication or those who are prescribed both anti-resorptive and anti-angiogenic drugs to manage their medical condition may be at higher risk.

2. Incidence of MRONJ in patients being treated for osteoporosis

Considered judgement on quality of evidence

Key question:	**Evidence table ref:**
What is the incidence of MRONJ in patients being treated with anti-resorptive drugs for osteoporosis?	Incidence – osteoporosis patients

1. Summary of evidence

Comment here on any issues concerning the quantity of evidence available on this topic and its methodological quality.

Systematic Reviews

Carmona et al. (2013)[10] systematically assessed the literature regarding the occurrence of osteonecrosis of the jaw in patients being treated with bisphosphonates for osteoporosis. The reviewers found 8 relevant systematic reviews but none of these gave an estimation of ONJ incidence. Cases of ONJ were observed but total numbers of patients are not quoted therefore a figure for incidence cannot be calculated. 8 clinical trials were identified, none of which reported ONJ as an adverse outcome. These trials were published in 2010 or earlier (2006-2010), so it may be that when the trials were taking place, there may have been less awareness of ONJ as a potential side effect. The timescale of the trials may also influence whether ONJ was observed, as the condition may be related to the dose/time the drug has been given and the trials may not have been long enough to observe this outcome. Also, ONJ in OP patients is likely to be very rare therefore the trials may not have been sufficiently powered to observe any cases. No cases of ONJ were associated with BPs in the meta-analyses of controlled clinical trials lasting at least one year for postmenopausal OP treatment with risedronate and alendronate. Authors performed assessment of study quality based on a modification of the Oxford Centre for Evidence-based Medicine Levels of Evidence however there is no assessment of potential sources of bias.

Solomon et al. (2013)[11] performed a systematic review and a separate cohort study to investigate the epidemiology of BONJ and to estimate the relative risk of BONJ in cohorts of bisphosphonate users with osteoporosis. In studies retrieved from the systematic review, the prevalence of ONJ varied **0.028% to 4.0%** (5 studies) with odds ratios of **7.2 and 9.2** (2 studies). Relative risks (3 studies) ranged from protective (odds ratio 0.65) to elevated (odds ratio 7.8). Only searched one data base (Medline) was searched, using very simple search terms. Study quality was assessed but sources of bias were not addressed and low quality studies were not excluded.

In the cohort study, the authors found very few cases of confirmed ONJ. The prevalence of ONJ was calculated as **0.02%** (cohort 1) and **0.007%** (cohort 2), with a prevalence of **0.002%** in osteoporosis patients not taking medication (cohort 2). The unadjusted prevalence ratio in cohort 2 was **4.10**. The authors used insurance-based health care claims (with surrogate outcomes/codes in cohort 1) and there are limitations to this method as it relies on accurate recording of diagnoses. The follow-up time was also quite short, compared to others' observations that ONJ may take longer than one year to develop in those taking oral BPs for osteoporosis. It should be noted however that the sample sizes for both cohorts were large (nearly 0.5 million patients).

Kuhl et al. (2012)[7] evaluated the literature published about bisphosphonate-related osteonecrosis of the jaws (BRONJ). 9 studies gave details on the incidence of BONJ after oral application; mean incidence was **0.12%** but varied from **0% to 4.3%** across studies. There was significant variance in study duration and the method used to calculate this value is not clear and may be skewed by high incidences observed in small studies (<250 patients). The biggest study included 305,000 patients, with 36 cases of ONJ observed (0.01%) while 5 studies observed no incidences of ONJ in a total of 1755 patients. There was variance in the design and duration of the studies so it may not have been appropriate to combine the data.

Guidelines

Khan et al. (2105)[8] investigated the incidence, pathophysiology, diagnosis, and treatment of

osteonecrosis of the jaw (ONJ), and to offer recommendations for its management based on multidisciplinary international consensus. The review found that the incidence of ONJ in the OP patient group is less than in the oncology patient population (abstract quotes **0.001% to 0.01%** while main text seems to suggest **0 to 0.1%**), There was no mention of grey/unpublished literature. The relevant studies were critically appraised and graded based on quality of evidence (this was done in duplicate; evidence appraisal does not seem to be particularly rigorous - based on study type rather than assessment of how well study was done. Also, potential sources of bias were not reported). The review itself does not appear to include any meta analysis and the evidence for each question is summarised in a literature review style, with subsequent recommendations proposed by the Task Force. The sections covering incidence and prevalence are not particularly easy to interpret and a letter from other researchers in the field highlight some of the shortcomings of this review, such as inadequate risk of bias assessment.

Ruggiero et al. (2014)[9] produced a position paper for the management of patients with, or at risk of, MRONJ. They note that medication-related risk factors vary based on the therapeutic indication (osteoporosis/ osteopaenia or malignancy) and type of medication (BP or non-BP). In patients treated with oral BPs for osteoporosis, MRONJ prevalence estimates range from **0.0004 to 0.1%**. In osteoporosis patients treated with yearly zoledronate or denosumab, the incidence is estimated at **0.017-0.04%** (similar to the risk of ONJ in placebo groups [**0 to 0.02%**]). There is evidence that incidence/risk increases as duration of drug treatment increases. The studies estimating MRONJ risk in this patient population have the weakest levels of evidence of the various study groups (e.g. survey or retrospective cohort studies), with ascertainment of disease based on a combination of examination or review of medical records. This position paper is not a systematic review and as such there is no information on how the included studies were retrieved and whether they were quality assessed before inclusion.

Hellstein et al. (2011)[12] performed a narrative review to update the ADA's 2008 advisory statement on ARONJ. MEDLINE and the Cochrane Central Register of Controlled Trials were searched but there is no mention of grey/unpublished literature or any assessment of study quality. There is a brief overview of the literature, including incidence and risk factors. The highest reliable estimate of antiresorptive agent-induced osteonecrosis of the jaw (ARONJ) prevalence in patients receiving treatment for osteoporosis is approximately **0.10 percent**. The authors note that prospective, well-controlled studies are needed to better determine the true prevalence of ARONJ worldwide.

There is no good quality evidence to inform an estimate of the risk of MRONJ in patients taking anti-resorptive drugs for the prevention or treatment of osteoporosis. This is mainly due to the extremely rare nature of the disease and associated study limitations such as small sample size, retrospective design, inadequate study durations and issues associated with voluntary reporting of cases.

The majority of studies covered in these reviews and guidelines are observational, where data has been collected either prospectively or retrospectively. This means that the evidence be associated with the results would be considered low quality by GRADE.

The estimate that appears to viewed as most reliable by the authors of guidelines above is based on a survey of patients with a history of chronic oral bisphosphonate use. Incidence in this group of patients was estimated at ~0.1% (9 cases /8572 controls). However, this is one study with a questionable design (would patients who had dental symptoms be more likely to reply?) and the value obtained is around 10 times higher than previous estimates, which had approximated 0.001 – 0.01%. Nonetheless, all three guidelines quote the 0.1% value, although some include a range with a lower limit as well.

2. Volume of evidence

Comment here on any issues concerning the quantity of evidence available on this topic and its methodological quality.

The majority of systematic reviews that have been performed in the field of MRONJ cover the incidence and prevalence of the disease. However, there appears to be much less data on which to base an estimate of prevalence/incidence in the osteoporosis patient population and the body of synthesised evidence that does exist is lacking in robustness, based on both the data from the primary studies and the methodology of the reviews themselves. Risk of bias is very rarely addressed in the reviews and the

methods by which some of the figures for incidence and prevalence have been calculated are not at all transparent and in some cases appears to be inappropriate. Some reviews include errors and inconsistencies between figures quoted in different parts of the articles.

These articles are useful as a guide but it is not possible to use this data as a basis for a definitive value for the risk of ONJ in osteoporosis patients treated with anti-resorptive or anti-angiogenic drugs, other than reporting the range of values quoted in the articles above.

3. Subgroup considerations

Comment here on any subgroup considerations e.g. should recommendations for patients at high or low risk be considered separately?

Patients with osteoporosis are considered a sub-group of the patient population to be covered by the guidance. However, there is evidence that MRONJ risk increases as the length of time patients are exposed to the drug increases and it may be that those who have taken the drug for >4 years should be considered as a subgroup, as should those who are taking other concurrent medications (e.g. steroids, combination therapy); both are considered to be at increased risk of MRONJ, although the risk is still small.

4. Consistency

Comment here on the degree of consistency demonstrated by the available of evidence. Where there are conflicting results, indicate how the group formed a judgement as to the overall direction of the evidence

There is not a great deal of evidence to inform an estimate of MRONJ risk in OP patients and I the evidence that is available, there is great variation in the estimates of ONJ incidence/prevalence. This may be due to heterogeneity in study design, size, reporting, disease classification and will be influenced by the rare nature of the disease also. The group may have to make decision on how the evidence should be communicated to patients.

5. Balance of Effects

Comment here on the desirable and undesirable effects of the intervention and how substantial the effects are. Indicate whether the overall balance of effects favours the intervention or comparison.

Not relevant for this clinical question.

6. Generalisability and applicability

Comment here on how reasonable it is to generalise from the results of the studies used as evidence to the target population for this guideline.

The data in these studies are directly applicable to a Scottish population and it would be reasonable to generalise from the results if these were consistent.

7. Values and preferences

How much do people value the main outcomes? Uncertainty about how much those affected value the outcomes of interest can be a reason not to make a strong recommendation and might affect the direction of a recommendation. Variability in how much those affected value the main outcomes (to the extent that individuals with different values would make different decisions) is also a reason not to make a strong recommendation.

An accurate assessment of the risk of MRONJ in this patient group is important as this is what will be used by clinicians when discussing risk with the patient. While it is important that patients are discouraged from taking their anti-resorptive medication or from undergoing dental treatment, it is also important that they can balance these against an accurate estimate of their individual MRONJ risk.

8. Acceptability

Is intervention acceptable to patients, caregivers and providers?

Not relevant for this clinical question.

9. Feasibility

Comment on cost effectiveness, resource implications and implementation considerations here, if applicable.

Not relevant for this clinical question.

10. Other factors

Indicate here any other factors that were taken into account when assessing the evidence base.

Clinical experience of group members and others suggests that MRONJ is very rare in this patient group. Patient representative note that this patient group may be disproportionately concerned about the risk of MRONJ.

9. Evidence statement *Please summarise the development group's synthesis of the evidence relating to this key question, taking all the above factors into account, and indicate the evidence level which applies.*	**Evidence Level** Low quality evidence

The Group agree that the range of values obtained from the included studies make it difficult to determine an overall incidence for MRONJ in osteoporosis patients.

There is a wide range in values quoted, with some studies reporting no cases of ONJ while others report values up to 4.3%. This is mainly due to the extremely rare nature of the disease and associated study limitations such as small sample size, retrospective design, inadequate study durations and issues associated with voluntary reporting of cases.

Studies are mostly observational with the data collected either retrospectively or prospectively. This means that the quality of the evidence would be rated LOW based on the GRADE classification of quality. The quality of the reviews/ guidelines was also variable, with very few addressing risk of bias.

The Group accept that it is difficult to obtain an accurate incidence figure for such a rare condition and that although observational studies are not considered to be as rigorous as RCTs, these types of studies are appropriate to determine incidence and prevalence of a disease. The Group agree that the incidence of MRONJ in patients being treated for osteoporosis is at least an order of magnitude less than the incidence in patients being treated for cancer.

10. Recommendation *What recommendation(s) does the guideline development group draw from this evidence? Please indicate the grade of recommendation(s) and any dissenting opinion within the group.*	**Grade of recommendation** **Strong** recommendation

The Group recommend that dentists should assign a level of risk to patients. Patients being treated with these drugs for osteoporosis should be assigned to the low risk group. There is some evidence that the risk in this patient group increases with increasing drug duration (applies to the bisphosphonates, not RANKL inhibitors) and also where anti-resorptive drugs are taken in combination with systemic corticosteroids or other immunosuppressive drugs therefore these patients would be considered to be at higher risk. The group agree patients who have taken bisphosphonate drugs for the treatment of osteoporosis for more than 5 years should be considered to be at higher risk.

KEY RECOMMENDATION:

Assess whether a patient taking anti-resorptive or anti-angiogenic drugs is at low risk or higher risk of developing MRONJ based on their medical condition, type and duration of therapy and any other complicating factors and record this in the patient's clinical notes.

Molar bullet point:

- Assign a level of risk based on an assessment of the medical condition that the patient is being treated for and any other complicating factors such as concurrent glucocorticoid medication and length of exposure to the drugs. See Table 3.1 for further information. Ensure that the assigned risk level is recorded in the patient's clinical record.

Advice in Table 3.1:

Low Risk if any of the following is present:

- Patients being treated for osteoporosis or other non-malignant diseases of bone (e.g. Paget's disease) with oral bisphosphonates for less than 5 years who are not concurrently being treated with systemic glucocorticoids
- Patients being treated for osteoporosis or other non-malignant diseases of bone with quarterly or

yearly infusions of intravenous bisphosphonates for less than 5 years who are not concurrently being treated with systemic glucocorticoids
- Patients being treated for osteoporosis or other non-malignant diseases of bone with denosumab who are not being treated with systemic glucocorticoids

Higher Risk if any of the following is present:

- Patients being treated for osteoporosis or other non-malignant diseases of bone (e.g. Paget's disease) with oral bisphosphonates or quarterly or yearly infusions of intravenous bisphosphonates for more than 5 years
- Patients being treated for osteoporosis or other non-malignant diseases of bone with bisphosphonates or denosumab for any length of time who are being concurrently treated with systemic glucocorticoids

The Group recommend that dentists should discuss the level of risk with patients, but should ensure the patient appreciates that the risk is low and is not discouraged from taking their medication or undergoing dental treatment.

- Advise the patient (or carer, where appropriate) that, due to the medication they are taking, there may be a risk of developing MRONJ but ensure that they understand that the risk is small. It is very important that a patient is not discouraged from taking their anti-resorptive or anti-angiogenic medication or from undergoing dental treatment. Record that this advice has been given. A list of points to cover in such a discussion can be found in Appendix 4.

From Appendix 4:

- Discuss the overall risk of MRONJ with the patient, based on the medical condition for which they are being treated, using language that they are able to understand. Stress that the risk is small and that the disease is an adverse effect of the medication and is not caused by dental treatment.
  - For patients taking oral anti-resorptive drugs for the prevention or management of non-malignant disease (e.g. osteoporosis, Paget's disease), the risk of MRONJ approximates 0.1% or less, which suggests that each patient has between a 1 in 1000 and 1 in 10,000 chance of developing the disease.
  - Patients who take concurrent glucocorticoid medication or those who are prescribed both anti-resorptive and anti-angiogenic drugs to manage their medical condition may be at higher risk.

3. Incidence of MRONJ after tooth extraction

Considered judgement on quality of evidence

Key question:	**Evidence table ref:**
What is the incidence of MRONJ in patients being treated with anti-resorptive or anti-angiogenic drugs after tooth extraction?	Incidence – tooth extraction

1. Summary of evidence

Comment here on any issues concerning the quantity of evidence available on this topic and its methodological quality.

Systematic Review

Gaudin et al. (2015)[13] explored the occurrence rate of MRONJ after dental extraction in patients treated with anti-resorptive drugs (ARD). 13 studies (9 case series, 2 cohort, 2 RCTs) were included. 5 studies considered IV administration, 3 oral and 5 both. 2662 patients underwent dental extractions, 2098 individuals (79%) were treated orally for osteoporosis and 564 (21%) were treated IV for oncological reasons.

10 studies reported MRONJ after tooth extractions in patients treated IV. 36 out of 564 patients had MRONJ, a risk of **3.2%** (95% CI: 1.7–4.7%). Two of the studies reported no cases of ONJ, but one had only 2 participants while the other had only 23.

8 studies reported on MRONJ after tooth extractions in patients treated orally. 9 cases out of 2098 were identified, a risk of **0.15%** (95% CI: 0.0–0.36%). It should be noted that no cases of ONJ were observed in 5 of the studies, including one with 700 participants.

Authors performed assessment of study quality (based on Cochrane Collaboration study-design-related forms) and reported the overall findings but did not report on the individual components of this such as randomisation. Studies assessed as low quality or having a high risk of bias were excluded from the review. It should be noted that the size of the studies assessing risk in patients treated with I.V. drugs were small, with most having <70 participants, and although the studies assessing risk in patients treated orally were bigger, only two had >500 participants. Because of this, it may be that these figures overestimate the risk of MRONJ following tooth extraction.

Guidelines

Ruggiero et al. (2014)[9] produced a position paper for the management of patients with, or at risk of, MRONJ. They note that dentoalveolar surgery is considered a major risk factor for developing MRONJ, with 52-61% of patients reporting tooth extraction as the precipitating event. They do not attempt to quantify the risk by combining data from several studies but merely report the results. There is no comment on the methodological quality of the individual studies.

In two observational studies of patients with cancer exposed to i.v. BPs (mostly zoledronate), tooth extraction was associated with a **16-fold** (odds ratio [OR] = 16.4; 95% CI, 3.4-79.6) and **33-fold** increased risk for ONJ. Risk estimates for developing ONJ after tooth extraction in patients with cancer exposed to IV BPs range from **1.6 to 14.8%**. In a retrospective cohort study composed of a sample of patients with cancer exposed to zoledronate (n = 27), 4 patients (14.8%) developed ONJ after tooth extraction and in a prospective cohort study composed of 176 patients with cancer who were exposed to zoledronate, 5 (2.8%) developed ONJ. In a prospective cohort study of 63 patients with a history of cancer and IV BP exposure who underwent extraction of at least 1 tooth, 1 patient (1.6%) developed ONJ. The estimates derived from the prospective studies should be weighted more heavily owing to the larger samples and more robust study designs.

They note that the best current estimate for the risk of ONJ in patients exposed to oral BPs after tooth extraction is **0.5%**, derived from a prospective evaluation of patients exposed to oral BPs who underwent extraction of at least 1 tooth (1 case/194 patients).

Hellstein et al. (2011)[12] performed a narrative review to update the ADA's 2008 advisory statement on ARONJ. They commented briefly on the incidence of MRONJ following tooth extraction in one study

which investigated the frequency of MRONJ in osteoporosis patients receiving BP therapy. The frequency of MRONJ was observed to range from **0.04% to 0.01%** when all patients were considered. However, when focussing on the population that underwent a dental extraction, the frequency of MRONJ was observed to range from **0.09% to 0.34%**. There is no comment on the methodological quality of the individual studies.

Only one systematic review addresses the risk of MRONJ following tooth extraction. Two guidelines discuss this briefly but the studies quoted are not quality assessed and only reported as part of a narrative.

The majority of studies covered in these reviews and guidelines are observational, where data has been collected either prospectively or retrospectively. This means that the evidence be associated with the results would be considered low quality by GRADE. Observational studies are often more useful in finding data for incidence and prevalence, especially with rare conditions like MRONJ, however some of the primary studies included were smaller than would be considered prudent. Due to the low frequency of MRONJ, studies with small samples (<500 patients) need to be interpreted cautiously.

2. Volume of evidence

Comment here on any issues concerning the quantity of evidence available on this topic and its methodological quality.

The majority of systematic reviews that have been performed in the field of MRONJ cover the incidence and prevalence of the disease. However, not many of these specifically address the incidence of MRONJ following tooth extraction. One systematic review of 10 studies was found and two guidelines also briefly cover this.

The authors of the systematic review (Gaudin et al.[13]) assessed study quality (based on Cochrane Collaboration study-design-related forms) and reported the overall findings but did not report on the individual components of this such as randomisation or other sources of bias. Studies assessed as low quality or having a high risk of bias were excluded from the review. However, it should be noted that most included studies were observational, with only 2 RCTs. The guidelines both quote data obtained from observational studies and do not assess the quality of the primary studies.

These articles are useful as a guide but it is not possible to use this data as a basis for a definitive value for the risk of ONJ following tooth extraction in patients treated with anti-resorptive or anti-angiogenic drugs, other than reporting the range of values quoted in the articles above.

3. Subgroup considerations

Comment here on any subgroup considerations e.g. should recommendations for patients at high or low risk be considered separately?

The results above do show that there is a difference in risk for patients being treated with i.v. drugs and those taking oral drugs and this will be reflected in the guidance.

4. Consistency

Comment here on the degree of consistency demonstrated by the available of evidence. Where there are conflicting results, indicate how the group formed a judgement as to the overall direction of the evidence

There is variation in the estimates of ONJ incidence/prevalence following tooth extraction in these patient groups. This may be due to heterogeneity in study design, size, reporting and disease classification. It is also likely that the rare nature of the disease contributes to this. The group may have to make decision on how the evidence should be communicated to patients.

5. Balance of Effects

Comment here on the desirable and undesirable effects of the intervention and how substantial the effects are. Indicate whether the overall balance of effects favours the intervention or comparison.

Not relevant for this clinical question.

6. Generalisability and applicability

Comment here on how reasonable it is to generalise from the results of the studies used as evidence to the target population for this guideline.

The data in these studies are directly applicable to a Scottish population and it would be reasonable to generalise from the results if these were consistent.

7. Values and preferences

How much do people value the main outcomes? Uncertainty about how much those affected value the outcomes of interest can be a reason not to make a strong recommendation and might affect the direction of a recommendation. Variability in how much those affected value the main outcomes (to the extent that individuals with different values would make different decisions) is also a reason not to make a strong recommendation.

An accurate assessment of the risk of MRONJ in this patient group is important as this is what will be used by clinicians when discussing risk with the patient. While it is important that patients are discouraged from taking their anti-resorptive or anti-angiogenic medication or from undergoing dental treatment, it is also important that they can balance these against an accurate estimate of their individual MRONJ risk.

8. Acceptability

Is intervention acceptable to patients, caregivers and providers?

Not relevant for this clinical question.

9. Feasibility

Comment on cost effectiveness, resource implications and implementation considerations here, if applicable.

Not relevant for this clinical question.

10. Other factors

Indicate here any other factors that were taken into account when assessing the evidence base.

The patient representatives were keen that patients should be given information about the risks of MRONJ in terms that they can understand. They reported anecdotally that some patients, particularly those prescribed anti-resorptive drugs for the prevention and treatment of osteoporosis, are disproportionately anxious about their risk of MRONJ. They hope that the guidance will address this by including recommendations or resources for practitioners to help reassure patients and, while not downplaying the risk, help them understand what this means for them.

9. Evidence statement *Please summarise the development group's synthesis of the evidence relating to this key question, taking all the above factors into account, and indicate the evidence level which applies.*	**Evidence Level** Low quality evidence

The Group agree that the volume of evidence is limited and that the values found for incidence of MRONJ following tooth extraction fall within the error bars of the values observed for all patients. However, it is likely that these overall incidence values include those who had invasive dental work and those who did not.

There does appear to be an increased MRONJ risk in patients taking these drugs who have an extraction, with one publication suggesting that around 50-60% of patients with MRONJ will have had a precipitating extraction. Although the guidance will stress the importance of avoiding extractions where possible in higher risk patients, the Group agrees that information on the incidence of ONJ following extractions should be provided for both low and higher risk patients to allow valid consent where extractions are required. The discussion with patients should also include information on the risks of stopping their medication, such as an increased risk of fractures, which greatly outweigh the risk of MRONJ. The group note that wherever values of risk are mentioned, these should be provided to patients in language that they will be able to comprehend (i.e. '1 in a thousand chance' is likely to be more understandable/relatable for patients than quoting an incidence rate of 0.1%).

10. Recommendation *What recommendation(s) does the guideline development group draw from this evidence? Please indicate the grade of recommendation(s) and any dissenting opinion within the group.*	**Grade of recommendation** **Strong** recommendation

The Group recommend that tooth extraction can be performed as normal in low risk patients, although patients should be encouraged to practice good oral hygiene to reduce the risk of extractions. Alternatives to extraction should be considered in higher risk patients wherever possible, although extractions are not contraindicated in this patient group. These patients should also be encouraged to have optimal oral hygiene practices to reduce the risk of extractions. Informed consent should be obtained from all patients who require extractions.

KEY RECOMMENDATIONS:

Carry out all routine dental treatment as normal and continue to provide personalised preventive advice in primary care.

- Perform straightforward extractions and other bone-impacting treatments in low risk patients in primary care.
- Adopt a more conservative approach in higher risk patients, giving greater consideration to other, less invasive alternative treatment options before performing extractions and other bone-impacting treatments in primary care.

Do not prescribe antibiotic or antiseptic prophylaxis following extractions or other bone-impacting treatments specifically to reduce the risk of MRONJ
(Strong recommendations; low quality evidence)

Low Risk Patients

Having made the patient as dentally fit as feasible:

- Carry out all routine dental treatment as normal and continue to provide personalised preventive advice.
  - If an extraction or another procedure that impacts on bone is required:
    - Discuss the risks and benefits associated with treatment with the patient (or carer, where appropriate) to ensure valid consent. See Appendix 4 for points to cover during this discussion;
    - Proceed with the treatment as clinically indicated;

Higher Risk Patients

Having made the patient as dentally fit as feasible:

- If an extraction is indicated, explore all possible alternatives where teeth could potentially be retained e.g. retaining roots in absence of infection.
  - If extraction remains the most appropriate treatment:
    - Discuss the risks and benefits associated with treatment with the patient (or carer, where appropriate) to ensure valid consent. See Appendix 4 for points to cover during this discussion;
    - Proceed with the extraction as clinically indicated;

4. Prevention of MRONJ

Considered judgement on quality of evidence

Key question:	**Evidence table ref:**
How should the risk of MRONJ be reduced in patients being treated with anti-resorptive or anti-angiogenic drugs?	Prevention of MRONJ

1. Summary of evidence

Comment here on any issues concerning the quantity of evidence available on this topic and its methodological quality.

Systematic Reviews

Gaudin et al. (2015)[13] investigated the occurrence rate of MRONJ after dental extraction in patients treated with anti-resorptive drugs (ARD) and compared extraction protocols to identify which were lowest risk.

Dental extractions performed with alveolectomy or use of a biological membrane significantly decreased MRONJ development in patients treated with BPs for cancer; no difference observed for primary or secondary intention closure in this patient group. Differences were not significant with any surgical parameter in the osteoporosis patient group

No. of MRONJ cases according to surgical parameters:

a) Alveolectomy vs. no alveolectomy
   Cancer: **1.5%** (0.1-2.9; n =404) vs. **5.9%** (2.2-9.5; n=158) **p =0.028**
   Osteoporosis: **0%** (0.0-0.26; n = 336) vs. **0.13%** (0.0-0.35 n = 1529) p=0.47
b) PRGF vs. no PRGF
   Cancer: **0.91%** (0.0-2.5; n = 218) vs. **4.4%** (2.1-6.6; n = 344) **p=0.015**
   Osteoporosis: no data vs. **0.08%** (0.0-0.24; n =1865) p=NA
c) First intention vs. second intention
   Cancer: **1.41%** (0.0-3.0; n =364) vs. **3.1%** (0.1-6.1; n = 103) p=0.32
   Osteoporosis: **0.12%** (0.0-0.35; n = 1286) vs. **0.01%** (0.0-0.27; n = 457) p=0.52

The majority of the patients received oral hygiene instructions and a full mouth scaling before the extractions, with post-operative mouth rinses (CHX 0.2%/iodine 10%) and a semi-liquid diet recommended. The majority of studies described antibiotic coverage but there was no standard protocol in terms of administration time and doses. Study quality was assessed using a checklist designed for each study type and low quality studies were excluded.

Kyrgidis et al. (2013)[14] aimed to identify interventions that may be effective in reducing the risk of ONJ in cancer patients receiving antiresorptive therapy. There was no significant difference in risk of ONJ between patients prescribed zoledronic acid or denosumab (**RR:0.71** [99% CI: 0.41-1.24]) based on three manufacturer sponsored RCTs. Four cohort studies suggest that pamidronate is at least 4 time less likely to induce ONJ compared to zoledronate (**RR:4.41** [99% CI: 1.90-10.24]) while an RCT and a cohort study favour clodronate over zoledronate (**RR:10.15** [99% CI: 2.43-42.35]) although it was noted that zoledronate is more effective at reducing bone morbidities.

Based on two cohort studies, dental extractions remain the most potent risk factor for ONJ (**RR:14.04**, [99% CI: 10.36-19.03]) and avoidance of extractions can be considered an effective risk-reductive intervention. Based on three cohort studies, dental prophylactic measures can reduce ONJ risk (**RR:0.45**, [99% CI: 0.23-0.85], I2=7%) however it was noted that one of these studies had a much higher than expected incidence of ONJ in the control arm. When this study is removed from the analysis, the result becomes non-significant based on the 99% confidence interval (RR: 0.55, [99% CI: 0.27-1.09).

Study quality was assessed using published instruments though it is not clear if this was taken into account when assessing the data. Heterogeneity and publication bias were also assessed but there is no mention of possible sources of bias. The authors note that the meta analyses in this review are

mostly underpowered and mostly based on non-randomised studies and suggest that more randomized clinical trials are needed.

Guidelines

Khan et al. (2015)[8] investigated the incidence, pathophysiology, diagnosis, and treatment of osteonecrosis of the jaw (ONJ) and offer recommendations for its management based on multidisciplinary international consensus. 13 studies addressed the prevention of ONJ and the role of drug interruption, none of which were judged to be of a high level of evidence (4 x level 3 [non-randomised controlled trial or cohort study]; 4 x level 4 [before-after study, cohort study with non-contemporaneous controls, case-control study]; 5 x level 5 [case series without controls]). The authors recommend that the risk of ONJ should be reduced by completing any required oral surgery before the commencement of antiresorptive therapy (based on 4 studies), the use of antibiotics before and after any procedures which are required while the patient is taking anti-resporptive medication (based on 6 studies), antimicrobial mouth rinsing (based on 3 studies), appropriate closure of the wound following tooth extraction (based on 3 studies) and maintenance of good oral hygiene (based on 6 studies). They also recommend that oncology patients taking anti-resorptive medication who undergo invasive oral surgery have the medication withheld following the procedure until soft tissue healing has occurred, although there is little evidence for this and it is known that BPs remain in bone for many years.

The relevant studies were critically appraised and graded based on quality of evidence (this was done in duplicate; evidence appraisal does not seem to be particularly rigorous - based on study type rather than assessment of how well study was done. Also, potential sources of bias were not reported). The review itself does not appear to include any meta analysis and the evidence for each question is summarised in a literature review style, with subsequent recommendations. A letter from other researchers in the field highlights some of the shortcomings of this review, such as inadequate risk of bias assessment.

Ruggiero et al. (2014)[9] produced a position paper for the management of patients with, or at risk of, MRONJ. The authors recommend that a multidisciplinary approach, including consultation with an appropriate dental professional when it is determined that a patient would benefit from an anti-resorptive or anti-angiogenic drug, should be adopted and that early screening and remedial dental work would benefit patients not just in terms of lowering their ONJ risk but also in improving their oral health.

They recommend that for patients being treated for cancer, initiation of drug therapy should be delayed until dental health is optimized if systemic conditions permit. Non-restorable teeth and those with a poor prognosis should be extracted and any other necessary elective dentoalveolar surgery completed, with extraction sites allowed to heal before antiresorptive/antiangiogenic therapy begins. Patients should be educated as to the importance of dental hygiene and regular dental evaluations and specifically instructed to report any pain, swelling, or exposed bone. Procedures that involve direct osseous injury should be avoided during treatment with antiresorptive/antiangiogenic drugs and any non-restorable teeth should be treated by removal of the crown and endodontic treatment of the remaining roots. Placement of dental implants should be avoided in these patients. Data are scant regarding the effect of drug holidays before invasive dental treatments. However, if ONJ develops, discuss with the oncologist the option of discontinuing antiresorptive therapy until soft tissue closure has occurred, depending on disease status.

For patients on antiresorptive treatment for osteoporosis, the risk of MRONJ increases when duration of oral antiresorptive therapy exceeds 4 years. Comorbidities, such as chronic corticosteroid use, may shorten this timeframe. At the initiation of treatment, patients should be educated as to the potential risks of MRONJ because the timeframe of antiresorptive therapy is likely to exceed 4 years. The importance of optimizing dental health throughout this treatment period and beyond should be stressed. Elective dentoalveolar surgery is not contraindicated in this group. It is recommended that patients be adequately informed of the very small risk (<1%) of compromised bone healing. There is currently no evidence that interrupting BP therapy alters the risk of ONJ in osteoporosis/osteopaenia patients after tooth extraction but a theoretical benefit may apply for those patients with extended exposure histories (>4 yrs)

This article is not a systematic review but includes an overview of the literature, a definition of the disease, risk factors, and recommendations for prevention and treatment of the condition. The recommendations for management do not appear to be based on a critical appraisal of the evidence and are merely accompanied by a reference to the relevant studies.

Hellstein et al. (2011)[12] performed an appraisal of the literature and make recommendations for the management of patients on anti-resorptive therapy for low bone mass (osteoporosis) on behalf of the American Dental Association Council on Scientific Affairs and updated the committee's 2008 advisory statement. The authors state that due to a paucity of clinical data regarding the dental care of patients receiving antiresorptive therapy, their recommendations are based primarily on expert opinion. They recommend that routine dental treatment should not be modified but that patients should be informed of the risks of ONJ (~0.10%). They also recommend that an oral health program consisting of sound hygiene practices and regular dental care may be the optimal approach for lowering ONJ risk. The authors conclude that the benefit provided by antiresorptive therapy outweighs the low risk of developing osteonecrosis of the jaw and that discontinuing bisphosphonate therapy may not lower the risk but may have a negative effect on low-bone-mass-treatment outcomes.

A search of two databases was performed however there is no mention of inclusion or exclusion criteria and it is not clear whether there was a quality assessment of the included studies and whether this was used as a basis to exclude poor quality studies. The guideline recommendations are not clearly stated separately but are buried within the main text. The guideline was compiled by the ADA and there are several authors but it is unclear if it was subject to peer review outwith the group who prepared it. The group does not appear to include any representatives from primary care dentistry and it is unclear whether patient views were sought as part of the development process.

There is no good quality evidence to inform measures to prevent MRONJ as the majority of studies covered in these reviews and guidelines are mostly observational, where data has been collected either prospectively or retrospectively. This means that the evidence be associated with the results would be considered low quality by GRADE. However, the evidence available does suggest that reaching and maintaining an optimum level of oral health as early in the patient's drug treatment as possible may help reduce the risk of extractions or procedures that impact on bone later on in their treatment, which are themselves risk factors for MRONJ.

2. Volume of evidence

Comment here on any issues concerning the quantity of evidence available on this topic and its methodological quality.

There are very few good quality randomised studies that investigate the prevention of MRONJ. The systematic review by Gaudin et al.[13] looks at different procedures for dental extractions in this patient group and the meta analysis does suggest that extractions performed with alveolectomy or with PRGF (biological membrane) reduce the risk of ONJ in patients being treated for cancer but the results were not significant for suture method in this patient group or for any of the techniques in patients with osteoporosis. Kyrgidis et al.[14] looked at the risk based on the type of drug prescribed to patients however, this is not likely to be relevant to prevention in the dental setting. Three cohort studies seemed to suggest that dental prophylactic measures can reduce ONJ however the significance of this result is not clear.

The review and guideline by Khan et al.[8] includes 13 studies that investigate prevention of MRONJ, however most of these are observational, with two trials that were controlled but not randomised. The characteristics of the included studies are not described at all in the main article (these are available as a separate appendix and are given an evidence rating based on study design only) and there is no meta analysis of the outcomes; the review merely makes recommendations and references the relevant studies. The guideline by Ruggiero et al.[9] gives an overview of studies which investigate prevention but again there is no description or critical appraisal of the included studies. Hellstein et al.[12] state that their recommendations for prevention are mainly based on expert opinion due to a lack of evidence.

The body of synthesised evidence that does exist for this topic is lacking in robustness, based on both the data from the primary studies and the methodology of the reviews themselves. Risk of bias is very rarely addressed in the reviews and as most studies were observational in nature, the body of evidence

would be rated **LOW** by GRADE.

3. Subgroup considerations

Comment here on any subgroup considerations e.g. should recommendations for patients at high or low risk be considered separately?

Patients who are being treated for malignant disease appear to be at higher risk of MRONJ, so this sub-group could be considered separately from those being treated for non-malignant disease. However, given the lack of high quality evidence to inform this, it is likely that the recommendations made will be the same for both patient groups.

4. Consistency

Comment here on the degree of consistency demonstrated by the available of evidence. Where there are conflicting results, indicate how the group formed a judgement as to the overall direction of the evidence

The evidence is consistent in that all recommend that achieving optimal oral health early on in the drug treatment is the ideal situation, but this recommendation is based mostly on expert opinion and the results of a few, mostly observational studies.

5. Balance of Effects

Comment here on the desirable and undesirable effects of the intervention and how substantial the effects are. Indicate whether the overall balance of effects favours the intervention or comparison.

Recommending that a patient's oral health be optimised is the overall goal for dentistry as a whole therefore it is difficult to foresee any undesirable effects.

6. Generalisability and applicability

Comment here on how reasonable it is to generalise from the results of the studies used as evidence to the target population for this guideline.

The data in these studies are directly applicable to a Scottish population and it would be reasonable to generalise from the results.

7. Values and preferences

How much do people value the main outcomes? Uncertainty about how much those affected value the outcomes of interest can be a reason not to make a strong recommendation and might affect the direction of a recommendation. Variability in how much those affected value the main outcomes (to the extent that individuals with different values would make different decisions) is also a reason not to make a strong recommendation.

It is likely that patients will find the recommendation acceptable, although it is known that it can be difficult to get those with poor oral hygiene to change their behaviour. Expressing this as being a way in which patients can affect (decrease) their risk of MRONJ may help deliver the oral hygiene message.

8. Acceptability

Is intervention (e.g. continuing on antiplatelet medication) acceptable to patients, caregivers and providers?

See comment above

9. Feasibility

Comment on cost effectiveness, resource implications and implementation considerations here, if applicable.

Not relevant for this clinical question.

10. Other factors

Indicate here any other factors that were taken into account when assessing the evidence base.

Prevention of dental disease by improving oral hygiene and reducing high risk behaviours, such as consumption of sugary snack and drinks, is a key message that is relevant to all dental patients.

9. Evidence statement	**Evidence Level**
Please summarise the development group's synthesis of the evidence relating to this key question, taking all the above factors into account, and indicate the evidence level which applies.	Low quality evidence

The Group agree that the evidence relating to prevention is low quality as the relevant studies are

generally observational with prospective or retrospective data collection. However, they agree that the body of evidence suggests that reaching and maintaining an optimum level of oral health as early in the patient's drug treatment as possible may help reduce the risk of extractions or procedures that impact on bone later on in their treatment, which are themselves risk factors for MRONJ.

10. Recommendation *What recommendation(s) does the guideline development group draw from this evidence? Please indicate the grade of recommendation(s) and any dissenting opinion within the group.*	**Grade of recommendation** **Strong** recommendation

The Group agree that patients prescribed anti-resorptive or anti-angiogenic drugs should be managed in a way that maximises preventive regimes and minimises the need for subsequent extractions and bone trauma, thereby reducing the likelihood of oral complications. They recommend that all patients who take anti-resorptive or anti-angiogenic drugs should be informed of their role in prevention and be given advice on optimising their oral health.

Initial Management of Patients Prescribed Anti-resorptive or Anti-angiogenic Drugs

KEY RECOMMENDATION:

Before commencement of anti-resorptive or anti-angiogenic drug therapy, or as soon as possible thereafter, aim to get the patient as dentally fit as feasible, prioritising preventative care. Higher risk cancer patients should preferably undergo a thorough dental assessment, with remedial dental treatment where required, prior to commencement of the drug therapy.
(Strong recommendation; low quality evidence)

- Give personalised preventive advice to help the patient optimise their oral health, emphasizing the importance of:
  - having a healthy diet and reducing sugary snacks and drinks;
  - maintaining excellent oral hygiene;
  - using fluoride toothpaste and fluoride mouthwash;
  - stopping smoking;
  - limiting alcohol intake;
  - regular dental checks;
  - reporting any symptoms such as exposed bone, loose teeth, non-healing sores or lesions, pus or discharge, tingling, numbness or altered sensations, pain or swelling as soon as possible.
- Prioritise care that will reduce mucosal trauma or may help avoid future extractions or any oral surgery or procedure that may impact on bone:
  - consider obtaining appropriate radiographs to identify possible areas of infection and pathology;
  - undertake any remedial dental work;
  - extract any teeth of poor prognosis without delay;
  - focus on reducing periodontal/dental infection or disease;
  - adjust or replace poorly fitting dentures to minimise future mucosal trauma;
  - consider prescribing high fluoride toothpaste.
- For medically complex patients for whom you would normally seek advice, including higher risk patients who are being treated with anti-resorptive or anti-angiogenic drugs for the management of cancer, consider consulting an oral surgery/special care dentistry specialist with regards to clinical assessment and treatment planning.

- Once the patient is dentally fit, undertake routine dental treatment as outlined in Section 4.2.
- In the situation where a patient presents with an established history of anti-resorptive or anti-angiogenic drug use (e.g. an existing patient who has not attended for some time or a patient new to your practice), follow the advice for extractions or other procedures which impact on bone in low or higher risk patients as outlined in Section 4.2.

Continuing Management of Patients Prescribed Anti-resorptive or Anti-angiogenic Drugs

KEY RECOMMENDATIONS:

Carry out all routine dental treatment as normal and continue to provide personalised preventive advice in primary care.

- Perform straightforward extractions and other bone-impacting treatments in low risk patients in primary care.
- Adopt a more conservative approach in higher risk patients, giving greater consideration to other, less invasive alternative treatment options before performing extractions and other bone-impacting treatments in primary care.

Do not prescribe antibiotic or antiseptic prophylaxis following extractions or other bone-impacting treatments specifically to reduce the risk of MRONJ.
(Strong recommendations; low quality evidence)

Low Risk Patients

Having made the patient as dentally fit as feasible:

- Carry out all routine dental treatment as normal and continue to provide personalised preventive advice.
  - If an extraction or another procedure that impacts on bone is required:
    - Discuss the risks and benefits associated with treatment with the patient (or carer, where appropriate) to ensure valid consent. See Appenix 4 for points to cover during this discussion.
    - Proceed with the treatment as clinically indicated;
    - Do not prescribe antibiotic or antiseptic prophylaxis unless required for other clinical reasons;
    - Advise the patient to contact the practice if they have any concerns, such as unexpected pain, tingling, numbness, altered sensation or swelling in the extraction area;
    - Review healing. If the extraction socket is not healed at **8 weeks** and you suspect that the patient has MRONJ, refer to an oral surgery/special care dentistry specialist as per local protocols.
- If you suspect a patient has spontaneous MRONJ, refer to an oral surgery/special care dentistry specialist as per local protocols.

Higher Risk Patients

Having made the patient as dentally fit as feasible:

- Carry out most routine dental treatment as normal and continue to provide personalised preventive advice.
- For medically complex patients for whom you would normally seek advice, including higher risk patients who are being treated with anti-resorptive or anti-angiogenic drugs for the management of cancer, consider consulting an oral surgery/special care dentistry specialist with regards to clinical assessment and treatment planning.
- If an extraction is indicated, explore all possible alternatives where teeth could potentially be

retained e.g. retaining roots in absence of infection.

- If extraction remains the most appropriate treatment:
  - Discuss the risks and benefits associated with treatment with the patient (or carer, where appropriate) to ensure valid consent. See Appenix 4 for points to cover during this discussion.
  - Proceed with the extraction as clinically indicated;
  - Do not prescribe antibiotic or antiseptic prophylaxis unless required for other clinical reasons;
  - Advise the patient to contact the practice if they have any concerns, such as unexpected pain, tingling, numbness, altered sensation or swelling in the extraction area;
  - Review healing. If the extraction socket is not healed at **8 weeks** and you suspect that the patient has MRONJ, refer to an oral surgery/special care dentistry specialist as per local protocols.

- If you suspect a patient has spontaneous MRONJ, refer to an oral surgery/special care dentistry specialist as per local protocols.

5. Effectiveness of antibiotic/antiseptic prophylaxis to prevent MRONJ

SDCEP	**Considered judgement on quality of evidence**

Key question:	**Evidence table ref:**
Is antibiotic/antiseptic prophylaxis effective at reducing the risk of MRONJ in patients being treated with anti-resorptive or anti-angiogenic drugs?	Prevention of MRONJ

1. Summary of evidence

Comment here on any issues concerning the quantity of evidence available on this topic and its methodological quality.

Systematic Reviews

There are no systematic reviews that directly address the clinical question.

Guidelines

Two clinical guidelines include information on antibiotic or antiseptic prophylaxis:

Khan et al. (2015)[8] includes reference to several primary studies but the quality of these is not appraised, other than an assessment of study design included in a separate Supporting Information document. The review does not specifically recommend antibiotic/antiseptic prophylaxis but lists these as interventions that have been investigated to reduce the risk of ONJ. It also summarises the results of one primary study (Montefusco, 2008) which appears to support the role of antibiotic prophylaxis in preventing MRONJ, but again does not comment on the quality of this study in the main text.

Hellstein et al. (2011)[12] provide recommendations for the care of patients taking anti-resorptive drugs for the prevention and treatment of osteoporosis. For those who require oral and/or maxillofacial surgery (including extractions), chlorhexidine mouthwash is recommended until healing is observed (commonly twice daily for 4-8 weeks). The authors do not specifically recommend antibiotic prophylaxis but do reference two studies which appear to support this intervention. The publication states that the recommendations are based on a critical evaluation of the relevant scientific evidence however details of this appraisal process are not included in the document.

Primary Studies

There are several primary studies which investigate the use of antibiotic or antiseptic prophylaxis in the prevention of MRONJ. Some of these are quoted by the guidelines mentioned above. A full quality appraisal has not been carried out for these studies. A summary of each study is listed below, along with a comment on the quality of the evidence.

Ferlito et al. (2011)[15] investigated the effectiveness of an extraction protocol to prevent ONJ in 43 patients receiving i.v. infusions of zoledronate. The protocol consisted of antibiotic prophylaxis pre- and post-surgery, local anaesthesia, creation of mucoperiosteal flap, tooth extraction, curettage, removal of adjacent alveolar bone and suturing. During the 12-month follow-up period, no signs of inflamed tissue or necrotic exposed bone were observed in any patient. This was a small study with no control group which included more than one intervention therefore it is not possible to determine whether antibiotic prophylaxis was effective in preventing MRONJ.

Kunchar & Goss (2008)[16] investigated the oral health status of a group of patients taking BPs for osteoporosis referred to their OMFS unit. Those who required extractions were given pre-extraction antibiotic cover, teeth were extracted with minimal trauma and the socket sutured. Patients were reviewed at one and eight weeks; delayed healing was observed in some cases but no ONJ was observed. This study was small and again had no control group. It is primarily an epidemiological study and there appear to be issues with the robustness of the study design. Additional information on the outcomes of patients who required an extraction are included but again there were multiple elements to the preventive regime used.

Lodi et al. (2010)[17] investigated a preventive extraction protocol in 23 patients treated with (either

currently or previously) i.v. BPs, no cases of BONJ were recorded. The protocol consisted of professional oral hygiene, where required, prior to extractions, use of pre-and post-surgical antibiotic cover and antiseptic rinses/gel, atraumatic extractions utilising a mucoperiosteal flap with debridement of extraction socket prior to suturing. The authors noted that 5 of the patients had previous history of ONJ and were considered high risk. This is another small study with no control group and multiple interventions.

Schubert et al. (2012)[18] described a preventive extraction procedure; only one (1.5%) case of ONJ was observed in 68 patients taking either i.v. or oral BPs who had dental extractions performed according to the procedure. The affected patient had received i.v. BPs and required complicated/difficult extraction surgery. The extraction protocol included pre- and post-surgery antibiotic cover, subperiostal flap, tooth extraction followed by bone smoothing, sutures and use of an antiseptic mouth rinse daily post-surgery. This is a slightly larger study but would still be considered smaller than would be desirable for such a rare condition. As with other studies there were multiple elements included in the preventive extraction procedure therefore it is not possible to determine whether antibiotic/antiseptic prophylaxis is effective in preventing ONJ.

Montefusco et al. (2008)[19] carried out a retrospective cohort study with oncology patients (multiple myeloma). 178 patients were included in the study. 64 patients did not undergo a dental procedure, and of these 1 patient (who had a previous dental abscess) developed ONJ (0.016%). 114 patients underwent dental procedures. 39 of these had dentures and were not given antibiotic prophylaxis; no cases of ONJ were observed in this group. 9 patients underwent low risk dental procedures (restorations, endodontics); 6 were given antibiotic prophylaxis, no cases of ONJ were observed in either group. A further 66 patients underwent high risk dental procedures (extractions, periodontal surgery etc.). 37 patients were given antibiotic prophylaxis before the dental procedure (1 day before, 3 days after, co-amoxiclav or levofloxacin). There were no cases of ONJ observed in this group but 8 cases of ONJ were observed in the 29 patients who were not given antibiotic prophylaxis (27.6%). This is a small, retrospective study and as such there may have been other differences between the patients that are not described here. However, in the patients undergoing high risk procedures, the only reported difference between groups is that one received antibiotic prophylaxis and one did not and there is a statistically significant difference between the outcomes of the two groups (p=0.012).

Mozzati et al. (2013)[20] compared two different surgical protocols with different degrees of invasiveness for tooth extraction in 700 patients treated with oral bisphosphonates (BPs). Patients were assigned randomly to receive either delicate surgery and closure by primary intention (n= 334) or non-traumatic avulsion and closure by secondary intention (n=366). All patients were prescribed pre- and post-operative antibiotic cover and received professional oral hygiene prior to the extractions. There was no evidence of postoperative bisphosphonate-associated osteonecrosis of the jaw in either study group at follow-up. This study is much larger than the previous studies listed and includes two randomised groups of patients. However, it is unlikely that either would be considered a typical control group as both groups received an intervention (composed of multiple elements) to prevent MRONJ.

2. Volume of evidence

Comment here on any issues concerning the quantity of evidence available on this topic and its methodological quality.

There are no systematic reviews or guidelines which directly address the use of antibiotic or antiseptic prophylaxis to prevent MRONJ after invasive dental procedures. The guidelines mentioned previously do include an overview of the evidence but there are no clear recommendations regarding the use of this intervention. The intervention is also included in some of the systematic reviews but antibiotic/antiseptic prophylaxis is always used as part of a larger group of preventive interventions (oral hygiene education, scale and polish, extraction technique, suturing etc.) therefore it is not possible to determine if prophylaxis is effective in preventing MRONJ from these studies.

The primary studies summarised previously are more likely to focus on antibiotic/antiseptic prophylaxis as an individual intervention (although some still looked at this within a larger group of preventive interventions). However, many of these studies were small and were often done retrospectively with no control groups and no randomisation. It is therefore not possible to determine whether

antibiotic/antiseptic prophylaxis is effective in preventing MRONJ after invasive dental treatments.

3. Subgroup considerations

Comment here on any subgroup considerations e.g. should recommendations for patients at high or low risk be considered separately?

Higher risk patients, such as those being treated with anti-resorptive/anti-angiogenic drugs for cancer, would likely benefit more from an intervention that is shown to help prevent MRONJ after invasive dental procedures. However, from the evidence presented previously it is not possible to determine if antibiotic/antiseptic prophylaxis is effective in this way.

4. Consistency

Comment here on the degree of consistency demonstrated by the available of evidence. Where there are conflicting results, indicate how the group formed a judgement as to the overall direction of the evidence

It is not possible to comment on the consistency of the evidence presented here as the data does not currently support the use of antibiotic/antiseptic prophylaxis to prevent MRONJ after invasive dental procedures.

5. Balance of Effects

Comment here on the desirable and undesirable effects of the intervention and how substantial the effects are. Indicate whether the overall balance of effects favours the intervention or comparison.

It is not possible to comment on the balance of effects of the intervention as the evidence does not currently support the use of antibiotic/antiseptic prophylaxis to prevent MRONJ after invasive dental procedures. It should be noted that it is not acceptable to expose patients to the adverse effects of antibiotic therapy without clear evidence that patients will benefit from the drugs and there is also the increasing threat of bacterial resistance at a population level to be considered.

6. Generalisability and applicability

Comment here on how reasonable it is to generalise from the results of the studies used as evidence to the target population for this guideline.

The groups included in these studies would be considered to be similar to a Scottish population and it would be reasonable to generalise from the results if the evidence were sufficient to make a recommendation.

7. Values and preferences

How much do people value the main outcomes? Uncertainty about how much those affected value the outcomes of interest can be a reason not to make a strong recommendation and might affect the direction of a recommendation. Variability in how much those affected value the main outcomes (to the extent that individuals with different values would make different decisions) is also a reason not to make a strong recommendation.

Although MRONJ is a serious complication of treatment with ant-resorptive or anti-angiogenic drugs, there is insufficient evidence to

8. Acceptability

Is intervention acceptable to patients, caregivers and providers?

See comment above

9. Feasibility

Comment on cost effectiveness, resource implications and implementation considerations here, if applicable.

Antibiotic/antiseptic prophylaxis is likely to have associated costs, to both the healthcare provider and perhaps the patient, therefore it should not be recommended unless there is clear evidence of its effectiveness.

10. Other factors

Indicate here any other factors that were taken into account when assessing the evidence base.

As stated previously, due to the threat of bacterial resistance and the numerous side effects associated with antibiotic therapy, it is unlikely that it would be acceptable to recommend antibiotic prophylaxis to prevent MRONJ after invasive dental procedures without clear evidence that it will benefit patients.

9. Evidence statement *Please summarise the development group's synthesis of the evidence relating to this key question, taking all the above factors into account, and indicate the evidence level which applies.*	**Evidence Level** Very low quality evidence
The Group agree that there is insufficient evidence to support a recommendation that antibiotic prophylaxis be given to reduce the risk of MRONJ following invasive dental procedures.	
10. Recommendation *What recommendation(s) does the guideline development group draw from this evidence? Please indicate the grade of recommendation(s) and any dissenting opinion within the group.*	**Grade of recommendation** **Strong** recommendation

Antibiotic Prophylaxis

Due to the increasing incidence of bacterial resistance and the numerous side effects associated with antibiotic therapy, antibiotics should only be prescribed where there is clear evidence that patients will benefit from them. A review of current literature found only observational studies, most of which were underpowered and in some cases had no control group, which generally only included antibiotic and/or antiseptic prophylaxis as one of a combination of measures to prevent MRONJ. There is currently insufficient evidence to support the use of antibiotic or topical antiseptic prophylaxis to reduce the risk of MRONJ following extractions or procedures that impact on bone.

Appendix 4 – Evidence Appraisal Forms

Systematic Review SR1: Gaudin et al., 2015[13]

<table>
<tr><td colspan="4">Systematic Review:
Gaudin et al. Occurrence and risk indicators of medication-related osteonecrosis of the jaw after dental extraction: a systematic review and meta analysis. Journal of Clinical Periodontology. 2015; 42: 922-32</td></tr>
<tr><td colspan="4">Aim of study: is there a clearly focussed question?
Yes – in patients treated with antiresortive drugs, what is the occurrence rate and what are the risk indicators of MRONJ after dental extraction? Two objectives:
1. to assess the occurrence rate of MRONJ after dental extraction in patients treated with antiresorptive drugs for osteoporosis or for oncological reasons;
2. to compare extraction techniques regarding the occurrence of MRONJ.</td></tr>
<tr><td>Patient/Problem: (target patients and actual participant characteristics)</td><td>Intervention or risk factors:</td><td>Comparison:</td><td>Outcomes: note which are critical/important (from patient perspective) for the guidance recommendation*</td></tr>
<tr><td>Human patients treated with antiresorptive drugs</td><td>Risk factor – dental extraction in patients treated with antiresorptive drugs; technique used in extraction</td><td>1. no comparison for incidence.
2. comparison of extraction techniques</td><td>1. Incidence of medication-related osteonecrosis of the jaw in patients being treated for
a) osteoporosis,
b) cancer
2. Incidence of medication related osteonecrosis of the jaw following different extraction techniques in the two patient groups:
a) Alveolectomy vs. no alveolectomy
b) PRGF (biological membrane) vs. no PRGF
c) First intention vs. second intention</td></tr>
<tr><td>Study Type:</td><td colspan="2">Search Strategy:</td><td>Study selection: No. of selectors: 2 plus one adjudicator</td></tr>
<tr><td>Appropriate study types?
Yes, no RCTs available
Correct components to address question?
Yes
Study no.s:
13 studies (9 case series, 2 cohort, 2 RCTs) were included. 5 studies considered IV administration, 3 oral and 5 both. 2662 patients</td><td colspan="2">Appropriate search terms? Yes
Appropriate databases? Yes – MEDLINE, EMBASE, LILACS
Unpublished studies? Not mentioned
Follow up of citations? Yes
Personal contact with experts? No</td><td>Inclusion criteria:
1.Prospective control trials, cohort studies and case series
2. Results on at least 20 patients treated with ARD therapy
3. Studies reporting a protocol used for dental extraction or comparing different extraction techniques in patients on ARD
4. Studies reporting data on MRONJ after a dental extraction.

Exclusion criteria:
1.Animal studies
2. Retrospective and cross-sectional studies</td></tr>
</table>

<table>
<tr><td>underwent dental extractions, 2098 individuals (79%) were treated orally for osteoporosis and 564 (21%) were treated IV for oncological reasons.</td><td></td><td colspan="2">3. Literature reviews
4. Case reports and studies involving less than 20 patients
5. Studies involving ONJ not related to ARD uptake
6. Studies, which did not include dental extractions</td></tr>
<tr><td colspan="4">Risk of bias/systematic error (study limitations that could cause systematic error): consider risk of bias for each important outcome</td></tr>
<tr><td>Randomisation: is it reported and appropriate?
Authors performed assessment of study quality and reported the overall findings but did not report on individual components of this such as randomisation.</td><td>Blinding: consider whether blinding of patients or assessors would be important for outcomes considered
Authors performed assessment of study quality and reported the overall findings but did not report on individual components of this such as blinding.</td><td colspan="2">Other limitations: e.g. attrition bias (incomplete accounting of patients and outcome events), reporting bias (selective outcome reporting), surrogate outcomes(?)
Authors performed assessment of study quality (based on Cochrane Collaboration study-design-related forms) and reported the overall findings but did not report on the individual components of this such as randomisation. Studies assessed as low quality (scoring <7/11) or having a high risk of bias were excluded from the review.</td></tr>
<tr><td>Inconsistency: Refers to unexplained heterogeneity in results.</td><td>Imprecision (random error):</td><td>Indirectness: consider implications for both systematic review and guidance</td><td>Publication bias:</td></tr>
<tr><td>Is heterogeneity analysis reported?
Heterogeneity of the studies was assessed by calculating the Q-statistic and the associated I^2 coefficient</td><td>Confidence intervals (95%) are reported
Results reported as significant do have narrow confidence intervals</td><td>The studies included were carried out according to strict protocols of care which might underestimate the rate of necrosis that might occur in routine dental practice.</td><td>e.g. when intervention is new and not many studies available- may be biased for positive results
Not reported by authors</td></tr>
<tr><td colspan="2">Meta analysis:
No. of data extractors:</td><td colspan="2">Overall results (for each outcome):</td></tr>
<tr><td colspan="2">Are results for individual studies shown? yes
Was it reasonable to combine study results? yes
Was an appropriate method used?
Results were expressed as mean and standard deviation (SD) for quantitative variables and as numbers and proportions for categorical findings. Proportions were weighted by their inverse variance and averaged to obtain the total proportion of MRONJ. The Z test was used to compare the proportions between groups.
Are reasons for variation in results discussed?
Heterogeneity was observed in the meta-analysis of patients with cancer (I^2 = 74.3%). This was due to one study (Lazarovici); removal of this study resulted in reduced heterogeneity (I^2 = 13.3%) and the overall incidence in these patients was reduced from 3.25 to 2.9% due to the small weight attributed to this study in the original analysis</td><td colspan="2">1. Overall incidence of MRONJ
d) osteoporosis 0.15 % (95% CI: 0 – 0.36) 8 studies, n=2098
e) cancer 3.2% (95% CI: 1.7-4.7) 10 studies, n=564
2. No. of MRONJ cases according to surgical parameters:
f) Alveolectomy vs. no alveolectomy
Cancer: 1.5% (0.1-2.9) vs. 5.9% (2.2-9.5) p =0.028
Osteoporosis: 0% (0.0-0.26) vs. 0.13% (0.0-0.35) p=0.47
g) PRGF vs. no PRGF
Cancer: 0.91% (0.0-2.5) vs. 4.4% (2.1-6.6) p=0.015
Osteoporosis: no data vs. 0.08% (0.0-0.24) p=NA
h) First intention vs. second intention
Cancer: 1.41% (0.0-3.0) vs. 3.1% (0.1-6.1) p=0.32</td></tr>
</table>

Would confounders affect overall result? Yes	Osteoporosis: **0.12%** (0.0-0.35) vs. **0.01%** (0.0-0.27) p=0.52 *Is the effect substantial?* N/A *Is there dose-response data?* N/A

Adverse events:	**Benefit/harm/cost considerations?**	**Values/preferences considerations?**
Outcome (MRONJ) is an adverse effect	Not considered	Not considered

Reviewer's comments:	**GRADE evidence quality rating:**
Include summary of main findings 10 studies reported MRONJ after tooth extractions in patients treated with IV antiresorptive drugs. 36 out of 564 patients had MRONJ, a risk of 3.2% (95% CI: 1.7–4.7%). 8 studies reported on MRONJ after tooth extractions in patients treated with oral antiresorptive drugs. 9 cases out of 2098 were identified, a risk of 0.15% (95% CI: 0.0–0.36%). Dental extraction performed with two of the adjusted extraction protocols (alveolectomy, use of a biological membrane) significantly decreased MRONJ development in patients treated with BPs for cancer. No significant difference was observed for primary or secondary intention closure in these patients or for alveolectomy or use of a biological membrane in patients being treated for osteoporosis. The majority of the patients received oral hygiene instructions and a full mouth scaling before the extractions, with post-operative mouth rinses (CHX 0.2%/iodine 10%) and a semi-liquid diet recommended. The majority of studies described antibiotic coverage but there was no standard protocol in terms of administration time and doses. The authors recommend that patients treated with BPs should be provided with preventive care and oral hygiene instruction. The authors recognise the limitations of this study: the studies included were carried out according to strict protocols of care which might underestimate the rate of necrosis that might occur in routine dental practice. There was inconsistency in the definitions of MRONJ and stage characterisation. Combining the results from different study designs included may also not be considered ideal. Data on other medications and co-morbidities was not provided in some studies and drug therapy was interrupted in 7/13 studies.	*Rating and brief explanation* **Low quality** because most studies were small and uncontrolled

Systematic Review SR2: Boquete-Castro et al., 2015[4]

Systematic Review:
Boquete-Castro et al. Denosumab and osteonecrosis of the jaw. A systematic analysis of events reported in clinical trials. *Clinical Oral Implants Research*. 00, 1-9, 2015.

Aim of study: *is there a clearly focussed question?*
To perform a systematic review of the relation between treatment with denosumab and the incidence of osteonecrosis of the jaw (ONJ) and to obtain information on dosage, first event apparition, and treatment approaches for patients with ONJ related to denosumab.

Patient/Problem: *(target patients and actual participant characteristics)*	**Intervention or risk factors:**	**Comparison:**	**Outcomes:** *note which are critical/important (from patient perspective) for the guidance recommendation**
Patients receiving denosumab therapy for osteoporosis and bone metastasis		Either patients taking placebo or zoledronic acid	Osteonecrosis of the jaw

Study Type:	**Search Strategy:**	**Study selection:**
Appropriate study types? Yes *Correct components to address question?* *Study no.s:* 8963 patients with a variety of solid tumours reported in seven randomized controlled trials (RCTs) were included in the systematic analysis.	*Appropriate search terms?* Too simple? *Appropriate databases?* Medline, Embase, Cochrane *Unpublished studies?* Not mentioned *Follow up of citations?* Yes *Personal contact with experts?* Not mentioned	*Inclusion criteria:* • Randomized Clinical Trials. • Studies realized in patients aged over 13. • Studies including at least 50 patients. • Studies including denosumab, descriptions of safety, and adverse events. *Exclusion criteria:* • Duplicated articles. • Review articles. • Studies published in a language other than English. • Animal studies.

Risk of bias/systematic error (study limitations that could cause systematic error): *consider risk of bias for each important outcome*

Randomisation: is it reported and appropriate?	*Blinding: consider whether blinding of patients or assessors would be important for outcomes considered*	*Other limitations: e.g. attrition bias (incomplete accounting of patients and outcome events), reporting bias (selective outcome reporting), surrogate outcomes(?)*
Not reported Inclusion criteria stated that studies had to be RCTs	Not reported	There does not appear have been any evaluation of the quality of the included studies or any consideration of potential sources of bias. A table containing the characteristics of the 35 articles which were reviewed in full contains a column for Jadad scores, but these are not reported for any of the studies.

Inconsistency: *Refers to unexplained heterogeneity in results.*	**Imprecision (random error):**	**Indirectness:** *consider implications for both systematic review and guidance*	**Publication bias:**
Is heterogeneity analysis reported? A funnel plot of the selected studies shows large dispersion of data and the authors state that this precluded meta analysis		The included studies most likely looked at the primary effects of denosumab on bones for osteoporosis/cancer and ONJ observed as an adverse effect so it is likely that this would reflect real life situation.	*e.g. when intervention is new and not many studies available- may be biased for positive results* Not specifically considered, a funnel plot was included but seems to have been used to identify heterogeneity

Meta analysis: *No. of data extractors:* N/A	**Overall results (for each outcome):**
Are results for individual studies shown? Yes *Was it reasonable to combine study results?* Meta-analysis was not possible due to substantial differences between studies. *Was an appropriate method used?* The overall incidence rates and 95% confidence intervals (CI) for ONJ were calculated employing fixed- and random-effects models, according to the heterogeneity of the studies included. *Are reasons for variation in results discussed?* 35 studies were retrieved for full text analysis, only seven reported cases of ONJ and were selected for the review. It is unclear whether the other studies just did not mention ONJ as a side effect or whether no cases were observed. If the latter, was it appropriate to rule out these studies? *Would confounders affect overall result?* Yes	Figures below are quoted in abstract only. Authors state in main text that meta analysis was not possible due to substantial differences between studies Assume that data was combined to give results below: 1. The overall incidence of ONJ in patients with cancer receiving denosumab was **1.7%** [95% CI: 0.9-3.1%]. 2. The use of denosumab was associated with a significantly increased risk of ONJ in comparison with BPs/placebo treatment (**RR 1.61**, 95% CI: 1.05-2.48, P = 0.029). 3. Subgroup analysis based on controlled therapies demonstrated an increased risk of ONJ in denosumab therapy, when compared with BPs (**RR 1.48**, 95% CI: 0.96-2.29, P = 0.078) or placebo (**RR 16.28**, 95% CI: 1.68-158.05, P = 0.017). Similar results were observed for prostate cancer (**RR 3.358**, 95% CI: 1.573-7.166, P = 0.002). Within the text, the authors state: *"ONJ incidence was low in all cases, ranging between 0 and 2% for periods from 13 to 21.4 months of treatment."* *"Random-effects model meta-analysis showed that for the total of 4985 patients under denosumab treatment, it could be expected that 1.945% of the patients would present ONJ."* *Is the effect substantial?* N/A *Is there dose-response data?* N/A

Adverse events:	**Benefit/harm/cost considerations?**	**Values/preferences considerations?**
Outcome (ONJ) is an adverse effect	Not considered	Not considered
Reviewer's comments:		**GRADE evidence quality rating:**
Include summary of main findings This does not appear to be a particularly well-conducted review. There are various errors in the text and the abstract and the main text contradict each other. The main results as quoted in the abstract do not appear in the main text, although it is possible that these have been calculated from the data retrieved from the seven included studies. The authors seem to suggest that the Jadad scale was used to assess the quality of the included studies but this is not reported and there does not appear to be any consideration of potential sources of bias. 28 studies were excluded from the analysis as they did not report on ONJ, but it is unclear whether this is because there were no cases of ONJ (in which case it would have been appropriate to include them) or whether data on adverse effects was not included in these articles. The abstract states that a total of 8963 patients with a variety of solid tumours reported in seven randomized controlled trials (RCTs) were included in the systematic analysis. The overall incidence of ONJ in patients with cancer receiving denosumab was calculated as 1.7% and the use of denosumab was associated with a significantly increased risk of ONJ in comparison with bisphosphonates or placebo (RR 1.61). Subgroup analysis demonstrated an increased risk of ONJ in denosumab therapy, when compared with BPs (RR 1.48) or placebo (RR 16.28). However, although it is stated that a random effects model was used, these figures are not quoted within the text of the article, nor are they included in the discussion. Authors conclude that denosumab, combined with risk factors such as dental extraction, poor oral hygiene, use of removable apparatus or chemotherapy, may favour ONJ development and that patients with these risk factors should be identified and preventive measures established to limit the development of ONJ.		*Rating and brief explanation* **Very low quality** as the review methodology appears to be unreliable

Systematic Review SR3: Qi et al., 2014[5]

Systematic Review: **Qi** et al. Risk of osteonecrosis of the jaw in cancer patients receiving denosumab: a meta-analysis of seven randomized controlled trials *Int. J. Clin. Oncol.* (2014) 19:403–410				
Aim of study: *is there a clearly focussed question?* The aim of this study was to gain a better understanding of the overall incidence and risk of osteonecrosis of the jaw (ONJ) in cancer patients receiving denosumab.				
Patient/Problem: *(target patients and actual participant characteristics)*	**Intervention or risk factors:**	**Comparison:**	**Outcomes:** *note which are critical/important (from patient perspective) for the guidance recommendation**	
Cancer patients (most with prostate or breast cancer)	Denosumab	Bisphosphonates or placebo	1. Incidence of osteonecrosis of the jaw 2. Relative risk of osteonecrosis of the jaw	
Study Type:	**Search Strategy:**		**Study selection:**	No. of selectors: Not stated
Appropriate study types? Yes, clinical trials *Correct components to address question?* Yes *Study no.s:* 7; 8963 patients	*Appropriate search terms?* Yes *Appropriate databases?* Pubmed, Embase, Cochrane library *Unpublished studies?* Not mentioned *Follow up of citations?* Yes *Personal contact with experts?* Not mentioned		*Inclusion criteria:* 1. prospective randomized phase II and III trials of patients with cancer; 2. participants assigned to treatment with denosumab (alone or in combination at any dosage or frequency); 3. data available on ONJ. *Exclusion criteria:* Non-English articles, studies that are not clinical trials	
Risk of bias/systematic error (study limitations that could cause systematic error): *consider risk of bias for each important outcome*				
Randomisation: is it reported and appropriate? Jadad scores are reported for each trial but the method of randomisation is not specified for each study	*Blinding: consider whether blinding of patients or assessors would be important for outcomes considered* Five trials were reported as Phase III double blind trials but this was not explained in any more detail. Two trials were described as Phase II trials with no information on blinding	*Other limitations: e.g. attrition bias (incomplete accounting of patients and outcome events), reporting bias (selective outcome reporting), surrogate outcomes(?)* There was no mention of potential sources of bias and, due to the trial, types, it is likely that there may have been some industry involvement, which does not mean that bias is inherent but it should be considered. Three trials reported on less patients than were enrolled but this was not explained, nor was it clear if analysis was done on an intention to treat basis.		

Inconsistency: *Refers to unexplained heterogeneity in results.*	**Imprecision (random error):**	**Indirectness:** *consider implications for both systematic review and guidance*	**Publication bias:**
Is heterogeneity analysis reported? Yes Heterogeneity was found to be significant therefore random effects analysis was used in the meta analysis	For one trial where there were no events in the control arm, a half-integer correction was used to calculate the RR and variance. No individual patient data analysis; this may overestimate treatment effects and makes confounders, due to differences in individual trials, more likely	Trials with short follow-up times may not be representative as ONJ incidence is thought to increase with increased follow-up times.	*e.g. when intervention is new and not many studies available- may be biased for positive results* No evidence of publication bias was detected for the relative risk of ONJ in this study by either Begg's or Egger's test (RR of ONJ: Begg's test P = 0.602; Egger's test P = 0.452).

Meta analysis: No. of data extractors: 2	**Overall results (for each outcome):**
Are results for individual studies shown? Yes *Was it reasonable to combine study results?* Yes *Was an appropriate method used?* Yes *Are reasons for variation in results discussed?* Yes *Would confounders affect overall result?* Yes Observed heterogeneity may be due to inclusion of patients with different cancer types; those with prostate cancer were found to have a higher risk of DONJ than patients with other cancers. Variation in follow-up periods may also influence this, with prostate cancer trials tending to last longer than non-prostate cancer trials	1. **Incidence = 1.7%** (95% CI: 0.9-3.1%; high heterogeneity; random effects). Incidence ranged from 0% to 4.6%. Seems to be higher in prostate cancer patients (2.3%; 95% CI: 0.9-5.7%) than non-prostate cancer (1.4%; 95%CI: 0.8-2.4%) 2. **Pooled RR = 1.613** (95% CI: 1.050-2.478; fixed effects) 3. Subgroup analysis found that there is an increased risk of developing ONJ in the denosumab group when compared with the BP group (RR 1.481, 95% CI: 0.957–2.293, P = 0.078) or placebo (RR 16.279, 95% CI: 1.677–158.050, P = 0.016). 4. The risk of DONJ in prostate cancer was significantly increased in comparison with controls (RR 3.358, 95 % CI: 1.573–7.166, P = 0.002), while there was a non-significantly increased risk of DONJ in non-prostate cancer (RR 1.142, 95 % CI: 0.678–1.921, P = 0.618) *Is the effect substantial?* N/A *Is there dose-response data?* N/A

Adverse events:	**Benefit/harm/cost considerations?**	**Values/preferences considerations?**
Outcome (ONJ) is an adverse event	Not considered	Not considered

Reviewer's comments:	**GRADE evidence quality rating:**
Include summary of main findings The use of denosumab is associated with a significantly increased risk of developing ONJ when compared with placebo. Although the overall incidence remains low, the RR is significant. The incidence of ONJ among patients receiving denosumab is 1.7 % (95 % CI: 0.9–3.1 %). Subgroup analysis based on tumour type shows that the incidence of DONJ in prostate cancer (2.3 %, 95 % CI: 0.9–5.7 %) is higher than that in non-prostate cancers (1.4 %, 95 % CI: 0.8–2.4 %). The use of denosumab significantly increases the risk of ONJ when compared with controls (RR 1.613, 95 % CI: 1.050–2.478, P = 0.029). Subgroup analysis based on controlled therapies found that there is an increased risk of developing ONJ in the denosumab group when compared with the BP group (RR 1.481, 95 % CI: 0.957–2.293, P = 0.078) or placebo (RR 16.279, 95 % CI: 1.677–158.050, P = 0.016). Subgroup analysis based on tumour types found that there is a significantly increased risk of DONJ in prostate cancer (RR 3.358, 95 % CI: 1.573–7.166, P = 0.002), while there is a non-significantly increased risk of DONJ in non-prostate cancers (RR 1.142, 95 % CI: 0.678–1.921, P = 0.618). This review has some limitations. There is no information on the randomisation or blinding process for any of the included studies and the authors do not consider any other sources of bias that may be present. There are is unexplained patient attrition in three of the studies. The authors do note some of the methodological weaknesses of their review. They highlight that their analysis of the data, which was collected prospectively, was done retrospectively and that their review is based on published data rather than individual patient data. They note that there may be potentially important differences among the studies that may account for the observed heterogeneity, including differing tumour types, dosages and administration schedules of denosumab, periods of study conduct and study investigators. This is a good review that gives useful information on the incidence and risk of ONJ in cancer patients treated with denosumab. There may be some methodological issues but it is unlikely that these have significantly biased the overall result.	*Rating and brief explanation* **Moderate quality** based on study types included in review (randomised controlled trials) and statistical significance of results. Some methodological issues with review noted.

Systematic Review SR4: Lee et al., 2014[6]

Systematic Review: **Lee** et al. Use of bisphosphonates and the risk of osteonecrosis among cancer patients: a systemic review and meta-analysis of the observational studies. *Supportive Care in Cancer*. 2014; 22(2): 553-560.				
Aim of study: *is there a clearly focussed question?* To evaluate the use of bisphosphonates (BPs) and risk of osteonecrosis of the jaw (ONJ) among cancer patients.				
Patient/Problem: *(target patients and actual participant characteristics)*	**Intervention or risk factors:**	**Comparison:**	**Outcomes:** *note which are critical/important (from patient perspective) for the guidance recommendation**	
Patients taking bisphosphonate drugs as part of their cancer treatment	Observational studies looking incidence of ONJ in patients taking bisphosphonates for cancer as compared to controls	Comparison of rates of ONJ in patients taking bisphosphonates for cancer compared to controls	Osteonecrosis of the jaw	
Study Type:	**Search Strategy:**		**Study selection:**	No. of selectors: 2
Appropriate study types? Yes *Correct components to address question?* Yes *Study no.s:* 8 studies met the inclusion criteria; two case-control and six cohort studies with a total of 1,035,065 patients. There were 569,620 controls and 1389 cases of ONJ were observed.	*Appropriate search terms?* Yes *Appropriate databases?* MEDLINE and EMBASE *Unpublished studies?* No *Follow up of citations?* Yes *Personal contact with experts?* No		*Inclusion criteria:* Observational studies where ONJ was analyzed as an outcome; Oral or intravenous use of BPs; Studies on human subjects who were 15 years or older; Studies on cancer patient populations; Cohort and case–control studies; *Exclusion criteria:* Case reports, case series, review articles, editorials, meta analysis, clinical guidelines, and randomized controlled trials excluded. Studies on osteoporosis or post-surgery patients excluded.	
Risk of bias/systematic error (study limitations that could cause systematic error): consider risk of bias for each important outcome				
Randomisation: is it reported and appropriate? Data was from non-randomised studies	*Blinding: consider whether blinding of patients or assessors would be important for outcomes considered* Not relevant for these study types	*Other limitations: e.g. attrition bias (incomplete accounting of patients and outcome events), reporting bias (selective outcome reporting), surrogate outcomes(?)* Diagnosis of osteonecrosis was based on medical records, clinical findings of exposed necrotic bone of jaw with compatible radiographic findings, or ICD-9 code or other diagnostic code in a health claim database. Surrogate outcomes may have been used in databases as there is no specific code for ONJ		

Inconsistency: *Refers to unexplained heterogeneity in results.*	**Imprecision (random error):**	**Indirectness:** *consider implications for both systematic review and guidance*	**Publication bias:**
Is heterogeneity analysis reported? Heterogeneity measured by the Cochran Q statistic ($p < 0.05$) and quantified with the I^2 statistic, with fixed effects models used for I^2 values <50 % and random effects models used for I^2 values >50 %. Meta-regression was used to evaluate heterogeneity in the subgroup analysis.	There is a possibility of exposure misclassification as most studies did not take into account that bone must be exposed for at least 6 weeks to fulfil a diagnosis of ONJ. The duration and dosage of BP use are important determinant factors for ONJ but have not been investigated in most of these studies.	Directly applicable to patients taking bisphosphonates for cancer	*e.g. when intervention is new and not many studies available- may be biased for positive results* Publication bias was assessed by utilizing two methods; Begg and Egger tests were used to quantify the publication bias, and funnel plots were used to visualize the potential publication bias. The authors conclude there is no compelling evidence of publication bias.

Meta analysis: No. of data extractors:	**Overall results (for each outcome):**
Are results for individual studies shown? Yes *Was it reasonable to combine study results?* Yes, subgroup analysis was also performed *Was an appropriate method used?* Yes, pooled estimates of odds ratios and 95% confidence intervals were derived by random effects meta-analysis. Subgroup analyses were carried out according to patients' characteristics and route of BP use. *Are reasons for variation in results discussed?* Yes. There was variation between sub-groups, with hospital-based studies giving a higher risk estimate than population-based studies. The diagnosis in the hospital-based studies may have been more reliable as it was based on assessment of clinical records while the population-based studies were based on medical databases which do not have a specific code for ONJ, therefore misclassification may occur when extrapolating from other surrogate outcomes *Would confounders affect overall result?* Yes	The use of BPs was associated with an increased risk of ON (pooled OR 4.25; 95 % confidence interval (CI) 3.67–5.36; I^2=0 %). Of the four studies which provided adjusted effect estimates, the pooled OR was slightly attenuated (4.22; 95 % CI 3.21–5.54; I^2 =0 %). Hospital-based studies were associated with higher risk estimates (pooled OR 3.62; 95 % CI 1.18–11.1) than population-based studies (pooled OR 2.15; 95 % CI 1.77–2.60). Six studies reported predisposing factors for ONJ; dental extractions or trauma, poor oral hygiene, concurrent use of chemotherapeutic or antiangiogenic agents, radiotherapy. *Is the effect substantial?* N/A *Is there dose-response data?* N/A

Adverse events:	**Benefit/harm/cost considerations?**	**Values/preferences considerations?**
Outcome (ONJ) is an adverse effect	Not relevant to the focussed question	Not relevant to the focussed question

Reviewer's comments:	**GRADE evidence quality rating:**
Include summary of main findings This systematic review has several limitations. The authors state that they recorded quality indicators of study designs, including the presence of appropriate controls, and that the majority of excluded studies were ruled out due to a lack of appropriate controls. However, there is no attempt to identify any sources of bias, other than possible misclassification of disease outcomes due to the way in which data for some of the studies was recorded. There was also no attempt to find grey literature. The authors state within the text that "*the eight included studies were comprised of 1,389 cases and 569,620 controls*" but do not state the total number of patients involved in the studies. This can be calculated from the summary table, which totals 1,035,065 patients, but later in the text the authors state "*in our study of 0.5 million people*" which seems to contradict the numbers stated previously. Use of BPs was associated with a significantly increased risk of ONJ (odds ratio (OR) 4.25). IV BPs were associated with higher risk (OR 4.27) than oral BPs (OR 1.18). However, the absolute risk is low. Subgroup analysis showed that hospital-based studies were associated with higher risk estimates than population-based studies, however this may be due to the way data about patients was recorded in these different settings. Six studies reported predisposing factors for ONJ; dental extractions or trauma, poor oral hygiene, concurrent use of chemotherapeutic or antiangiogenic agents, radiotherapy. The authors recommend that before starting BP therapy, a comprehensive dental examination should be carried out and all potential sites of infection be eliminated so that the patient attains a state of good oral health during the course of BP therapy. For cancer patients who have already commenced IV BP therapy, avoiding dental extractions is recommended; for those that are unavoidable, some experts recommend the withdrawal of BP therapy for 3 months before surgery (will not affect BP already deposited in bone but may limit anti-angiogenic effects of BPs). Good oral hygiene, along with regular dental care, is considered to be the best way to lower risk.	*Rating and brief explanation* **Low quality** based on included study types (non-randomised cohort and case-control) and issues with the methodology and reporting in the review.

Systematic Review SR5: Solomon et al., 2013[11]

<table>
<tr><td colspan="4">Systematic Review:
Solomon et al. Defining the epidemiology of bisphosphonate-associated osteonecrosis of the jaw: prior work and current challenges Osteoporosis International (2013) 24: 237-244</td></tr>
<tr><td colspan="4">Aim of study: is there a clearly focussed question?
i) to perform a systematic review of the literature to investigate the epidemiology of BONJ
ii) to estimate the relative risk of BONJ in cohorts of bisphosphonate users with osteoporosis</td></tr>
<tr><td>Patient/Problem: (target patients and actual participant characteristics)</td><td>Intervention or risk factors:</td><td>Comparison:</td><td>Outcomes: note which are critical/important (from patient perspective) for the guidance recommendation*</td></tr>
<tr><td>Osteoporosis patients taking bisphosphonate drugs</td><td>Study aims to investigate whether bisphosphonate drugs are a risk factor for ONJ in patients with osteoporosis</td><td>Osteoporosis patients not taking bisphosphonate drugs/the general population</td><td>i) clinically confirmed cases of ONJ
ii) clinically confirmed cases of ONJ</td></tr>
<tr><td>Study Type:</td><td colspan="2">Search Strategy:</td><td>Study selection: No. of selectors: 2 independent</td></tr>
<tr><td>Appropriate study types?
The authors excluded case series and some cohort groups
Correct components to address question?
Not sure
Study no.s: 9; 7 x case-control and 2 x cohort</td><td colspan="2">Appropriate search terms? Too simple?
Appropriate databases? Only searched Medline
Unpublished studies? Not mentioned/done
Follow up of citations? Yes
Personal contact with experts? Not mentioned/done</td><td>Systematic review
Inclusion criteria:
Articles containing primary epidemiologic data regarding BONJ among non-cancer patients.
Exclusion criteria:
Case series; cohorts with an unclear denominator or source population or if it was a selected group of dental patients i.e. dental implants.
Cohort study
Inclusion criteria:
Both cohorts included three groups of patients 1) those who initiated bisphosphonates; (2) those who initiated another medication for osteoporosis; and (3) those who had a diagnosis of osteoporosis or a fracture but started no osteoporosis-related medications.
Exclusion criteria:
Diagnosis of solid organ malignancy or multiple myeloma. Use of a bisphosphonate or another medication during the 1 year prior to the start of follow-up.</td></tr>
</table>

<table>
<tr><td colspan="4">Risk of bias/systematic error (study limitations that could cause systematic error): consider risk of bias for each important outcome</td></tr>
<tr><td>Randomisation: is it reported and appropriate?
Not considered but may not be appropriate for these study types</td><td>Blinding: consider whether blinding of patients or assessors would be important for outcomes considered
Not applicable</td><td colspan="2">Other limitations: e.g. attrition bias (incomplete accounting of patients and outcome events), reporting bias (selective outcome reporting), surrogate outcomes(?)
Surrogate outcomes/coding when assessing insurance databases</td></tr>
<tr><td>Inconsistency: Refers to unexplained heterogeneity in results.</td><td>Imprecision (random error):</td><td>Indirectness: consider implications for both systematic review and guidance</td><td>Publication bias:</td></tr>
<tr><td>Is heterogeneity analysis reported?
The designs and quality of the included studies were so heterogeneous that no attempt was made to meta-analyze the results.</td><td>Cohort study relies on correct coding of ONJ or the authors interpretation of surrogate outcomes/coding</td><td>Results may be applicable to those taking BPs for the treatment of osteoporosis.</td><td>e.g. when intervention is new and not many studies available- may be biased for positive results
Not addressed</td></tr>
<tr><td colspan="2">Meta analysis: No. of data extractors: 2</td><td colspan="2">Overall results (for each outcome):</td></tr>
<tr><td colspan="2">Are results for individual studies shown? Yes
Was it reasonable to combine study results? Not combined
Was an appropriate method used? Not combined
Are reasons for variation in results discussed? Yes
Would confounders affect overall result? Yes</td><td colspan="2">1. Systematic review
• 5 studies gave an estimate of the incidence of BONJ, ranging from 0.028% to 4.0%.
• 2 studies estimated the relative risk of ONJ among bisphosphonate users compared with non-users, with odds ratios of 7.2 and 9.2.
• 3 studies using insurance claims data examined the relationship of bisphosphonate use to miscellaneous jaw lesions and found relative risks that ranged from protective (odds ratio 0.65) to elevated (odds ratio 7.8).
2. Cohort study
Cohort 1 – 1 case of ONJ (from 4934 BP users) confirmed from dental records and dentist responses, a prevalence of 0.02 % (95 % CI 0.004 %–0.11 %).
Cohort 2 – 7 possible cases of ONJ (from 100,109 BP users) plus 6 possible cases of ONJ in one of the control arms (351,623 patients receiving no treatment for osteoporosis) but none of these cases could be confirmed from dental records. Based on the unconfirmed cases, the estimated prevalence of BONJ among BP users was 0.007% (95% CI 0.0007%–0.014%) and the estimated incidence rate among patients not taking osteoporosis medication was 0.002 % (95 % CI 0.0008 %–0.004 %). The unadjusted prevalence ratio was 4.10 (95 % CI 1.37–12.2).
Is the effect substantial? N/A
Is there dose-response data? N/A</td></tr>
</table>

Adverse events:	**Benefit/harm/cost considerations?**	**Values/preferences considerations?**
Outcome (ONJ) is an adverse event.	Not done	Not done
Reviewer's comments:		**GRADE evidence quality rating:**
Include summary of main findings In studies retrieved from the systematic review, the prevalence of ONJ varied 0.028% to 4.0% (5 studies) with odds ratios of 7.2 and 9.2 (2 studies). Relative risks (3 studies) ranged from protective (odds ratio 0.65) to elevated (odds ratio 7.8). In the cohort study, the authors found very few cases of confirmed ONJ. The prevalence of ONJ was calculated as 0.02% (cohort 1) and 0.007% (cohort 2), with a prevalence of 0.002% in osteoporosis patients not taking medication (cohort 2). The unadjusted prevalence ratio in cohort 2 was 4.10. For the systematic review portion of the article, the authors only searched one data base (Medline) and used very simple search terms (osteonecrosis of the jaw AND bisphosphonates AND osteoporosis). They state that they assessed study quality using a system adapted from recommendations for the conduct of systematic reviews however the source of these is not referenced and the system does not take into account any sources of bias that may be relevant. The authors do not use the results of this assessment to exclude low quality studies. The authors found nine relevant articles which varied both in methodology and quality. Differences between the studies included the definition of the source population, the definition of BONJ and the examination of co-morbidities and co-medications. For the cohort investigation portion of the article, the authors used insurance-based health care claims in a single state (cohort 1) and across multiple states (cohort 2) with a follow-up of 13 months for both. The authors had to use surrogate outcomes/codes when examining the insurance database for cohort 1 as no specific code was available to record cases of ONJ at that time. They attempted to contact the relevant oral and maxillofacial surgeons to confirm any suspected diagnosis of ONJ. There was a relevant code for ONJ available for the second cohort and if any evidence of possible ONJ was found, the authors attempted to confirm this through dental records. There are limitations to this method of estimating prevalence as it relies on the accurate recording of diagnoses in databases, and for cohort 1 the authors had to use surrogates for this as no code for ONJ existed at that time. The follow-up time is also quite short, compared to others' observations that ONJ may take longer than one year to develop in those taking oral BPs for osteoporosis. It should be noted however that the sample sizes for both cohorts were large (nearly 0.5 million patients).		*Rating and brief explanation* **Low quality** based on study types included in review portion of paper (non-randomised case-control or cohort) and inconsistencies in results. Main cohort study also considered to provide **low quality** evidence due to study type and methodological shortcomings.

Systematic Review SR6: Kyrgidis et al., 2013[14]

<table>
<tr><td colspan="4">Systematic Review:
Kyrgidis et al. An evidence-based review of risk-reductive strategies for osteonecrosis of the jaws among cancer patients. Current Clinical Pharmacology. 2013; 8(2): 124-134.</td></tr>
<tr><td colspan="4">Aim of study: is there a clearly focussed question?
To elucidate any interventions that are effective in reducing the risk for development of ONJ in cancer patients receiving bone antiresorptive therapy and to quantify the effectiveness of such inteventions</td></tr>
<tr><td>Patient/Problem: (target patients and actual participant characteristics)</td><td>Intervention or risk factors:</td><td>Comparison:</td><td>Outcomes: note which are critical/important (from patient perspective) for the guidance recommendation*</td></tr>
<tr><td>Oncology patients</td><td>Some studies investigated whether dental extractions were risk factors and others looked at whether dental prophylactic measures can reduce ONJ risk.</td><td>1. patients prescribed zoledronic acid or denosumab
2. patients prescribed zoledronic acid or pamidronate
3. patients prescribed zoledronic acid or clodronate plus other comparisons</td><td>1. Relative risk (RR) of ONJ after bone antiresorptive agent exposure
2. RR of ONJ after bisphosphonate type exposure
3. RR of ONJ after antiresorptive agent dose exposure
4. RR of ONJ after BP prescription indication exposure
5. RR of ONJ after dental extractions exposure
6. RR of ONJ after denture/rootcanal/VitD/smoking exposure
7. RR of ONJ after periodontal disease exposure
8. RR of ONJ after dental preventive measures exposure</td></tr>
<tr><td>Study Type:</td><td colspan="2">Search Strategy:</td><td>Study selection: No. of selectors: 2 plus third adjudicator</td></tr>
<tr><td>Appropriate study types?
Yes
Correct components to address question?
Yes
Study no.s:
12 eligible studies identified; 5 x RCTs and 7 x cohort studies
3 RCTs excluded from meta-analysis due to insufficient data for the required comparisons</td><td colspan="2">Appropriate search terms? Yes
Appropriate databases? Yes MEDLINE, EMBASE, CENTRAL
Unpublished studies? Yes
Follow up of citations? Yes
Personal contact with experts? Yes</td><td>Inclusion criteria:
Oncology patients treated with at least 1 antiresorptive for >12 months;
Studies which report the incidence of adverse effects;
Comparison of ONJ incidence between two different treatments, antiresorptive agents or intervention to reduce the risk of ONJ;
RCTs.
Exclusion criteria:
Cohort studies unless there were no higher evidence studies reporting on the modality.</td></tr>
</table>

<table>
<tr><td colspan="4">Risk of bias/systematic error (study limitations that could cause systematic error): consider risk of bias for each important outcome</td></tr>
<tr><td>Randomisation: is it reported and appropriate?
Jadad instrument is used to assess quality of RCTS; of the 7 RCTs included in the SR, all had a Jadad score of ≥3. All SRs are described as randomized but the randomization methods are not stated.
Observational studies quality assessed using Newcastle-Ottawa scale</td><td>Blinding: consider whether blinding of patients or assessors would be important for outcomes considered
4 of the SRs are described as double blind.</td><td colspan="2">Other limitations: e.g. attrition bias (incomplete accounting of patients and outcome events), reporting bias (selective outcome reporting), surrogate outcomes(?)
ONJ overall incidence in the treatment and control groups was evaluated by intention to treat analysis.
Most of the calculations are likely to be underpowered due to the small number (2-4) of studies included for each outcome. The authors sought to address this by using random effects model for all analyses and assuming 99% confidence intervals but the results should still be treated with caution
The three RCTs include in the study were all funded by the same pharmaceutical company but it is noted that they were not designed to assess ONJ directly, this is reported as an adverse event</td></tr>
<tr><td>Inconsistency: Refers to unexplained heterogeneity in results.</td><td>Imprecision (random error):</td><td>Indirectness: consider implications for both systematic review and guidance</td><td>Publication bias:</td></tr>
<tr><td>Is heterogeneity analysis reported?
Examined by Chi-square tests for significance and presented by I^2 test. Random effects model was used for all calculations, regardless of the heterogeneity between studies, to obtain conservative estimates of effect.</td><td>Risk Ratios were reported at the 99% confidence interval to try to counteract type 1 errors.</td><td>The results are likely to be directly applicable to cancer patients being treated with antiresorptive agents</td><td>e.g. when intervention is new and not many studies available- may be biased for positive results
The authors state that funnel plots were used to assess the extent of publication bias but do not elaborate upon this any further in the discussion and no funnel plot is included in the article</td></tr>
<tr><td colspan="2">Meta analysis: No. of data extractors: 2</td><td colspan="2">Overall results (for each outcome):</td></tr>
<tr><td colspan="2">Are results for individual studies shown? Yes
Was it reasonable to combine study results?
Unsure. Results from RCTs and cohort studies were combined
Was an appropriate method used?
The authors have tried to use statistical methods that reduce the probability of errors
Are reasons for variation in results discussed?
The authors note that there is considerable heterogeneity in the cohort study populations but that the control group in each was matched to the exposed cohort. The authors attempt to address any observed variation in the discussion of each comparison/outcome</td><td colspan="2">1. No significant difference in ONJ risk ONJ between patients prescribed zoledronate or denosumab (RR: 0.71 [99% CI: 0.41-1.24], I^2=0%; 3 RCTs).
2. Zolendronate is more likely to induce ONJ compared to palmidronate (RR: 4.41 [99% CI: 1.90-10.24], I^2=16%; 4 cohorts) and clodronate (RR: 10.15 [99% CI: 2.43-42.35], I^2=0%; RCT + cohort) but zoledronate is more effective at reducing bone morbidities.
3. The crude incidence of ONJ among zoledronic acid patients is 1.3% for those prescribed monthly compared to 0.1% for those prescribed biannually (RR: 9.23 [99% CI: 2.23-38.23])
4. No significant difference was found for prescription indication.
5. Dental extractions remain the most potent risk factor for ONJ (RR: 14.04, [99% CI:</td></tr>
</table>

Would confounders affect overall result?	10.36-19.03], I^2=0%; 2 cohort). 6. No data to support an association, except for dentures where there may be an increased risk 7. Two cohort studies were unable to find an association between periodontal disease and ONJ (RR: 0.95, [99% CI: 0.45-2.00]) 8. Based on three cohort studies, dental prophylactic measures can reduce ONJ risk (RR: 0.45, [99% CI: 0.23-0.85], I^2=7%) however it was noted that one of these studies had a much higher than expected incidence of ONJ in the control arm. When this study is removed from the analysis, the result becomes non-significant based on the 99% confidence interval (RR: 0.55, [99% CI: 0.27-1.09, I^2 = 0%).

Adverse events:	**Benefit/harm/cost considerations?**	**Values/preferences considerations?**
Outcome (ONJ) is an adverse effect	Not considered	Not considered

Reviewer's comments:	**GRADE evidence quality rating:**
Include summary of main findings The aim of this systematic review was to identify interventions that may be effective in reducing the risk of ONJ in cancer patients receiving antiresorptive therapy. There are some limitations to the review. Study quality was assessed using published instruments though it is not clear if this was taken into account when assessing the data. Heterogeneity and publication bias were also assessed, although the result of the publication bias assessment was not reported, but there is no mention of possible sources of bias other than a comment that three of the RTCs were funded by the same pharmaceutical company. The authors note that the meta analyses in this review are mostly underpowered and mostly based on non-randomised studies and suggest that more randomized clinical trials are needed. They report results as significant at the 99% CI level to counteract type I error inflation and used random effects model for all analyses in an attempt to avoid overstating the effects. The authors found no significant difference in risk of ONJ between patients prescribed zoledronic acid or denosumab (RR:0.71 [99% CI: 0.41-1.24], I^2=0%) based on three manufacturer sponsored RCTs. Four cohort studies suggest that pamidronate is at least 4 time less likely to induce ONJ compared to zoledronate (RR:4.41 [99% CI: 1.90-10.24], I^2=16%) while an RCT and a cohort study favour clodronate over zoledronate (RR:10.15 [99% CI: 2.43-42.35], I^2=0%) although it was noted that zoledronate is more effective at reducing bone morbidities. Dental extractions remain the most potent risk factor for ONJ (RR: 14.04, [99% CI: 10.36-19.03], I^2=0%), based on two cohort studies, and avoidance of extractions can be considered an effective risk-reductive intervention. The results of three cohort studies suggest that dental prophylactic measures can reduce ONJ risk (RR: 0.45, [99% CI: 0.23-0.85], I^2=7%) however it was noted that one of these studies had a much higher than expected incidence of ONJ in the control arm. When this study is removed from the analysis, the result becomes non-significant based on the 99% confidence interval (RR: 0.55, [99% CI: 0.27-1.09, I^2 = 0%).	*Rating and brief explanation* **Low quality** based on the mostly non-randomised studies which are included in the meta analyses.

Systematic Review SR7: Carmona et al., 2013[10]

Systematic Review: **Carmona** et al. Systematic Literature Review of Biphosphonates and Osteonecrosis of the Jaw in Patients With Osteoporosis *Reumatología Clínica* 2013; 9 (3): 172-177				
Aim of study: *is there a clearly focussed question?* To systematically assess the literature related to the occurrence of osteonecrosis of the jaw (ONJ) using bisphosphonates (BP) in the treatment of osteoporosis (OP).				
Patient/Problem: *(target patients and actual participant characteristics)*	**Intervention or risk factors:**	**Comparison:**	**Outcomes:** *note which are critical/important (from patient perspective) for the guidance recommendation**	
Patients >18 years of both sexes with osteoporosis treated with bisphosphonates (i.v. and oral)		placebo or active drug	Presence of ONJ	
Study Type:	**Search Strategy:**		**Study selection:**	No. of selectors: 2 independent plus mentor
Appropriate study types? Yes *Correct components to address question?* Yes *Study no.s:* 18 8 systematic reviews, 8 clinical trials and 2 meta analyses	*Appropriate search terms?* Yes, MeSH and free text *Appropriate databases?* Medline, EMBASE, Cochrane, Central *Unpublished studies?* Not mentioned *Follow up of citations?* Yes *Personal contact with experts?* Not mentioned		*Inclusion criteria:* Patients ≥18 years with osteoporosis of non-malignant etiology; Treatment with BPs (alendronate, etidronate disodium, ibandronic acid, pamidronate, risedronate and zoledronic acid) or strontium ranelate; Meta-analysis, systematic review or clinical trial; ONJ as an outcome. *Exclusion criteria:* Animal and basic science studies.	
Risk of bias/systematic error (study limitations that could cause systematic error): *consider risk of bias for each important outcome*				
Randomisation: is it reported and appropriate? Not applicable	*Blinding: consider whether blinding of patients or assessors would be important for outcomes considered* Not applicable	*Other limitations: e.g. attrition bias (incomplete accounting of patients and outcome events), reporting bias (selective outcome reporting), surrogate outcomes(?)* Study quality is assessed and commented on (Oxford scale)		
Inconsistency: *Refers to unexplained heterogeneity in results.*	**Imprecision (random error):**	**Indirectness:** *consider implications for both systematic review and guidance*	**Publication bias:**	
Is heterogeneity analysis reported? No. There are more ONJ cases reported in the systematic reviews than the trials, but this may be due to the nature of the studies	There may be under- or over-reporting of cases due to confounding factors in the patient population. Also, the definition of ONJ may vary across studies. If ONJ was an adverse event, this	Data is probably directly applicable to patients being treated with BPs for osteoporosis, although it should be noted that those individuals who take part in clinical trials do not always	*e.g. when intervention is new and not many studies available- may be biased for positive results* Not addressed	

included in the reviews (case reports etc.).	may not have been reported evenly.	represent the general population in terms of co-morbidities.	

Meta analysis: No. of data extractors: not stated	**Overall results (for each outcome):**
Are results for individual studies shown? Yes *Was it reasonable to combine study results?* Not combined *Was an appropriate method used?* See above *Are reasons for variation in results discussed?* See above *Would confounders affect overall result?*	1. Systematic reviews: One review identified 368 cases of ONJ from 30 case series, with 15 (4%) occurring in patients with OP treated with oral BPs. Another, looking at OP patients only, identified 26 cases of ONJ in 11 studies. A third review identified 57 cases, most associated with iv BPs for OP. Other reviews found a progressive increase in cases of ONJ in patients receiving BP for the treatment of OP. The most recent review found 2408 cases of ONJ associated with BPs, of which 178 corresponded to patients with OP. 2. Clinical trials: In zoledronate trials including over 10,000 patients treated for OP, no cases of ONJ were observed. Treatment included different regimens of zoledronate compared to placebo or risdronate. Further investigation in one study suggested that 2 patients (one in the experimental group and one in the placebo group) did experience adverse effects that could be attributed to ONJ (delayed healing). In two ibandronate trials (~1500 patients treated for OP), no cases of ONJ were reported. A study which followed 1099 women who had been treated with alendronate for 5 years after treatment was discontinued observed no cases of ONJ. A trial which compared the outcome of 220 dental implants placed in 50 women with post-menopausal OP (50% were treated with weekly BP [alendronate 70 mg or risedronate 35 mg], remainder received no treatment) observed no cases of ONJ or differences in the loss of implants. 3. Meta-analysis: there were no cases of ONJ associated with BPs in the meta-analyses of controlled clinical trials lasting at least one year for postmenopausal OP treatment with risedronate and alendronate.

Adverse events:	**Benefit/harm/cost considerations?**	**Values/preferences considerations?**
Outcome (ONJ) is an adverse event	Not considered	No considered

Reviewer's comments:	**GRADE evidence quality rating:**
Include summary of main findings This review aims to systematically assess the literature regarding the occurrence of osteonecrosis of the jaw in patients being treated with bisphosphonates for osteoporosis. The review limits eligible study types to meta analyses, systematic reviews and clinical trials and finds limited occurrence of ONJ in patients with osteoporosis. Most of these are associated with iv administration, with very few associated with oral BPs. The authors conclude that there is insufficient evidence to suggest that iv or oral BP treatment of OP leads to a significant risk of ONJ and that the benefits of the drugs for the treatment of osteoporosis much outweigh the risks. The review has several limitations. The narrative is slightly confusing and in some places does not match exactly to the data in the tables. This is most likely due to the translation from Spanish to English. This reviewer therefore had to spend a significant amount of time re-extracting data from the individual study results. The data tables themselves are not particularly straightforward to interpret. In some cases, particularly the systematic reviews, the authors include data on number of cases of ONJ observed but not the total number of patients who did not develop the condition so it is difficult to grasp what the incidence may be based on these numbers. This may be due to the type of studies included in the reviews (e.g. case studies, case series). There are hardly any cases of ONJ observed in the clinical trials, but these would have been mostly reported as adverse events as the primary aim of the trials was not to investigate ONJ. The timescale of the trials may also influence whether ONJ was observed, as the condition may be related to the dose/time the drug has been given and the trials may not have been long enough to observe this outcome. Also, ONJ in OP patients is likely to be very rare therefore the trials may not have been sufficiently powered to observe any cases.	*Rating and brief explanation* **Low quality** based on the methodology and reporting of the review. Occurrence of ONJ was not a primary outcome for the RCTs and it is questionable whether this study type is appropriate to determine incidence of what is thought to be a rare side effect of drug treatment.

Systematic Review SR8: Kuhl et al., 2012[7]

Systematic Review: **Kuhl** et al. Bisphosphonate-related osteonecrosis of the jaws – A review. Oral Oncology 48 (2012) 938-947				
Aim of study: *is there a clearly focussed question?* To (a) assess the number of publications per year; (b) evaluate the type of journals for publication; (c) determine the level of evidence of published trials for classification; (d) retrieve information on the incidence; and (e) the treatment strategies and results related to BRONJ.				
Patient/Problem: *(target patients and actual participant characteristics)*	**Intervention or risk factors:**	**Comparison:**	**Outcomes:** *note which are critical/important (from patient perspective) for the guidance recommendation**	
All patients with bisphosphonate-related osteonecrosis of the jaw	Any intervention as treatment. Risk factors not addressed by this review	There is a narrative comparing outcomes for patients receiving different treatments but no direct comparison	The authors were looking for incidence of bisphosphonate-related osteonecrosis of the jaw. They also compiled data on treatment and the number of patients who fully recovered or experienced resolution of their clinical symptoms.	
Study Type:	**Search Strategy:**		**Study selection:**	No. of selectors: Not stated
Appropriate study types? All study types retrieved due to aim of study *Correct components to address question?* *Study no.s:* 671 relevant articles retrieved, 176 classified to determine grade of evidence	*Appropriate search terms?* *'Bisphosphonate'* and '*osteonecrosis of the jaw'* used as search terms. Was this sufficient? *Appropriate databases?* Medline/Pubmed, Cochrane *Unpublished studies?* Not appropriate for this review *Follow up of citations?* Cited literature was evaluated and manual search/library research performed *Personal contact with experts?* Not mentioned		*Inclusion criteria:* All studies retrieved were included to address aims a) and b) of the review. All clinical studies were extracted and the grade of evidence classified. *Exclusion criteria:* Not applicable for this review	
Risk of bias/systematic error (study limitations that could cause systematic error): *consider risk of bias for each important outcome*				
Randomisation: is it reported and appropriate? Not applicable for this review	*Blinding: consider whether blinding of patients or assessors would be important for outcomes considered* Not applicable for this review	*Other limitations: e.g. attrition bias (incomplete accounting of patients and outcome events), reporting bias (selective outcome reporting), surrogate outcomes(?)* Not applicable for this review		

Inconsistency: *Refers to unexplained heterogeneity in results.*	**Imprecision (random error):**	**Indirectness:** *consider implications for both systematic review and guidance*	**Publication bias:**
Is heterogeneity analysis reported? Not applicable for this review	Not applicable for this review	Not applicable for this review	*e.g. when intervention is new and not many studies available- may be biased for positive results* Not applicable for this review

Meta analysis: No. of data extractors: not stated	**Overall results (for each outcome):**
Are results for individual studies shown? Not applicable for this review *Was it reasonable to combine study results?* Not applicable for this review *Was an appropriate method used?* Not applicable for this review *Are reasons for variation in results discussed?* Not applicable for this review *Would confounders affect overall result?*	a) 671 relevant publications found b) 26.7% of the publications appeared in general dental journals; 20.1% appeared in OMFS journals; 19.1% were found in clinical oncology journals; 13.3% appeared in general medical journals; 13.0% were published in journals of internal medicine and 3.6 % in other journals. c) A total of 176 publications out of 671 could be classified. Only one study with evidence level Ia was found; 8 publications had evidence level Ib; 9 studies had a level of evidence grade IIa; 25 studies had a level of evidence grade IIb; 101 publications had evidence grade III and 32 publications had evidence grade IV. d) The mean incidence of BRONJ after intravenous application (47 studies) was **7%**, with a high variation from 0.0% up to 27.5%. The mean incidence of BRONJ after oral bisphosphonate application (9 studies) was **0.12%**, ranging from 0.0% to 4.3%. e) In 15 studies of 403 BRONJ patients, 123 patients had conservative treatment, 255 patients had surgical treatment and the remaining 25 patients were treated with a combination of both. 388 of the 403 patients were given antibiotics. 240 patients (59.7%) were treated with radical surgery combined with antibiotics; the lesions healed in 141 (58.8%) of these patients, with improvement and resolution of clinical symptoms observed in another 47 patients (19.6%). 10 patients (4.2%) had refractory or new BRONJ.103 patients were treated conservatively in combination with administration of antibiotics. 66 (64.1%) of these patients had healing of their lesions with six patients (5.8%) experiencing an improvement with resolution of their clinical symptoms. Eight patients (7.8%) had refractory or new BRONJ. 27 patients were treated with antibiotics only and improvement with resolution of clinical symptoms was observed in 18 (66.7%) of these patients.

Adverse events:	**Benefit/harm/cost considerations?**	**Values/preferences considerations?**
Outcome (BRONJ) is an adverse event	Not applicable for this review	Not applicable for this review
Reviewer's comments:		**GRADE evidence quality rating:**
Include summary of main findings The aim of this systematic review was to evaluate the literature published about bisphosphonate-related osteonecrosis of the jaws (BRONJ). MEDLINE, Pubmed and the Cochrane register of controlled clinical trials were searched, with additional manual searching, from Jan 2003 to March 2010. The amount of publications per year, the type of journal for publication, and the evidence level of the trial were evaluated. Next to this the incidences and the success of treatment strategies for BRONJ were identified. 671 publications were found and, as would be expected, the number of publications increased year on year and were most likely to be found in the dental literature. The studies showed a wide variety in design, most of them being retrospective. 176 of the publications classified by grade of evidence (Shekelle et al.), with the majority found to be Grade III or IV (descriptive studies or expert opinion). Only one grade Ia study was found. 47 studies gave details on the incidence of BONJ after IV application; mean incidence was 7% but varied from 0% to 27.5% across studies. There was also variance in the design and duration of these studies. 9 studies gave details on the incidence of BONJ after oral application; mean incidence was 0.12% but varied from 0% to 4.3% across studies. Again, there was significant variance in study duration. The authors also assessed treatment outcomes across 15 of the identified studies (403 patients). Treatment was either conservative or surgical, with or without antibiotic therapy, with surgical treatment judged to more effective in those with advanced ONJ. There is no scientific data to sufficiently support any specific treatment protocol for the management of BRONJ and the authors conclude that further clinical studies are needed to evaluate the incidence and treatment strategies at a higher level of evidence. Therefore, uniform study protocols would be favourable. This review gives a useful overview of the studies published on BRONJ to end 2009 but does not provide any information on risk factors or interventions to prevent the condition. The information on incidence is likely to be superseded by more recent data.		*Rating and brief explanation* **Low quality** based on the variation between incidences observed and the variance in study designs and study durations. Studies included were at the lower end of the evidence level scale.

Systematic Review SR9: Diniz-Freitas et al., 2013[21]

<table>
<tr><td colspan="4">Systematic Review:
Diniz-Freitas, M. and J. Limeres (2016). "Prevention of medication-related osteonecrosis of the jaws secondary to tooth extractions. A systematic review." Medicina oral, patologia oral y cirugia bucal 21(2): e250-e259.</td><td>Ref. No.:
Reviewer(s):</td></tr>
<tr><td colspan="5">Aim of study: is there a clearly focussed question?
Yes – What is the most effective procedure for reducing the risk of ONJ after tooth extraction in patients receiving treatment with anti-resorptive or anti-angiogenic drugs?</td></tr>
<tr><td>Patient/Problem: (target patients and actual participant characteristics)</td><td colspan="2">Intervention or risk factors:</td><td>Comparison:</td><td>Outcomes: note which are critical/important (from patient perspective) for the guidance recommendation*</td></tr>
<tr><td>Patients treated with oral or intravenous anti-resorptive or anti-angiogenic drugs who had tooth extractions</td><td colspan="2">Protocol to reduce the incidence of ONJ after tooth extraction</td><td>None</td><td>Osteonecrosis of the jaw</td></tr>
<tr><td>Study Type:</td><td colspan="3">Search Strategy:</td><td>Study selection:
No. of selectors: 2</td></tr>
<tr><td>Appropriate study types?
No RCTs included, only case series or cohorts
Correct components to address question?
Yes
Study no.s: 13; 634 patients</td><td colspan="3">Appropriate search terms? Yes
Appropriate databases? Only two, Medline and Scopus
Unpublished studies? Not mentioned
Follow up of citations? Yes
Personal contact with experts? Not mentioned</td><td>Inclusion criteria: studies had to include information on type of anti-resorptive or antiangiogenic treatment used, administration route, indication of treatment, clear definition of the presence of ONJ, duration of follow-up, specific details of prevention protocol

Exclusion criteria: studies in patients under 18; case series with <10 patients; animal studies</td></tr>
<tr><td colspan="5">Risk of bias/systematic error (study limitations that could cause systematic error): consider risk of bias for each important outcome</td></tr>
<tr><td>Randomisation: is it reported and appropriate?
Not applicable for the included study types</td><td colspan="2">Blinding: consider whether blinding of patients or assessors would be important for outcomes considered
Not applicable for the included study types</td><td colspan="2">Other limitations: e.g. attrition bias (incomplete accounting of patients and outcome events), reporting bias (selective outcome reporting), surrogate outcomes(?)
Not applicable for the included study types</td></tr>
<tr><td>Inconsistency: Refers to unexplained heterogeneity in results.</td><td colspan="2">Imprecision (random error):</td><td>Indirectness: consider implications for both systematic review and guidance</td><td>Publication bias:</td></tr>
<tr><td>Is heterogeneity analysis reported?
Not applicable for the included study types</td><td colspan="2">Not applicable for the included study types</td><td>The results of this review would be directly applicable to the patient population covered by the guidance</td><td>e.g. when intervention is new and not many studies available- may be biased for positive results
Not addressed</td></tr>
<tr><td colspan="3">Meta analysis: no meta analysis performed
No. of data extractors: 2</td><td colspan="2">Overall results (for each outcome):</td></tr>
</table>

Are results for individual studies shown? Yes *Was it reasonable to combine study results?* This was not done, other than to calculate an incidence figure *Was an appropriate method used?* *Are reasons for variation in results discussed?*	1. I.V. BPs: ONJ prevalence 6.9% (634 patients, range 0-34.7%) 2. Oral BPs: ONJ prevalence 0.47% (1261 patients, range 0-2.5%) 3. No studies found for other anti-resorptive or anti-angiogenic drugs

Adverse events:	**Benefit/harm/cost considerations?**	**Values/preferences considerations?**
Outcome (ONJ) is an adverse event	Not considered	Not considered

Reviewer's comments:	**GRADE evidence quality rating:**
Include summary of main findings Strategies to prevent ONJ in patients treated with i.v. bisphosphonates included antibiotic prophylaxis; atraumatic tooth extraction with the raising of a flap to allow first-intention closure and healing, minimizing direct contact of the oral bacteria with the socket; and the local application of antiseptic products. However, the composition of the antimicrobials used, the dosage and the duration of treatment varied considerably. Some studies also investigated the use of adjusted extraction techniques, plasma rich in growth factors and laser therapy. The authors note: *Although randomized trials would be needed to determine the true efficacy of antibiotic prophylaxis in patients subjected to extraction and treated with antiresorptive or antiangiogenic drugs, antibiotics do appear to exert a certain preventive effect, as demonstrated by some studies in animals and retrospective studies in patients with multiple myeloma*. Studies which investigated the prevention of ONJ in patients treated with oral bisphosphonates were also based on local and systemic infection control. There is no evidence that the interruption of oral BPs prior to invasive dental procedures (drug holiday) eliminates the risk of ONJ and temporary suspension of the medication may have a negative impact in terms of bone resorption. Authors conclude: *No conclusive scientific evidence is available to date on the efficacy of ONJ prevention protocols in patients subjected to tooth extraction and treated with antiresorptive or antiangiogenic drugs. In practical terms, and until future studies are able to define the ideal protocol, adoption of the preventive measures proposed by the international expert committees has weak scientific justification, but could afford some coverage from the medical-legal perspective.* This is as good a review as the current literature allows and agrees with this reviewer's previous appraisal of the evidence. As the authors note: *Most articles on the efficacy of preventive measures before tooth extraction in patients treated with antiresorptive or antiangiogenic drugs have methodological shortcomings, are not randomized or controlled, involve an insufficient sample size, and apply very heterogeneous preventive protocols – combining common sense initiatives such as antibiotic treatment with other much more sophisticated strategies such as platelet rich plasma or low-power laser irradiation. This heterogeneity and the limitations of the reviewed studies therefore do not allow quantitative analysis (meta-analysis).*	*Rating and brief explanation* **Low quality** based on the non-randomised studies which are included in the review.

Guideline G1: Khan et al., 2015[8]

Title: Diagnosis and management of osteonecrosis of the jaw: A systematic review and international consensus		
Authors/organisation: Khan et al. (on behalf of the International Task Force on Osteonecrosis of the Jaw)		
Date of publication/revision: 2015	Original version: 2015	Source: *Journal of Bone and Mineral Research*. 2015; 30(1):3-23. http://onlinelibrary.wiley.com/doi/10.1002/jbmr.2405/epdf

Aim(s) of guidance:
The aim of the article is to provide a systematic review of the literature pertaining to the incidence, pathophysiology, diagnosis and treatment of osteonecrosis of the jaw (ONJ) and offers recommendations for its management based on multidisciplinary international consensus.

Key recommendations: *relevant to SDCEP guidance*

Nine key questions were formulated by the task force. 3 were felt to be particularly relevant to the SDCEP guidance topic:

2. How common is ONJ?

In patients with osteoporosis the incidence of ONJ is estimated to be 1.04-69 per 100,000 patient-years. This is thought to be only slightly higher than the incidence of ONJ lesions in the general population.

Incidence of ONJ in the oncology patient population is approximately from 0-12,222 per 100,000 patient-years. The greater frequency of ONJ in this patient population appears to be related to the intensive use of anti-resorptive therapies as well as associated comorbidity and concurrent medications often used in this patient population.

Type: evidence-based. **Grade of recommendation:** C*.

3. Who develops ONJ? What are the risk factors and co-morbidity?

Risk factors for developing ONJ in the osteoporosis population are listed in order of decreasing association: suppuration, any BP use, dental extraction and oral BP use

Type: evidence-based. **Grade of recommendation:** D*.

Risk factors for developing ONJ in the oncology population are listed in order of decreasing association: IV BPs (zoledronic acid and pamidronate risk impacted by dose and duration of therapy), denosumab, radiation therapy, dental extraction, chemotherapy , periodontitis, oral BP use, osteoporosis, local suppuration, glucocorticoid therapy, diabetes, denture use, erythropoietin therapy, smoking tobacco, hyperthyroidism, renal dialysis, cyclophosphamide therapy, etidronate and age.

Type: evidence-based. **Grade of recommendation:** D*.

7. Can ONJ be prevented and what is the role of drug interruption?

Identification and treatment of dental disease prior to initiation of anti-resorptive therapy if possible is recommended. Evolving data suggest optimizing oral hygiene prior to initiating anti-resorptive therapy may reduce the incidence of ONJ.

Type: evidence-based. **Grade of recommendation:** C*.

There is insufficient evidence to suggest that interrupting anti-resorptive therapy before a minor oral surgical procedure will alter the risk of developing ONJ.

In those at high risk for the development of ONJ including cancer patients receiving high-dose BP or Dmab therapy consideration should be given to withholding anti-resorptive therapy following extensive oral surgery until the surgical site heals with mature mucosal coverage.

Type: consensus-based. **Grade of recommendation:** D*.

Therapy can be resumed following clinical evidence of mature soft tissue closure.

Type: consensus-based. **Grade of recommendation:** D*.

Geographical setting for guidance:	**Healthcare setting for guidance:** *users and patients*	**Is guidance currently used?**
International	Primary care dental practice	Yes

Basis for recommendations: *e.g. published evidence, expert opinion etc.*
If evidence based, review evidence in sections below

Based on a review of the literature plus expert opinion

Description of evidence questions for recommendations (if applicable):

Patient/Problem: *(target patients and actual participant characteristics)*	Intervention or risk factors:	Comparison:	Outcomes: *note which are critical/important (from patient perspective) for the guidance recommendation**
Patients being treated for cancer or osteoporosis	Antiresorptive agents (bisphosphonates or denosumab)		Osteonecrosis of the jaw

Details of evidence search: *search strategy, study selection, study types*	**Study limitations:** *risk of bias, limitations, inconsistency, imprecision, indirectness*
A search strategy combining medical subject headings and/or text words was used and all searches were limited to human studies published in the English language and excluded reviews, editorials, and letters. The electronic search was conducted in Medline, EMBASE and the Cochrane Database of Systematic Reviews. A manual search of the bibliography of identified published articles was also performed. In order to obtain additional unpublished data, personal communication with relevant experts was conducted and pharmaceutical companies were invited to submit relevant information. A total of 46 records were included from manual searches and expert communication. The total number of references were reviewed was 933 and from these, 599 papers were reviewed in full.	The relevant texts from the literature search were critically appraised and graded based on quality of evidence in duplicate, with disagreements discussed between reviewers until consensus was achieved. If no consensus was possible, a third reviewer was available to provide the final decision. The evidence from each article was graded based on the study design (see footnote*), with each recommendation graded based on the evidence underpinning it. Risk of bias and other limitations not explicitly considered for each study. No heterogeneity analysis or investigation of publication bias was performed.

Meta analysis:	**Evidence:** *for each outcome or recommendation as applicable*
No formal meta-analysis was performed	*2. How common is ONJ*? 88 studies were found to be relevant to this question. The study designs varied from RCTs to case series. The prevalence of ONJ in patients prescribed oral BPs for the treatment of osteoporosis ranges from 0% to 0.04%, with the majority being below 0.001%. The prevalence of ONJ in those prescribed high dose i.v. BPs is significantly higher than that seen with low dose i.v. or oral BPs, with prevalence rates of 0% to 0.348% and the majority being under 0.005%. One study noted a prevalence of ONJ in patients treated with BPs for osteoporosis of<1/100,000 while another found the prevalence of ONJ in those receiving BPs for more than 2 years to range from 0.05% to 0.21% and this appeared to be related to duration of exposure. A survey of oral surgeons found the prevalence of ONJ in those on BPs to be approximately 0.001%. A case-control

	study noted an association between oral BPs and ONJ, with an odds ratio (OR) of 12.2 (95% CI] 4.3-35). This study, however, included patients with cancer on oncologic doses of BPs, which likely increased the incidence of ONJ. A historical cohort study evaluated jaw-related events in BP users with nonusers and noted a hazard ratio (HR) of 3.15 (95% CI, 1.44-6.87) with alendronate use. *3. Who develops ONJ? What are the risk factors and co-morbidity?* 36 studies were found to be relevant to this question. Epidemiological data on the prevalence and incidence of ONJ are limited and, when available, typically not based on prospective studies or population-based surveys. Significant risk factors for the development of ONJ in the oncology population, in declining order of importance, include: i.v. BPs (both dose of BP and duration of exposure impact ONJ risk) (based on 1 study); zoledronic acid (based on 5 studies); pamidronate (based on 1 study); Dmab (from incidence and prevalence data); radiation therapy (based on 1 study); dental extraction (based on 5 studies); chemotherapy (based on 1 study); periodontal disease (based on 1 study); oral BP use (based on 1 study); osteoporosis (based on 1 study); local suppuration (based on 1 study); glucocorticoid therapy (based on 1 study); diabetes (based on 1 study); denture use (based on 3 studies); erythropoietin therapy (based on 1 study); tobacco use (based on 1 study); hyperthyroidism (based on 1 study); renal dialysis (based on 1 study); cyclophosphamide therapy (based on 1 study); etidronate (based on 1 study); and increasing age (based on 2 studies). Significant risk factors for the development of ONJ in the osteoporosis patient population, in declining order of importance, include: suppuration (based on 1 study); BP use (based on 1 study); dental extraction (based on 1 study); and anemia (based on 1 study). *7. Can ONJ be prevented and what is the role of drug interruption?* 13 studies were included for this question, none of which were judged to be of a high level of evidence (4 x level 3 [non-randomised controlled trial or cohort study]; 4 x level 4 [before-after study, cohort study with non-contemporaneous controls, case-control study]; 5 x level 5 [case series without controls]). 4 studies support the completion of necessary oral surgery prior to initiation of antiresorptive therapy, six studies support the use of antibiotics before and/or after the procedure, three studies support antimicrobial mouth rinsing, three studies support appropriate closure of the wound following tooth extraction and six studies support the maintenance of good oral hygiene to reduce the risk of ONJ. In patients taking high doses of antiresorptive drugs, there is little evidence to support the recommendation to withhold antiresorptive therapy after invasive oral surgery until soft tissue healing has occurred. There also little evidence to support stopping antiresorptive therapy in patients who may require extensive invasive oral surgery, as well as those with multiple risk factors for ONJ (diabetes, periodontal disease, glucocorticoid treatment, immune deficiencies, smoking, etc.) or to support drug holidays.
Benefit/harm/resource considerations?	**Values/preferences considerations?**
Not discussed	Not discussed

Overall quality of guidance (AGREE II) and explanation:	**Rating of recommendations:** *Should the recommendations made be considered for SDCEP guidance?*
AGREEII rating: 2/7 This article does not set out to be a guideline but does include recommendations for the management of patients at risk of MRONJ. There does appear to have been a search of more than one database and inclusion and exclusion criteria have been drawn up for each clinical question. However, it is not clear how the authors assessed the quality of included publications, apart from a rating based on the study type, and whether potential sources of bias were considered. The layout of the text within the guideline is dense, with recommendations not easy to identify. However, this will in part be due to the requirements of the journal in which the article was published. The guideline was compiled as an International Consensus and there is a long list of authors but it is unclear if it was subject to peer review outwith the group who prepared it, apart from the usual journal review process. It is also unclear whether patient views were sought as part of the development process.	The evidence which informs the recommendations in this publication was not appraised for quality using GRADE methods and the strength of the guideline recommendations is not stated in the main text. All of the recommendations are graded as C or D. However, due to the paucity of evidence in this area, the recommendations made within this publication may be useful in informing recommendations in SDCEP guidance.
Reviewer's comments:	
The paper takes on the not insubstantial task of addressing 9 questions related to the incidence, pathophysiology, diagnosis, and treatment of osteonecrosis of the jaw and to offer recommendations for its management based on multidisciplinary international consensus. A total of 599 relevant articles were retrieved in a search of the literature and data extracted to support the formulation of recommendations. Manual searching was also performed but there was no mention of grey/unpublished literature. The relevant studies were critically appraised and graded based on quality of evidence (this was done in duplicate, evidence appraisal does not seem to be particularly rigorous - based on study type rather than assessment of how well study was done. Also, potential sources of bias were not reported). The review itself does not appear to include any meta analysis, except perhaps for the figures quoted for incidence/prevalence, and the evidence for each question is summarised in a literature review style, with subsequent recommendations proposed by the Task Force. As with other groups, they found that high quality evidence is mostly lacking regarding prevention and treatment; this may be related to the low incidence of the disease, especially in the osteoporosis population. Where evidence is lacking, the authors have made recommendations based on a consensus of expert opinion.	

*The criteria used to assign a level of evidence to articles covering treatment or prevention were:

1+ Systematic overview of meta-analysis of RCTs
1 1 randomized controlled trial with adequate power
2+ Systematic overview or meta-analysis of level 2 RCTs
2 RCT that does not meet level 1 criteria
3 Non-randomized controlled trial or cohort study
4 Before-after study, cohort study with non-contemporaneous controls, case-control study
5 Case series without controls
6 Case report or case series of <10 patients

Recommendations were graded as follows:

A Supportive level 1 or 1+ evidence plus consensus
B Supportive level 2 or 2+ evidence plus consensus
C Supportive level 3 evidence plus consensus
D Any lower evidence supported by consensus

Guideline G2: Ruggiero et al., 2014[9]

Title: American Association of Oral and Maxillofacial Surgeons Position Paper on Medication-Related Osteonecrosis of the Jaw - 2014 Update		
Authors/organisation: Ruggiero et al. on behalf of the American Association of Oral and Maxillofacial Surgeons		
Date of publication/revision: 2014	Original version: 2007; 2009	Source: J. Oral and Maxillofac. Surg. 72(10) 2014, 1938–1956

Aim(s) of guidance:

To appraise the current literature and revise the AAOMS guidelines to reflect current knowledge for strategies for management of patients with, or at risk for, medication-related osteonecrosis of the jaw (MRONJ).

The purpose of this updated position paper is to provide:

- Risk estimates of developing MRONJ
- Comparisons of the risks and benefits of medications related to ONJ to facilitate medical decision making for the treating physician, dentist, dental specialist, and patients
- Guidance to clinicians regarding:
    - The differential diagnosis of MRONJ in patients with a history of exposure to antiresorptive or antiangiogenic agents
    - MRONJ prevention measures and management strategies for patients with MRONJ based on disease stage

The guidance includes a disclaimer which states that the position paper is informational in nature and is not intended to set standards of care, that the strategies described are not practice parameters or guidelines and may not be suitable for every, or any, purpose or application and that the position paper cannot substitute for the individual judgment brought to each clinical situation by the patient's oral and maxillofacial surgeon.

Key recommendations: *relevant to SDCEP guidance*

Patients may considered to have MRONJ if all the following characteristics are present:

- Current or previous treatment with antiresorptive or antiangiogenic agents
- Exposed bone or bone that can be probed through an intra-oral or extra-oral fistula in the maxillofacial region that has persisted for longer than 8 weeks
- No history of radiation therapy to the jaws or obvious metastatic disease to the jaws

Medication-related risk factors appear to vary based on the therapeutic indication (osteoporosis/osteopaenia or malignancy) and type of medication (BP or non-BP).

- Patients with cancer treated with zoledronate or denosumab have 50-100 times higher risk of ONJ compared to those treated with placebo (incidence 1-2%)
- The risk of ONJ in patients with cancer treated with bevacizumab is 0.2% and the risk may increase in patients concurrently treated with zoledronate
- In patients treated with oral BPs for osteoporosis, MRONJ prevalence estimates range from 0.0004 to 0.1%
- In osteoporosis patients treated with yearly zoledronate or denosumab, the incidence is estimated at 0.017-0.04% (similar to the risk of ONJ in placebo groups [0 to 0.02%])
- There is evidence that incidence/risk increases as duration of drug treatment increases
- Local risk factors include dentoalveolar surgery, anatomic factors (denture use) and concomitant oral disease (e.g. periodontal disease)
- Age, gender and concurrent medication, particularly steroids, are also considered risk factors and possible genetic risk factors are currently being investigated

Management strategies

For patients on IV antiresorptive or antiangiogenic treatment for cancer, delay initiation of antiresorptive therapy until dental health is optimized if systemic conditions

permit.

- Extract non-restorable teeth and those with a poor prognosis and complete any other necessary elective dentoalveolar surgery.
- Allow the extraction site to heal before antiresorptive/antiangiogenic therapy begins.
- Examine patients with full or partial dentures for areas of mucosal trauma, especially along the lingual flange region and
- Educate patients as to the importance of dental hygiene and regular dental evaluations and specifically instructed to report any pain, swelling, or exposed bone.
- During treatment with antiresorptive/antiangiogenic drugs, avoid procedures that involve direct osseous injury. Treat non-restorable teeth by removal of the crown and endodontic treatment of the remaining roots. Avoid placement of dental implants in these patients.
- Data are scant regarding the effect of drug holidays before invasive dental treatments. However, if ONJ develops, discuss with the oncologist the option of discontinuing antiresorptive therapy until soft tissue closure has occurred, depending on disease status.

For patients on antiresorptive treatment for osteoporosis, the risk of MRONJ increases when duration of oral antiresorptive therapy exceeds 4 years. Comorbidities, such as chronic corticosteroid use, may shorten this timeframe. At the initiation of treatment, patients should be educated as to the potential risks of MRONJ because the timeframe of antiresorptive therapy is likely to exceed 4 years. The importance of optimizing dental health throughout this treatment period and beyond should be stressed.

- Elective dentoalveolar surgery is not contraindicated in this group. It is recommended that patients be adequately informed of the very small risk (<1%) of compromised bone healing.
- Sound recommendations based on strong clinical research designs are still lacking for patients taking oral BPs. The committee's strategies outlined below are based on clinical studies that have shown a low prevalence of disease however the level of evidence is not strong. There is currently no evidence that interrupting BP therapy alters the risk of ONJ in osteoporosis/ osteopaenia patients after tooth extraction but a theoretical benefit may apply for those patients with extended exposure histories (>4 yrs)
    - For patients who have taken an oral BP for less than 4 years and have no clinical risk factors, no alteration or delay in the planned surgery is necessary.
    - For those patients who have taken an oral BP for less than 4 years and have taken corticosteroids or antiangiogenic medications concomitantly, or those patients who have taken an oral BP for longer than 4 years with or without any concomitant medical therapy, the prescribing provider should be contacted to consider discontinuation of the antiresorptive for at least 2 months before oral surgery, if systemic conditions permit. The antiresorptive should not be restarted until osseous healing has occurred. However, long-term prospective studies are still required to establish the efficacy of drug holidays in decreasing the risk of MRONJ for these patients.

There are further recommendations on staging and treatment but these are not relevant to the SDCEP guidance.

Geographical setting for guidance:	**Healthcare setting for guidance:** *users and patients*	**Is guidance currently used?**
US but likely to be used worldwide	Primary care dental practice	Yes

Basis for recommendations: *e.g. published evidence, expert opinion etc.*
If evidence based, review evidence in sections below

Based on a review of the evidence plus expert opinion.

<table>
<tr><td colspan="4">Description of evidence questions for recommendations (if applicable):</td></tr>
<tr><td>Patient/Problem: (target patients and actual participant characteristics)
Patients taking antiresorptive or antiangiogenic drugs for osteoporosis or cancer treatment</td><td>Intervention or risk factors:

Antiresorptive or antiangiogenic drugs</td><td>Comparison:

Patients not taking these drugs</td><td>Outcomes: note which are critical/important (from patient perspective) for the guidance recommendation*
Osteonecrosis of the jaw</td></tr>
<tr><td colspan="2">Details of evidence search: search strategy, study selection, study types</td><td colspan="2">Study limitations: risk of bias, limitations, inconsistency, imprecision, indirectness</td></tr>
<tr><td colspan="2">No details provided in the article.</td><td colspan="2">No details provided in the article, other than a description of study type and occasionally information on patient numbers etc.</td></tr>
<tr><td>Meta analysis:</td><td colspan="3">Evidence: for each outcome or recommendation as applicable</td></tr>
<tr><td>Not done</td><td colspan="3">1. Management/prevention strategies before initiation of antiresorptive or antiangiogenic medications: The implementation of dental screening and appropriate dental measures before initiating antiresorptive therapy lowered the risk of ONJ in several prospective studies when compared in a retrospective fashion to patients who did not undergo dental preventive measures. One study found a statistically significant, almost 3-fold, decrease in the incidence of osteonecrosis in patients when preventive measures were applied. Another did not report any new cases of ONJ in patients who received dental screening and necessary dental treatment before initiating IV BP treatment. A third study found the incidence rate of developing ONJ decreased by 50% in patients who were screened and received preventive dental care before initiating drug therapy.
2. Management/prevention strategies after initiation of antiresorptive or antiangiogenic medications:
Oncology patients: Although a small percentage of patients receiving antiresorptive medications develop ONJ spontaneously, most affected patients develop this complication after dentoalveolar surgery. Therefore, if systemic conditions permit, initiation of antiresorptive therapy should be delayed until dental health is optimized.
Osteoporosis patients: these patients are also at risk for developing MRONJ, but to a much lesser degree than those treated with IV antiresorptive therapy. The risk of developing MRONJ associated with oral BPs increases when duration of therapy exceeds 4 years. This time frame may be shortened in the presence of certain comorbidities, such as chronic corticosteroid or antiangiogenic use.
3. Drug holidays: there is currently no evidence that interrupting BP therapy alters the risk of ONJ in patients after tooth extraction. One paper proposes several alternatives to a drug holiday in BP-exposed patients who require invasive dental treatment based on bone physiology and pharmacokinetics of the antiresorptive medications and merit consideration (Level 5 evidence). They noted that because 50% of serum BP undergoes renal excretion, the major reservoir of BP is the osteoclast whose life span is 2 weeks.</td></tr>
</table>

	Thus, the majority of free BP within the serum would be extremely low 2 months after the last dose of an oral BP and a 2-month drug-free period should be adequate before an invasive dental procedure.
Benefit/harm/resource considerations?	**Values/preferences considerations?**
Not discussed	Not discussed

Overall quality of guidance (AGREE II) and explanation:	**Rating of recommendations:** *Should the recommendations made be considered for SDCEP guidance?*
AGREEII rating: 2/7 This article does not set out to be a guideline but does include recommendations for the management of patients at risk of MRONJ. There is no information about whether the literature search was systematic and no mention of inclusion or exclusion criteria. It is not clear whether there was a quality assessment of the included studies and whether this was used as a basis to exclude poor quality studies. The guideline recommendations are not clearly stated on their own but are buried within the main text. However, as with other guidelines published in clinical journals, this will in part be due to the requirements of the journal in which the article was published. The guideline was compiled by the AAOMS and there are several authors but it is unclear if it was subject to peer review outwith the group who prepared it, apart from the usual journal review process. The group does not appear to include any representatives from primary care dentistry and it is unclear whether patient views were sought as part of the development process.	The evidence which informs the recommendations in this publication was not appraised for quality using GRADE methods and the strength of the guideline recommendations is not stated. However, due to the paucity of evidence in this area, the recommendations made within this publication may be useful in informing recommendations in SDCEP guidance.

Reviewer's comments:

This article is not a systematic review but includes an overview of the literature, a definition of the disease, risk factors, and recommendations for prevention and treatment of the condition. The authors recommend that the term medication-related osteonecrosis of the jaw (MRONJ) be used to take into account the other anti-resorptive and anti-angiogenic drugs implicated in ONJ.
The article begins with an overview of the current literature with regards to the indicated medication and the pathophysiology of the disease. A review of the literature with regards to risk is then presented, which includes estimates of MRONJ risk for various patient groups based on data from published studies, with patients being treated for cancer found to be at higher risk than those being treated for osteoporosis. There is also a discussion of potential risk factors, such as length of drug treatment, dental extractions or concomitant corticosteroid therapy. The article then goes on to make recommendations for the management of patients taking antiresorptive or antiangiogenic drugs.
The authors recommend that prior to commencement of anti-resorptive or anti-angiogenic therapy for cancer treatment, patients should undergo a thorough dental exam, with drug treatment postponed, if possible, until the patient is dentally fit. Invasive treatment should be avoided once the patient has commenced anti-resorptive or anti-angiogenic treatment, where possible, with non-restorable teeth treated with removal of the crown and endodontic treatment of the remaining roots. Implant placement is not recommended for these patients. Patients about to start taking anti-resorptive drugs for osteoporosis do not require in-depth review of their oral

health but should be informed of potential risks of MRONJ and be encouraged to optimize their oral hygiene to prevent any dental conditions that may require invasive dental treatment in future. Elective dentoalveolar surgery is not contraindicated in these patients once treatment with anti-resorptive drugs has commenced but patients should be fully informed of the risk of MRONJ, which may be higher in those who have taken the medication for >4 years or who have other co-morbidities, such as chronic corticosteroid use. The authors suggest that drug holidays may be considered for this group of patients in consultation with the prescribing physician.
There are also recommendations on the staging system and treatment strategies for patients for MRONJ but these are not relevant to the scope of the SDCEP guidance so are not covered in depth in this overview. Recommendations for future research are also included.
This position paper is from a well respected source and is considered authoritative. However, there are several methodological issues with the article. There is no information on the literature search or inclusion and exclusion criteria, nor any assessment of study quality other than describing study types. The authors do comment on the lack of high quality studies to inform their recommendations and note that most are made based on expert opinion, especially those relevant to patients taking oral antiresorptive drugs.

The article provides information on risk of ONJ among patients taking antiresorptive or antiangiogenic drugs and risk factors; there are no recommendations associated with this data but it may be of use to the development of SDCEP guidance.

Risk of ONJ

In cancer patients in placebo groups: 0 to 0.019% (3 studies).
Cancer patients exposed to zoledronate: 0.7 to 6.7% (5 studies). When limited to the 4 studies with Level 1 evidence (SRs or RCTs) the risk is~ 1%.
Cancer patients exposed to denosumab: 0.7 to 1.9% (2 studies).
Cancer patients exposed to bevacizumab: 0.2% (1 study). The risk may be higher in patients exposed to bevacizumab and zoledronate (0.9%; 1 study)
The studies estimating MRONJ risk in patients with osteoporosis have the weakest levels of evidence of the various study groups (e.g. survey or retrospective cohorts)
In osteoporosis patients in placebo groups: 0 to 0.02% (2 studies)
In osteoporosis patients exposed to oral BPs: 0.004% - 0.1% (based on 2 studies; may increase the longer patients are exposed to oral BPs)
In osteoporosis patients exposed to iv BP or RANKL inhibitors: 0.017% (based on 1 study; may not increase the longer patients are exposed)
In osteoporosis patients exposed to denosumab: 0.04% (1 study).
In osteoporosis patients treated with yearly zoledronate : 0.017% (1 study; similar to placebo)

Risk Factors

Duration of treatment: in patients with cancer exposed to zoledronate or denosumab, the incidence of developing ONJ was increases as treatment time increases, with the risk for ONJ in denosumab-exposed patients plateauing between years 2 and 3. For patients receiving oral BP therapy to manage osteoporosis, the prevalence of ONJ increases over time, from nearly 0% at baseline to 0.21% after at least 4 years of BP exposure.
Dentoalveolar surgery: The best current estimate for the risk of ONJ in patients exposed to oral BPs after tooth extraction is 0.5%. Estimates for developing ONJ after tooth extraction in patients with cancer exposed to IV BPs ranges from 1.6 to 14.8%. There is no data for implant placement or endodontic/periodontal procedures.
Anatomic factors: Denture use has been associated with an increased risk for ONJ in patients with cancer exposed to zoledronate (OR = 4.9; 95% CI, 1.2-20.1). In another study patients with cancer treated with i.v. BPs showed a 2-fold increased risk for ONJ in denture wearers.
Concomitant oral disease: in patients with cancer and MRONJ, pre-existing inflammatory dental disease was a risk factor in 50% of cases.
Demographic, systemic and other medication factors: Age and gender are reported as risk factors, likely due a reflection of the underlying disease for which the agents are being prescribed (ie, osteoporosis, breast cancer). Corticosteroids and antiangiogenic agents given in addition to antiresorptive medications, are associated

with an increased risk of ONJ. Comorbid conditions in patients with cancer that are inconsistently reported to be associated with an increased risk for MRONJ include anaemia and diabetes. Cancer type also is variably reported as a risk factor. There is inconsistent evidence with regards to tobacco use as a risk factor for MRONJ.
Genetic factors: Some studies suggest that a germline sensitivity to BPs may exist.

Management/Prevention Strategies

Before initiation of antiresorptive or antiangiogenic medications

A multidisciplinary approach to the treatment of patients taking antiresorptive or antiangiogenic medications is recommended, with initiation of appropriate dental care where required.
Patients should be informed of the low risk associated with these drug therapies and the risk incurred by not undergoing recommended dental preventive measures before consenting to treatment.
Initiation of antresorptive or antiangiogenic treatment for cancer therapy should be delayed until dental health is optimised. Nonrestorable teeth and those with a poor prognosis should be extracted and other necessary elective dentoalveolar surgery also should be completed at this time, with antiresorptive or antiangiogenic therapy delayed, if systemic conditions permit, until the extraction site has mucosalized or until there is adequate osseous healing. Dental prophylaxis, caries control, and conservative restorative dentistry are critical to maintaining functionally sound teeth, with this level of care continued indefinitely. Patients with full or partial dentures should be examined for areas of mucosal trauma, especially along the lingual flange region. It is critical that patients be educated as to the importance of dental hygiene and regular dental evaluations and specifically instructed to report any pain, swelling, or exposed bone.
Patients about to initiate antresorptive treatment for osteoporosis should be educated as to the potential risks of MRONJ because the antiresorptive therapy is likely to exceed beyond 4 years. The importance of optimizing dental health throughout this treatment period and beyond should be stressed.

During treatment with antiresorptive or antiangiogenic medications

Patients receiving iv BP or antiangiogenic drugs for cancer should be educated about the importance of maintaining good oral hygiene and regular dental care to prevent dental disease that may require dentoalveolar surgery. Procedures that involve direct osseous injury should be avoided. Nonrestorable teeth may be treated by removal of the crown and endodontic treatment of the remaining roots. Placement of dental implants should be avoided in the oncologic patient receiving IV antiresorptive therapy or antiangiogenic medications. There are no data regarding the risk of ONJ associated with implant placement in patients receiving antiangiogenic medications.
For patients receiving antiresorptive therapy for osteoporosis who have taken an oral BP for less than 4 years and have no clinical risk factors, no alteration or delay in planned dental surgery is necessary. This includes any and all procedures common to oral and maxillofacial surgeons, periodontists, and other dental providers. It is suggested that if dental implants are placed, informed consent should be provided related to possible long-term implant failure and the low risk of developing ONJ if the patient continues to take an antiresorptive agent. Such patients should be placed on a regular recall schedule. In addition, it is advisable to contact the provider who originally prescribed the oral BP and suggest monitoring such patients and considering alternate dosing of the BP, drug holidays, or an alternative to the BP therapy.
For patients receiving antiresorptive therapy for osteoporosis who have taken an oral BP for less than 4 years but have taken corticosteroids or antiangiogenic medications concomitantly, the prescribing provider should be contacted to consider discontinuation of the oral BP (drug holiday) for at least 2 months before oral surgery, if systemic conditions permit. The antiresorptive should not be restarted until osseous healing has occurred.
For patients receiving antiresorptive therapy for osteoporosis who have taken an oral BP for longer than 4 years with or without any concomitant medical therapy, the prescribing provider should be contacted to consider discontinuation of the antiresorptive for 2 months before oral surgery, if systemic conditions permit. The BP should not be restarted until osseous healing has occurred.

Guideline G3: Hellstein et al., 2011[12]

Title: Managing the care of patients receiving antiresorptive therapy for prevention and treatment of osteoporosis.		
Authors/organisation: Hellstein et al. for the American Dental Association Council on Scientific Affairs Expert Panel on Antiresorptive Agents		
Date of publication/revision: 2011	Original version: 2008	Source: *J. American Dent. Assoc.* 2011; 142(11): 1243-1251 http://jada.ada.org/article/S0002-8177(14)62814-2/pdf Full version at: www.aae.org/uploadedfiles/publications_and_research/endodontics_colleagues_for_excellence_newsletter/bonj_ada_report.pdf
Aim(s) of guidance: The purpose of this report is to help dentists make treatment decisions based on the current best evidence when available, and on expert opinion when necessary, for patients being treated with antiresorptive agents.		
Key recommendations: *relevant to SDCEP guidance* • Routine dental treatment should not be modified solely because of the use of antiresorptive agents. • Patients for whom antiresorptive agents have been prescribed and who are not receiving regular dental care would benefit from a comprehensive oral examination before or early in their treatment. • A discussion of the risks and benefits of dental care with patients receiving antiresorptive therapy is appropriate. • Where dental treatment is required, the dental care provider should inform the patient of the dental treatment needed, alternative treatments, the way in which any treatment relates to the risk of ARONJ, other risks associated with various treatment options and the risk of forgoing dental treatment even temporarily. • Patients who receive treatment with antiresorptive agents should be instructed to contact their dentist if any problem develops in the oral cavity. • A patient with active dental or periodontal disease should be treated despite the risk of developing ARONJ, because the risks and consequences of no treatment likely outweigh the risks of developing ARONJ. A discussion of the risks, benefits and treatment options with the patient should take place and be documented. • Dental implants are not currently contraindicated in such patients • Use of CHX and antibiotics before and after surgical procedures may be appropriate • Prosthodontic appliances should be adjusted to avoid ulceration. • There is no evidence that drug holidays are of any benefit.		
Geographical setting for guidance:	**Healthcare setting for guidance:** *users and patients*	**Is guidance currently used?**
USA	Primary care dental practice	Yes

Basis for recommendations: *e.g. published evidence, expert opinion etc.*
If evidence based, review evidence in sections below

The authors performed a literature search of Medline and the Cochrane Central Register but note that because of a paucity of clinical data regarding the dental care of these patients, the recommendations are based primarily on expert opinion.
A narrative summary of the evidence found is provided in the full guideline but not in the JADA paper. The authors note that study limitations such as small sample size, retrospective design, inadequate study duration, and issues associated with voluntary reporting of cases have hindered accurate estimation of incidence and prevalence of ARONJ in the general population. They also note that some studies were performed before a consensus on the definition of ARONJ was reached, meaning that cases may have been misdiagnosed. They conclude that prospective, well-controlled studies are needed to better determine the true prevalence of ARONJ worldwide.

Description of evidence questions for recommendations (if applicable):

Patient/Problem: *(target patients and actual participant characteristics)*	Intervention or risk factors:	Comparison:	Outcomes: *note which are critical/important (from patient perspective) for the guidance recommendation**
Patients receiving antiresorptive therapy for prevention and treatment of osteoporosis	Antiresorptive therapy		Development of osteonecrosis of the jaw

Details of evidence search: *search strategy, study selection, study types*	**Study limitations:** *risk of bias, limitations, inconsistency, imprecision, indirectness*
The authors searched two databases, Medline and the Cochrane Central Register of Controlled Trials. There are no inclusion/exclusion criteria specified and they do not describe the results of the search (no. of publications retrieved etc.).	The authors do not report on any quality assessment of the relevant studies, however they do state that the studies focussing on ARONJ incidence and prevalence are limited by small sample size, retrospective design, inadequate study duration, and issues associated with voluntary reporting of cases. The only details of included studies (other than narratively within the main text) is a table summarising studies estimating ARONJ risk.
Meta analysis:	**Evidence:** *for each outcome or recommendation as applicable*
Not done	The authors note that because of a paucity of clinical data regarding the dental care of these patients, the recommendations are based primarily on expert opinion. There is a section which includes a review of the literature and some of the recommendations are accompanied by references to relevant studies but there is no specific summary of the evidence underpinning each recommendation.
Benefit/harm/resource considerations?	**Values/preferences considerations?**
The authors stress that the benefits of antiresorptive medication outweigh the risks	Not discussed

Overall quality of guidance (AGREE II) and explanation:	**Rating of recommendations:** *Should the recommendations made be considered for SDCEP guidance?*
AGREEII rating: 3/7 This article includes recommendations for the management of patients on anti-resorptive therapy for low bone mass. A search of two databases was performed however there is no mention of inclusion or exclusion criteria and it is not clear whether there was a quality assessment of the included studies and whether this was used as a basis to exclude poor quality studies. The guideline recommendations are not clearly stated on their own but are buried within the main text. The guideline was compiled by the ADA and there are several authors but it is unclear if it was subject to peer review outwith the group who prepared it. The group does not appear to include any representatives from primary care dentistry and it is unclear whether patient views were sought as part of the development process.	The evidence which informs the recommendations in this publication was not appraised for quality using GRADE methods and the strength of the guideline recommendations is not stated. However, due to the paucity of evidence in this area, the recommendations made within this publication may be useful in informing recommendations in SDCEP guidance.

Reviewer's comments:

This narrative review is based on an appraisal of the literature by an advisory committee of the American Dental Association Council on Scientific Affairs and updates the committee's 2008 advisory statement. MEDLINE and the Cochrane Central Register of Controlled Trials were searched from May 2008 to February 2011. There is no mention of grey/unpublished literature or any assessment of study quality. There is a brief overview of the literature, including incidence and risk factors. The highest reliable estimate of antiresorptive agent-induced osteonecrosis of the jaw (ARONJ) prevalence in patients receiving treatment for osteoporosis is approximately 0.10 percent. The authors state that due to a paucity of clinical data regarding the dental care of patients receiving antiresorptive therapy, their recommendations are based primarily on expert opinion. They recommend that routine dental treatment should not be modified but that patients should be informed of the risks of ONJ (~0.10%). They also recommend that an oral health program consisting of sound hygiene practices and regular dental care may be the optimal approach for lowering ARONJ risk. The authors conclude that the benefit provided by antiresorptive therapy outweighs the low risk of developing osteonecrosis of the jaw and that discontinuing bisphosphonate therapy may not lower the risk but may have a negative effect on low-bone-mass-treatment outcomes.

The recommendations in this guideline are based mainly on expert opinion due to a lack of good evidence to underpin the committee's advice.

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