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Interventions for preventing oral mucositis in patients with cancer receiving treatment: cytokines and growth factors (Protocol)

Riley P, Glenny AM, Worthington HV, Littlewood A, Clarkson JE, McCabe MG

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[Intervention Protocol]

Interventions for preventing oral mucositis in patients with cancer receiving treatment: cytokines and growth factors

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the effects of cytokines and growth factors for preventing oral mucositis in patients with cancer who are receiving treatment.

BACKGROUND

Description of the condition

Treating cancer with chemotherapy, radiotherapy of the head and neck, or targeted therapy can cause toxic oral side effects (Al-Dasooqi 2013; Scully 2006; Sonis 2004). Perhaps the most widely researched of these side effects is oral mucositis (Al-Dasooqi 2013), which affects at least 75% of high risk patients (those receiving head and neck radiotherapy or high-dose chemotherapy) (Scully 2006). Oral mucositis may be under-reported in lower risk groups for various reasons: their tendency to be outpatients with less observation; less reporting of moderate mucositis; or patients and clinicians wishing to avoid any disruption to optimal cancer treatment (Scully 2006).

Simply put, oral mucositis affects the oral mucosa (the mucous membrane of moist tissue lining the oral cavity) and can lead to the

development of lesions (ulcers). However, the process that leads to oral mucositis is complex and multifactorial, with Sonis' five phase model being the currently accepted explanation for the sequence of events underlying the condition (Sonis 2004; Sonis 2009).

1. Initiation: DNA damage caused by chemotherapy or radiotherapy results in the loss of ability to proliferate in the basal cells of the epithelium (the external layers of cells lining the oral mucosa). This produces reactive oxygen species (ROS).

2. Primary damage response: Radiotherapy, chemotherapy, ROS, and DNA strand breaks all contribute to the activation of transcription factors such as nuclear factor kappa beta (NF- κ B), and sphingomyelinases. All this leads to the upregulation of pro-inflammatory cytokines (e.g. tumour necrosis factor alpha - TNF- α), nitric oxide, ceramide, and matrix metalloproteinases, resulting in the thinning of the epithelium through tissue injury and cell death, culminating with the destruction of the oral mucosa.

3. Signal amplification: Some of the molecules in the previous phase can lead to the exacerbation and prolonging of tissue injury through positive or negative feedback (e.g. TNF- α can positively feedback on NF- κ B thus inducing more pro-inflammatory cytokine production).

4. Ulceration: Bacteria colonise ulcers and their cell wall products infiltrate the submucosa (the connective tissues beneath the oral mucosa), activating tissue macrophages (white blood cells that respond to infection or damaged/dead cells), which results in further production of pro-inflammatory cytokines, inflammation, and pain.

5. Healing: Signalling from the extracellular matrix of the submucosa results in epithelial proliferation and differentiation, and thus a thickening of the epithelium. The local oral flora are reinstated.

Understanding of the pathobiology leading to mucosal toxicity as a result of targeted therapies (e.g. mammalian target of rapamycin (mTOR) inhibitor-associated stomatitis - mIAS) is currently limited, but it is thought to differ from chemotherapy- and radiotherapy-induced mucositis, and the clinical presentation of the ulcers is more similar to aphthous stomatitis (Al-Dasooqi 2013; Boers-Doets 2013; Peterson 2015).

Chemotherapy-induced oral mucositis is regarded as an acute condition, with ulceration normally occurring one week after treatment, and resolving within three weeks of treatment (Sonis 2009). Radiotherapy-induced oral mucositis is chronic in nature, with ulceration normally occurring around two weeks into a seven-week treatment cycle, and resolving three to four weeks after treatment has ended (Sonis 2009).

Ulceration is the most significant phase as it leads to pain of varying severity, and difficulties with eating, swallowing, and talking (Scully 2006). This in turn leads to the consumption of pain relief medication, nutritional support (i.e. nasogastric or intravenous feeding), treatment of the oral mucositis, specialist oral hygiene care, increased medical appointments and use of staff and resources, and, in some instances, hospitalisation (Jensen 2014; Miller 2001; Trotti 2003). Thus the negative impact on the quality of life of cancer patients, when they are already suffering, is severe (Elting 2008; Epstein 1999). Further problems can occur in immunosuppressed patients if whole bacteria on the ulcer surface cross into the underlying submucosa, potentially leading to bacteraemia and sepsis, which require antibiotics and hospitalisation, and can cause death (Jensen 2014; Peterson 2015; Scully 2006). Therefore, oral mucositis can be a dose-limiting condition, disrupting a patient's optimal cancer treatment plan (Jensen 2014; Peterson 2015; Sonis 2004). The additional costs associated with oral mucositis are significant, with one study reporting a median incremental cost of USD 18,515 per patient (Nonzee 2008). These costs have been reported to be as much as USD 42,749 more per patient when ulcerative oral mucositis is present (Sonis 2001).

Description of the intervention

As described above, oral mucositis occurs partly as result of the loss of regenerative ability of the oral epithelial cells. Growth factors and anti-inflammatory cytokines are used to counteract the biological processes leading to this loss of proliferative ability. Growth factors and anti-inflammatory cytokines include (Raber-Durlacher 2013):

- keratinocyte growth factor;
- colony-stimulating factors;
- epidermal growth factor;
- transforming growth factor-beta;
- whey-derived growth factor;
- interleukin-11;
- ATL-104;
- trefoil factor.

How the intervention might work

The growth factors described here are proteins that bind to receptors of target cells and either increase the proliferation of the epithelial cells that form the mucous membrane lining of the oral cavity, or promote the recovery of the white blood cells that contribute to the maintenance of oral health following conventional or high dose chemotherapy (with or without radiotherapy) (Raber-Durlacher 2013). Anti-inflammatory cytokines are also proteins or glycoproteins that bind to receptors of target cells, and are thought to alter the complex balance of pro- and anti-inflammatory cytokines involved in the pathogenesis of oral mucositis (Raber-Durlacher 2013).

Currently, evidence-based guidelines recommend growth factors for the prevention of oral mucositis in patients with haematological cancers undergoing high-dose chemotherapy and total body irradiation prior to haematopoietic stem cell transplantation (Lalla 2008). It has been postulated that tumour cells may also have receptors accommodating cytokines and growth factors, thus encouraging the proliferation of cancer cells in solid tumours (Lalla 2008; von Bültzingslöwen 2006). A 2010 systematic review suggested that the risk of acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) is increased in people with various cancers receiving chemotherapy with granulocyte colony-stimulating factor (G-CSF) when compared to those receiving chemotherapy without G-CSF (Lyman 2010). The authors concluded that it was not clear whether the increased AML/MDS risk was due to G-CSF or due to the increased chemotherapy dose-intensity in those patients. However, the review also reported a reduction in overall mortality for those receiving G-CSF.

As there is currently no clear consensus on this issue, the use of cytokines and growth factors for the prevention of oral mucositis is not limited to haematological cancer patients in practice.

Why it is important to do this review

This review is part of a series that will replace the previously published Cochrane review covering all interventions for the prevention of oral mucositis in patients with cancer receiving treatment (Worthington 2011). The Mucositis Study Group (MSG) of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) is a group that was set up in 1998 for the purpose of producing international evidence-based clinical practice guidelines for managing mucositis (both oral and gastrointestinal), which they first published in 2004, with the latest update published in 2014 (Lalla 2014). In order to facilitate the future updating of Cochrane reviews on this topic, and also to make them more usable to clinicians, guideline developers, and consumers, we have decided to divide the original Cochrane review into the same intervention categories as those used by MASCC/ISOO, which are as follows:

- basic oral care/good clinical practice;
- growth factors and cytokines;
- anti-inflammatory agents;
- antimicrobials, mucosal coating agents, anaesthetics, and analgesics;
- laser and other light therapy;
- cryotherapy;
- natural and miscellaneous agents.

We believe that following the MASCC/ISOO structure will better enable the Cochrane reviews to feed into such guidelines. We can also be more thorough and rigorous in our assessment and summarising of the evidence in each of the categories, which was not feasible in a single Cochrane review approaching 150 included studies.

It is also important to do this review as it is consistently shown to be the most used review produced by the Cochrane Oral Health Group (in terms of full-text downloads). It was also ranked by an expert panel of oral medicine specialists as being the most important topic in the field of oral medicine in an international prioritisation exercise carried out by the Cochrane Oral Health Group in 2014 (Worthington 2015).

OBJECTIVES

To assess the effects of cytokines and growth factors for preventing oral mucositis in patients with cancer who are receiving treatment.

METHODS

Criteria for considering studies for this review

Types of studies

We will include all randomised controlled trials (RCTs) of parallel design. It is possible to conduct cross-over studies in this area as patients may receive several treatment sessions/cycles, with any mucositis completely healing in the periods between the sessions. However, we will not include cross-over data as we cannot discount any period effects, with mucositis risk increasing as patients receive further cycles of treatment (Scully 2006; Sonis 2009). Instead, we will use the first-period data only and treat such studies as parallel studies.

Types of participants

We will include all patients with cancer who are receiving treatment.

Types of interventions

We will include studies comparing growth factors and cytokines for the prevention of oral mucositis (we will also include targeted therapy-induced stomatitis) against usual care, no treatment, or any other treatment to prevent oral mucositis. We will also include studies comparing different growth factors and cytokines or different regimens of growth factors and cytokines against each other (head-to-head studies).

We will exclude studies with 'complex' interventions for the prevention of mucositis, such as lasers plus growth factors and cytokines versus lasers. We will exclude studies assessing different cancer treatments where the primary outcome is survival/cure, with mucositis as a toxicity.

Types of outcome measures

We are in agreement with Williamson 2012 that, if clinical trials and systematic reviews are to be utilised, the outcomes assessed should be those considered important to patients, healthcare professionals, and other key stakeholders. If outcomes and outcome measures are inconsistent across studies, it will not be possible to compare and summarise research, and there is potential for outcome reporting bias, with the selective reporting of results based on statistical significance and favourability (Clarke 2007; Dwan 2008; Williamson 2005). This can lead to exaggerated estimates of effect in systematic reviews of interventions, leading to an incorrect belief that an intervention is more beneficial than it truly is (Clarke 2007). It is thought that the way to address this problem is to develop disease- or condition-specific core outcome sets to be used as a minimum when conducting and reporting clinical trials (Clarke 2007; Williamson 2012).

Therefore we will use the core outcome set produced by Bellm 2002, which is registered on the COMET (Core Outcome Measures in Effectiveness Trials) Initiative's website (www.comet-initiative.org), and is the only core outcome set for oral mucositis known to us.

Primary outcomes

Mucositis (at all levels of severity) using an appropriate, objective scale. We will use mucositis measured on a 0 to 4 point scale (none to severe) and dichotomise it as any mucositis (0 versus 1+), moderate to severe mucositis (0 to 1 versus 2+), and severe mucositis (0 to 2 versus 3+).

Some studies measure mucositis using a composite scale. If it is possible to extract the 'mucositis only' data from the total score, we will include the data in the analyses. If it is not possible, we will record the composite data in an additional table.

Secondary outcomes

- Interruptions to cancer treatment.
- Oral pain.
- Quality of life.
- Normalcy of diet (including use of percutaneous endoscopic gastrostomy (PEG) feeding tubes or total parenteral nutrition (TPN)).
- Adverse events.
- Number of days in hospital.
- Number of days of treatment with opioid analgesics.
- Number of days unable to take medicine orally.

Search methods for identification of studies

For the identification of studies included or considered for this review, we will develop detailed search strategies. These will be based on the search strategy for MEDLINE (Ovid) ([Appendix 1](#)), which will be revised appropriately for each database. The MEDLINE search strategy has a combination of controlled vocabulary and free text terms and will be linked with the Cochrane Highly Sensitive Search Strategy (CHSSS) for identifying randomised trials (RCTs) in MEDLINE: sensitivity maximising version (2008 revision) as referenced in Chapter 6.4.11.1 and detailed in box 6.4.c of the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011) ([Higgins 2011](#)).

Due to the Cochrane Embase Project to identify all clinical trials on the database and add them to CENTRAL, only the last six months of the Embase database will be searched. Please *see* the [searching page on the Cochrane OHG website](#) for more information. No other restrictions will be placed on the language or date of publication when searching the electronic databases.

Electronic searches

We will search the following electronic databases:

- the Cochrane Oral Health Group Trials Register (to date);
- the Cochrane Central Register of Controlled Trials (CENTRAL; current issue);
- MEDLINE via Ovid (1946 to date) ([Appendix 1](#));
- Embase via Ovid (six months previous to date);

- CANCERLIT via PubMed (1950 to date);
- CINAHL via EBSCO (1937 to date).

Searching other resources

We will search the following databases for ongoing trials:

- US National Institutes of Health Trials Registry (clinicaltrials.gov) (to date);
- World Health Organization (WHO) International Clinical Trials Registry Platform (apps.who.int/trialsearch/default.aspx) (to date).

We will only include handsearching done as part of the Cochrane Worldwide Handsearching Programme and uploaded to CENTRAL.

Data collection and analysis

Selection of studies

Two review authors will independently screen the titles and abstracts retrieved from the electronic searches. We will obtain full text copies of all studies that appear to meet the inclusion criteria of the review, or where there is insufficient information in the title or abstract to make a clear judgement. Two review authors will independently assess the full text copies for eligibility and attempt to resolve any disagreements through discussion. We will consult a third review author if we are unable to resolve disagreements.

On assessing the full text article, we will discard any studies that clearly do not meet the inclusion criteria. We will record all other studies that do not meet the inclusion criteria, along with reasons for exclusion, in the 'Characteristics of excluded studies' table.

Data extraction and management

Two review authors will independently extract the data from each included study using a specially designed data extraction form, which will first be piloted on a small sample of studies. We will contact study authors for clarification or missing data where necessary and feasible. We will resolve any disagreements through discussion, consulting a third review author to achieve consensus when necessary.

We will record the following data for each included study in the 'Characteristics of included studies' table.

- Trial design, location, number of centres, recruitment period.
- Inclusion/exclusion criteria, age and gender of participants, number randomised/analysed, any other potentially important prognostic factors (e.g. cancer type, cancer treatment, etc.).
- Detailed description of the intervention and comparator, including timing and duration. Information on compliance with the intervention.

- Details of the outcomes reported, including method of assessment and time(s) assessed.
- Details of sample size calculations, adverse effects, funding sources, declarations/conflicts of interest.

Assessment of risk of bias in included studies

Two review authors will independently assess the risk of bias of each included study using the Cochrane domain-based, two-part tool as described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will contact study authors for clarification or missing information where necessary and feasible. We will resolve any disagreements through discussion, consulting a third review author to achieve consensus when necessary.

We will complete a 'Risk of bias' table for each included study. For each domain of risk of bias, we will first describe what was reported to have happened in the study. This will provide the rationale for our judgement of whether that domain is at low, high, or unclear risk of bias.

We will assess the following domains:

1. sequence generation (selection bias);
2. allocation concealment (selection bias);
3. blinding of participants and personnel (performance bias);
4. blinding of outcome assessment (detection bias);
5. incomplete outcome data (attrition bias);
6. selective outcome reporting (reporting bias);
7. other bias.

We will categorise the overall risk of bias of individual studies. Studies will be categorised as being at low, high, or unclear risk of bias according to the following criteria:

- low risk of bias (plausible bias unlikely to seriously alter the results) if all domains are at low risk of bias;
- high risk of bias (plausible bias that seriously weakens confidence in the results) if one or more domains are at high risk of bias; or
- unclear risk of bias (plausible bias that raises some doubt about the results) if one or more domains are at unclear risk of bias.

We will also present the 'Risk of bias' summary graphically.

Measures of treatment effect

For continuous outcomes (e.g. oral pain on a visual analogue scale) where studies use the same scale, we will use the mean values and standard deviations (SDs) reported in the studies in order to express the estimate of effect as mean difference (MD) with 95% confidence interval (CI). Where different scales are used, we will consider expressing the treatment effect as standardised mean difference (SMD) with 95% CI.

For dichotomous outcomes (e.g. mucositis of any severity/no mucositis), we will express the estimate of effect as a risk ratio (RR) with 95% CI.

Unit of analysis issues

The participant will be the unit of analysis.

Dealing with missing data

We will attempt to contact the author(s) of all included studies, where feasible, for clarification, missing data, and details of any other outcomes that may have been measured but not reported. We will use the methods described in Section 7.7.3 of the *Cochrane Handbook for Systematic Reviews of Interventions* to estimate missing SDs (Higgins 2011). We will not use any other statistical methods or perform any further imputation to account for missing data.

Assessment of heterogeneity

If a sufficient number of studies are included in any meta-analyses, we will assess clinical heterogeneity by examining the characteristics of the studies, the similarity between the types of participants, the interventions, and the outcomes. We will also assess heterogeneity statistically using a Chi² test, where a P value < 0.1 indicates statistically significant heterogeneity. We will quantify heterogeneity using the I² statistic. A guide to interpretation of the I² statistic given in Section 9.5.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* is as follows (Higgins 2011):

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

Assessment of reporting biases

If at least 10 studies are included in a meta-analysis, we will assess publication bias according to the recommendations on testing for funnel plot asymmetry (Egger 1997), as described in Section 10.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). If asymmetry is identified, we will examine possible causes.

Data synthesis

We will only carry out meta-analyses where there are studies of similar comparisons reporting the same outcomes. We will combine MDs for continuous data, and RRs for dichotomous data. Our general approach will be to use a random-effects model. With this approach, the CIs for the average intervention effect will be wider than those that would be obtained using a fixed-effect approach, leading to a more conservative interpretation.

We will use an additional table to report the results from studies not suitable for inclusion in a meta-analysis.

Subgroup analysis and investigation of heterogeneity

We will carry out subgroup analyses according to type of cancer treatment and age group (children versus adults).

Sensitivity analysis

We will test the robustness of our results by performing sensitivity analyses based on excluding the studies at unclear or high risk of bias from the analyses.

If any meta-analyses include several small studies and a single very large study, we will undertake a sensitivity analysis comparing the effect estimates from both random-effects and fixed-effect models. If these are different we will report on both analyses as part of the results section, and we will consider possible interpretation.

Presentation of main results

We will produce a 'Summary of findings' table for each comparison that includes more than one study, and for the main outcomes (listed below). We will use GRADE methods (GRADE 2004), and the GRADEpro online tool for developing 'Summary of findings'

tables (www.guidelinedevelopment.org). We will assess the quality of the body of evidence for each comparison and outcome by considering the overall risk of bias of the included studies, the directness of the evidence, the inconsistency of the results, the precision of the estimates, and the risk of publication bias. We will categorise the quality of each body of evidence as high, moderate, low, or very low.

Main outcomes:

- mucositis incidence;
- interruptions to cancer treatment;
- oral pain;
- quality of life;
- normalcy of diet;
- adverse events;
- number of days in hospital.

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* Indicates the major publication for the study

APPENDICES

Appendix I. MEDLINE (Ovid) search strategy

1. exp NEOPLASMS/
2. exp RADIOTHERAPY/
3. exp Antineoplastic agents/
4. Anti-neoplastic combined chemotherapy protocols/
5. Bone Marrow Transplantation/
6. Hematopoietic Stem Cell Transplantation/
7. (neoplasm\$ or cancer\$ or leukaemi\$ or leukemi\$ or tumour\$ or tumor\$ or malignan\$ or neutropeni\$ or carcino\$ or adenocarcinoma\$ or lymphoma\$).ti,ab.
8. (radioth\$ or radiat\$ or irradiat\$).ti,ab.
9. ((bone adj marrow adj5 transplant\$) or "hematopoietic stem cell transplant\$" or "haematopoietic stem cell transplant\$" or HSCT).ti,ab.
10. chemo\$.ti,ab.
11. or/1-10
12. exp STOMATITIS/
13. Candidiasis, Oral/
14. stomatitis.ti,ab.
15. mucositis.ti,ab.
16. (oral adj6 mucos\$).ti,ab.
17. (mycosis or mycotic).ti,ab.
18. mIAS.ti,ab.
19. or/12-18
20. ((growth adj factor\$) or (growth adj substance\$) or (immunologic adj factor\$)).ti,ab.
21. Fibroblast growth factor 7/
22. "fibroblast growth factor".ti,ab.
23. (keratinocyte\$ or cytokine\$).ti,ab.
24. (palifermin\$ or KGF or FGF).ti,ab.
25. (kepivance or velafermin or repifermin).ti,ab.
26. glycoprotein\$.ti,ab.
27. exp Colony-stimulating factors/
28. ("colony-stimulat\$" or "macrophage-granulocyte inducer\$" or "myeloid cell-growth inducer\$" or "protein inducer MGI").ti,ab.
29. (GM-CSF or G-CSF).ti,ab.
30. (molgramostim or Growgen-GM or Leucomax or Molcass or Gramostim or Leucocitim or Mielogen or Meustim or Bagomol or Gramal).ti,ab.
31. Epidermal growth factor/
32. (rhEGF or "recombinant epithelial growth factor\$" or "epidermal growth factor\$" or EGF).ti,ab.
33. Platelet-derived growth factor/
34. ("platelet-derived growth factor\$" or PDGF or "platelet lysate").ti,ab.
35. Transforming Growth Factor beta/
36. ("transforming growth factor\$" or "bone-derived transforming growth factor\$" or "milk growth factor\$" or "platelet transforming growth factor" or TGF-beta or TGFbeta).ti,ab.
37. Hepatocyte growth factor/
38. ("hepatocyte growth factor\$" or hepatopietin or "scatter factor").ti,ab.
39. exp Somatomedin/
40. (somatomedin\$ or "insulin-like growth factor\$" or "sulfation factor" or Mecasermin or Increlex or Iplex or IGF-1 or IGF1).ti,ab.
41. erythropoietin\$.ti,ab.
42. Thrombopoietin/

43. (thrombopoietin\$ or “mpl Ligand” or “megakaryocyte colony stimulating factor\$” or “megakaryocyte growth and development factor\$” or “MGDF factor” or “myeloproliferative leukemia virus oncogene ligand” or “thrombocytopoiesis-stimulating factor” or thrombocytopoietin\$).ti,ab.
44. Ghrelin/
45. Interleukin 11/
46. (“interleukin 11” or “Adipogenesis Inhibitory Factor\$” or IL-11 or IL11).ti,ab.
47. (ghrelin\$ or “GHRL protein” or obestatin).ti,ab.
48. (ATL-104 or ATLL104).ti,ab.
49. (whey or (“milk derived” adj (protein or growth factor))).ti,ab.
50. Glucagon-Like Peptide 2/
51. (“glucagon-like peptide 2” or (amino adj acid\$) or proglucagon or GLP-2 or teduglutide or Gattex or Revestive).ti,ab.
52. Glutathione/
53. (“trefoil factor” or “carcinoembryonic antigen cell adhesion molecule 1” or glutathione or isethion).ti,ab.
54. Vascular endothelial growth factors/
55. (“vascular endothelial growth factor\$” or VEGF\$).ti,ab.
56. Molecular targeted therapy/
57. (targeted adj3 (therap\$ or agent\$)).ti,ab.
58. (biologic\$ adj therap\$).ti,ab.
59. or/20-58
60. 11 and 19 and 59

The above subject search will be linked to the Cochrane Highly Sensitive Search Strategy (CHSSS) for identifying randomised trials in MEDLINE: sensitivity maximising version (2008 revision) as referenced in Chapter 6.4.11.1 and detailed in box 6.4.c of the *Cochrane Handbook for Systematic Reviews of Interventions*, Version 5.1.0 [updated March 2011] ([Higgins 2011](#)).

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. drug therapy.fs.
6. randomly.ab.
7. trial.ab.
8. groups.ab.
9. or/1-8
10. exp animals/ not humans.sh.
11. 9 not 10

WHAT'S NEW

Date	Event	Description
26 January 2016	Amended	Minor edit (hyperlink)

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Philip Riley: writing the Background and Methods sections.

Anne-Marie Glenny: writing the Methods section.

Helen V Worthington: writing the Methods section.

Anne Littlewood: writing the Methods section.

Jan E Clarkson: providing a clinical perspective.

Martin G McCabe: providing a clinical perspective.

DECLARATIONS OF INTEREST

Philip Riley: I am a salaried member of the Cochrane Oral Health Group editorial team.

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- Cochrane Oral Health Group Global Alliance, Other.

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