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[Intervention Protocol]

Topical and oral steroids for otitis media with effusion (OME) in children

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To assess the effects (benefits and harms) of topical and oral steroids for otitis media with effusion (OME) in children.

BACKGROUND

Description of the condition

Otitis media with effusion (OME) is a common condition in early childhood. The condition, also known as 'glue ear' or serous otitis media, is defined as "the presence of fluid in the middle ear without signs or symptoms of acute infection" (Rosenfeld 2016).

A key clinical feature of OME is hearing loss, due to decreased mobility of the tympanic membrane and consequent loss of sound conduction (Rosenfeld 2016). Other symptoms that may be attributable to OME include balance (vestibular) problems and ear discomfort (Rosenfeld 2016). When symptoms persist, they may lead to poor school performance and affect a child's daily activities, social interactions and emotions, possibly leading to a poorer quality of life for the child (Rosenfeld 2000).

It is thought that up to 80% of children have had OME by the age of four years, but a decline in its prevalence is observed for children beyond six years of age (Williamson 2011). Most episodes of OME in children resolve spontaneously within three months, however approximately 35% of children will have more than one episode of OME and, furthermore, 5% to 10% of episodes will last for more than a year (Rosenfeld 2016). Children with OME following an episode of untreated acute otitis media (AOM) have a 59% rate of resolution by one month rising to 74% by three months, while children with newly diagnosed OME of unknown duration demonstrate a resolution rate of 28% by three months and up to 42% by six months (Rosenfeld 2003). The condition is more prevalent in children with Down syndrome or cleft palate (Flynn 2009; Maris 2014). Atopy has been considered a potential risk factor for OME in children (Kreiner-Møller 2012; Marseglia 2008; Zernotti 2017).

Diagnosis of OME is typically by clinical examination including (pneumatic) otoscopy and/or tympanometry in primary care. Following diagnosis, there will often be a period of active observation for at least three months. During the observation period the care provider may offer a non-surgical intervention such as hearing aids or autoinflation. The National Institute for Health and Care Excellence (NICE) and the American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS) do not currently recommend the use of antibiotics, antihistamines, decongestants or corticosteroids for OME as there is insufficient evidence to suggest they are effective treatments (NICE 2008; Rosenfeld 2016). If OME has not resolved within the three-month observation period, the child may be referred for further management/active intervention. This may include hearing aid provision or review by an ENT surgeon for consideration for myringotomy, ventilation tubes insertion and/or adenoidectomy. The choice of active intervention varies considerably. Earlier active intervention may be considered for children at increased risk of developmental difficulties (see Rosenfeld 2016 for a list of 'at-risk' factors).

This Cochrane Review focusses on topical and oral steroids as treatment for OME in children. This review forms part of a suite of five reviews of OME treatment, which will address those interventions identified in a prioritisation exercise as being most important and in need of up-to-date Cochrane Reviews, namely ventilation tubes, adenoidectomy with or without ventilation tubes, autoinflation, antibiotics, and topical and oral steroids (Cochrane ENT 2020).

Description of the intervention

Steroids have been used with the intention of reducing the inflammatory cascade that causes Eustachian tube dysfunction and middle ear effusion (Vanneste 2019). They have been administered systemically as an oral preparation and topically as a nasal spray.

How the intervention might work

Chronic infection in the middle ear creates an inflammatory response and the production of inflammatory mediators, including arachidonic acid metabolites. Steroids may exert a beneficial effect on middle ear effusion by stabilising membrane phospholipid breakdown, thus preventing the formation of arachidonic acid and, in turn, inflammatory mediators (Rosenfeld 1991). In addition, steroids may have an effect on OME by shrinking peritubal lymphoid tissue, promoting secretion of Eustachian tube surfactant, and reducing the viscosity of middle ear fluid (Rosenfeld 1991). Topical intranasal steroids may be safer than systemic steroids as the active preparation is quickly degraded in the nasal mucosa. In contrast, systemic steroids are more likely to reach the middle ear than topical intranasal steroids.

Why it is important to do this review

A Cochrane Review assessing topical and oral steroids for hearing loss associated with OME was published in 2011 (Simpson 2011). This review included 12 studies (nine for oral steroids and three for topical intranasal steroids), none of which documented hearing loss associated with OME prior to randomisation. The authors concluded that "while oral steroids, especially when used in combination with an oral antibiotic, lead to a quicker resolution of OME in the short term, there is no evidence of a longer-term benefit and no evidence that they relieve symptoms of hearing loss". The authors also found no evidence of short- or long-term benefit from the use of topical intranasal steroids either alone or in combination with an antibiotic.

Since the Cochrane Review was published (Simpson 2011), the findings from a number of randomised controlled trials (RCTs) have been published including those from the OSTRICH study (Francis 2018), a RCT of the effects of a short course of oral steroids for hearing loss in 389 children with persistent OME, and from a second RCT that evaluated the effects of oral and intranasal steroids in 290 children with OME (Hussein 2017).

A prioritisation exercise undertaken in 2020 identified a review of topical and oral steroids as a top priority (Cochrane ENT 2020). It is therefore timely to update the evidence.

OBJECTIVES

To assess the effects (benefits and harms) of topical and oral steroids for otitis media with effusion (OME) in children.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs) and quasi-randomised trials (where trials were designed as RCTs, but the sequence generation for allocation of treatment used methods such as alternative allocation, birth dates and alphabetical order). We will include studies that randomised by participant or by cluster. Due to the self-limiting nature of the condition, studies that use a cross-over design are unlikely to be appropriate. However, if we do identify any such studies, we will use data from the first phase only.

Types of participants

Children aged 6 months to 12 years with unilateral or bilateral OME. If a study includes children aged younger than 6 months and older than 12 years, we will include the study if the majority of children fit our inclusion criteria or only if the trialists present outcome data by age group. We will include all children regardless of any comorbidity such as Down syndrome or cleft palate.

Clinical diagnosis of OME will be confirmed by oto(micro)scopy or tympanometry or both.

Types of interventions

Intervention

Topical (intranasal) and oral steroids.

Comparator

The comparators are placebo or no treatment.

We are interested in the following comparisons:

- topical (intranasal) steroids versus placebo;
- topical (intranasal) steroids versus no topical treatment;
- oral steroids versus placebo;
- oral steroids versus no oral treatment.

If study participants have received other treatments, for example antibiotics, mucolytics or decongestants, we will include these studies if both arms received identical treatments.

Types of outcome measures

We will analyse the following outcomes in the review, but we will not use them as a basis for including or excluding studies. We will assess all outcomes at very short term (< 6 weeks), short term (≤ 3 months), medium term (> 3 months to ≤ 1 year) and long term (> 1 year).

Primary outcomes

- Hearing, measured as:
  - Proportion of children whose hearing has returned to normal, with normal hearing defined as 20 dB HL or less (assessed using age-appropriate tests).
  - Hearing threshold.

It is anticipated that study data for these outcomes may be derived from a variety of assessment methods. To avoid loss of important evidence, we will extract all such data for analysis. However, we will give consideration to the appropriateness of pooling different types of data in meta-analysis. Our selection of primary outcomes is based principally upon clinical importance, but also permits applicability across a variety of age-appropriate assessment methods, and considers the types of outcome data that are most likely to be available. Accordingly, we regard the proportion of participants whose hearing has returned to normal as the most important measure of hearing impact. We consider medium- and long-term outcome data as the most clinically important.

- Disease-specific quality of life measured using a validated instrument, for example:
  - OM8-30 (Haggard 2003);
  - Otitis Media-6 (Rosenfeld 1997).
- Adverse events - systemic corticosteroid side effects.

Secondary outcomes

- Presence/persistence of OME.
- Adverse events - local nasal side effects.
- Receptive language skills, measured using a validated scale, for example:
  - Peabody Picture Vocabulary Test - Revised (Dunn 2007);
  - relevant domains of the Reynell Developmental Language Scales (Reynell 1985);
  - relevant domains of the Preschool Language Scale (PLS) (Zimmerman 1992);
  - relevant domains of the Sequenced Inventory of Communication (SCID) (Hedrick 1984).
- Speech development, or expressive language skills, measured using a validated scale, for example:
  - Schlichting test (Schlichting 2010);
  - Lexi list (Schlichting 2007);
  - relevant domains of the Reynell Developmental Language Scales (Reynell 1985);
  - relevant domains of the PLS (Zimmerman 1992);
  - relevant domains of the SCID (Hedrick 1984).
- Cognitive development, measured using a validated scale, for example:
  - Griffiths Mental Development Scales (Griffiths 1996);
  - McCarthy General Cognitive Index (McCarthy 1972);
  - Bayley Scales of Infant and Toddler Development (Bayley 2006).
- Psychosocial outcomes, measured using a validated scale, for example:
  - the Social Skills Scale of the Social Skills Rating System (Gresham 1990);
  - Child Behaviour Checklist (Achenbach 2011);
  - Strengths and Difficulties Questionnaire (Goodman 1997);
  - Pediatric Symptom Checklist (Jellinek 1988).
- Listening skills, for example listening to stories and instructions effectively. Given that there are few validated scales to assess listening skills in children with OME, we will include any methods used by trialists.

- Generic health-related quality of life assessed using a validated instrument, for example:
  - EQ-5D (Rabin 2001);
  - TNO AZL Children's QoL (TACQOL) (Verrips 1998);
  - TNO AZL Pre-school children QoL (TAPQOL) (Fekkes 2000);
  - TNO AZL Infant Quality of Life (TAIQOL) (TNO 1997);
  - Infant Toddler Quality of Life Questionnaire (ITQOL) (Landgraf 1994);
  - Child Heath Questionnaire (CHQ) (Landgraf 1996).
- Parental stress, measured using a validated scale, for example:
  - Parenting Stress Index (Abidin 1995).
- Vestibular function:
  - balance;
  - co-ordination.
- Number of doctor-diagnosed acute otitis media episodes within a specified time frame.

These outcomes were identified as the most important in two studies that aimed to develop a core outcome set for children with OME (Bruce 2015; Liu 2019). As this review forms part of a suite of reviews of interventions for OME, not all outcomes will be relevant for all reviews.

Search methods for identification of studies

The Cochrane ENT Information Specialist will conduct systematic searches for randomised controlled trials and controlled clinical trials. There will be no language, publication year or publication status restrictions. We may contact original authors for clarification and further data if trial reports are unclear and we will arrange translations of papers where necessary.

Electronic searches

The Cochrane ENT Information Specialist will search the following databases from their inception to identify published, unpublished and ongoing RCTs:

- the Cochrane ENT Register (search via the Cochrane Register of Studies to date);
- the Cochrane Central Register of Controlled Trials (CENTRAL) (search via the Cochrane Register of Studies to date);
- Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) (1946 to date);
- Ovid EMBASE (1974 to date);
- Web of Science, Web of Science (1945 to date);
- ClinicalTrials.gov, www.clinicaltrials.gov:
  - search via the Cochrane Register of Studies to date;
  - search via www.clinicaltrials.gov to date;
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP), https://trialsearch.who.int;
  - search via the Cochrane Register of Studies to date;
  - search via https://apps.who.int/trialsearch/ to date.

The subject strategies for databases will be modelled on the search strategy designed for CENTRAL, Ovid MEDLINE and Ovid Embase (Appendix 1). The search strategies were designed to identify all relevant studies for a suite of reviews on various interventions for otitis media with effusion. Where appropriate, these will be combined with subject strategy adaptations of the highly sensitive search strategy designed by Cochrane for identifying randomised controlled trials and controlled clinical trials (as described in the Technical Supplement to Chapter 4 of the *Cochrane Handbook for Systematic Reviews of Interventions* version 6.1; Lefebvre 2020).

Searching other resources

We will scan the reference lists of identified publications for additional trials and contact trial authors if necessary. In addition, the Information Specialist will search Ovid MEDLINE to retrieve existing systematic reviews relevant to this systematic review, so that we can scan their reference lists for additional trials. The Information Specialist will also run non-systematic searches of Google Scholar to retrieve grey literature and other sources of potential trials.

We will not perform a separate search for adverse effects. We will consider adverse effects described in included studies only.

We will contact original authors for clarification and further data if trial reports are unclear and we will arrange translations of papers where necessary.

Data collection and analysis

Selection of studies

We will consider using Cochrane's Screen4Me workflow to help assess the search results, depending on the number of results retrieved from the database searches. Screen4Me comprises three components:

1. Known assessments – a service that matches records in the search results to records that have already been screened in Cochrane Crowd and been labelled as 'a RCT' or as 'not a RCT'.
2. The machine learning classifier (RCT model) (Wallace 2017), available in the Cochrane Register of Studies (CRS-Web), which assigns a probability of being a true RCT (from 0 to 100) to each citation. For citations that are assigned a probability score below the cut-point at a recall of 99% we will assume these to be non-RCTs. For those that score on or above the cut-point we will either manually dual screen these results or send them to Cochrane Crowd for screening.
3. Cochrane Crowd is Cochrane's citizen science platform where the Crowd help to identify and describe health evidence. For more information about Screen4Me and the evaluations that have been done, please go to the Screen4Me website on the Cochrane Information Specialist's portal and see Marshall 2018, McDonald 2017, Noel-Storr 2018 and Thomas 2017.

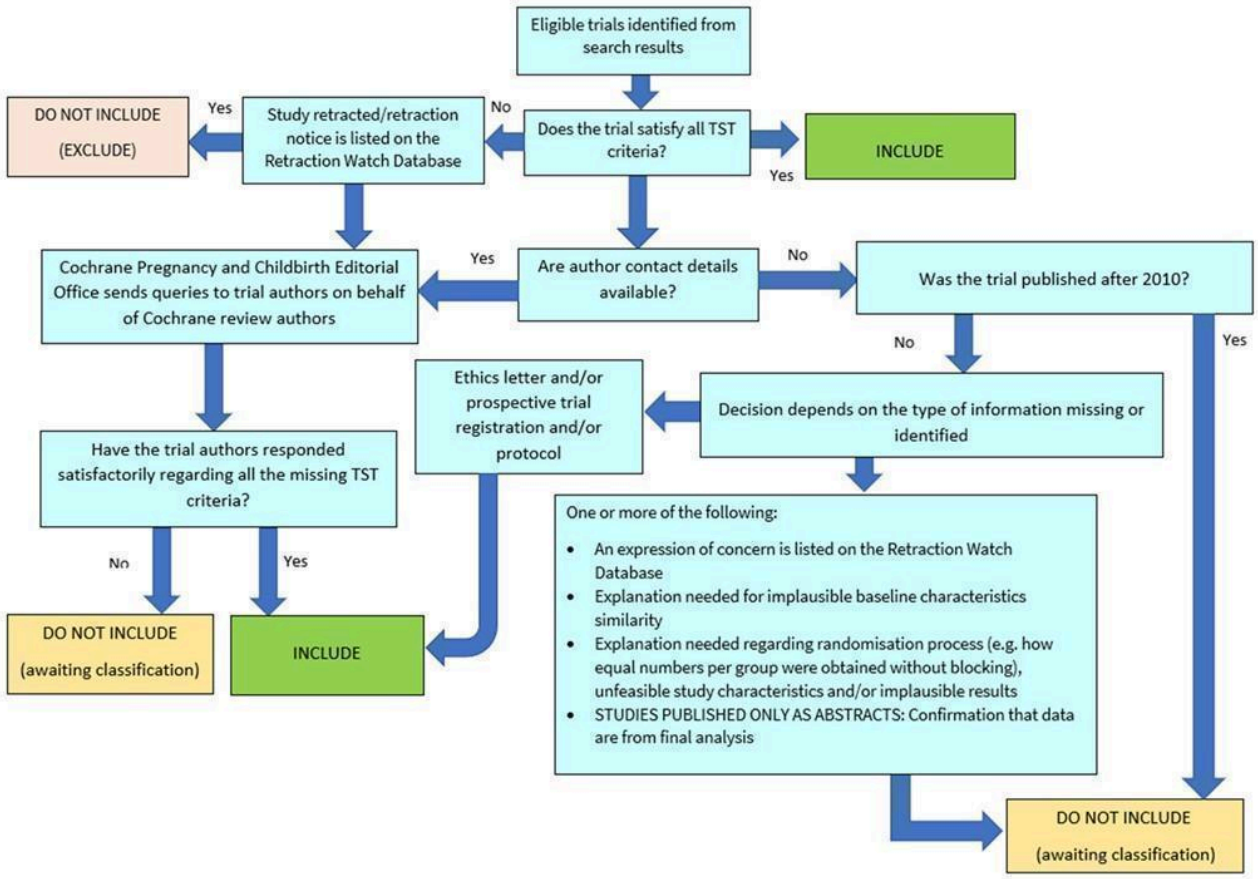
At least two review authors will independently screen titles and abstracts retrieved by the search to identify potentially relevant studies. At least two review authors will independently evaluate the full text of each potentially relevant study to determine whether it meets the inclusion/exclusion criteria for this review. Any differences will be resolved by discussion and consensus, with the involvement of a third author where necessary.

Screening eligible studies for trustworthiness

Two review authors will appraise all studies meeting our inclusion criteria for trustworthiness using a screening tool developed by Cochrane Pregnancy and Childbirth. This tool includes specified criteria to identify studies that are considered sufficiently

trustworthy to be included in the review (see Appendix 2). If any studies are assessed as being potentially 'high risk', we will attempt to contact the study authors to obtain further information or address any concerns. If we are unable to contact the authors, or there is persisting uncertainty about the study then it will not be included in the review. The study will remain in 'awaiting classification' and the reasons for concern and communication with the authors will be described in full. The process is outlined in Figure 1. We will perform a sensitivity analysis to assess the effect on our findings of including/excluding studies considered at high risk of lack of trustworthiness.

Figure 1. The Cochrane Pregnancy and Childbirth Trustworthiness Screening Tool



Data extraction and management

Two review authors will independently extract outcome data from each study using a standardised data collection form. Where a study has more than one publication, we will retrieve all publications to ensure complete extraction of data. Any discrepancies in the data extracted by the two authors will be checked against the original reports, and differences will be resolved through discussion and consensus, with recourse to a third author where necessary. If required, we will contact the study authors for clarification. We will include key characteristics of the studies, such as the study design, setting, sample size, population and the methods for defining or collecting outcome data in the studies.

We will extract data on study findings according to treatment assignment, irrespective of whether study participants complied with treatment or received the treatment to which they were randomised.

In addition to extracting pre-specified information about study characteristics and aspects of methodology relevant to risk of bias, we will extract the following summary statistics for each trial and outcome:

- For continuous data: the mean values, standard deviation and number of patients for each treatment group at the different time points for outcome measurement. Where endpoint data are not available, we will extract the values for change-from-baseline data instead. If values for the individual treatment groups are not reported, where possible we will extract summary statistics (e.g. mean difference) from the studies.
- For binary data: we will extract information on the number of participants experiencing an event, and the number of participants assessed at that time point. If values for the individual treatment groups are not reported, where possible we will extract summary statistics (e.g. risk ratio) from the studies.
- For ordinal scale data: we do not anticipate identifying ordinal data which is of relevance for our outcomes. However, if this is identified and if the data appear to be normally distributed, or if the analysis performed by the investigators indicates that parametric tests are appropriate, then we will treat the outcome

measure as continuous data. Alternatively, if data are available, we will convert these to binary data for analysis.

We have pre-specified time points of interest for the outcomes in this review. Where studies report data at multiple time points, we will take the longest available follow-up point within each of the specific time frames. For example, if a study reports an outcome at 4 months, 8 months and 12 months of follow-up then the 12-month data will be included for the time point > 3 months to ≤ 1 year. For adverse events, some studies may report frequency data for events and it may not be possible to determine whether these events occurred in one patient on one occasion or more than one occasion. In such circumstances we will report the data narratively.

Assessment of risk of bias in included studies

Two authors will undertake assessment of the risk of bias of the included studies independently, with the following taken into consideration, as guided by the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011):

- sequence generation;
- allocation concealment;
- blinding;
- incomplete outcome data;
- selective outcome reporting; and
- other sources of bias.

We will use the Cochrane risk of bias tool in RevMan 5.3 (RevMan 2014), which involves describing each of these domains as reported in the study and then assigning a judgement about the adequacy of each entry: 'low', 'high' or 'unclear' risk of bias.

Measures of treatment effect

We will summarise dichotomous data, such as presence of OME, as risk ratios (RR) and 95% confidence intervals (CI) and we will summarise continuous data as a mean difference (MD) and 95% CI. For the outcomes to be presented in the summary of findings tables, we will provide both the relative and absolute measures of effect. Where the same outcome has been assessed using different scales we will present continuous data as a standardised mean difference (SMD). If individual patient data (IPD) are available we will use these in our analyses.

Unit of analysis issues

For this review the unit of analysis will be the child. If we identify cluster-randomised trials, we will assume that the data from participants is no longer independent and adjust our analyses accordingly using the design effect.

Dealing with missing data

We will attempt to contact study authors by email where data on an outcome of interest to the review are not reported but the methods described in the paper suggest that the outcome was assessed. We will do the same if not all data required for meta-analysis have been reported. If standard deviation data are not available, we will approximate these using the standard estimation methods from P values, standard errors or 95% CIs if these are reported, as detailed in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021).

Assessment of heterogeneity

We will assess clinical heterogeneity by examining the included studies for potential differences between them in the types of participants recruited, interventions or controls used, and the outcomes measured. We will assess statistical heterogeneity by considering both the I^2 statistic, which calculates the percentage of variability that is due to heterogeneity rather than chance, with values over 50% suggesting substantial heterogeneity, and the P value from the Chi^2 test (Higgins 2021).

Assessment of reporting biases

We will assess reporting bias as within-study outcome reporting bias and between-study publication bias.

Outcome reporting bias (within-study reporting bias)

We will assess within-study reporting bias by comparing the outcomes reported in the published report against the study protocol or trial registry, when this can be obtained. If the protocol or trial registry entry is not available, we will compare the outcomes reported to those listed in the methods section of the published report. If results are mentioned but not reported in a way that allows analysis (e.g. the report only mentions whether the results were statistically significant or not), we will seek further information from the study authors. If no further information can be found, we will note this as being a 'high' risk of bias. If there is insufficient information to judge the risk of bias we will note this as an 'unclear' risk of bias (Handbook 2011).

Publication bias (between-study reporting bias)

If we are able to pool 10 or more studies in a single analysis, we will produce a funnel plot to explore possible publication biases. We will test for asymmetry using Egger's test (Egger 1997).

Data synthesis

Where two or more studies report the same outcome we will perform a meta-analysis using Review Manager 5 (RevMan 2014). We will report pooled effect measures for dichotomous outcomes as a risk ratio (RR) using the Mantel-Haenszel methods. For continuous outcomes measured using the same scales we will report a mean difference (MD) and if studies have assessed the same outcomes using different scales we will report the standardised mean difference (SMD). We will use a random-effects model.

Where it is not possible to pool the findings from studies in a meta-analysis, we will present the results of each study and provide a narrative synthesis of findings. We will use the SWiM guidelines to guide us through this process (Campbell 2020). We will group the studies according to what seem to be appropriate groupings once we have identified included studies that do not provide data suitable for meta-analysis. We will then identify the standardised metric for each outcome and calculate an intervention effect using the appropriate transformation.

Subgroup analysis and investigation of heterogeneity

We propose the following subgroup analyses if sufficient data are available in trial reports:

- children with mild hearing loss versus moderate or worse;

- children with allergy versus those without (using the trialists own definition);
- children aged up to four years versus children aged four years and over;
- children with previous ventilation tubes versus those without ventilation tubes;
- children with cleft palate versus children without;
- children with Down syndrome versus children without.

Unless studies report these subgroups, it will be necessary to carry out the subgroup analysis at the study level, i.e. group the studies according to the characteristics of the majority of their participants.

Sensitivity analysis

We will carry out sensitivity analyses to assess whether our findings are robust to decisions made regarding the analyses and inclusion of studies. We will perform sensitivity analyses to assess the following:

- impact of model chosen: we will compare the results using a random-effects versus a fixed-effect model;
- inclusion of studies at high risk of bias: we will compare the results including all studies versus excluding studies at overall high risk of bias, that is four or more of the seven domains of bias are rated as high risk (see Assessment of risk of bias in included studies).
- inclusion of studies considered at high risk of trustworthiness, as assessed by the Trustworthiness Screening Tool (Figure 1).

Summary of findings and assessment of the certainty of the evidence

Two independent authors will use the GRADE approach to rate the overall certainty of evidence using GRADEpro GDT (https://gradepro.org/). The certainty of evidence reflects the extent to which we are confident that an estimate of effect is correct and we will apply this in the interpretation of results. There are four possible ratings: high, moderate, low and very low. A rating of high certainty of evidence implies that we are confident in our estimate of effect and that further research is very unlikely to change our confidence in the estimate of effect. A rating of very low certainty implies that any estimate of effect obtained is very uncertain.

The GRADE approach rates evidence from RCTs that do not have serious limitations as high certainty. However, several factors can lead to the downgrading of the evidence to moderate, low or very low. The degree of downgrading is determined by the seriousness of these factors:

- study limitations (risk of bias);
- inconsistency;
- indirectness of evidence;
- imprecision; and
- publication bias.

We will include a summary of findings table, constructed according to the recommendations described in Chapter 14 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021), for the following comparisons:

- topical (intranasal) steroids versus placebo;
- topical (intranasal) steroids versus no topical treatment;
- oral steroids versus placebo;
- oral steroids versus no oral treatment.

We will include the following four outcomes in the summary of findings tables:

- hearing;
- disease-specific quality of life;
- presence/persistence of OME;
- adverse events - systemic corticosteroid side effects.

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APPENDICES

Appendix 1. Draft search strategies

The search strategies were designed to identify all relevant studies for a suite of reviews on various interventions for Otitis Media with Effusion.

CENTRAL (CRS)	MEDLINE (Ovid)	Embase (Ovid)
1 MESH DESCRIPTOR Otitis Media with Effusion EXPLODE ALL AND CENTRAL:TARGET 39 2 ("otitis media" adj6 effusion):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 730 3 (OME):TI,TO AND CENTRAL:TARGET 0 4 (Secretory otitis media):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 264 5 (Serous otitis media):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 49 6 (Middle-ear effusion):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 238 7 (glue ear):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 62	MEDLINE (Ovid MEDLINE® Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE®) 1946 to present 1 exp Otitis Media with Effusion/ 5807 2 ("otitis media" adj6 effusion).ab,ti. 3451 3 OME.ti. 469 4 Secretory otitis media.ab,ti. 953 5 Serous otitis media.ab,ti. 567 6 Middle-ear effusion.ab,ti. 1444 7 Glue ear.ab,ti. 303 8 middle-ear perfusion.ab,ti. 3 9 Otitis Media/ 17663 10 "otitis media".ti. 11554 11 9 or 10 21726 12 ((effusion or Recurrent or persistent or serous or secretory or perfusion) adj3 otitis).ab,ti. 6178 13 11 and 12 4299	Embase 1974 to present 1 exp secretory otitis media/ 5885 2 ("otitis media" adj6 effusion).ab,ti. 3999 3 OME.ti. 540 4 Secretory otitis media.ab,ti. 1051 5 Serous otitis media.ab,ti. 615 6 Middle-ear effusion.ab,ti. 1627 7 glue ear.ab,ti. 351 8 middle-ear perfusion.ab,ti. 3 9 otitis media/ 21684 10 otitis media.ti. 12337 11 9 or 10 27117 12 ((effusion or Recurrent or persistent or serous or secretory or perfusion) adj3 otitis).ab,ti. 7383 13 11 and 12 5219 14 1 or 2 or 4 or 5 or 6 or 7 or 8 or 13 9824 15 (random* or factorial* or placebo* or assign* or allocat* or crossover*).tw. 2194998 16 (control* adj group*).tw. 724788 17 (trial* and (control* or comparative)).tw. 701811

(Continued)

8 (middle-ear perfusion):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 1
9 MESH DESCRIPTOR Otitis Media AND CENTRAL:TARGET 784
10 (otitis media):TI,TO AND CENTRAL:TARGET 1653
11 #9 OR #10 AND CENTRAL:TARGET 1911
12 (((effusion or Recurrent or persistent or serous or secretory or perfusion) adj3 otitis)):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 1010
13 #11 AND #12 AND CENTRAL:TARGET 766
14 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #13 AND CENTRAL:TARGET 1066

14 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 13 8976
15 randomized controlled trial.pt. 542809
16 controlled clinical trial.pt. 94373
17 randomized.ab. 533045
18 placebo.ab. 221237
19 drug therapy.fs. 2370147
20 randomly.ab. 365421
21 trial.ab. 567106
22 groups.ab. 2243598
23 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 5110951
24 exp animals/ not humans.sh. 4882975
25 23 not 24 4445451
26 14 and 25 2367

18 ((blind* or mask*) and (single or double or triple or treble)).tw. 288542
19 (treatment adj arm*).tw. 22835
20 (control* adj group*).tw. 724788
21 (phase adj (III or three)).tw. 67227
22 (versus or vs).tw. 2371156
23 rct.tw. 43341
24 crossover procedure/ 68008
25 double blind procedure/ 187232
26 single blind procedure/ 43636
27 randomization/ 91740
28 placebo/ 370427
29 exp clinical trial/ 1625769
30 parallel design/ 14463
31 Latin square design/ 394
32 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 5531900
33 exp ANIMAL/ or exp NONHUMAN/ or exp ANIMAL EXPERIMENT/ or exp ANIMAL MODEL/ 29428557
34 exp human/ 22679343
35 33 not 34 6749214
36 32 not 35 4834087
37 14 and 36 1820

Appendix 2. Tool for screening eligible studies for scientific integrity/trustworthiness

This screening tool has been developed by Cochrane Pregnancy and Childbirth. It includes a set of predefined criteria to select studies that, based on available information, are deemed to be sufficiently trustworthy to be included in the analysis.

Criteria questions	Assessment		Comments and concerns
	High risk	Low risk	
Research governance			
Are there any retraction notices or expressions of concern listed on the Retraction Watch Database relating to this study?	Yes	No	
Was the study prospectively registered (for those studies published after 2010) If not, was there a plausible reason?	No	Yes	
When requested, did the trial authors provide/share the protocol and/or ethics approval letter?	No	Yes	
Did the trial authors engage in communication with the Cochrane Review authors within the agreed timelines?	No	Yes	
Did the trial authors provide IPD data upon request? If not, was there a plausible reason?	No	Yes	
Baseline characteristics			
Is the study free from characteristics of the study participants that appear too similar?	No	Yes	

(Continued)

(e.g. distribution of the mean (SD) excessively narrow or excessively wide, as noted by Carlisle 2017)		
Feasibility		
Is the study free from characteristics that could be implausible? (e.g. large numbers of women with a rare condition (such as severe cholestasis in pregnancy) recruited within 12 months)	No	Yes
In cases with (close to) zero losses to follow-up, is there a plausible explanation?	No	Yes
Results		
Is the study free from results that could be implausible? (e.g. massive risk reduction for main outcomes with small sample size)?	No	Yes
Do the numbers randomised to each group suggest that adequate randomisation methods were used (e.g. is the study free from issues such as unexpectedly even numbers of women 'randomised' including a mismatch between the numbers and the methods, if the authors say 'no blocking was used' but still end up with equal numbers, or if the authors say they used 'blocks of 4' but the final numbers differ by 6)?	No	Yes
For abstracts only:		
Have the study authors confirmed in writing that the data to be included in the review have come from the final analysis and will not change?	No	Yes

CONTRIBUTIONS OF AUTHORS

Caroline A Mulvaney: drafted the protocol. She will screen search results and select relevant studies, extract data, carry out statistical analyses, draft the review and edit the review.

Kevin Galbraith: drafted the protocol. He will screen search results and select relevant studies, extract data, carry out statistical analyses, draft the review and edit the review.

Samuel MacKeith: drafted the protocol. He will screen search results and select relevant studies, extract data, carry out statistical analyses, draft the review and edit the review.

Tal Marom: reviewed the protocol. He will review the findings of the analyses.

Mat Daniel: reviewed the protocol. He will review the findings of the analyses.

Roderick P Venekamp: co-wrote and edited the protocol. He will interpret the results, and co-write and edit the review.

Anne GM Schilder: co-wrote and edited the protocol. She will interpret results, and co-write and edit the review.

DECLARATIONS OF INTEREST

Caroline A Mulvaney: none known.

Kevin Galbraith: none known.

Samuel MacKeith: treats patients with OME in his NHS and private practice and is Assistant Co-ordinating Editor of Cochrane ENT but has not been involved in the editorial process for this protocol.

Tal Marom: none known.

Mat Daniel: has a financial interest in Aventamed, a company that produces a ventilation tube insertion device.

Roderick P Venekamp: is an Editor for Cochrane Acute Respiratory Infections and Cochrane ENT, but had no role in the editorial process for this protocol.

Anne GM Schilder: Professor Anne Schilder was joint Co-ordinating Editor of Cochrane ENT until April 2020, but had no role in the editorial process for this review. Her evidENT team at the UCL Ear Institute is supported by the National Institute of Health Research (NIHR) University College London Hospitals (UCLH) Biomedical Research Centre (BRC), with research projects being supported by the NIHR, Wellcome Trust, RNiD, ENT UK and industry. She is the National Specialty Lead for the NIHR Clinical Research Network ENT and Surgical Specialty Lead for ENT for the Royal College of Surgeons of England's Clinical Research Initiative. In her role as director of the NIHR UCLH BRC Deafness and Hearing Problems Theme, she advises CRO, biotech and pharma companies in the hearing field on clinical trial design and delivery.

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