

## Systemic corticosteroids for acute otitis media in children

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## Systemic corticosteroids for acute otitis media in children (Protocol)

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[Intervention Protocol]

# Systemic corticosteroids for acute otitis media in children

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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 corticosteroids, with and without antibiotics, for AOM in children.

## BACKGROUND

### Description of the condition

Acute otitis media (AOM) is a common complication of an acute respiratory infection (ARI); it mostly affects children aged six to 12 months (Lieberthal 2013; SACHCN 2014).

A 2015 update of a clinical practice guideline on the diagnosis and management of AOM states that “Clinicians should diagnose AOM in children who present with moderate-to-severe bulging of the tympanic membrane or new onset of otorrhoea not due to acute otitis externa; and may diagnose AOM in children who present with mild bulging of the tympanic membrane and recent (< 48 hours) onset of ear pain (holding, tugging, rubbing of the ear in a nonverbal child) or intense erythema of the tympanic membrane” (Pichichero 2015). The 2014 New South Wales

Health (Australia) clinical practice guideline defines AOM as an “acute onset of middle ear inflammation characterised by 1) distinct otalgia (ear pain) that interferes with normal activity or sleep; 2) bulging tympanic membrane and erythema; and 3) possible perforation and otorrhoea (ear discharge)” (NSW Health 2014). In young children aged from six months to three years the overall incidence of AOM as a complication of ARIs (mostly caused by rhinovirus and adenovirus) was shown to be 37% in a prospective, longitudinal cohort study (Chonmaitree 2008). Fifty per cent of acute symptoms (pain and systemic symptoms) resolve within 24 hours and 80% within 72 hours. Children aged up to two years often experience more severe and protracted illness (Chonmaitree 2008). Studies from Europe and the US have reported that 62% of children aged up to 12 months, and 83% of children aged between one and three years, experience at least one episode of AOM. Among these children, between 10% and 30% experience

recurrent AOM, and 2% to 25% experience persistent middle ear effusion for three months, many requiring ventilation tube (grommet) insertion (Gribben 2012; Kitamura 2015).

The prevalences of AOM are slightly varied across Asian countries. In Korea, a 1991 national survey reported a point prevalence of 0.08% for AOM in children aged up to 15 years (Lee 2012); in Malaysia, 9% of children aged from three months to 12 years experienced AOM over the previous three years (Tikaram 2012). A 2005 study in Taiwan found that 13.2% of children aged up to seven years had experienced AOM (Ting 2012). In East Jakarta, Indonesia, the point prevalence of AOM in children aged from two to five years was 5.4% (Umar 2013).

As the risk of AOM increases in the indigenous population, a cluster survey in Indigenous versus non-Indigenous children in Australia found that severe otitis media was more prevalent in Indigenous children (7.9%) compared to non-Indigenous children (1.7%) (Gunasekera 2007).

Pain is one of the most common and distressing symptoms of AOM. Many clinical practice guidelines have recommended analgesic (e.g. paracetamol, ibuprofen) as an initial treatment option for pain management in AOM (Lieberthal 2013; NSW Health 2014; SACHCN 2014). A study on the use of ibuprofen versus acetaminophen and placebo for the symptoms of AOM in children showed no significant differences between treatment groups in the improvement of tympanic membrane inflammation, rectal temperature, appetite, sleep and playing activity 48 hours after treatment (Bertin 1996). However, there was a modest benefit of ibuprofen over placebo in reducing pain. There was no significant difference between acetaminophen and placebo. Topical analgesics have limited evidence of efficacy in reducing ear pain (Foxlee 2011).

Antibiotics are also commonly prescribed in the treatment for AOM. Antibiotics have a modest effect in reducing pain at two to three days, with a number needed to treat to benefit (NNTB) of 20 children (Venekamp 2015). Despite using antibiotics, 11% to 19% of children with AOM experience persistent symptoms for more than six days (Lieberthal 2013). Ear effusions may persist in 30% to 60% of children for up to one month, and in 15% to 25% of children for up to three months (Chonmaitree 2003). Almost one-third of these children do not have bacterial growth from their MEE. One-third of affected children experience recurrence within a month (Chonmaitree 2003). Nevertheless, the clinical practice guideline of the American Academy of Pediatrics strongly recommends antibiotics for children aged six months and older with bilateral or unilateral AOM and severe signs or symptoms. Antibiotics are also recommended for children younger than two years with bilateral AOM without severe signs or symptoms (Lieberthal 2013).

An alternative strategy for the management of AOM in children is close observation through follow-up, based on joint decision-making with the parent or caregiver. However, close observation requires accessible follow-up and continuity of care (Lieberthal

2013; Pichichero 2015). Observation alone may not be suitable for high-risk or vulnerable populations such as Indigenous children in remote settings or those with complications such as cleft palate, Down syndrome or immunodeficiency syndromes (Morris 2009; NSW Health 2014).

Other treatments, such as decongestants or antihistamines, are not recommended for children due to the risk of adverse events and the lack of benefit. There is limited evidence on the use of decongestant/antihistamine combinations for AOM in children: a Cochrane review found a small statistical benefit from the combination medication, but the clinical significance was minimal and the contributing studies may have been biased (Coleman 2008). However, the 2015 Japanese clinical practice guideline on the diagnosis and management of AOM in children recommended use of complementary nasal treatment for children with AOM associated with nasal disease (Kitamura 2015). A study on the use of intranasal steroid spray (triamcinolone acetonide) for otitis media with effusion and negative middle ear pressure showed there was no statistically significant difference in the normalization of the tympanometric findings between intranasal steroid group and placebo in six weeks (Gluth 2011). A Cochrane review on the use of topical intranasal steroids for otitis media effusion in children also found no evidence of benefit in terms of symptoms (including ear symptoms that are crucial in the management of AOM) either at short- or longer-term follow-up (Simpson 2011).

## Description of the intervention

Corticosteroids are natural steroid hormones produced by the adrenal cortex, which can be synthetically manufactured. They have an important anti-inflammatory role (Gupta 2008), and they have been used for a wide range of both acute and chronic inflammatory illnesses in adults and children (Coutinho 2011).

There are concerns about the possible risks associated with corticosteroid use, such as increased appetite, weight gain, fluid retention, gastritis, headache, mood swings, increased blood glucose and Addisonian crisis from abrupt stopping of the corticosteroid, all of which can occur with protracted use. However, in general, short-term use (one week or less) does not cause these harms or require dose-tapering (Deshmukh 2007). A randomised controlled trial (RCT) of corticosteroids for AOM found no correlation between the emergence of viral infection and corticosteroid use (Chonmaitree 2003). A Cochrane review on the use of systematic corticosteroids for acute sinusitis found no serious side effects (Venekamp 2014).

## How the intervention might work

Persistent middle ear effusion (MEE) after resolution of AOM is a concern. MEE has been found in 60% to 70% of children two weeks after successful antibiotic treatment of AOM. Presentation

decreases to 10% to 25% at three months, but in 5% to 10% of cases MEE is present one year later (Lee 2012; Lieberthal 2013; Lighthall 2015; Mahadevan 2012; Rosenfeld 2001). One cause of MEE is dysfunction of the Eustachian tube due to the inflammation process. The Eustachian tube has an important role in maintaining ventilation and protecting the middle ear cavity, and in the drainage of middle ear fluid (Coticchia 2013). MEE is also caused by dysfunction of the epithelial sodium channel (ENaC) in controlling the periciliary fluid that is essential for maintaining a fluid-free middle ear cavity. An in vitro study showed that interleukin-1 $\beta$  (IL-1 $\beta$ ), an important inflammatory cytokine mostly found in the MEE, inhibits fluid absorption by suppressing ENaC in various epithelia including airway epithelial cells (Choi 2006; Choi 2007).

Despite the benefits of using antibiotics for some ear infections, they have several consequences due to bacterial death and the release of inflammatory bacterial products. This may induce and prolong inflammation in the middle ear and lead to otitis media with effusion (OME) and further episodes of AOM (Principi 2013). This suggests that the inflammatory mechanism may be involved in the basic pathogenesis of AOM. This mechanism is induced by both cellular and chemical mediators in the middle ear. These mediators (i.e. cytokines, chemokines, mast cells, prostaglandins, leukotrienes) contribute by altering vascular permeability, increasing mucous glycoprotein secretion and stimulating the chemotaxis process, epithelial secretion activity and other mediators (Juhn 2008).

Based on this pathogenesis, an intervention that suppresses the inflammatory process could have an important role in the resolution of AOM, including inhibition of the interleukin-1 (IL-1) and tumour necrosis factor-alpha (TNF- $\alpha$ ) early-response cytokines that are commonly found in children. Corticosteroids play an important role in inhibiting the inflammation process through genomic and non-genomic mechanisms, including inhibition of mediators that are involved in middle ear inflammatory processes (Juhn 2008). An animal study showed that AOM inflammatory disease generally peaks between three and five days and resolves by 10 to 14 days (MacArthur 2006). However, a randomised controlled trial (RCT) has shown no significant clinical benefits of the use of corticosteroids for AOM (Chonmaitree 2003). A temporary improvement in tympanometry in patients who received corticosteroids suggested the possibility that discontinuation after a five-day course of corticosteroid induced a rebound effect due to ongoing middle ear inflammation, which indicated the need for a longer duration of treatment (Chonmaitree 2003).

Corticosteroids have been found to be effective in some ARIs, for example when combined with antibiotics for patients with sore throat (Hayward 2012). A recent study has shown that the use of oral corticosteroids as an additional treatment to antibiotics for AOM with discharge through tympanostomy tubes shortened the duration of otorrhoea (McCormick 2003). However, a few small trials on the use of corticosteroids as an additional treatment

to antibiotics for AOM in children have reported varied results (Wang 2007).

As a monotherapy, oral corticosteroids are not effective for adults with clinically diagnosed acute sinusitis (Venekamp 2014). Nevertheless, when combined with antibiotics, oral corticosteroids may have a modest beneficial effect (Venekamp 2014). An RCT also reported no significant difference between oral prednisolone as a standalone therapy and placebo in hospitalised patients with acute viral mild-to-moderate wheezing (Panickar 2009). However, as close observation (without antibiotic administration) is a treatment option for AOM, there is a risk of persistent and recurrent AOM in some cases, and there is involvement of an inflammatory mechanism in the middle ear, it is worthwhile identifying the effects of corticosteroids as a monotherapy for AOM in children.

### Why it is important to do this review

The therapeutic options for the management of AOM in children are currently unsatisfactory. An effective treatment modality is needed and systemic corticosteroids may fill that role, either as a monotherapy or in addition to antibiotics. A recent literature review concluded that there was insufficient evidence to recommend corticosteroids for AOM (Principi 2013). However, potentially relevant studies were not included in that review and therefore there is need for a further systematic assessment (McCormick 2003; Ruohola 1999; Wang 2007). An up to date Cochrane review is warranted to assess the effects of corticosteroids, as another treatment option, for the treatment of AOM in children.

## OBJECTIVES

To assess the effects of corticosteroids, with and without antibiotics, for AOM in children.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

We will include randomised controlled trials (RCTs).

#### Types of participants

We will include children aged up to 15 years with AOM. AOM often correlates with immaturity of the immune system, therefore we will set the age limit at 15 years because maturation of the B-

cells involved in the immune system commences at that point and beyond (McKenna 2001).

AOM is defined as “the rapid onset of ear pain accompanied with bulging and/or hyperaemic tympanic membrane and the presentation of middle ear effusion” (Lieberthal 2013; Pichichero 2015). We will include both unilateral and bilateral AOM. Participants will be included irrespective of the setting from which they were recruited.

We will exclude children with contraindications to corticosteroid therapy (e.g. immunodeficient or immunocompromised, or both), children with anatomic or physiological disorders of the ear or nasopharynx and those with chronic MEE. We will also exclude children with ventilation tubes because this procedure is principally used for non-acute (chronic) otitis media with effusion.

### Types of interventions

We will include studies that compare any type of systemic corticosteroids (e.g. oral, parenteral) with placebo, either without antibiotics (i.e. corticosteroid versus placebo) or with antibiotics (i.e. antibiotics plus corticosteroid versus antibiotics plus placebo).

We will exclude studies using any type of topical corticosteroids (e.g. intranasal).

For symptomatic treatment, patients may have received acetaminophen as an antipyretic and analgesic treatment (Bertin 1996).

### Types of outcome measures

#### Primary outcomes

1. Proportion of children with pain at various time points (24 hours; two to three days; and four to seven days - time points taken from Venekamp 2015).

2. Reduction of overall or specific symptoms (e.g. ear discomfort, hearing loss, irritability, sleep disturbance, diminished appetite). Reduction of overall or specific symptoms may be measured using visual analogue scales or validated symptom scales specific to otitis media such as the Acute Otitis Media Severity of Symptoms Scale (AOM-SOS), Otitis Media Outcome-22 questionnaire (OMO-22), Otitis Media-6 quality of life survey (OM-6), or others (Timmerman 2007).

3. Reduction in overall or specific symptom duration.

4. Adverse effects.

#### Secondary outcomes

1. Changes in tympanometry measurements at various time points as an objective assessment of the resolution of AOM (e.g. middle ear pressure, tympanogram curve types).

2. Tympanic membrane perforation.

3. Contralateral otitis (in children with unilateral infection).

4. AOM recurrence, which is defined as the occurrence of AOM episodes within one month after completion of antibiotic therapy (Pichichero 2000).

5. Serious complications related to AOM such as mastoiditis and meningitis.

### Search methods for identification of studies

#### Electronic searches

We will search the following databases from inception to the present:

1. Cochrane Central Register of Controlled Trials (CENTRAL);
2. MEDLINE (Ovid);
3. Embase (Elsevier);
4. CINAHL (EBSCO);
5. Web of Science (Thomson Reuters); and
6. LILACS (BIREME).

We will combine the search terms set out in Appendix 1 with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity and precision-maximising version (2008 revision) (Lefebvre 2011). We will assess whether we need to apply a filter for retrieving studies in children (Boluyt 2008). This will depend on the number of search results retrieved. We will not impose language or publication restrictions.

#### Searching other resources

We will also conduct a search of ClinicalTrials.gov ([www.ClinicalTrials.gov](http://www.ClinicalTrials.gov)) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (<http://apps.who.int/trialsearch/>). We will check the reference lists of all primary studies and review articles for additional references. We will contact experts in the field to identify additional unpublished materials.

### Data collection and analysis

#### Selection of studies

Three review authors (RR, YP, EDS) will independently screen the titles and abstracts of all potential studies identified as a result of the searches. We will retrieve full-text study reports of potentially relevant studies. Three review authors (RR, YP, EDS) will independently screen the retrieved reports to identify studies for inclusion and they will record the reasons for exclusion of ineligible studies. We will resolve disagreements through discussion or, if required, consult with a third review author (EMB or CDM). We

will identify and exclude duplicates and collate multiple reports of the same study so that each study rather than each report is assessed in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram (Moher 2010).

### Data extraction and management

We will use a data collection form, which has been piloted on at least one study in the review, to collate study characteristics and outcome data. Three review authors (RR, YP, EDS) will independently extract study characteristics from included studies. We will extract the following study characteristics:

1. methods: study design, total duration of study, details of any 'run-in' period, number of study centres and location, study setting, withdrawals and date of study;
2. participants: number, mean age, age range, gender, severity of condition, diagnostic criteria, inclusion criteria and exclusion criteria;
3. interventions: intervention, comparison, concomitant medications and excluded medications;
4. outcomes: primary and secondary outcomes specified and collected, and time points reported; and
5. notes: funding for trial and notable conflicts of interest of trial authors.

Three review authors (RR, YP, EDS) will independently extract outcome data from the included studies. We will note in the 'Characteristics of included studies' table if outcome data were not reported in a usable way. We will resolve disagreements by consensus. A review author (RR) will input data into the Review Manager software (RevMan 2014). We will double-check that data are entered correctly by comparing the data presented in the systematic review with the study reports. Two review authors (YP, EDS) will spot-check study characteristics for accuracy against the trial report.

### Assessment of risk of bias in included studies

Three review authors (RR, YP, EDS) will independently assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will resolve any disagreements by discussion with another review author (EMB or CDM). We will assess the risk of bias according to the following domains:

1. random sequence generation;
2. allocation concealment;
3. blinding of participants and personnel;
4. blinding of outcome assessment;
5. incomplete outcome data;
6. selective outcome reporting; and
7. other bias.

We will grade each potential source of bias as high, low or unclear and we will provide a quote from the study report together with a

justification for our judgement in the 'Risk of bias' table. We will summarise the risk of bias judgements across different studies for each of the domains listed. We will consider blinding separately for different key outcomes, where necessary. Where information on risk of bias relates to unpublished data or correspondence with a trialist, we will note this in the 'Risk of bias' table.

We will take into account the risk of bias for the studies that contribute to that outcome when considering treatment effects.

### Measures of treatment effect

We will enter the outcome data for each study into the data tables in RevMan 2014 to calculate the treatment effects. We will use the risk ratio (RR) with 95% confidence interval (CI) for dichotomous outcomes and the mean difference (MD) or standardised mean difference (SMD) for continuous outcomes.

We will undertake meta-analyses only where this is meaningful, i.e. if the treatments, participants and the underlying clinical question are similar enough for pooling to make sense.

### Unit of analysis issues

We do not expect any trials in this area to have applied cross-over or cluster-randomised designs.

For studies with more than two intervention groups, where more than two of the groups are eligible for this review, we will follow the methods in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). That is, in studies with more than one control group or more than one intervention group, we will combine the results of the control or intervention groups, respectively.

### Dealing with missing data

We will contact trial authors to verify key study characteristics and to obtain missing numerical outcome data where possible (e.g. when a study is identified as an abstract only). Where this is not possible, and the missing data are thought to introduce serious bias, we will explore the impact of including such studies in the overall assessment of results using the 'Risk of bias' assessment.

If numerical outcome data are missing, such as standard deviations (SDs) or correlation coefficients, and they cannot be obtained from the trial authors, we will calculate the missing parameters from other available statistics such as P values according to the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). If values are imputed (e.g. correlation coefficients), rather than calculated, we will perform sensitivity analyses to assess how sensitive the results are to reasonable changes in the assumptions that are made in the imputation.



### Assessment of heterogeneity

We will use the Chi<sup>2</sup> test and the I<sup>2</sup> statistic to measure heterogeneity among the studies in each analysis. If we identify substantial heterogeneity (over 50% as explained in the *Cochrane Handbook for Systematic Reviews of Interventions*; Higgins 2011), we will report this and explore the possible causes by conducting prespecified subgroup analysis. Nonetheless, we are aware that there is uncertainty in the I<sup>2</sup> statistic measurement when there are few studies in a meta-analysis. In that case, we will use a P value of 0.10 rather than 0.05 in the Chi<sup>2</sup> test to determine statistical heterogeneity (Higgins 2011).

### Assessment of reporting biases

If we are able to pool more than 10 trials, we will create and examine a funnel plot to explore possible small study and publication biases.

### Data synthesis

We will pool data from studies that we judge to be clinically homogeneous using RevMan 2014, with a fixed-effect model. If a single true effect is not plausible, due to variation in populations and interventions or substantial heterogeneity, we will use a random-effects model instead (DerSimonian and Laird method) (Higgins 2011). If more than one study provides usable data in any single comparison, we will perform a meta-analysis. We will analyse primary outcomes at three time points, namely 24 hours; two to three days; and four to seven days.

### GRADE and 'Summary of findings' table

We will create a 'Summary of findings' table using the following primary outcomes: proportion of children with pain at various time points (24 hours; two to three days; and four to seven days); reduction of overall or specific symptoms; reduction in overall or specific symptom duration; and adverse effects of corticosteroids. We will use the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of a body of evidence as it relates to the studies that contribute data to the meta-analyses for the pre-specified outcomes (Atkins 2004; GRADE 2004). We will use the methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), using GRADEproGDT software

(GRADEproGDT 2015). We will justify all decisions to downgrade or upgrade the quality of studies using footnotes and we will make comments to aid readers' understanding of the review where necessary.

### Subgroup analysis and investigation of heterogeneity

We plan to carry out the following subgroup analyses if there are sufficient studies:

1. short- versus long-term use of corticosteroids ( $\leq$  one week versus  $>$  one week);
2. type of corticosteroids (i.e. prednisolone, dexamethasone, etc.); and
3. corticosteroids as monotherapy versus adjuvant to antibiotics.

We will use the Chi<sup>2</sup> test to test for subgroup interactions in Review Manager (RevMan 2014).

### Sensitivity analysis

We plan to carry out sensitivity analyses by identifying and excluding studies with high risk of bias or low methodological quality based on the Cochrane 'Risk of bias' assessment, if there are sufficient included studies to make this feasible.

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\* Indicates the major publication for the study

## **APPENDICES**

### **Appendix I. MEDLINE (Ovid) search strategy**

#### **MEDLINE (Ovid)**

- 1 exp Otitis Media/ (22799)
- 2 otitis media.tw. (17913)
- 3 (middle ear adj5 (infect\* or inflam\*)).tw. (1878)
- 4 (ome or aom).tw. (7702)
- 5 or/1-4 (33474)
- 6 exp Adrenal Cortex Hormones/ (355953)
- 7 adrenal cortex hormone\*.tw,nm. (56917)
- 8 corticosteroid\*.tw,nm. (83470)
- 9 corticoid\*.tw,nm. (5657)
- 10 steroid\*.tw,nm. (284604)
- 11 glucocorticoid\*.tw,nm. (92417)
- 12 exp Pregnenediones/ (173193)
- 13 pregnenedione\*.tw,nm. (2108)
- 14 pregnenolone\*.tw,nm. (6726)
- 15 hydrocortisone.tw,nm. (70460)
- 16 hydroxypregnenolone.tw,nm. (928)
- 17 tetrahydrocortisol.tw,nm. (471)
- 18 cortodoxone.tw,nm. (779)
- 19 cortisone.tw,nm. (22609)
- 20 corticosterone.tw,nm. (30378)
- 21 triamcinolone.tw,nm. (10351)

- 22 prednisone.tw,nm. (47956)
- 23 prednisolone.tw,nm. (41014)
- 24 paramethasone.tw,nm. (246)
- 25 methylprednisolone.tw,nm. (22772)
- 26 dexamethasone.tw,nm. (62108)
- 27 clobetasol.tw,nm. (1395)
- 28 beclomethasone.tw,nm. (3662)
- 29 betamethasone.tw,nm. (6960)
- 30 budesonide.tw,nm. (5108)
- 31 (efcortisol or hydrocortone or solu-cortef).tw,nm. (35)
- 32 (betnelan or betnesol).tw,nm. (25)
- 33 (deflazacort or calcort).tw,nm. (486)
- 34 (medrone or solu-medrone or depo-medrone).tw,nm. (17)
- 35 kenalog.tw,nm. (185)
- 36 (novolizer or pulmicort or symbicort).tw,nm. (328)
- 37 (beclometasone or aerobec or asmabec or beclazone or becodisks or becotide or clenil modulite or qvar or becloforte).tw,nm. (287)
- 38 cortisol.tw,nm. (51031)
- 39 or/6-38 (712225)
- 40 5 and 39 (1017)

## CONTRIBUTIONS OF AUTHORS

Respati W Ranakusuma (RR) drafted the protocol and will contribute as a primary review author, select studies for inclusion, extract data, enter data into RevMan, and carry out and interpret the analysis.

Eka Dian Safitri (EDS) will select studies for inclusion and extract data.

Yupitri Pitoyo (YP) will select studies for inclusion and extract data.

Sarah Thorning (ST) will develop and run the search strategy, and obtain copies of studies.

Elaine M Beller (EMB) will carry out and interpret the analysis, contribute as the third review author for disagreements on methodological/statistical issues and check the correct use of grammar.

Sudigdo Sastroasmoro (SS) drafted the protocol, will contribute to drafting the final review and will check the correct use of grammar.

Chris B Del Mar (CDM) drafted the protocol and will contribute as the third review author for disagreements on clinical issues, draft the final review and check the correct use of grammar.

## DECLARATIONS OF INTEREST

Respati W. Ranakusuma: none known

Yupitri Pitoyo: none known

Eka Dian Safitri: none known

Sarah Thorning: none known

Elaine M Beller: this review was supported by a grant from the NHMRC, Australia, to the Centre for Research in Evidence-Based Practice, Bond University

Sudigdo Sastroasmoro: none known

Chris B Del Mar: none known