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Azithromycin for treatment of bronchiolitis obliterans syndrome in adult lung transplant recipients (Protocol)

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Azithromycin for treatment of bronchiolitis obliterans syndrome in adult lung transplant recipients

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ABSTRACT

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

This review aims to look at the benefits and harms of azithromycin for the treatment of BOS in adult lung transplant recipients.

BACKGROUND

Description of the condition

Lung transplantation is potentially the only life-prolonging treatment available for end-stage chronic lung disease. However, despite significant advances in recipient selection, surgical technique, and immunosuppressant therapy, which have led to improvements in survival, the median survival remains poorer than other solid organ transplants at 5.7 years ([ISHLT Report 2015](#)). Bronchiolitis obliterans syndrome (BOS) is a major subtype of the recently termed Chronic Lung Allograft Dysfunction (CLAD) or late graft failure after lung transplantation. BOS is estimated to develop in 50% of adult lung transplant recipients within 5 years of transplantation and in 76% by 10 years ([ISHLT Report 2015](#)), and was the most common indication for adult lung re-transplantation during January 1995 to June 2013 ([ISHLT Report 2014](#)), internationally.

As defined by the International Society for Heart and Lung Transplantation (ISHLT) guidelines, BOS is a delayed allograft dysfunction, characterised by a persistent (more than three weeks) obstructive lung function with a decline in forced expiratory volume in one second (FEV₁), which is not caused by other known and potentially reversible causes of post-transplant loss of lung function ([Meyer 2014](#)). Obliterative bronchiolitis (OB) is the hallmark of BOS on histopathology ([Verleden 2014](#)), although, it is difficult to diagnose on transbronchial lung biopsy, the most commonly used biopsy method in clinical practice. BOS is graded according to the severity of FEV₁ decline, as per the 2001 diagnostic criteria ([Estenne 2002](#)):

- BOS 0: FEV₁ > 90% of baseline and FEF_{25–75} > 75% of baseline post transplant (FEF_{25–75} = forced expiratory flow at 25% to 75% of forced vital capacity)
- BOS 0-p: FEV₁ 81% to 90% of baseline and/or FEF_{25–75} ≤ 75% of baseline
- BOS 1: FEV₁ 66% to 80% of baseline post-transplant

FEV₁

- BOS 2: FEV₁ 51% to 65% of baseline post-transplant FEV₁
- BOS 3: FEV₁ 50% or less of baseline post-transplant FEV₁

There are two main CLAD phenotypes: classic BOS and restrictive allograft syndrome (RAS). RAS is characterised by total lung capacity (TLC) \leq 90% of stable baseline value, normal or increased FEV₁ to forced vital capacity (FVC) ratio (FEV₁/FVC), with FEV₁ and/or FVC decline \leq 90% of stable baseline value, infiltrates on high resolution computed tomography (HRCT) with/without bronchiectasis and air trapping, and parenchymal or pleural fibrosis on biopsy with/without OB. RAS is progressive and may start/coincide with BOS. Approximately 40% of patients with BOS respond to azithromycin with an increase in their FEV₁ of at least 10% after two to three months of treatment, and some patients may experience complete reversal of their FEV₁ decline and return to BOS stage 0. This phenotype has been termed azithromycin-responsive allograft dysfunction (ARAD) or azithromycin-responsive BOS, which can only be diagnosed retrospectively after the decline in FEV₁ has been diagnosed, and has subsequently responded to azithromycin. It is unclear whether ARAD will progress to BOS eventually. BOS remains the physiologic surrogate for OB, and the most common phenotype of obstructive CLAD (Kapila 2015; Verleden 2014).

This review uses the term BOS as described in the 2001 diagnostic criteria, which is the criteria used in clinical studies, while acknowledging that ARAD, as defined by Verleden 2014, poses a retrospective challenge to the diagnostic pathway. We note that there remains debate within the field. Whilst we use the 2001 diagnostic pathway for practical reasons, we note that, as the field evolves, future versions of this review may use an updated diagnostic pathway.

Description of the intervention

Currently there is no gold standard treatment for BOS; this has resulted in a range of therapies being tried, which have included switching immunosuppressants, total lymphoid irradiation (McKay 2014), and Nissen's fundoplication in cases of gastro-oesophageal reflux disease (Meyer 2014). Azithromycin is a macrolide antibiotic, which was initially trialled for the treatment of BOS in early 2000s (Gerhardt 2003; Verleden 2004), noting the success of maintenance macrolide therapy in management of Japanese panbronchiolitis (Hui 2013), asthma (Brusselle 2013), and chronic obstructive pulmonary disease (COPD) (Albert 2011).

How the intervention might work

Azithromycin is currently hypothesised to primarily impact BOS via its immunomodulatory and anti-inflammatory pathway (Vos

2012). BOS is a heterogeneous entity with a variable natural history. There are at least two distinct subsets, which are characterised by neutrophilic or fibroproliferative phenotypes (Vanaudenaerde 2008). Patients with the neutrophilic subset of BOS may respond to azithromycin, and have reduced bronchoalveolar lavage neutrophil count following three to six months of azithromycin maintenance therapy (Gottlieb 2008; Vanaudenaerde 2008; Verleden 2006). Additionally, azithromycin reduces interleukin-8 levels (Verleden 2006) modulating the immune system. Furthermore, azithromycin may reduce airway inflammation by enhancing oesophageal motility and accelerating gastric emptying, reducing gastric content aspiration (an established risk factor for development and progression of BOS) (Corris 2015; Mertens 2009; Vos 2012).

Why it is important to do this review

BOS is the Achilles heel of lung transplantation; it is the major cause of late graft failure after lung transplantation and mortality. Therapeutic approaches for BOS have ranged from switching immunosuppression to total lymphoid irradiation, which have had variable and modest impact on the rate of decline in graft function in BOS (Fisher 2005; Verleden 2009), but are often associated with significant iatrogenic complications, such as bone marrow failure and death in the case of total lymphoid irradiation (Diamond 1998). Maintenance low dose azithromycin, often administered orally three times/week, has been in use for over a decade. It has a good safety profile, with cardiac dysrhythmias (Albert 2014; Ray 2012) and hearing impairment (Mick 2007) as the main complications. Furthermore, studies have reported development of macrolide resistance with the prolonged use of azithromycin (Hansen 2009; Pomares 2011), but it remains to be seen whether this resistance is of clinical significance. There is also concern that long-term use of azithromycin in patients with nontuberculous mycobacteria infection could lead to resistance, further complicating its treatment (Mogayzel 2013). There have been a number of studies published, with results ranging from no improvement in lung function (Porhownik 2008) to slowing the progression of disease (Shitrit 2005) and improved life expectancy (Jain 2010; Yates 2005). More recently, randomised controlled trials (RCTs) have also been published that have investigated azithromycin for either treatment of BOS or as a prophylaxis against development of BOS (Corris 2015; Vos 2011). Therefore, in light of the new evidence supporting the use of azithromycin in BOS and the potential complication associated with its long-term use, this Cochrane review aims to assess the efficacy of azithromycin for treatment of BOS in adult lung transplant recipients.

OBJECTIVES

This review aims to look at the benefits and harms of azithromycin for the treatment of BOS in adult lung transplant recipients.

METHODS

Criteria for considering studies for this review

Types of studies

All RCTs and quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) looking at azithromycin for BOS in adult lung transplant recipients.

Types of participants

Adult lung transplant recipients, both male and female, who have been diagnosed with BOS, as per 2001 criteria ([Estenne 2002](#)), will be included.

Inclusion criteria

- Lung transplant recipients, including single lung, double lung, re-do transplants, and heart and lung transplant recipients.
- Male and female patients.
- Age 18 years and over.

Exclusion criteria

- Lung transplant recipients under the 18 years of age will be excluded as azithromycin has not been established for treatment of BOS in the paediatric lung transplant recipient cohort.

Types of interventions

- We will compare the daily dosing regimen to three times a week regimen.
- We will compare long term (eight weeks and more) oral azithromycin therapy, 250 mg three times/week and 500 mg three times/week, to:
 - Placebo
 - Monoclonal antibody
 - Alternate dose

Azithromycin in capsule, tablet, and oral suspension formulation is accepted. It is expected for the patients diagnosed with BOS to receive high dose intravenous methylprednisolone followed by a tapering course of oral steroids, and optimisation of immunosuppressant therapy, as standard treatment.

Types of outcome measures

Primary outcomes

1. Lung function improvement, defined as $\geq 10\%$ improvement in FEV₁
2. Progression to BOS stage 3

Secondary outcomes

1. Absolute change in FEV₁
2. Decision to re-transplant
3. Survival
4. All adverse events, including hearing impairment, cardiac dysrhythmias, prolonged QT interval on ECG, and hepatotoxicity.

Search methods for identification of studies

Electronic searches

We will search the [Cochrane Kidney and Transplant Specialised Register](#) through contact with the Information Specialist using search terms relevant to this review. The Cochrane Kidney and Transplant Specialised Register contains studies identified from several sources.

1. Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL)
2. Weekly searches of MEDLINE OVID SP
3. Handsearching of kidney-related journals and the proceedings of major kidney conferences
4. Searching of the current year of EMBASE OVID SP
5. Weekly current awareness alerts for selected kidney and transplant journals
6. Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Studies contained in the Specialised Register are identified through search strategies for CENTRAL, MEDLINE, and EMBASE based on the scope of Cochrane Kidney and Transplant. Details of these strategies, as well as a list of handsearched journals, conference proceedings and current awareness alerts, are available in the Specialised Register section of information about [Cochrane Kidney and Transplant](#).

See [Appendix 1](#) for search terms used in strategies for this review.

Searching other resources

1. Reference lists of review articles, relevant studies and clinical practice guidelines.

2. Letters seeking information about unpublished or incomplete trials to investigators known to be involved in previous studies.

Data collection and analysis

Selection of studies

The search strategy described will be used to obtain titles and abstracts of studies that may be relevant to the review. The titles and abstracts will be screened independently by two authors, who will discard studies that are not applicable; however, studies and reviews that might include relevant data or information on trials will be retained initially. Two authors will independently assess retrieved abstracts and, if necessary the full text, of these studies to determine which studies satisfy the inclusion criteria. Any disagreements will be resolved by discussion, and, if necessary, arbitration by the third or fourth author.

Data extraction and management

Data extraction will be carried out independently by two authors using standard data extraction forms. Studies reported in non-English language journals will be translated before assessment. Where more than one publication of one study exists, reports will be grouped together and the publication with the most complete data will be used in the analyses. Where relevant outcomes are only published in earlier versions these data will be used. Any discrepancy between published versions will be highlighted.

Assessment of risk of bias in included studies

The following items will be independently assessed by two authors using the risk of bias assessment tool (Higgins 2011) (see Appendix 2).

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?
- Was knowledge of the allocated interventions adequately prevented during the study?
 - Participants and personnel (performance bias)
 - Outcome assessors (detection bias)
- Were incomplete outcome data adequately addressed (attrition bias)?
 - Are reports of the study free of suggestion of selective outcome reporting (reporting bias)?
 - Was the study apparently free of other problems that could put it at a risk of bias?

Measures of treatment effect

For dichotomous outcomes (reversal of BOS, halted progression of BOS, progression to next BOS stage, re-transplantation, and death) results will be expressed as risk ratio (RR) with 95% confidence intervals (CI). Where continuous scales of measurement are used to assess the effects of treatment (FEV₁), the mean difference (MD) will be used, or the standardised mean difference (SMD) if different scales have been used.

Where death or re-transplantation are reported as a time to event data, these will be analysed as per the Cochrane Handbook, using summary statistics from individual trial reports. If estimates of log hazard ratios and standard errors are available from Cox proportional hazards are available, these will be analysed by the generic inverse-variance method. If O-E and variance data, or if log rank methods are reported, these will be analysed with Peto's method. If standard deviations of changes from baseline (such as for FEV₁) are missing, these will be calculated if other information (such as P values) are available. If this is not possible, we will impute standard deviations using the methods from the Cochrane Handbook Chapter 16.

Unit of analysis issues

For cross-over studies, where possible, we will use the first treatment cycle prior to the 'cross-over', to avoid the effect of treatment 'hangover'. Where multiple groups are investigated in one study, we will use each group only once in meta-analysis, to remove the impact of unit of analysis issues. Where possible, we will combine groups to make a single pair-wise comparison. Other approaches which will be taken are (i) removing interventions not relevant to this review, (ii) splitting a shared group into multiple groups and including these in the meta-analysis or (iii) including correlated comparisons, and using appropriate methods for accounting with the correlation.

Dealing with missing data

Any further information required from the original author will be requested by written correspondence (e.g. emailing corresponding authors) and any relevant information obtained in this manner will be included in the review. Evaluation of important numerical data such as screened, randomised patients as well as intention-to-treat, as-treated and per-protocol population will be carefully performed. Attrition rates, for example drop-outs, losses to follow-up and withdrawals will be investigated. Issues of missing data and imputation methods (for example, last-observation-carried-forward) will be critically appraised (Higgins 2011).

Assessment of heterogeneity

We will first assess the heterogeneity by visual inspection of the forest plot. Heterogeneity will then be analysed using a Chi² test on

N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance and with the I^2 test (Higgins 2003). A guide to the interpretation of I^2 values will be as follows:

- 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.

The importance of the observed value of I^2 depends on the magnitude and direction of treatment effects and the strength of evidence for heterogeneity (e.g. P-value from the Chi^2 test, or a CI for I^2) (Higgins 2011).

Assessment of reporting biases

If possible, funnel plots will be used to assess for the potential existence of publication bias (Higgins 2011).

Data synthesis

Data will be pooled using the random-effects model but the fixed-effect model will also be used to ensure robustness of the model chosen and susceptibility to outliers.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis will be used to explore possible sources of heterogeneity (e.g. studies with or without blinding). Heterogeneity among participants could be related to the type of transplant (e.g. single versus double versus heart-lung transplant). Heterogeneity in treatments could be related to prior agent(s) used and the dose and duration of therapy (e.g. azithromycin 250 mg versus 500 mg). Adverse effects will be tabulated and assessed with descriptive techniques. Where possible, the risk difference with 95% CI will be calculated for each adverse effect, either compared to no treatment or to another agent.

Sensitivity analysis

We will perform sensitivity analyses in order to explore the influence of the following factors on effect size.

- Repeating the analysis excluding unpublished studies
- Repeating the analysis taking account of risk of bias, as specified

- Repeating the analysis excluding any very long or large studies to establish how much they dominate the results
- Repeating the analysis excluding studies using the following filters: diagnostic criteria, language of publication, source of funding (industry versus other), and country
- Repeating the analysis excluding quasi-RCTs.

'Summary of findings' tables

We will present the main results of the review in 'Summary of findings' tables. These tables present key information concerning the quality of the evidence, the magnitude of the effects of the interventions examined, and the sum of the available data for the main outcomes (Schunemann 2011a). The 'Summary of findings' tables also include an overall grading of the evidence related to each of the main outcomes using the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach (GRADE 2008). The GRADE approach defines the quality of a body of evidence as the extent to which one can be confident that an estimate of effect or association is close to the true quantity of specific interest. The quality of a body of evidence involves consideration of within-trial risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias (Schunemann 2011b). We plan to present the following outcomes in the 'Summary of findings' tables.

- Lung function improvement, defined as $\geq 10\%$ improvement in FEV_1
- Proportion of patients progressing to BOS stage 3
- Decision to re-transplant
- Survival
- Adverse events, including hearing impairment, cardiac dysrhythmias, prolonged QT interval on ECG, and hepatotoxicity.

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* Indicates the major publication for the study

APPENDICES

Appendix I. Electronic search strategies

Database	Search terms
CENTRAL	<ol style="list-style-type: none"> 1. MeSH descriptor: [Lung Transplantation] explode all trees 2. MeSH descriptor: [Organ Transplantation] this term only 3. lung transplant*:ti,ab,kw (Word variations have been searched) 4. {or #1-#3} 5. MeSH descriptor: [Bronchiolitis Obliterans] this term only 6. bronchiolitis obliterans or obliterative bronchiolit* or obliterating bronchiolit*:ti,ab,kw (Word variations have been searched) 7. proliferative bronchioliti*:ti,ab,kw (Word variations have been searched) 8. constrictive bronchioliti*:ti,ab,kw (Word variations have been searched) 9. exudative bronchioliti*:ti,ab,kw (Word variations have been searched) 10. {or #5-#9} 11. MeSH descriptor: [Azithromycin] this term only 12. azithromycin:ti,ab,kw (Word variations have been searched) 13. sumamed:ti,ab,kw (Word variations have been searched) 14. toraseptol:ti,ab,kw (Word variations have been searched) 15. azadose:ti,ab,kw (Word variations have been searched) 16. ultreon:ti,ab,kw (Word variations have been searched) 17. vinzam:ti,ab,kw (Word variations have been searched) 18. zentavion:ti,ab,kw (Word variations have been searched) 19. zithromax:ti,ab,kw (Word variations have been searched) 20. zitromax:ti,ab,kw (Word variations have been searched) 21. {or #11-#20} 22. {and #4, #10, #21}
MEDLINE	<ol style="list-style-type: none"> 1. exp Lung Transplantation/ 2. Organ Transplantation/ 3. lung transplant\$.tw. 4. or/1-3 5. Bronchiolitis Obliterans/ 6. (bronchiolitis obliterans or obliterative bronchioliti\$ or obliterating bronchioliti\$).tw. 7. proliferative bronchioliti\$.tw. 8. constrictive bronchioliti\$.tw. 9. exudative bronchioliti\$.tw. 10. or/5-9

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	<ol style="list-style-type: none"> 11. Azithromycin/ 12. azithromycin.tw. 13. (cp-62993 or cp62993).tw. 14. sumamed.tw. 15. toraseptol.tw. 16. azadose.tw. 17. ultreon.tw. 18. vinzam.tw. 19. zentavion.tw. 20. zithromax.tw. 21. zitromax.tw. 22. or/11-21 23. and/4,10,22
EMBASE	<ol style="list-style-type: none"> 1. exp lung transplantation/ 2. organ transplantation/ 3. lung transplant\$.tw. 4. or/1-3 5. bronchiolitis obliterans/ 6. (bronchiolitis obliterans or obliterative bronchioliti\$ or obliterating bronchioliti\$.tw. 7. proliferative bronchioliti\$.tw. 8. constrictive bronchioliti\$.tw. 9. exudative bronchioliti\$.tw. 10. or/5-9 11. azithromycin/ 12. azithromycin.tw. 13. (cp-62993 or cp62993).tw. 14. sumamed.tw. 15. toraseptol.tw. 16. azadose.tw. 17. ultreon.tw. 18. vinzam.tw. 19. zentavion.tw. 20. zithromax.tw. 21. zitromax.tw. 22. or/11-21 23. and/4,10,22

Appendix 2. Risk of bias assessment tool

Potential source of bias	Assessment criteria
Random sequence generation Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence	<i>Low risk of bias:</i> Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimisation (minimisation may be implemented without a random element, and this is considered to be

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	<p>equivalent to being random)</p> <hr/> <p><i>High risk of bias:</i> Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention</p> <hr/> <p><i>Unclear:</i> Insufficient information about the sequence generation process to permit judgement</p>
<p>Allocation concealment Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment</p>	<p><i>Low risk of bias:</i> Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes)</p> <hr/> <p><i>High risk of bias:</i> Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure</p> <hr/> <p><i>Unclear:</i> Randomisation stated but no information on method used is available</p>
<p>Blinding of participants and personnel Performance bias due to knowledge of the allocated interventions by participants and personnel during the study</p>	<p><i>Low risk of bias:</i> No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken</p> <hr/> <p><i>High risk of bias:</i> No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding</p> <hr/> <p><i>Unclear:</i> Insufficient information to permit judgement</p>
<p>Blinding of outcome assessment Detection bias due to knowledge of the allocated interventions by outcome assessors</p>	<p><i>Low risk of bias:</i> No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken</p>

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	<p><i>High risk of bias:</i> No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding</p> <p><i>Unclear:</i> Insufficient information to permit judgement</p>
<p>Incomplete outcome data Attrition bias due to amount, nature or handling of incomplete outcome data</p>	<p><i>Low risk of bias:</i> No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods</p> <p><i>High risk of bias:</i> Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; ‘as-treated’ analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation</p> <p><i>Unclear:</i> Insufficient information to permit judgement</p>
<p>Selective reporting Reporting bias due to selective outcome reporting</p>	<p><i>Low risk of bias:</i> The study protocol is available and all of the study’s pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon)</p> <p><i>High risk of bias:</i> Not all of the study’s pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. sub-scales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear jus-</p>

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	tification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study
	<i>Unclear:</i> Insufficient information to permit judgement
Other bias Bias due to problems not covered elsewhere in the table	<i>Low risk of bias:</i> The study appears to be free of other sources of bias. <i>High risk of bias:</i> Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem <i>Unclear:</i> Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias

HISTORY

Protocol first published: Issue 9, 2017

Date	Event	Description
3 August 2016	Amended	Protocol reviewed by all authors

CONTRIBUTIONS OF AUTHORS

1. Draft the protocol: SS, APP
2. Study selection: SS, APP
3. Extract data from studies: SS, APP
4. Enter data into RevMan: SS
5. Carry out the analysis: SS, APP
6. Interpret the analysis: SS, APP
7. Draft the final review: SS, APP
8. Disagreement resolution: IPH, JP
9. Update the review: SS

DECLARATIONS OF INTEREST

None known.