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Magnesium sulfate for acute exacerbations of chronic obstructive pulmonary disease (Protocol)

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[Intervention Protocol]

Magnesium sulfate for acute exacerbations of chronic obstructive pulmonary disease

Han Ni[1], Cho Naing[2,3], Swe Zin Aye[4]

[1]Faculty of Medicine, SEGi University, Sibu, Malaysia. [2]International Medical University, Kuala Lumpur, Malaysia. [3]Division of Tropical Health and Medicine, James Cook University, Townsville, Australia. [4]Department of Paediatrics and Child Health, Quest International University Perak, Ipoh, Malaysia

Contact address: Han Ni, Faculty of Medicine, SEGi University, Hospital Sibu, Jalan Ulu Oya, Sibu, Sarawak, 96000, Malaysia. hanni.dr@gmail.com.

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ABSTRACT

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

To assess the effects of magnesium sulfate for acute exacerbations of chronic obstructive pulmonary disease in adults.

BACKGROUND

Description of the condition

Chronic obstructive pulmonary disease (COPD) refers to a group of lung diseases characterised by airflow obstruction that interferes with normal breathing (American Lung Association 2013). Clinical diagnosis of COPD is considered in people who experience breathlessness, chronic cough or sputum production, with a history of exposure to known risk factors (WHO 2017). Smoking and ambient particulate matter are the main risk factors for COPD (GBD 2017). Confirmation of COPD requires spirometry to demonstrate persistent airflow limitation according to the criterion of a post-bronchodilator forced expiratory volume in one second (FEV1)/ forced vital capacity (FVC) ratio of less than 0.7 (GOLD 2019).

According to the Global Burden of Disease (GBD) study, 251 million people had COPD worldwide in 2016; with an estimated 3.17 million COPD-related deaths accounting for 5% of total deaths globally in 2015 (WHO 2017). This indicates that COPD caused 2.6% of disability-adjusted life years in 2015 alone (GBD 2017). In 2016, chronic respiratory diseases contributed to 8.96% of worldwide non-communicable disease deaths, of which 2.93 million deaths were due to COPD (Ngahavi 2017). In the 1990s, COPD was the sixth leading cause of death; it has become the fourth leading cause since 2000, and is expected to be the third by the year 2020, with an estimated 4.7 million deaths out of 68 million deaths globally (GOLD 2019; Lopez-Campos 2016). The principal causes of death in people with mild to moderate COPD are lung cancer (26.5%) and cardiovascular disease (21.6%), while acute respiratory failure (25.8%) is the main cause of death in people with very severe COPD, based on the analysis of 2,826 deaths in 13 Spanish centres (Soto-Campos 2013). Morbidity due to COPD is also high worldwide, with 29.4 million years lost due to disability in 2015 (Lopez-Campos 2016).

The chronic and progressive course of COPD is often punctuated by episodes of exacerbations. Exacerbations are defined as "an acute worsening of respiratory symptoms that result in additional therapy" (GOLD 2019; O'Donnell 2006; Wedzicha 2017). COPD exacerbations are more frequent in the winter months for people living in temperate climates (Jenkins 2012), and are mainly triggered by respiratory infections (Wedzicha 2007). People experience worsening symptoms, including breathlessness or cough with increased sputum volume or purulence, and require increased use of maintenance medications. Mild exacerbations can be treated with short-acting bronchodilators only, whereas more severe exacerbations require the addition of a course of systemic steroids or antibiotics, hospitalisation or an emergency room visit (GOLD 2019). These exacerbations, especially when frequent, can compromise quality of life (Connors 1996; David 2012; Miravitlles 2004; Seemungal 1998; Spencer 2001), accelerate lung function decline (Anzueto 2009; Celli 2008; Donaldson 2002), reduce physical capacity (Donaldson 2005; Pitta 2006), result in hospital admissions (Mullerova 2015) and increase mortality (Almagro 2002; Groenewegen 2003; Soler-Cataluna 2005). In addition, severe COPD exacerbations that require hospital admission exert a direct and independent effect on survival, with a reported mortality rate of 50% within five years, similar to an oncologic mortality rate (Garcia-Aymerich 2011; Nannini 2012).

Acute COPD exacerbations are reported to be more frequent in people with severe disease, with an annual exacerbation frequency of 3.43, compared with 2.68 for those with moderate disease (Anzueto 2010). Similarly, in the ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points) study, exacerbation rates in the first year of follow-up were 0.85, 1.34 and 2.00 per person for people with GOLD (Global Initiative for Chronic Obstructive Lung Disease) stage 2, 3 and 4 respectively while 22%, 33% and 47% were reported to have two or more exacerbations over the same period (Hurst 2010). However, most of the COPD exacerbation data have been estimated in populations with moderate to severe COPD requiring hospital care, thus leading to the possibility of higher number of less severe forms being under-diagnosed (Borrell 2009).

Description of the intervention

Magnesium is the second most common intracellular cation in the body, found principally in bone (53%), muscle (27%) and soft tissues (19%); less than 1% of total body magnesium is present in the blood (Elin 1988; Fawcett 1999). It is involved in many biological actions, such as energy production, glycolysis (breakdown of glucose), synthesis of nucleic acids and proteins, transmembrane ion flux, regulation of adenylate cyclase, muscle contraction and neuronal activity (Costello 2016; Grober 2015; Romani 2013). It acts as a physiological calcium channel antagonist, stimulates prostacyclin and nitric oxide production, and diminishes vascular reactivity to a variety of pressor agents (drugs to increase blood pressure) (Fawcett 1999; Laires 2004). Magnesium prevents calcium ion movement into vascular and bronchial smooth muscle cells via voltage-dependent calcium channels, so it is believed to play a major role in vasodilatation and bronchodilatation (Gourgoulianis 2001; Kew 2014; Spivey 1990). Magnesium also inhibits the release of acetylcholine from cholinergic nerve endings and histamine from mast cells, leading to possible anticholinergic and antihistamine effects (Del-Castillo 1954). Furthermore, some evidence suggests that magnesium may reduce the neutrophilic burst of inflammatory response with a possible beneficial anti-inflammatory effect (Cairns 1996).

Recent clinical guidelines advise that a single dose of intravenous magnesium sulfate can be considered for adults with severe life-threatening asthma exacerbations, adults and children who fail to respond to initial treatment with persistent hypoxaemia, and children who fail to achieve 60% of predicted FEV1 value after one hour of care. The recommended dosage of intravenous magnesium sulfate for adults is 1.2 g to 2 g, delivered by infusion over 20 minutes (BTS/SIGN 2019; GINA 2018). However, routine use of magnesium sulfate in acute exacerbations of asthma is not recommended (GINA 2018). Similarly, nebulised magnesium sulfate is not routinely recommended for adults with acute asthma or children with mild to moderate asthma attacks, although 150 mg of nebulised magnesium sulfate can be considered as an adjunct to nebulised salbutamol and ipratropium in the first hour for children with severe asthma exacerbations (BTS/SIGN 2019).

How the intervention might work

The characteristic response in COPD exacerbations is increased airway inflammation, hyperinflation and gas trapping, with reduced expiratory flow accounting for increased breathlessness. Treatment of acute exacerbation of COPD aims to minimise the negative impact of the episode and prevent subsequent events. The current guidelines recommend the use of short-acting beta$_2$-agonists (SABA), muscarinic antagonists, systemic corticosteroids,

antibiotics and non-invasive ventilation for COPD exacerbations (GOLD 2019).

Magnesium sulfate may have potential benefits as an adjunct therapy in acute exacerbations of COPD. This is because low serum magnesium levels are reported to be associated with an increased risk of exacerbation in people with COPD, according to a retrospective study (Aziz 2005), and a small prospective study (Gumus 2014). Moreover, studies have reported that hypomagnesaemia (low serum magnesium level) is an independent predictor of frequent readmission for acute exacerbations of COPD (Bhatt 2008), or exacerbation frequency in people with COPD (Gumus 2014).

Intravenous magnesium sulfate, in addition to bronchodilators, reduces hospital admissions and improves lung function when the response to bronchodilators during acute asthma exacerbations is inadequate (Kew 2014; Rowe 2000). However, evidence for the use of inhaled magnesium sulfate during acute exacerbations of asthma, either alone or in addition to bronchodilators, does not demonstrate clinically important benefits, and further trials are needed to establish its usefulness (Knightly 2017).

Over the past few years, there has been a marked interest in a subset of people with airways disease who have features of both asthma and COPD, known as asthma-COPD overlap (ACO) (Cosio 2018). People who have asthma and smoke are reported to have more symptoms than people with asthma who do not smoke (Leung 2017). In the absence of a standard definition for ACO diagnosis, the prevalence estimates vary from 3.2% in the United States of America (Kumbhare 2016), to 11.1% in Italy (Sorino 2016). The prevalence of ACO ranges from 6% to 55% in cohorts of people with COPD, and from 10% to 31% in cohorts of people with asthma (Leung 2017). People with ACO have more severe and frequent exacerbations; and have thicker airway walls than people with COPD alone (Hardin 2014), leading to more hospitalisations and emergency department visits (Kumbhare 2016). Furthermore, they have a significantly lower quality of life (Kauppi 2011), a more rapid decline in lung function (Lange 2016), higher disease burden (including respiratory symptoms and activity limitation) (Hines 2017), and a higher mortality rate compared to people with asthma or COPD alone (Gibson 2009; Sorino 2016). As some people with COPD may also have asthmatic features, it is reasonable to assume there may be some benefits of magnesium sulfate for acute exacerbations of COPD, as well as for acute asthma. Moreover, bronchodilatation (Spivey 1990), anticholinergic (Del-Castillo 1954) and anti-inflammatory properties of magnesium (Cairns 1996) could lead to potential therapeutic effects for acute exacerbations of COPD.

Why it is important to do this review

Exacerbations play a major role in the morbidity and mortality of people with COPD, resulting in a significant health burden. Therefore, a potentially effective add-on treatment would be useful for people with COPD and healthcare providers. The potential clinical benefits of intravenous or nebulised magnesium sulfate for acute exacerbations of COPD have been studied, however, published studies have found conflicting and inconclusive results for its effectiveness. A non-Cochrane systematic review on magnesium sulfate reported that it appeared to potentiate the bronchodilatory effect of inhaled beta$_2$-agonists, but did not find significant differences in dyspnoea scores, hospital admission rates, or emergency department readmission rates, compared to placebo (Shivanthan 2014). Currently, standard guidelines do not recommend magnesium sulfate as a treatment for acute exacerbation of COPD, but it is nonetheless used by some clinicians in practice. Thus, we would like to establish evidence regarding its usage as an adjunct treatment for acute exacerbations of COPD in people not responding to conventional measures, based on current available data from randomised clinical trials.

OBJECTIVES

To assess the effects of magnesium sulfate for acute exacerbations of chronic obstructive pulmonary disease in adults.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs) with a parallel-group design. We will include studies reported in full text, those published as an abstract only and unpublished data. We will exclude studies with a cross-over design, due to the carry-over effects of the intervention.

Types of participants

We will include adults aged 40 years and older with acute exacerbations of COPD (defined as a worsening of a previously stable condition with increasing respiratory symptoms, particularly dyspnoea, cough, sputum production and increased sputum purulence). We will include studies where diagnosis of COPD is physician-diagnosed or guideline-based, according to the criteria of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) (GOLD 2019), the American Thoracic Society (ATS) and European Respiratory Society (ERS) (ATS/ERS 2011), the Thoracic Society of Australia and New Zealand (TSANZ) (Yang 2019) or the UK National Institute for Health and Care Excellence (NICE) (NICE 2019).

We will also include trials that assess participants with mixed COPD and asthma features (asthma-COPD overlap, ACO), based on the consensus published by the Global Initiative for Asthma (GINA) and GOLD (GOLD ACO 2015), provided that the trials report outcomes separately for the different participant groups. We will exclude participants with the following comorbidities or characteristics: pneumothorax, bronchiectasis, cystic fibrosis, other chronic lung diseases or heart failure.

If we find trials in which only a subset of participants has a diagnosis of COPD, we will include these participants if we can obtain disaggregated data from the trial authors.

Types of interventions

The intervention of interest is magnesium sulfate, given at any dose and by any route of administration (intravenous or inhalation), as an adjunct to standard therapy for acute exacerbation of COPD. We will compare this with standard therapy alone, either with or without a placebo. We will include any co-interventions as standard therapy, provided that they are not part of the randomised treatment: e.g. systemic corticosteroids; antibiotics; short acting bronchodilators, such as salbutamol or ipratropium bromide; mucolytics; intravenous aminophylline or oxygen therapy.

For intravenous magnesium sulfate, we will study the following comparisons.

1. Intravenous magnesium sulfate + standard care versus placebo + standard care
2. Intravenous magnesium sulfate + standard care versus standard care

For inhaled/nebulised magnesium sulfate, we will study the following comparisons.

1. Inhaled magnesium sulfate + standard care versus placebo + standard care
2. Inhaled magnesium sulfate + standard care versus standard care

Types of outcome measures

Primary outcomes

1. Hospital admissions (from the emergency room)
2. Need for non-invasive ventilation (NIV), assisted ventilation or admission to intensive-care unit (ICU)
3. Serious adverse events

Secondary outcomes

1. Length of hospital stay (inpatients) or time to emergency room discharge (outpatients)
2. All-cause mortality
3. Adverse events/side effects
4. Arterial-blood gas measurements: arterial partial pressure of carbon dioxide ($PaCO_2$), arterial partial pressure of oxygen (PaO_2) and pH
5. Lung function measurements: forced expiratory volume in the first second (FEV1), if available, or peak expiratory flow rate (PEFR) if the trial does not report FEV1
6. Symptom scores measuring breathlessness, cough and sputum production using validated scales; e.g. Exacerbations of Chronic Pulmonary Disease Tool (EXACT) total score

If the trial measured arterial-blood gas, lung function and symptom scores at multiple time points, we will use the data at (or as close as possible to) 60 minutes post-baseline for meta-analysis. We chose this time point as we expect that most participants will have a response to treatment within an hour, and to maximise the homogeneity of pooled results. Reporting one or more of the outcomes listed here in the study is not an inclusion criterion for the review.

Search methods for identification of studies

Electronic searches

We will identify studies from searches of the following databases and trial registries:

1. Cochrane Airways Trials Register (Cochrane Airways 2019), via the Cochrane Register of Studies, all years to date;
2. Cochrane Central Register of Controlled Trials (CENTRAL), via the Cochrane Register of Studies, all years to date;
3. MEDLINE OvidSP, 1946 to date;
4. Embase OvidSP, 1974 to date;
5. US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov);
6. World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch).

Appendix 1 contains the proposed search strategy for the Cochrane Airways Trials Register. We will adapt this for use in the other databases. The Cochrane Airways Information Specialist developed the search strategy, in collaboration with the authors.

We will search all databases and trials registries from their inception to the present, and will place no restriction on language or type of publication. Handsearched conference abstracts and grey literature will be searched for through the Cochrane Airways Trials Register and the CENTRAL database.

Searching other resources

We will check the reference lists of all primary studies and review articles for additional references. In addition, we will search relevant manufacturers' websites for study information.

We will also search on PubMed for errata or retractions from included studies published in full text, and report the date that we did this in the review.

Data collection and analysis

Selection of studies

Two review authors (HN and CN) will screen the titles and abstracts of the search results independently, and code them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We will retrieve the full-text study reports of all potentially eligible studies, and two review authors (HN and CN) will independently screen them for inclusion, recording the reasons for exclusion of ineligible studies. We will resolve any disagreement through discussion or, if required, we will consult a third review author (SZA). We will identify and exclude duplicates and collate multiple reports of the same study so that each study, rather than each report, is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram and 'Characteristics of excluded studies' table (Moher 2009).

Data extraction and management

We will use a data collection form for study characteristics and outcome data, which we will pilot on at least one study in the review. Two review authors (HN and SZA) will extract the following study characteristics from the included studies.

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: N, mean age, age range, gender, severity of condition, diagnostic criteria, baseline lung function, smoking history, 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.
5. Notes: funding for studies and notable conflicts of interest of trial authors.

Two review authors (HN and CN) will independently extract outcome data from included studies. We will note in the 'Characteristics of included studies' table if a trial did not report outcome data in a usable way. We will resolve disagreements by consensus or by involving a third review author (SZA). One review author (HN) will transfer data into the Review Manager file (RevMan 2014). We will double-check that we entered the data correctly by comparing the data presented in the systematic review with the study reports. A second review author (SZA) will spot-check study characteristics for accuracy against the study report.

Assessment of risk of bias in included studies

Two review authors (HN and SZA) will assess risk of bias independently for each study, using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019). We will resolve any disagreements by discussion or by involving another author (CN). 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;
7. other bias.

We will judge each potential source of bias as high, low or unclear, and 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 (e.g. for unblinded outcome assessment, risk of bias for all-cause mortality may be very different than for a participant-reported pain scale). 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.

When considering treatment effects, we will take into account the risk of bias for the studies that contribute to that outcome.

Assessment of bias in conducting the systematic review

We will conduct the review according to this published protocol and justify any deviations from it in the 'Differences between protocol and review' section of the systematic review.

Measures of treatment effect

We will analyse dichotomous data as odds ratios (OR) and continuous data as the mean difference (MD) or standardised mean difference (SMD). If we combine data from rating scales in a meta-analysis, we will ensure they we enter these with a consistent direction of effect (e.g. lower scores always indicate improvement).

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

We will describe skewed data narratively (for example, as medians and interquartile ranges for each group).

If a trial reports both change-from-baseline and endpoint scores for continuous data, we will use change-from-baseline. If a study reports outcomes at multiple time points, we will use the data collected at or as close as possible to 60 minutes post-baseline.

We will use intention-to-treat (ITT) or 'full analysis set' analyses where trials report these (i.e. those where trialists have imputed data for participants who were randomly assigned, but did not complete the study), instead of completer or per-protocol analyses.

Unit of analysis issues

For dichotomous outcomes, we will use participants, rather than events, as the unit of analysis (i.e. the number of participants with a hospital admission rather than the number of admissions per participant). However, if a study reports rate ratios, we will analyse them on the basis of events rather than participants.

Where a single study reports multiple trial arms, we will include only the relevant arms. If we combine two comparisons in the same meta-analysis (e.g. intravenous magnesium sulfate versus placebo and inhaled magnesium sulfate versus placebo), we will halve the control group to avoid double-counting.

Dealing with missing data

We will contact investigators or study sponsors in order to verify key study characteristics and obtain missing numerical outcome data where possible (e.g. when we only identify a study as an abstract). Where this is not possible, and we think the missing data could introduce serious bias, we will take this into consideration in the GRADE rating for affected outcomes.

Assessment of heterogeneity

We will use the I^2 statistic to measure heterogeneity among the studies in each analysis, and will interpret this following Higgins 2019, as:

- 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.

If we identify substantial heterogeneity ($I^2 > 50\%$), we will report it and explore the possible causes by prespecified subgroup analysis.

Assessment of reporting biases

If we are able to pool more than 10 studies, we will create and examine a funnel plot to explore possible small study and publication biases (Higgins 2019).

Data synthesis

We will use a random-effects model, and perform a sensitivity analysis with a fixed-effect model. As we expect to gather data from a series of studies performed by different researchers operating independently, it would be unlikely that all the studies were functionally equivalent with a common effect estimate. Therefore, the random-effects model is more justified than the fixed-effect model.

Subgroup analysis and investigation of heterogeneity

We plan to carry out the following subgroup analyses:

1. concomitant treatment with systemic corticosteroids (yes versus no);
2. blood eosinophil count (≥ 300/µL versus < 300/µL);
3. COPD versus asthma-COPD overlap.

We will use the following outcomes in subgroup analyses:

1. need for admission to hospital (from the emergency department);
2. need for NIV, assisted ventilation or admission to ICU;
3. length of hospital stay (inpatients) or time to emergency room discharge (outpatients).

We will use the formal test for subgroup interactions in Review Manager (RevMan 2014).

Sensitivity analysis

We will include all trials, irrespective of risk of bias, in the primary analysis.

We plan to carry out the following sensitivity analyses for the primary outcomes:

1. removing studies with unclear or high risk of performance or detection bias due to lack of appropriate blinding;
2. comparing the results from inclusion and exclusion of imputed data values;
3. comparing the results from a fixed-effect model with those from a random-effects model.

This will show whether lack of blinding in trials has any impact on the effect estimates. Also, the analysis will show whether inclusion of imputed data values has any impact on the effect estimates.

Summary of findings and assessment of the certainty of the evidence

We will create a 'Summary of findings' table using the following outcomes:

1. hospital admissions (from the emergency room);
2. need for NIV, assisted ventilation or admission to ICU;
3. serious adverse events;
4. length of hospital stay (inpatients) or time to emergency room discharge (outpatients);
5. arterial-blood gas measurements, e.g. $PaCO_2$;
6. symptom scores, as measured by validated scales; e.g. EXACT total score;
7. lung function measurements, such as changes in FEV1.

We will use the five GRADE considerations (risk of bias, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence in relation to the studies that contribute data for the prespecified outcomes. We will use the methods and recommendations described in Chapter 14 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019), using GRADEpro software (GRADEpro GDT). We will justify all decisions to downgrade the quality of studies using footnotes, and make comments to aid the reader's understanding of the review where necessary.

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APPENDICES

Appendix 1. Search strategy for Cochrane Airways Trials Register

Searched via Cochrane Register of Studies

#1 MeSH DESCRIPTOR Pulmonary Disease, Chronic Obstructive Explode All
#2 MeSH DESCRIPTOR Bronchitis, Chronic
#3 (obstruct*) near3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)
#4 COPD:MISC1
#5 (COPD OR AECOPD):TI,AB,KW
#6 #1 OR #2 OR #3 OR #4 OR #5
#7 MESH DESCRIPTOR Magnesium
#8 MESH DESCRIPTOR Magnesium Sulfate
#9 magnesium*:ti,ab,kw
#10 (MgSO4 or MG SO4):ti,ab,kw
#11 #7 OR #8 OR #9 OR #10
#12 #11 AND #6

CONTRIBUTIONS OF AUTHORS

Han Ni (HN)*:* designed the work, conducted the literature search, wrote the protocol and revised the manuscript critically for important intellectual content.

Cho Naing (CN)*:* critically commented on the draft protocol and revised the manuscript.

Swe Zin Aye (SZA): conducted the literature search for the background section and drafted the protocol.

All authors reviewed and agreed on the protocol prior to submission for editorial review.

Contributions of editorial team

Rebecca Fortescue (Co-ordinating Editor): edited the protocol; advised on methodology.
Chris Cates (Co-ordinating Editor) checked the planned methods, approved the protocol prior to publication.
Brian Rowe (Editor): edited the protocol; advised on content.
Emma Dennett (Managing Editor): co-ordinated the editorial process; advised on content; edited the protocol.
Emma Jackson (Assistant Managing Editor): conducted peer review; edited the references and other sections of the protocol.
Elizabeth Stovold (Information Specialist): designed the search strategy.

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Han Ni: none known

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