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Postnatal corticosteroids for transient tachypnea of the newborn (Protocol)

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TABLE OF CONTENTS

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[Intervention Protocol]

Postnatal corticosteroids for transient tachypnea of the newborn

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ABSTRACT

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

The objective of this review is to assess benefits and harms of postnatal administration of corticosteroids for the management of transient tachypnea of the newborn.

BACKGROUND

Description of the condition

Transient tachypnea of the newborn (TTN) is characterized by a respiratory rate greater than 60 breaths per minute (tachypnea) and signs of respiratory distress (grunting, flaring of nostrils, and retraction of skin underneath or between ribs when breathing). The incidence of TTN can reach up to 13% in late preterm and in term infants delivered by elective cesarean section (Hibbard 2010; Kumar 1996; Mahoney 2013; Morrison 1995; Sengupta 2013). Common risk factors for TTN include delivery before 39 weeks of gestational age, precipitous delivery (expulsion of the fetus within less than 3 hours from the start of contractions), fetal distress, maternal sedation and gestational diabetes (Edwards 2013). TTN was originally described in 1966 as the clinical manifestation of delayed clearance of fetal lung fluid (Avery 1966). The clinical features typically appear immediately after birth or within the first two hours of life, in term and late preterm newborns. TTN is a clinical diagnosis, and is supported by findings from chest radiographs, such as increased lung volumes with flat diaphragms, mild cardiomegaly (heart enlargement) and prominent vascular markings in a sunburst pattern originating at the hilum (medial area of the lung where blood vessels and bronchi exit towards heart and trachea). In term and late preterm newborns, TTN is the most common cause of respiratory distress (Clark 2005). Other causes of respiratory distress include surfactant deficiency (respiratory distress syndrome), pneumonia, meconium aspiration syndrome, asphyxia (oxygen deprivation), pneumothorax (a collapsed lung caused by air between the lungs and chest wall) and congenital heart disease (Ma 2010). Affected infants often undergo evaluation through chest radiography, laboratory tests and close cardiorespiratory monitoring. Although TTN is usually a self-limiting condition, a large retrospective study reported that TTN is

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associated with wheezing syndromes in late childhood (Birnkrant 2006; Liem 2007). Rarely, affected infants may present with persistent pulmonary hypertension (increased blood pressure within the arteries of the lungs) or a pulmonary air leak requiring mechanical ventilation (Miller 1980; Tudehope 1979).

Description of the intervention

Maternal administration of corticosteroids is the only pharmacological antenatal intervention associated with a relevant reduction in TTN incidence. Antenatal corticosteroids have been used for decades, in case of risk of an imminent delivery before 34 weeks' gestational age (GA), and results in great benefits in terms of mortality and morbidity in the offspring (NIH 1994). More recently, corticosteroids have been administered in late preterm labor (34 to 36 weeks' GA) and before elective term cesarean section.

In cases concerning very preterm infants with chronic lung disease, postnatal corticosteroids may be administered through intravenous, enteral and inhalation routes. The latter approach results in systemic absorption, though its extent has not been determined in newborns. Adverse effects of corticosteroid treatment include hyperglycemia (high glucose levels? ? ? ? ? ? ? ? ? ? ? ? ? ? ? ? ? ? ?)? ? ? , gastrointestinal bleeding, infections and impaired neurodevelopment (Linsell 2016; Stark 2001). However, most of these data have been obtained from either antenatal use or postnatal use in extreme preterm infants to treat chronic lung disease, and not from late preterm or full-term infants.

How the intervention might work

Immediately after birth, the clearance of lung fluid is promoted by activation of beta-adrenergic receptors located in the alveolar type-II cells, and by sodium absorption from increased epithelial sodium channels (a cellular membrane protein which promotes the reabsorption of sodium and water from alveolar space) and sodium-potassium adenosine triphosphatase activity (the source of energy for the channels) (Barker 2002). As sodium is transported in the interstitium (support tissues within lung), it also carries chloride and water passively through the paracellular and intracellular pathways (Guglani 2008). The poor ability of the fetal lungs to switch from fluid secretion to fluid absorption, and the immaturity in expression of epithelial sodium channels, may play important roles in the development of TTN (Davies 2004). Disruption of sodium transport through epithelial sodium channels may impair transepithelial movement of alveolar fluid, thus causing TTN. Of note, expression of the sodium channels increases through gestation and is completed in late preterm infants (Smith 2000). In the alveolar epithelia, dexamethasone may stimulate transcription of sodium channels in the fetal rat (O'Brodovich 1990), and in the fetal human lung (Venkatesh 1997), thus inducing sodium reabsorption in the lung. Similar findings have been reported in the preterm lamb, with betamethasone increasing the responsiveness of lungs to beta-adrenergic agents (Jobe 1997). It is possible that exogenous administration of corticosteroids might partly compensate for the impaired hormonal changes which occur when infants are delivered late preterm, or at term before the onset of spontaneous labor (elective cesarean section). Compared with vaginal delivery, both late preterm and elective cesarean delivery are associated with reduced glucocorticoid-inducible kinase 1 mRNAs (Janer 2015). This could mean that administration of endogenous cortisol and exogenous corticosteroids might improve sodium transport and clearance of lung liquid. During TTN, administration of steroids may result in reduced? ? ? ? effort required to breathe? and improvement of respiratory distress, the severity of which can be assessed using specific neonatal scales (Silverman 1956; Wood 1972).

Why it is important to do this review

The last update of the Cochrane Review "Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth" included 12 trials of gestations greater than 35 weeks, and reported reduced rates of respiratory distress syndrome (RDS) (Roberts 2017). For late preterm deliveries, the 2015 National Institute for Health and Care Excellence (NICE) guidelines on preterm labour and birth suggest considering corticosteroids in the following scenarios: suspected, diagnosed or established preterm labour; prior to planned preterm births; or in mothers with preterm premature rupture of membranes (P-PROM) (NICE 2015). However, the WHO recommendations on interventions to improve preterm birth outcomes do not recommend antenatal corticosteroid therapy in women undergoing planned cesarean section at late preterm gestations (conditional recommendation based on very low-quality evidence) (WHO 2015). A systematic review reported that antenatal administration of steroids led to a dramatic reduction in rates of RDS and TTN amongst offspring in late preterm and full-term births reported , though there was a higher incidence of neonatal hypoglycemia (Saccone 2016). However, universal prevention of TTN in this population (i.e. greater than 34 weeks' GA) would expose many women and fetuses to steroids, and their potential side-effects, unnecessarily. In other words, the number of women who need to be treated to prevent TTN in the offspring would be high and unfavorable. A more targeted strategy might consist of early postnatal treatment with corticosteroids during the first few hours of onset of symptoms.

Several factors are associated with an increased incidence of TTN, including cesarean section, macrosomia (birth weight greater than two standard deviations for gestational age), maternal diabetes, a family history of asthma and twin pregnancy (Hansen 2008). Since

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these prenatal risk factors are widespread, the majority of TTN occurs in level 1 neonatal units, where resources for immediate respiratory support may be suboptimal and expertise for its use might be lower. Therefore, it would be advantageous to identify an effective and safe procedure that can be applied in this setting, which would improve the management of TTN and subsequently reduce the need for intensive care with or without transfer to a level 3 neonatal intensive care unit.. Postnatal steroids might affect neurodevelopmental outcomes, however studies involving late preterm and term newborn infants are lacking.

Many supportive therapies have been proposed, and some have been evaluated or are in the process of being evaluated in Cochrane Reviews. These include fluid restriction (Gupta 2015), furosemide (Kassab 2015), salbutamol (Moresco 2016a), and epinephrine (Moresco 2016b). No systematic reviews have been conducted on postnatal corticosteroids for TTN management.

OBJECTIVES

The objective of this review is to assess benefits and harms of postnatal administration of corticosteroids for the management of transient tachypnea of the newborn.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomized controlled trials (RCTs), quasi-randomized controlled trials, and cluster-randomized trials.

We will exclude cross-over trials.

Types of participants

We will include infants that meet the following criteria.

- Born at 34 weeks' gestational age or more
- Less than three days of age
- Suffering from transient tachypnea of the newborn, defined as the presence of respiratory distress starting within six hours after birth, with::
    - X-ray findings such as increased lung volumes with flat diaphragms, mild cardiomegaly, and prominent vascular markings in a sunburst pattern originating at the hilum; or
    - a normal chest X-ray with no other apparent reason for respiratory distress (we plan to exclude infants with pneumonia, surfactant deficiency, aspiration syndromes, congenital diaphragmatic hernia, pneumothorax or congenital heart disease).

If necessary, we will contact the authors of studies to ascertain details of their enrolled population so we can determine whether the study should be included in our review.

Types of interventions

We will include any type of corticosteroids, e.g. dexamethasone, budesonide, beclomethasone dipropionate, flunisolide, fluticasone propionate betamethasone, hydrocortisone, or others.

We will include any dose, mode of administration and duration of therapy in this review. Our comparisons will be as follows.

Corticosteroids versus no treatment or placebo

- Systemic corticosteroids versus no treatment or placebo (comparison 1)
- Inhaled corticosteroids versus no treatment or placebo (comparison 2)

Head-to-head comparison of different corticosteroids

- One type of systemic steroid versus another type of systemic steroid (comparison 3)
- One type of inhaled steroid versus another type of inhaled steroid (comparison 4)
- Inhaled corticosteroids versus other inhaled corticosteroids (comparison 5)

Since TTN begins in the very first hours of life and its course is self-limited, we will included trials in which the intervention was started within the first 72 hours of life.

We will investigate the effects of different corticosteroid preparations (e.g. dexamethasone, budesonide, beclomethasone dipropionate, flunisolide, fluticasone propionate, betamethasone, hydrocortisone) in the subgroup analysis (see Subgroup analysis and investigation of heterogeneity).

Types of outcome measures

Primary outcomes

- Need for nasal continuous positive airway pressure (yes/no)
- Need for mechanical ventilation (yes/no)

Secondary outcomes

- Duration of hospital stay (days)
- Duration of supplemental oxygen therapy (hours)
- Duration of mechanical ventilation (hours)
- Pneumothorax (anytime after intervention) (diagnosis on chest X-ray)
- Culture-proven sepsis (anytime after intervention) (yes/no)
- Initiation of oral feeding (days)

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- Duration of tachypnea, defined as number of hours with respiratory rate greater than 60 breaths per minute
- Silverman or Downes' score greater than 6 (indicative of impending respiratory failure) (yes/no), 24 and 48 hours after study entry (Silverman 1956; Wood 1972)
- Silverman or Downes' score greater than 4 (indicative of moderate distress) (yes/no), 24 and 48 hours after study entry
- Persistent pulmonary hypertension diagnosed clinically, with or without at least one of the following echocardiographic findings: high right ventricular systolic pressure, right to left or bidirectional shunt at the patent foramen ovale or patent ductus arteriosus, severe tricuspid regurgitation (anytime after intervention)
- Hyperglycemia, defined as blood glucose greater than 10 millimoles per liter (mmol/L) during the course of intervention
- Gastrointestinal bleed, defined as presence of bloody nasogastric or orogastric aspirate (anytime after intervention)
- Hypertension, defined as systolic or diastolic blood pressure more than two standard deviations (SDs) above the mean for the infant's gestational and postnatal age (Zubrow 1995) during the course of intervention
- Major neurodevelopmental disability: cerebral palsy, developmental delay (Bayley Mental Developmental Index (Bayley 1993; Bayley 2006) or Griffiths Mental Development Scale (Griffiths 1954) assessment more than two SDs below the mean), intellectual impairment (intelligence quotient (IQ) more than two SDs below the mean), blindness (vision less than 6/60 in both eyes), or sensorineural deafness requiring amplification (Jacobs 2013). We plan to assess data separately for children aged 18 to 24 months and those aged three to five years.

Search methods for identification of studies

We will use the criteria and standard methods of Cochrane and Cochrane Neonatal (see the Cochrane Neonatal search strategy for specialized register). We will search for errata or retractions from included studies published in full-text on PubMed (www.ncbi.nlm.nih.gov/pubmed) and report the date this was done within the review.

Electronic searches

We will conduct a comprehensive search including: the Cochrane Central Register of Controlled Trials (CENTRAL, current issue) in the Cochrane Library; MEDLINE via PubMed (1996 to current); Embase (1980 to current); and CINAHL (1982 to current), using the following search terms: (transient tachypnea of the newborn[MeSH] OR transient tachypnea OR transitory tachypnea OR TTN OR TTNB), plus database-specific limiters for RCTs and neonates (see Appendix 1 for the full search strategies for each database). We will not apply any language restrictions. We will search clinical trials registries for ongoing or recently completed trials (clinicaltrials.gov; the World Health Organization's International Trials Registry and Platform, and the ISRCTN Registry).

Searching other resources

We will review the reference lists of all identified articles for relevant reports not identified in the primary search.

Data collection and analysis

We will record the selection process in sufficient detail to complete a PRISMA flow diagram (Moher 2009), and 'Characteristics of excluded studies' table.

Selection of studies

Two review authors (MB, LM) will independently search and identify eligible trials that meet the inclusion criteria. We will screen the titles and abstracts to identify potentially relevant citations. We will retrieve the full texts of all potentially relevant articles; we will independently assess the eligibility of the studies by filling out eligibility forms designed in accordance with the specified inclusion criteria. We will review studies for relevance based on study design, types of participants, interventions and outcome measures. We will resolve any disagreements by discussion and, if necessary, by consulting a third review author (MGC). We will provide details of studies excluded from the review in the 'Characteristics of excluded studies' table, along with the reasons for their exclusion. We will contact the trial authors if the details of the primary trial reports are not clear.

Data extraction and management

Two review authors (LM, MGC) will independently extract data using a data extraction form which has been integrated with a modified version of the data collection checklist from the Cochrane Effective Practice and Organisation of Care Group (EPOC 2013). We will extract the following characteristics from each included study.

- Administrative details: author(s); published or unpublished; year of publication; year in which study was conducted; details of other relevant papers cited.
- Details of the study: study design; method of randomization, blinding, stratification; duration and completeness of follow-up; country and location of study; informed consent and ethics approval.
- Details of participants: sex; birth weight; gestational age; and number of participants.
- Details of intervention: initiation, dose, duration and type of corticosteroid.
- Details of outcomes, as listed above in Types of outcome measures.

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We will resolve any disagreements by discussion. If we identify any ongoing studies from our search, we will record the primary author, research question(s), methods and outcome measures, together with an estimate of the reporting date.
Should we have any queries about a study, or require additional data, we will contact study investigators/authors for clarification. For each study, one review author (MGC) will enter data into Cochrane's statistical software, Review Manager 5 (Review Manager 2014), and a second review author (MB) will check the entered data.

Assessment of risk of bias in included studies

Two review authors (MB, MGC) will independently assess the risk of bias (low, high, or unclear) of all included trials, using the Cochrane 'Risk of bias' tool (Higgins 2017). We will assess the following domains.

- Sequence generation (selection bias)
- Allocation concealment (selection bias)
- Blinding of participants and personnel (performance bias)
- Blinding of outcome assessment (detection bias)
- Incomplete outcome data (attrition bias)
- Selective reporting (reporting bias)
- Any other bias

Any disagreements will be resolved by discussion or by a third assessor (MB). See Appendix 2 for a more detailed description of risk of bias for each domain.

Measures of treatment effect

For categorical variables, we will use risk ratios (RRs) and risk differences (RDs). For statistically significant results, we will calculate the number needed to treat for an additional beneficial outcome (NNTB) or number needed to treat for an additional harmful outcome (NNTH). We will use mean differences (MDs) and standardized mean differences (SMDs) for continuous variables. We plan to replace any within-group standard error of the mean (SEM) reported in a trial with its corresponding standard deviation (SD), using the formula SD = SEM x $\sqrt{N}$. We will report 95% confidence intervals (CIs) for each statistic. We will perform the statistical analyses using Review Manager 5 (RevMan 2014).

Unit of analysis issues

The unit of analysis will be individual infants. If we find any cluster-RCTs, we will adjust them for effects that result from their design using the methods stated in the*Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017).

Dealing with missing data

We will obtain a dropout rate for each study. If we find a significant dropout rate (e.g. more than 20%), we will contact study author(s) to request additional data. We will perform a sensitivity analysis to evaluate the overall results with and without inclusion of studies with a significant dropout rate. If a study reports outcomes only for participants completing the trial, or only for participants who followed the protocol, we will contact the study author(s) to ask them to provide additional information to facilitate an intention-to-treat analysis; in instances when this is not possible, we will perform a complete case analysis. We will address the potential impact of missing data on the findings of the review in the 'Discussion' section.

Assessment of heterogeneity

We plan to assess clinical heterogeneity by comparing the distribution of important participant factors between trials and trial factors (a? llocation concealment, ? b? ? linding of participants and personnel, b? ? ? linding of outcome assessment, ? i? ncomplete outcome data, s? ? elective reporting, treatment type, cointerventions). We will assess statistical heterogeneity by examining the I^2 statistic (Higgins 2017), a quantity that describes the proportion of variation in point estimates that is due to variability across studies rather than sampling error.
We will interpret the I^2 statistic as follows, in accordance with Higgins 2003:

- less than 25%: no heterogeneity;
- 25 to 49%: low heterogeneity;
- 50 to 74%: moderate heterogeneity;
- 75% or greater: high heterogeneity.

In addition, we will employ the Chi^2 test of homogeneity to determine the strength of evidence that heterogeneity is genuine. We will consider a threshold of P value less than 0.1 as an indicator of whether heterogeneity (genuine variation in effect sizes) is present.

Assessment of reporting biases

We will examine the possibility of within-study selective outcome reporting for each study included in the review. We will search for protocols of included trials on electronic sources such as PubMed, ClinicalTrials.gov, and the WHO International Clinical Trials Registry Platform, in order to assess whether outcome reporting seems to be sufficiently complete and transparent. We will investigate publication bias by using funnel plots if we include 10 or more clinical trials in the systematic review (Egger 1997; Higgins 2017).

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Data synthesis

We will perform statistical analyses according to the recommendations of the Cochrane Neonatal Review Group (neonatal.cochrane.org/en/index.html). We will analyze all infants randomized on an intention-to-treat basis. We will analyze treatment effects in the individual trials. In the first instance, we will use a fixed-effect model to combine the data. We plan to analyze and interpret individual trials separately when we judge meta-analysis to be inappropriate.

Quality of evidence

Two review authors will independently use the GRADE approach, as outlined in the GRADE Handbook (Schünemann 2013), to assess the quality of the evidence for the following (clinically relevant) outcomes: duration of hospital stay; need for mechanical ventilation; pneumothorax; duration of tachypnea; persistent pulmonary hypertension; hyperglycemia; gastrointestinal bleed.

We will consider evidence from RCTs as high quality, but will downgrade the evidence by one level for serious (or two levels for very serious) limitations based upon the following: design (risk of bias), consistency across studies, directness of the evidence, precision of estimates, and presence of publication bias. We will use the GRADEpro Guideline Development Tool (GRADEpro GDT) to create a 'Summary of findings' table to report the quality of the evidence.

The GRADE approach results in an assessment of the quality of a body of evidence, according to one of the following four grades.

1. High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
2. Moderate quality: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
3. Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
4. Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Subgroup analysis and investigation of heterogeneity

We will consider the following groups for subgroup analysis for the primary outcomes ? ? ? ? ? ? ? ? where data are available.

- Gestational age: term (37 weeks or greater); late preterm infants (34 weeks to less than 37 weeks).
- Birth weight: less than 2500 grams; 2500 grams or greater.
- Antenatal steroids: (yes/no)
- Type of corticosteroids: e.g. dexamethasone, budesonide, beclomethasone dipropionate, flunisolide, fluticasone propionate, betamethasone, hydrocortisone

Sensitivity analysis

We will conduct sensitivity analyses to explore the effect of the methodological quality of the trials, checking to ascertain if studies with a high risk of bias overestimate the effect of treatment. Differences in study design between included trials might affect the results of the systematic review. We plan to perform a sensitivity analysis to compare the effects of ? postnatal steroids? in truly randomized trials as opposed to quasi-randomized trials.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Cochrane Neonatal standard search strategy

PubMed: ((infant, newborn[MeSH] OR newborn OR neonate OR neonatal OR premature OR low birth weight OR VLBW OR LBW or infan* or neonat*) AND (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals [mh] NOT humans [mh]))
Embase: ((exp infant) OR (infan* OR newborn or neonat* OR premature or very low birth weight or low birth weight or VLBW or LBW).mp AND (human not animal) AND (randomized controlled trial or controlled clinical trial or randomized or placebo or clinical trials as topic or randomly or trial or clinical trial).mp
CINAHL: (infan* OR newborn OR neonat* OR premature OR low birth weight OR VLBW OR LBW) AND (randomized controlled trial OR controlled clinical trial OR randomized OR placebo OR clinical trials as topic OR randomly OR trial OR PT clinical trial)
Cochrane Library: (infan* or newborn or neonat* or premature or preterm or very low birth weight or low birth weight or VLBW or LBW)

Appendix 2. Risk of bias tool

We will use the standard methods of Cochrane and Cochrane Neonatal to assess the methodological quality of the trials. For each trial, we will seek information regarding the method of randomization, blinding and reporting of all outcomes of all the infants enrolled in the trial. We will assess each criterion as being at a low, high, or unclear risk of bias. Two review authors will separately assess each study. We will resolve any disagreement by discussion. We will add this information to the table Characteristics of included studies. We will evaluate the following issues and enter the findings into the risk of bias table:

1. Sequence generation (checking for possible selection bias). Was the allocation sequence adequately generated?

For each included study, we will categorize the method used to generate the allocation sequence as:

- low risk (any truly random process e.g. random number table; computer random number generator);
- high risk (any non-random process e.g. odd or even date of birth; hospital or clinic record number); or
- unclear risk.

2. Allocation concealment (checking for possible selection bias). Was allocation adequately concealed?

For each included study, we will categorize the method used to conceal the allocation sequence as:

- low risk (e.g. telephone or central randomization; consecutively numbered sealed opaque envelopes);
- high risk (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth); or

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- unclear risk

3. Blinding of participants and personnel (checking for possible performance bias). Was knowledge of the allocated intervention adequately prevented during the study?

For each included study, we will categorize the methods used to blind study participants and personnel from knowledge of which intervention a participant received. Blinding will be assessed separately for different outcomes or class of outcomes. We will categorize the methods as:

- low risk, high risk or unclear risk for participants; and
- low risk, high risk or unclear risk for personnel.

4. Blinding of outcome assessment (checking for possible detection bias). Was knowledge of the allocated intervention adequately prevented at the time of outcome assessment?

For each included study, we will categorize the methods used to blind outcome assessment. Blinding will be assessed separately for different outcomes or class of outcomes. We will categorize the methods as:

- low risk for outcome assessors;
- high risk for outcome assessors; or
- unclear risk for outcome assessors.

5. Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations). Were incomplete outcome data adequately addressed?

For each included study and for each outcome, we will describe the completeness of data including attrition and exclusions from the analysis. We will note whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomized participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information is reported or supplied by the trial authors, we will re-include missing data in the analyses. We will categorize the methods as:

- low risk (< 20% missing data);
- high risk ($\geq$ 20% missing data); or
- unclear risk.

6. Selective reporting bias. Are reports of the study free of suggestion of selective outcome reporting?

For each included study, we will describe how we investigated the possibility of selective outcome reporting bias and what we found. For studies in which study protocols were published in advance, we will compare prespecified outcomes versus outcomes eventually reported in the published results. If the study protocol was not published in advance, we will contact study authors to gain access to the study protocol. We will assess the methods as:

- low risk (where it is clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review have been reported);
- high risk (where not all the study's prespecified outcomes have been reported; one or more reported primary outcomes were not prespecified outcomes of interest and are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported); or
- unclear risk.

7. Other sources of bias. Was the study apparently free of other problems that could put it at a high risk of bias?

For each included study, we will describe any important concerns we had about other possible sources of bias (for example, whether there was a potential source of bias related to the specific study design or whether the trial was stopped early due to some data-dependent process). We will assess whether each study was free of other problems that could put it at risk of bias as:

- low risk;
- high risk;
- unclear risk

If needed, we plan to explore the impact of the level of bias through undertaking sensitivity analyses.

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CONTRIBUTIONS OF AUTHORS

MB and LM reviewed the literature and wrote the protocol.

MGC and OR commented on and reviewed the protocol.

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MB: no conflict of interest.

LM: no conflict of interest.

MGC: no conflict of interest.

OR: no conflict of interest.

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