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Superoxide dismutase for preventing bronchopulmonary dysplasia (BPD) in preterm infants (Protocol)

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[Intervention Protocol]

Superoxide dismutase for preventing bronchopulmonary dysplasia (BPD) in preterm infants

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ABSTRACT

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

To determine the efficacy and safety of superoxide dismutase (SOD) in the prevention and treatment of bronchopulmonary dysplasia on mortality and other complications of prematurity in infants at risk for or having bronchopulmonary dysplasia.

BACKGROUND

Description of the condition

Survival of preterm infants has increased in the previous 30 years due to a variety of antenatal and postnatal interventions (Horbar 2012; Soll 2013). Despite these significant advances in neonatal intensive care, bronchopulmonary dysplasia (BPD) still occurs in a significant proportion of preterm infants (Horbar 2012). BPD is a common morbidity in preterm infants, affecting 22% to 38% of extremely low gestational age neonates (gestational age < 28 weeks) (Poets 2018). Annually in the USA, there are approximately 10,000 to 15,000 new cases of BPD each year; BPD is typically more prevalent in infants that weigh less than 1250 grams (Balany 2015). BPD has long-lasting adverse effects including chronic respiratory difficulties, recurrent infection, prolonged and recurrent hospitalizations, increased evidence of neurodevelopmental disabilities, growth restriction and death (O'Brodovich 1985; Anderson 2006; Bhandari 2006).

The history of bronchopulmonary dysplasia (BPD) is ever evolving and elucidation of its pathophysiology has great potential to provide life-saving treatments for preterm infants (Northway 1967; Bancalari 1979; Farrell 1997). Northway was the first to describe this disease in infants who had used mechanical ventilation or had high oxygen requirements (Northway 1967). In the decades that followed, multiple definitions of BPD were proposed, many focusing on clinical and radiographic characteristics that were present at 1 month of age (Ehrenkranz 2005). In 1988, Shennan proposed a new definition, which is widely used now, of an oxygen requirement at 36 weeks' postmenstrual age (PMA) because it is more accurate in predicting the long-term pulmonary consequences of BPD (Shennan 1988; Isayama 2017).

The etiology of chronic lung disease in preterm infants is thought to be multifactorial. In his original report in 1967, Northway hy-

pothesized that oxygen toxicity, pulmonary healing in the setting of severe respiratory distress, and poor ventilation were implicated in BPD (Northway 1967). Currently, pathogenesis of BPD is also thought to be a multifactorial event that encompasses prenatal, postnatal, genetic, and environmental factors that act on immature lungs (Sampath 2015). Events such as infection can cause localized inflammation that can persist and are exacerbated by the use of mechanical ventilation or assistance with oxygen (Balany 2015). Increased ventilation and oxygen generate production of free radicals, which further elicit inflammation and injury to the mucosal surface of the lung (Sampath 2015). Balany postulated that these injuries cause immune dysregulation, and subsequent remodeling of the premature lung, which later progress to BPD (Balany 2015).

Given the multifaceted nature of the pathogenesis of BPD, it is not surprising that multiple interventions have been tested to prevent or treat BPD, and met with variable success. Antenatal infections can cause chorioamnionitis from organisms, such as *Ureaplasma* species, which can cause dysregulation of lung growth through inflammatory effects (Kallapur 2013). Antenatal corticosteroids work by stimulating growth of the immature lung (Roberts 2017). It has been shown that antenatal steroids reduce respiratory distress syndrome and mortality; however there seems to be no significant statistical reduction in BPD alone (Jain 2014; Goldstein 2017). In contrast, postnatal steroids administered in the first few weeks of life to infants at risk of BPD have reduced the use of assisted ventilation and BPD (Doyle 2017a; Doyle 2017b). However, both the short-term and longer-term complications of postnatal steroid exposure (including increased risk of cerebral palsy) have led to curtailed use in very low birth weight infants (AAP 2010).

Other potential strategies to reduce BPD in preterm infants include managing respiratory support. Trials have shown that use of high frequency ventilation, non-invasive respiratory support (continuous positive airway pressure [CPAP] or non-invasive positive pressure ventilation pressure [NIPPV]), permissive hypercapnia, and reduced oxygen support do not produce any statistically significant reductions in the incidence of BPD (Jain 2014; Ma 2016). However, volume controlled ventilation, as well as exogenous surfactant, have been shown to reduce rates of BPD and mortality of preterm infants (Seger 2009; Klingbenberg 2017).

Multiple pharmacologic agents have been proposed to treat BPD with varying degrees of success. Current pharmacologic interventions include systemic corticosteroids (Doyle 2017a; Doyle 2017b), caffeine (Schmidt 2006), and vitamin A (Ghanta 2013; Darlow 2016). Interestingly, caffeine has been used for apnea of prematurity; however studies have found that it decreases rates of BPD and reduces the need for ventilation in the first seven days of life (Schmidt 2006). Intramuscular vitamin A is another agent that has shown efficacy in reducing the rates of chronic lung disease and mortality, with no known long-term effects on neurodevelopmental disease (Darlow 2016). Inhaled nitric oxide (iNO) is another pharmacological treatment that has been suggested for preventing BPD; however, a meta-analysis of trials in various preterm populations found that there is no significant reduction in mortality or incidence of BPD (Barrington 2017).

Antioxidant therapy has also been a suggested for treatment of BPD. Vitamin E has been shown to function as a scavenger for free radicals protecting cells from oxidant injury (Biniwale 2006). Consequently, other antioxidant therapies, such as superoxide dismutase (SOD), have great potential to mitigate or reduce BPD by blocking the effects of free radicals.

Description of the intervention

Superoxide dismutase (SOD) is an intracellular enzyme that converts the extremely toxic superoxide radical into potentially less toxic hydrogen peroxide (Pham-Huy 2008). Superoxide dismutase appears in two forms: one in the cytoplasm of the cell or in the extracellular spaces with two subunits, each with one equivalent of Cu^{2+} and Zn^{2+}; the other in the mitochondria with Mn^{2+} as its subunit.

How the intervention might work

Arguably, oxygen is the most essential element in the human body. It is involved in maintaining basic life process, but if unregulated can cause severe damage in the form of free radicals. A free radical is an atom or molecule that contains an unpaired electron. Radicals produced endogenously in the body include the superoxide and hydroxyl radicals, hydrogen peroxide, hypochlorous acid, peroxynitrite, and nitric oxide. Free radicals are produced in abundance in all cells. This type of oxidative stress causes cell damage and at a molecular level, DNA and RNA damage (Wojtunik-Kulesza 2016).

In healthy humans a balance exists between oxygen-derived free-radical production and their inactivation by antioxidant defenses. Typically the body can counteract free radicals; however if there is an inability to reduce them via anti-oxidative enzymes, then catastrophic tissue damage can occur (Wojtunik-Kulesza 2016). In adults, oxidative stress is implicated in aging, cardiovascular disease, cataracts, neurodegenerative disorders, neoplasia, and other disorders (Knight 1998; Pham-Huy 2008).

Disturbances in this balance may contribute to the pathogenesis of certain disease processes seen in the preterm infant such as chronic lung disease (Saugstad 1990; Kelly 1993; Fardy 1995), retinopathy of prematurity (Saugstad 1990; Kelly 1993), intraventricular hemorrhage (Kelly 1993), and periventricular leukomalacia (Volpe 1997). Preterm infants are often exposed to excessive oxidative stress because they are exposed to high oxygen concentrations due to surfactant deficiency and immature lungs. In addition, preterm infants have inadequate antioxidant defenses and are not able to induce antioxidant enzymes in response to oxidative stress (Davis 1998; Saugstad 1998). Also, inflammation and infection, which

are closely linked to oxidative stress, are more common in preterm infants (Saugstad 1998).

However numerous natural defenses exist either to prevent the formation of free radicals, or to neutralize them once they are produced. Anti-oxidants, including SOD, play a key role in mitigating the damage caused by free radicals. It is thought that infants have a reduction or a deficiency in these enzymes due to prematurity, which results in increased susceptibility to oxidative damage to growing tissue. It has been hypothesized that providing exogenous antioxidants in the form of SOD can potentially prevent BPD and other secondary outcomes by reducing the increased oxidative stress experienced by preterm infants born to a hyperoxic environment.

Why it is important to do this review

BPD remains an ongoing problem in preterm infants with few safe treatments available. On-going research into anti-oxidant therapies, including SOD, hold great promise for future treatment. This systematic review will review all randomized trials of exogenously administered SOD for the prevention of chronic lung disease in preterm infants receiving mechanical ventilation. It is an update of the original Suresh 2001 review.

OBJECTIVES

To determine the efficacy and safety of superoxide dismutase (SOD) in the prevention and treatment of bronchopulmonary dysplasia on mortality and other complications of prematurity in infants at risk for or having bronchopulmonary dysplasia.

METHODS

Criteria for considering studies for this review

Types of studies

We will include only randomized (RCTs) or quasi-randomized controlled studies (QRCTs) or cluster-randomized controlled trials where subjects were randomly allocated to receive superoxide dismutase (SOD) (any dose, any route) versus placebo or no treatment.

Types of participants

We will include studies conducted in preterm infants of 32 weeks' gestation or less, or very low birth weight infants (VLBW) weighing less than 1500 grams who are at risk of BPD (regardless of respiratory support), or with early respiratory insufficiency who require respiratory support, including conventional ventilation, high frequency ventilation, NIPPV, NCPAP or supplemental oxygen.

Types of interventions

We will include studies in which SOD was administered in any form, by any route, and at any time in the first six months of life compared to placebo or no treatment in the control group.

Comparison 1: SOD versus no treatment or placebo in preterm infants at risk for BPD.

Comparison 2: SOD versus no treatment or placebo in preterm infants with early respiratory insufficiency.

Types of outcome measures

Primary outcomes

1. BPD defined as an oxygen requirement at 28 days
2. BPD defined as oxygen at 36 weeks' postmenstrual age
3. Neonatal mortality
4. Mortality prior to discharge
5. BPD or death at 36 weeks' postmenstrual age

Secondary outcomes

1. Hemodynamically significant patent ductus arteriosus (Arlettaz 2017)
2. Patent ductus arteriosus (PDA) requiring treatment
3. Sepsis (with proven culture)
4. Necrotizing enterocolitis (Bell ≥ stage 2)(Bell 1978)
5. Intraventricular hemorrhage (IVH) (any)(Papile)
6. Severe intraventricular hemorrhage (IVH) (grades III-IV)(Papile 1978)
7. Periventricular leukomalacia (PVL)
8. Retinopathy of prematurity (any stage)(ICROP 1984)
9. Severe retinopathy of prematurity (stage II or greater)
10. Duration of assisted ventilation (days)
11. Duration of oxygen dependence (days)
12. Duration of hospital stay (days)
13. Moderate to severe neurodevelopmental outcome at 18 to 24 months (any of the following complications):

i) cerebral palsy, developmental delay (Bayley or Griffith assessment > 2 standard deviations (SD) below the mean);

ii) intellectual impairment (intelligence quotient [IQ] > 2 SD below the mean);

iii) blindness (vision < 6/60 in both eyes);
iv) sensorineural deafness requiring amplification)

14. Components of moderate to severe neurodevelopmental outcomes at 18 to 24 months, including:
i) cerebral palsy;
ii) developmental delay (Bayley or Griffith assessment > 2 SD below the mean);
iii) intellectual impairment (IQ > 2 SD below the mean);
iv) blindness (vision < 6/60 in both eyes);
v) sensorineural deafness requiring amplification

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) in The Cochrane Library; MEDLINE via PubMed (1966 to present); Embase (1980 to present); and CINAHL (1982 to present) using the following search terms: anti-oxidant; antioxidant; superoxide dismutase; free radical injury, CuZnSOD; rhSOD, plus database-specific limiters for RCTs and neonates (see Appendix 1 for the full search strategies for each database). We will not apply 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

In addition to the electronic searches described above, we will review the reference lists of all relevant articles we identify for references to relevant articles not identified in the primary search.

Data collection and analysis

We will collect information regarding the method of randomization, blinding, drug intervention, stratification, and whether the trial was single- or multicentered for each included study. We will note the information regarding trial participants including gestational age criteria, birth weight criteria, and other inclusion or exclusion criteria. We will analyze the information on primary and secondary clinical outcomes noted above.

Selection of studies

We will include all randomized and quasi-randomized controlled trials fulfilling the selection criteria described in the previous section. Both superiority trials and non-inferiority trials are eligible for inclusion. All review authors will review the results of the search and select the studies for inclusion separately. The review authors will resolve any disagreement by discussion.

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

Data extraction and management

RRG and RFS will extract, assess, and code all data for each study, using a form designed specifically for this review. We will replace any standard error of the mean with the corresponding standard deviation. We will resolve any disagreement by discussion. For each study, final data will be entered into Review Manager 5 (RevMan 5) by one review author (RRG) and then checked by the other review author (RFS) (Review Manager 2014). All authors will review the protocol, analysis and draft manuscript.

Assessment of risk of bias in included studies

Independently, two review authors (RRG and RFS) will assess the risk of bias (low, high, or unclear) of all included trials using the Cochrane 'Risk of bias' tool for the following domains (Higgins 2017).

1. Sequence generation (selection bias)
2. Allocation concealment (selection bias)
3. Blinding of participants and personnel (performance bias)
4. Blinding of outcome assessment (detection bias)
5. Incomplete outcome data (attrition bias)
6. Selective reporting (reporting bias)
7. Any other bias

We will resolve any disagreements by discussion or with the input of a third assessor. See Appendix 2 for a more detailed description of risk of bias for each domain.

Measures of treatment effect

We will perform the statistical analyses using RevMan 5 software (Review Manager 2014). We will analyze categorical data using risk ratio (RR), and risk difference (RD). For statistically significant outcomes we will calculate the number needed to treat for an beneficial outcome (NNTB) or number needed to treat for an additional harmful outcome (NNTH). For continuous data, we will calculate mean differences (MDs) between treatment groups where outcomes are measured in the same way; where outcomes are measured differently, we will report data as standardized mean differences (SMD). We will report 95% confidence intervals (CIs) for all outcomes.

Unit of analysis issues

The unit of analysis will be the participating infant in individually randomized trials, and each infant will be considered only once in the analyses. The participating neonatal unit or section of a neonatal unit or hospital will be the unit of analysis in cluster-randomized trials. We will analyze them using an estimate of the intra-cluster correlation coefficient (ICC) derived from the trial (if possible), or from a similar trial or from a study with a similar population as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Section 16.3.6) (Higgins 2011). If we use ICCs from a similar trial or from a study with a similar population we will report this and conduct a sensitivity analysis to investigate the effect of variation in the ICC.

If we identify both cluster-randomized trials and individually randomized trials, we will only combine the results if there is little heterogeneity between the study designs, and interaction between the effect of the intervention and the choice of randomization unit is considered to be unlikely.

We will acknowledge any possible heterogeneity in the randomization unit and perform a sensitivity analysis to investigate possible effects of the randomization unit.

Dealing with missing data

Where feasible, we intend to carry out analysis on an intention-to-treat basis for all outcomes. We will analyze all participants in the treatment group to which they were randomized, regardless of the actual treatment received, whenever possible. If important missing data (in the outcomes) or unclear data are identified, we will request the missing data by contacting the original investigators. We will make explicit the assumptions of any methods we use to cope with missing data. We may perform sensitivity analyses to assess how sensitive results are to reasonable changes in the assumptions that are made. We will address the potential impact of missing data on the findings of the review in the 'Discussion' section.

Assessment of heterogeneity

We will estimate the treatment effects of individual trials and examine heterogeneity among trials by inspecting the forest plots and quantifying the impact of heterogeneity using the I^2 statistic. We will grade the degree of heterogeneity according to the I^2 value thus: less than 25% indicates no heterogeneity; 25% to 49% indicates low heterogeneity; 50% to 75% indicates moderate heterogeneity; and over 75% indicates substantial heterogeneity. If statistical heterogeneity (I^2 > 50%) is noted, we will explore the possible causes (for example, differences in study quality, participants, intervention regimens, or outcome assessments).

Assessment of reporting biases

We intend to conduct a comprehensive search for eligible studies and we will be alert for duplication of data. If we identify 10 or more trials for meta-analysis, we will assess possible publication bias by inspection of a funnel plot. If we uncover reporting bias that could, in the opinion of the authors, introduce serious bias, we plan to conduct a sensitivity analysis to determine the effect of including and excluding these studies in the analysis.

Data synthesis

If multiple studies are identified and thought to be sufficiently similar, we will perform meta-analysis using Review Manager 2014, supplied by Cochrane. For categorical (dichotomous) outcomes we will calculate the typical estimates of RR and RD, each with its 95% CI; and for continuous outcomes we will calculate the weighted mean difference (WMD) or a summary estimate for the SMD, each with its 95% CI. We will use a fixed-effect model to combine data where it is reasonable to assume that studies are estimating the same underlying treatment effect. If we judge that performing meta-analysis will be inappropriate, we will analyze and interpret individual trials separately. If there is evidence of clinical heterogeneity, we will try to explain this on the basis of the different study characteristics and subgroup analyses.

Quality of evidence

We will use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, as outlined in the GRADE Handbook (Schünemann 2013), to assess the quality of evidence for the following (clinically relevant) outcomes:

1. BPD defined by an oxygen requirement at 28 days or an oxygen at 36 weeks' postmenstrual age;
2. Mortality (neonatal mortality at 28 days and death prior to discharge);
3. BPD or death at 36 weeks' postmenstrual age;
4. Need for supplemental oxygen (days);
5. Retinopathy of prematurity (ROP) defined by any stages or zones reported (stage 2 or greater)(ICROP 1984);
6. Moderate to severe neurodevelopmental outcome at 18 to 24 months (any of the following complications):cerebral palsy, developmental delay (Bayley or Griffith assessment > 2 standard deviations (SD) below the mean);intellectual impairment (intelligence quotient [IQ] > 2 SD below the mean);blindness (vision < 6/60 in both eyes);sensorineural deafness requiring amplification)

Independently, two authors will assess the quality of the evidence for each of the outcomes above. We will consider evidence from randomized controlled trials as high quality, but downgrade the evidence 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 GDT Guideline Development Tool 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 in one of four grades.

1. High: we are very confident that the true effect lies close to that of the estimate of the effect.
2. Moderate: 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: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
4. Very low: 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

Gestational age, the type and dose of SOD used, age at enrollment, respiratory status (assisted ventilation, CPAP, NIPPV), age at treatment (less than 32 weeks' gestation).

Sensitivity analysis

Where we identify substantial heterogeneity, we will conduct sensitivity analysis to determine whether the findings are affected by inclusion of only those trials considered to have adequate methodology with a low risk of bias (selection and performance bias). We will report results of sensitivity analyses for primary outcomes only.

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The methods section of this review is based on a standard template used by Cochrane Neonatal.

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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

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
- 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 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 we will categorize the methods used to blind outcome assessment. Blinding will be assessed separately for different outcomes or class of outcomes. We 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 was reported or supplied by the trial authors, we will re-include missing data in the analyses. We 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 will explore the impact of the level of bias through undertaking sensitivity analyses.

WHAT'S NEW

Date	Event	Description
23 August 2018	New citation required and major changes	This review will replace the existing Cochrane Neonatal review of "Superoxide dismutase for preventing chronic lung disease in mechanically ventilated preterm infants."

CONTRIBUTIONS OF AUTHORS

RRG drafted the protocol update. RS worked with RRG on the initial draft. DE and GS reviewed the updated protocol and will help with data validation and review of the upcoming systematic review.

DECLARATIONS OF INTEREST

None.

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