Different magnesium sulphate regimens for neuroprotection of the fetus for women at risk of preterm birth (Protocol)

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Different magnesium sulphate regimens for neuroprotection of the fetus for women at risk of preterm birth (Protocol)  
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Different magnesium sulphate regimens for neuroprotection of the fetus for women at risk of preterm birth

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Editorial group: Cochrane Pregnancy and Childbirth Group.


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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

The aim of this review is to assess the comparative effectiveness and adverse effects of different magnesium sulphate regimens for neuroprotection of the fetus in women considered at risk of preterm birth.
**BACKGROUND**

**Preterm birth and neurologic outcome**

Infants born preterm (less than 37 weeks) have an increased risk of mortality during their first few weeks of life (Saigal 2008). Whilst survival rates for preterm infants have improved (Doyle 2004), those infants who survive may have a greater risk of neurodevelopmental impairments including cerebral palsy (CP), cognitive dysfunction, and sensory impairments (blindness and deafness) (Doyle 2004; Drummond 2002; Lorenz 1998; Petriti 2009; Saigal 2008) and in turn a significant risk of substantial disability (Doyle 2001; Saigal 2008). Along with very low birthweight (VLBW), very preterm birth (less than 34 weeks) is a principal risk factor for CP (Lorenz 1998); the prevalence of CP increases significantly with decreasing gestational age (Drummond 2002; Hagberg 2001; Himpens 2008; Petriti 2009; Saigal 2008). Decreasing gestational age is associated with increased vulnerability of cerebral white matter, and is consequently predictive of an increasing risk of white matter damage such as periventricular leukomalacia (PVL), and of intraventricular haemorrhage (IVH) (Larroque 2003) - established risk factors for the development of CP and other disabilities (Saliba 2001).

**Magnesium sulphate for women at risk of preterm birth**

An association between maternal administration of magnesium sulphate and a reduction in the risk of IVH was first described by Kuban and colleagues. A significantly lower risk of IVH was found among babies born to mothers who had received magnesium sulphate regardless of whether they had pre-eclampsia (Kuban 1992). Nelson and Grether later described an association between antenatal magnesium sulphate and a reduced risk of CP in VLBW infants (less than 1500 g) (Nelson 1995). In their case-control study, in utero exposure to magnesium sulphate whether given as a tocolytic, to suppress preterm labour, or for pre-eclampsia, was more frequent in controls than in children with CP; the odds ratio (OR) (OR 0.14; 95% confidence interval (CI) 0.05 to 0.51) suggested a significant protective effect of magnesium sulphate (Nelson 1995).

Additional observational studies have supported such findings. Antenatal magnesium sulphate has been reported to be associated with protective effects for PVL (FineSmith 1997), IVH (Perlman 1997), CP (Hauth 1995; Matsuda 2000; Schendel 1996), and perinatal mortality (Grether 1998). Inconsistencies have existed, however, with a number of observational studies not reporting beneficial effects for antenatal magnesium sulphate for the risk of PVL (Canterino 1999), IVH (Canterino 1999; Kimberlin 1999; Weintraub 2001), CP (Boyle 2000; Costantine 2007; Grether 2000; O’Shea 1998; Paneth 1997; Wilson-Costello 1998), and perinatal mortality (Kimberlin 1999).

In order to establish reliable evidence, a number of randomised controlled trials have been undertaken assessing the effects of in utero exposure to magnesium sulphate for preventing perinatal cerebral injuries, CP, and perinatal mortality, when given to women at risk of preterm birth. The Doyle 2009 Cochrane systematic review included five randomised controlled trials (6145 infants) comparing magnesium sulphate with placebo or no treatment. The primary aim of four included studies, two from the United States (Mittendorf 2002; Rouse 2008), one from Australia and New Zealand (Crowther 2003), and one from France (Marret 2007b), was fetal neuroprotection, although one trial had a second tocolytic arm of the study (Mittendorf 2002). The primary aim of the fifth study (Mappie 2007), conducted worldwide, was the prevention of eclampsia; however long-term neurological outcomes were reported for the infants.

In the Doyle 2009 review, magnesium sulphate administered to the mother specifically with neuroprotective intent was associated with a 15% relative reduction in the risk of death or CP (risk ratio (RR) 0.85, CI 0.74 to 0.98; four trials; 4446 infants). Overall antenatal magnesium sulphate treatment was associated with a 32% relative reduction in the risk of CP (RR 0.68, 95% CI 0.54 to 0.87; five trials; 6145 infants). This review confirmed the neuroprotective role for antenatal magnesium sulphate given to women at risk of preterm birth, showing that 63 babies (95% CI 44 to 155) would need to be treated to benefit one baby by avoiding CP, and 42 babies (95% CI 24 to 346) would need to be treated to benefit one baby by avoiding death or CP (Doyle 2009).

**Different regimens for magnesium sulphate**

The optimal antenatal magnesium sulphate regimen for fetal neuroprotection in terms of dose, duration, timing, and whether repeat dosing should be permitted remains unclear. As the association between magnesium sulphate and a reduced risk of CP was first noted in observational studies in which magnesium sulphate was given for tocolysis or pre-eclampsia, the treatment regimens used for these intentions largely guided the regimens used in the randomised trials for fetal neuroprotection.

Whilst in all of the trials, intravenous magnesium sulphate was used, there was variation in the loading and maintenance dose regimens, the durations, and timings of therapy, and whether repeat treatment was permitted. Loading dose regimens varied from 4 g over 10 to 15 minutes (Mappie 2007) to 6 g over 20 to 30 minutes (Rouse 2008), with maintenance dose regimens varying from none (Mittendorf 2002; Marret 2007b), to 1 g per hour (Crowther 2003), to 2 g per hour (Rouse 2008). Duration of infusion varied from 12 to 24 hours, and in all but one trial (Rouse 2008) repeat dosing was not permitted. The time magnesium sulphate was planned to be given prior to preterm birth similarly varied in the trials; in two trials magnesium sulphate was given when birth was planned or expected within 24 hours, with median times from randomisation to birth of three hours 47 minutes...
(Crowther 2003) and one hour 38 minutes (Marret 2007b). In a further trial, most women were given magnesium sulphate for preterm premature rupture of membranes, with a 25-hour median time to birth (Rouse 2008); in one trial the timing was not specified (Mittendorf 2002).

As differences in death and CP by regimen are unclear at present, no particular regimen has been judged to have a greater or lesser impact than another. The ideal treatment regimen has not been established.

**Adverse maternal effects of magnesium sulphate**

Due to the widespread use of magnesium sulphate in obstetrics, the potential for adverse maternal effects following administration is well recognised, and has been noted in the Cochrane reviews assessing the various antenatal indications (Crowther 2009; Doyle 2009; Duley 2010a; Duley 2010b; Han 2010).

Whilst life-threatening magnesium toxicity in obstetrics is extremely rare, and should not occur with correct administration (Lu 2000), consequences of severe hypermagnesemia, including respiratory and cardiac arrest, have been detailed in case reports (Bohman 1990; McCubbin 1981; McDonnell 2009; Morisaki 2000; Richards 1985; Wax 1995).

More frequently noted, however, are occurrences of minor adverse effects with antenatal magnesium sulphate therapy. Such adverse effects are well recognised and include pain in the arm during intravenous infusion, and flushing, warmth, and sweating, due to the peripheral vasodilatory effects of magnesium. Further adverse effects associated with therapy include nausea, vomiting, headaches, muscle weakness, and blurred vision (Lu 2000).

In the randomised trials for neuroprotection of the fetus, and on meta-analysis in the Doyle 2009 review, serious maternal complications of therapy, such as death, cardiac arrest, and respiratory arrest were not more frequent among women exposed to magnesium sulphate. As expected, however, significantly higher rates of minor maternal adverse effects were observed among women exposed to magnesium sulphate as compared to control women; an approximate 50% increase of both hypotension and tachycardia were reported. Additional adverse effects including flushing, nausea or vomiting, sweating, and problems at injection site, were more frequent among women exposed to magnesium sulphate, as compared to control women. Importantly, significantly more women receiving magnesium sulphate ceased therapy because of adverse effects (RR 3.26, 95% CI 2.46 to 4.31) (Doyle 2009).

As administration of antenatal magnesium sulphate for fetal neuroprotection is associated with a risk of adverse maternal effects and therapy cessation, it is important to determine the ideal treatment regimen, which maintains effectiveness whilst minimising adverse effects.

**Mode of action for magnesium sulphate**

The precise mechanism of action of magnesium sulphate for neuroprotection of the fetus is not known. Experimental evidence and animal studies have supported several possible neuroprotective effects of magnesium (Marret 2007a).

In humans, magnesium in essential for health, through key cellular processes including protein synthesis, lipid and nucleic acid metabolism, glycolysis, oxidative phosphorylation, and the maintenance of membrane integrity (McIntosh 1989). Magnesium is vital for normal functioning of CNS cells, activating ATP-ase, enhancing phosphorylation, and controlling calcium flow as the endogenous regulator of N-methyl-D-aspartate (NMDA) receptor calcium channel activity (Vink 2009).

Animal studies have revealed that magnesium is neuroprotective during perinatal brain injury (Hoffman 1994; Mami 2006; Marret 1995; McDonald 1990). The developing brain is regarded as particularly sensitive to glutamate-mediated damage, proposed to be associated with an up-regulation of NMDA receptors with enhanced function (Johnston 2002). It is thus plausible that magnesium can protect against hypoxic/ischemic perinatal brain injury and neurological dysfunction through inhibiting glutamate-mediated NMDA receptor activation, consequently reducing calcium influx, and subsequent excitotoxic cell injury (Antonov 1999; Gathwala 2001; McIntosh 1989; Nowak 1984).

**Rationale for the review**

The effectiveness of antenatal magnesium sulphate for neuroprotection of the fetus, infant, and child has now been established (Doyle 2009). Implementation would be strengthened if recommendations for practice could be based on reliable evidence about the comparative effectiveness and adverse effect profiles of different magnesium sulphate regimens.

As administration of higher doses of magnesium sulphate may be associated with a greater risk of adverse effects, and the duration of therapy affects the requirement for costly supervision by trained staff, it is important to assess the optimal regimen and minimum effective dose. No review assessing studies making head-to-head comparisons of different regimens of magnesium sulphate for fetal neuroprotection has been identified.

**OBJECTIVES**

The aim of this review is to assess the comparative effectiveness and adverse effects of different magnesium sulphate regimens for neuroprotection of the fetus in women considered at risk of preterm birth.

**METHODS**

Different magnesium sulphate regimens for neuroprotection of the fetus for women at risk of preterm birth (Protocol)
Criteria for considering studies for this review

Types of studies
We will include all published, unpublished, and ongoing randomised trials with reported data that compare different magnesium sulphate regimens used for neuroprotection of the fetus in women at risk of preterm birth. The trials must use some form of random allocation. We will include cluster trials. We will exclude quasi-randomised trials and those with a crossover design. We will include trials published in abstract form only.

Types of participants
We will include women expected to give birth preterm (before 37 weeks), regardless of the reason, number of babies in utero, and parity.

Types of interventions
We will include all randomised comparisons of different antenatal magnesium sulphate regimens for neuroprotection of the fetus given to women at risk of preterm birth. Comparisons could include different routes of administration, different loading or maintenance doses, different durations of therapy, timings of therapy, and whether re-treatment is permitted. We will exclude trials where magnesium sulphate was compared with placebo or no treatment, as those trials are covered in a separate review (Doyle 2009).

Types of outcome measures

Primary outcomes
Primary outcomes will be those most representative of the clinically important measures of effectiveness and safety, including serious outcomes for women and their infants.

For the infant/child
- Death (fetal, neonatal, or later death up to the time of follow-up)
- Cerebral palsy (abnormality of tone with motor dysfunction, or as defined by trialists)
- Death or cerebral palsy (as they are competing outcomes this combined outcome is often considered the most clinically relevant for assessing neuroprotection)

For the woman
- Serious adverse cardiovascular or respiratory outcome related to therapy (respiratory arrest, cardiac arrest, death)
- Adverse effect(s) severe enough to stop treatment
- Need for calcium gluconate

Secondary outcomes
Secondary outcomes will include other measures of effectiveness and safety.

For the infant
- Intraventricular haemorrhage (IVH)
- Grade 3 or 4 IVH
- Periventricular leukomalacia
- Apgar score (less than seven at five minutes)
- Need for active resuscitation at birth (assisted ventilation via an endotracheal tube)
- Neonatal convulsions
- Neonatal hypotonia
- Use of respiratory support (mechanical ventilation or continuous positive airways pressure, or both)
- Chronic lung disease (need for continuous, supplemental oxygen at 28 days postnatal age or 36 weeks' postmenstrual age)
- Use of postnatal corticosteroids

For the infant/child
- Cerebral palsy (mild, moderate or severe, evaluated separately, as defined by trialists)
- Other neurological impairments
  - Developmental delay or intellectual impairment (developmental quotient or intelligence quotient less than one standard deviation (SD) below the mean)
  - Blindness (corrected visual acuity worse than 6/60 in the better eye)
  - Deafness (hearing loss requiring amplification or worse)
- Substantial gross motor dysfunction (child was not walking at two years, or was unable to grasp and release a small block with both hands)
- Major neurologic disability
  - Moderate or severe cerebral palsy (as defined by trialists)
  - Moderate or severe neurological impairment: developmental delay or intellectual impairment (developmental quotient or intelligence quotient less than two SD below the mean)
  - Legal blindness
  - Sensorineural deafness requiring hearing aids
- Death or any neurological impairment
- Death or substantial gross motor dysfunction
- Death or any major neurologic disability

For the child
- Growth assessments at childhood follow-up (weight, head circumference, height)
- Educational achievements
For the woman

● Any adverse effects of therapy
● Clinical adverse effects of therapy (reduced or absent tendon reflexes, hypotension, respiratory depression, tachycardia, postpartum haemorrhage, hypocalcaemia, pulmonary oedema, other)
  ● Self-reported adverse effects or symptoms of therapy (arm discomfort with infusion, blurred vision, dizziness, headache, mouth dryness, muscle weakness, nausea or vomiting, sleepiness or drowsiness, sweating, warmth over body or flushing, other)
● Mode of birth
● Induction or augmentation of labour
● Length of labour
● Satisfaction with therapy

Use of health services

● Admission to intensive care unit for the mother
● Length of postnatal hospitalisation for the women
● Admission to neonatal intensive care
● Length of stay in neonatal intensive care unit
● Length of neonatal hospitalisation

Search methods for identification of studies

Electronic searches

We will contact the Trials Search Co-ordinator to search the Cochrane Pregnancy and Childbirth Group’s Trials Register. The Cochrane Pregnancy and Childbirth Group’s Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:
  1. quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
  2. weekly searches of MEDLINE;
  3. weekly searches of EMBASE;
  4. handsearches of 30 journals and the proceedings of major conferences;
  5. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL, MEDLINE and EMBASE, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the ‘Specialized Register’ section within the editorial information about the Cochrane Pregnancy and Childbirth Group.

Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

We will not apply any language restrictions.

Data collection and analysis

Selection of studies

Two review authors will independently assess for inclusion all the potential studies we identify as a result of the search strategy. We will resolve any disagreement through discussion or, if required, we will consult the third author.

Data extraction and management

We will design a form to extract data. For eligible studies, two review authors will extract the data using the agreed form. We will resolve discrepancies through discussion or, if required, we will consult the third author. We will enter data into Review Manager software (RevMan 2011) and check for accuracy.

When information regarding any of the above is unclear, we will attempt to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors will independently assess risk of bias for each study using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). We will resolve any disagreement by discussion or by involving a third assessor.

(1) Random sequence generation (checking for possible selection bias)

We will describe for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We will assess the method as:
  ● low risk of bias (any truly random process, e.g. random number table; computer random number generator);
  ● high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number); or
  ● unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

We will describe for each included study the method used to conceal allocation to interventions prior to assignment and will assess whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We will assess the methods as:
  ● low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
  ● high risk of bias (open random allocation; unsealed or non-opaque envelopes; alternation; date of birth); or
  ● unclear risk of bias.
(3.1) Blinding of participants and personnel (checking for possible performance bias)

We will describe for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We will consider that studies are at low risk of bias if they were blinded, or if we judge that the lack of blinding would be unlikely to affect results. We will assess blinding separately for different outcomes or classes of outcomes.

We will assess the methods as:
- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel.

(3.2) Blinding of outcome assessment (checking for possible detection bias)

We will describe for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We will assess blinding separately for different outcomes or classes of outcomes.

We will assess methods used to blind outcome assessment as:
- low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

We will describe for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We will state whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomised 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 can be supplied by the trial authors, we will re-include missing data in the analyses which we undertake.

We will assess methods as:
- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups and is unlikely to influence the outcome; missing data have been imputed using appropriate methods);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; ‘as treated’ analysis done with substantial departure of intervention received from that assigned at randomisation);
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

We will describe for each included study how we investigated the possibility of selective outcome reporting bias and what we found. We will assess the methods as:
- low risk of bias (where it is clear that all of the study’s pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study’s pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest 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);
- unclear risk of bias.

(6) Other bias (checking for bias due to problems not covered by (1) to (5) above)

We will describe for each included study any important concerns we have about other possible sources of bias.

We will assess whether each study was free of other problems that could put it at risk of bias:
- low risk of other bias;
- high risk of other bias;
- unclear whether there is risk of other bias.

(7) Overall risk of bias

We will make explicit judgements about whether studies are at high risk of bias, according to the criteria given in the Handbook (Higgins 2011). With reference to (1) to (6) above, we will assess the likely magnitude and direction of the bias and whether we consider it is likely to impact on the findings. We will explore the impact of the level of bias through undertaking sensitivity analyses - see Sensitivity analysis.

Measures of treatment effect

Dichotomous data

For dichotomous data, we will present results as summary risk ratio with 95% confidence intervals.

Continuous data

For continuous data, we will use the mean difference if outcomes are measured in the same way between trials. We will use the standardised mean difference to combine trials that measure the same outcome, but use different methods.

Unit of analysis issues

Cluster-randomised trials

We will include cluster-randomised trials in the analyses along with individually randomised trials. We will adjust their sample sizes...
using the methods described in the Handbook using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial, or from a study of a similar population. If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomised trials and individually-randomised trials, we plan to synthesise the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely. We will also acknowledge heterogeneity in the randomisation unit and perform a sensitivity analysis to investigate the effects of the randomisation unit.

**Crossover trials**

We consider crossover designs inappropriate for this research question.

**Dealing with missing data**

For included studies, we will note levels of attrition. We will explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis.

For all outcomes, we will carry out analyses, as far as possible, on an intention-to-treat basis, i.e. we will attempt to include all participants randomised to each group in the analyses, and analyse all participants in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial will be the number randomised minus any participants whose outcomes are known to be missing.

**Assessment of heterogeneity**

We will assess statistical heterogeneity in each meta-analysis using the $T^2$, $I^2$, and Chi² statistics. We will regard heterogeneity as substantial if $I^2$ is greater than 30% and either $T^2$ is greater than zero, or there is a low P value (less than 0.10) in the Chi² test for heterogeneity.

**Assessment of reporting biases**

If there are 10 or more studies in the meta-analysis we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually, and use formal tests for funnel plot asymmetry. For continuous outcomes we will use the test proposed by Egger 1997, and for dichotomous outcomes we will use the test proposed by Harbord 2006. If asymmetry is detected in any of these tests or is suggested by a visual assessment, we will perform exploratory analyses to investigate it.

**Data synthesis**

We will carry out statistical analysis using the Review Manager software (RevMan 2011). We will use fixed-effect meta-analysis for combining data where it is reasonable to assume that studies are estimating the same underlying treatment effect; i.e. where trials are examining the same intervention, and the trials’ populations and methods are judged sufficiently similar. If there is clinical heterogeneity sufficient to expect that the underlying treatment effects differ between trials, or if substantial statistical heterogeneity is detected, we will use random-effects meta-analysis to produce an overall summary if an average treatment effect across trials is considered clinically meaningful. The random-effects summary will be treated as the average range of possible treatment effects and we will discuss the clinical implications of treatment effects differing between trials. If the average treatment effect is not clinically meaningful we will not combine trials.

If we use random-effects analyses, we will present the results as the average treatment effect with 95% confidence intervals, and the estimates of $T^2$ and $I^2$.

**Subgroup analysis and investigation of heterogeneity**

We will perform separate comparisons for different types of regimens, i.e. different routes of administration, loading and maintenance doses, durations, timings, or whether repeat dosing was permitted.

If we identify substantial heterogeneity, we will investigate it using subgroup analyses and sensitivity analyses. We will consider whether an overall summary is meaningful, and if it is, use random-effects analysis to produce it.

Maternal characteristics are likely to affect health outcomes. We plan to carry out subgroup analyses, if sufficient data are available, based on:

- reason the woman was considered to be at risk of preterm birth (such as presence of ruptured membranes versus preterm labour versus pre-eclampsia);
- number of babies in utero: singleton versus multiple;
- gestational age at which treatment was given: before 28 weeks versus before 34 weeks versus before 37 weeks (at randomisation);
- use of prenatal corticosteroids: in more than 50% of those at risk versus in less than 50% of those at risk.

We will use primary outcomes in subgroup analyses.

For fixed-effect inverse variance meta-analyses, we will assess differences between subgroups by interaction tests. For random-effects and fixed-effect meta-analyses using methods other than inverse variance, we will assess differences between subgroups by inspection of the subgroups’ confidence intervals; non-overlapping confidence intervals indicate a statistically significant difference in treatment effect between the subgroups.
Sensitivity analysis

We will carry out sensitivity analysis to explore the effects of trial quality assessed by allocation concealment and other risk of bias components, by omitting studies rated as 'high risk of bias' for these components. We will restrict this to the primary outcomes.

ACKNOWLEDGEMENTS

As part of the pre-publication editorial process, this protocol has been commented on by three peers (an editor and two referees who are external to the editorial team), a member of the Pregnancy and Childbirth Group’s international panel of consumers and the Group’s Statistical Adviser.

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Different magnesium sulphate regimens for neuroprotection of the fetus for women at risk of preterm birth (Protocol)

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Marret 2007a

Marret 2007b

Matsuda 2000

McCubbin 1981

McDonald 1990

McDonnell 2009

McIntosh 1989

Mittendorf 2002

Morisaki 2000

Nelson 1995

Nowak 1984

O’Shea 1998

Paneth 1997

Perlman 1997

Petriti 2009

RevMan 2011

Richards 1985

Rouse 2008

Saigal 2008

Saliba 2001

Schenkel 1996

Vink 2009

Wax 1995
Wax JR, Segna RA, Vandersloot JA. Magnesium toxicity and resuscitation - an unusual cause of postcesarean evisceration.
Weintraub 2001

Wilson-Costello 1998

* Indicates the major publication for the study

**HISTORY**
Protocol first published: Issue 9, 2011

**CONTRIBUTIONS OF AUTHORS**
Emily Bain wrote the first draft of the protocol, with Caroline Crowther and Philippa Middleton making comments and contributing to subsequent drafts.

**DECLARATIONS OF INTEREST**
The three review authors (Emily Bain, Philippa Middleton, and Caroline Crowther) are investigators in the IRIS trial (Different Infusion Rates of Magnesium Sulphate before Preterm Birth for Neuroprotection Trial), which may be included in a future update of the review. Trial eligibility, data extraction and the risk of bias for this trial will therefore be carried out by two individuals independent to the trial.

**SOURCES OF SUPPORT**

**Internal sources**
- ARCH, Robinson Institute, The University of Adelaide, Australia.

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External sources

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