Antenatal Magnesium Sulphate Prior to Preterm Birth for Neuroprotection of the Fetus, Infant and Child

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Prepared by the
Antenatal Magnesium Sulphate
For Neuroprotection
Guideline Development Panel

National Clinical Practice Guidelines

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Email: researchhub@auckland.ac.nz

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Disclaimer

These guidelines are a general guide to appropriate practice to be used subject to the health practitioner's clinical judgement and the individual woman's preference. The document is designed to give information to assist clinical decision-making and is based on the best available evidence at the time of release.

Publication Approval

Australian Government
National Health and Medical Research Council

These guidelines were approved by the Chief Executive Officer of the National Health and Medical

These guidelines were approved by the Chief Executive Officer of the National Health and Medical Research Council (NHMRC) on 17 November 2010 under Section 14A of the National Health and Medical Research Council Act 1992. In approving these guidelines the NHMRC considers that they meet the NHMRC standard for clinical practice guidelines in that they are based on the systematic identification and synthesis of the best available scientific evidence and make clear recommendations for health professionals practising in an Australian health care setting. The NHMRC expects that all guidelines will be reviewed no less than once every five years.

This publication reflects the views of the authors and not necessarily the views of the Australian Government.

CONTENTS

Abbreviations

ACMI	Australian College of Midwives Inc.
ACNN	Australian College of Neonatal Nurses
ACP	Australian College of Pharmacy
ARCH	Australian Research Centre for Health of Women and Babies, The University of Adelaide
BP	Blood pressure
CI	Confidence interval
DNA	Deoxyribonucleic acid
g	Gram/s
IPD	Individual patient data
IQR	Interquartile range
IV	Intravenous
IVH	Intraventricular haemorrhage
$MgSO_4$	Magnesium sulphate
mL	Millilitre
mm Hg	Millimetres of mercury
mmol/L	Millimoles per litre
NHMRC	National Health and Medical Research Council
NNTB	Number needed to treat to benefit
NZCOM	New Zealand College of Midwives
NZGG	New Zealand Guidelines Group
PPROM	Preterm prelabour rupture of the membranes
RANZCOG	Royal Australian and New Zealand College of Obstetrics and Gynaecology
RCNA	Royal College of Nursing, Australia
RCOG	Royal College of Obstetricians and Gynaecologists
RCPA	Royal College of Pathologists Australasia
RCT	Randomised controlled trial
RNA	Ribonucleic acid
RR	Risk ratio
SOGC	Society of Obstetricians and Gynaecologists of Canada
SOMANZ	Society of Obstetric Medicine of Australia and New Zealand
soln	Solution
US	United States
WHA	Women's Hospitals Australasia
WHO	World Health Organization

Glossary of Terms

Adverse event	An adverse outcome that occurs during or after the use of a drug or other intervention but is not necessarily caused by it.
Antenatal	Occurring before birth; concerned with the care and treatment of the unborn child and pregnant women.
Antenatal corticosteroids	Betamethasone and dexamethasone are corticosteroids, also called glucocorticoids, given before birth (antenatally) to improve lung development and function in the fetus at risk of preterm birth.
Antepartum haemorrhage	Bleeding from the vagina during pregnancy from 20 weeks' gestation to birth.
Applicability	The degree to which a body of evidence is relevant to a particular health care context.
Arm (of a clinical study)	Group of individuals within a study who are allocated to one particular intervention, for example the placebo arm.
Bias	Systematic (as opposed to random) – deviation of the results of a study from the 'true' results.
Biological plausibility	A method of reasoning to suggest a causal association between a biologic factor and a particular disease or health outcome.
Bolus	A large dose of a drug given by injection for the purpose of rapidly achieving the needed therapeutic concentration in the bloodstream.
Calcium channel	A structure in the body which allows cells to transmit electrical charges to each other. These charges are carried on a calcium ion which can travel freely back and forth through the calcium channel.
Case-control study	A study that compares people with a specific disease or outcome of interest (cases) to people from the same population without that disease or outcome (controls), and which seeks to find associations between the outcome and prior exposure to particular risk factors. This design is particularly useful where the outcome is rare and past exposure can be reliably measured. Case-control studies are usually retrospective.
Cerebral palsy	Cerebral palsy describes a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to nonprogressive disturbances that occurred in the developing fetal or infant brain. The motor disorders of cerebral palsy are often accompanied by disturbances of sensation, perception, cognition, communication, and behaviour, by epilepsy, and by secondary musculoskeletal problems.
Clinical impact	Measure of potential benefit from application of the guideline to a population.
Cochrane Library	A regularly updated electronic collection of evidence-based healthcare databases, including the Cochrane Database of Systematic Reviews.
Cochrane Review/Cochrane Systematic Review	A systematic review of the evidence usually from randomised controlled trials relating to a particular health problem or healthcare intervention, produced by the Cochrane Collaboration. Available electronically as part of the Cochrane Library.
Cognitive dysfunction	Poor mental function, such as, difficulties with lack of attention, memory and problem solving.
Confidence interval	Gives a range of values for an unknown population outcome estimated from a study. It will depend on the number of study recruits and the variation in the outcome data. A 95% confidence interval (CI) means that if the study was repeated 100 times with a different sample of recruits and a CI calculated each time, the interval would contain

	the 'true' value of the population outcome 95 times.
Controls	A group of patients recruited into a study that receives no treatment, a treatment of known effect, or a placebo (dummy treatment) – in order to provide a comparison for a group receiving an experimental treatment, such as a new drug.
Deoxyribonucleic Acid	The molecules inside cells that carry genetic information and pass it from one generation to the next.
Developmental delay	Any significant lag in a child's physical, cognitive, behavioural, emotional, or social development, in comparison with norms.
Eclampsia	Seizures (convulsions) in a pregnant woman related to hypertensive disease in pregnancy.
Evidence-based	The best available evidence gained from the scientific method to inform medical decision making. It seeks to assess the quality of evidence of the risks and benefits of treatments (including lack of treatment).
Evidence statement	A table summarising the results of a collection of studies which, taken together, represent the evidence supporting a particular recommendation or series of recommendations in a guideline.
Fetal	Of or pertaining to a fetus or to the period of its development.
Fetal compromise	The fetus not being well.
Fetus	The unborn young.
Gestational age	The period of time between last menstrual period and birth.
Glutamate	A neurotransmitter normally involved in learning and memory. It also is an excitatory neurotransmitter, which means it stimulates areas in the brain or other parts of the nervous system.
Harms	Adverse effects.
Higher order	More than two fetuses in the womb.
Hypermagnesaemia	An abnormally elevated concentration of magnesium in the blood.
Hyporeflexia	The condition of below normal or absent reflexes.
Hypotension	Abnormally low blood pressure.
Hypotonia	A condition of low muscle tone (the amount of tension or resistance to movement in a muscle), often involving reduced muscle strength.
Individual patient data	The central collection, validation and re-analysis of 'raw' data from existing trials addressing the same research question to allow further exploration of patient factors or groups that are more or less likely to benefit from treatment.
Intellectual impairment	A condition where powers of comprehension and information processing abilities are affected to the point where it impairs the person's ability to perform.
Interquartile range	Difference between the first quartile (25^{th} percentile) and the third quartile (75^{th} percentile) of an ordered range of data.
Intraventricular haemorrhage	Bleeding inside or around the ventricles, the spaces in the brain containing the cerebrospinal fluid. Intraventricular haemorrhage can be graded based on the severity of the haemorrhage. Grades 3 and 4 represent more severe haemorrhage causing ventriculomegaly or venous infarction of the brain respectively and are more likely to be associated with neurologic disability.
In utero	Within the uterus.
Loading dose	One or a series of doses that may be given at the onset of therapy with the aim of achieving the target concentration rapidly.
Maternal neuroprotective intent	Magnesium sulphate given to a pregnant woman with the intention of preventing eclampsia.

Mechanical ventilation	To mechanically assist or replace spontaneous breathing.
Necrotising enterocolitis	A medical condition primarily seen in premature infants, where portions of the bowel undergo tissue death (necrosis).
Neonatal	Pertaining to the newborn period which is the first four weeks after birth.
Neonate	An infant in the first 4 weeks of life.
Neurologic impairment	A group of disorders that relate to the central nervous system (brain and spinal cord). Among the more common diagnostic categories for children are cerebral palsy, epilepsy, blindness, deafness and developmental delay. A neurological impairment may affect an individual's speech, motor skills, vision, memory, hearing, muscle actions and learning abilities.
Neurons	Primary, impulse conducting cells of the nervous system; nerve cells.
Neuroprotection	A therapeutic strategy aimed at protecting neurons from injury or degeneration.
Neuroprotective intent	Magnesium sulphate given to women at risk of preterm birth helps to protect the baby's brain and improve long-term outcomes.
Nifedipine	Vasodilator agent (calcium channel blocker).
Number needed to treat to benefit	The number of patients who need to be treated with the new or intervention treatment (rather than the control treatment) for one patient to benefit from the new treatment.
Observational studies	A study in which the investigators do not seek to intervene, and simply observe the course of events. Changes or differences in one characteristic (e.g. whether or not people received the intervention of interest) are studied in relation to changes or differences in other characteristic(s) (e.g. whether or not they died), without action by the investigator. There is a greater risk of selection bias than in experimental studies.
Odds	In a simple situations the odds of an outcome are given by the number with the outcome divided by the number without the outcome.
Odds ratio	The odds of the outcome in the intervention group to the odds of an outcome in the control group.
Oxidative phosphorylation	The process during which nutrients are broken down into ATP (adenosine triphosphate) using the oxygen we breathe.
Parity	The number of times a women has given birth to a fetus with a gestational age of 20 weeks or more, regardless of whether the child was born alive or was stillborn.
Peripheral vasodilator	Medicines that act directly on muscles in blood vessel walls to make blood vessels widen (dilate).
Periventricular leukomalacia	A form of brain injury characterised by the death of white matter near the cerebral ventricles in newborns due to damage and softening of the brain tissue.
Placebo	An inactive substance or preparation used as a control in an experiment or test to determine the effectiveness of a medicinal drug.
Plasma membrane integrity	Integrity of body cell walls.
Post hypoxic brain injury	Damage to the brain that impairs normal functions due to lack of oxygen.
Pre-eclampsia	A pregnancy-induced condition, which can occur in the second half of pregnancy. It is characterised by high blood pressure, swelling that happens suddenly along with rapid weight gain due to fluid retention, and protein in the urine.
Preterm birth	The birth of a baby of less than 37 weeks' gestational age.
Preterm labour	Labour before 37 weeks' gestation.
Protein synthesis	The process by which the genetic code puts together proteins in the cell.
p-value	Used in hypothesis testing where initially it is assumed that there is no difference between two treatments. The p-value is the probability that the difference observed

	in a study between the two treatments might have occurred by chance. Small p-values indicate evidence against an assumption of no difference. Large p-values indicate insufficient evidence against the assumption of no difference between treatments NOT that there is actually no difference between the treatments. P-values will depend on study size; large studies can detect small differences for instance.
Randomised controlled trial	A comparative study in which participants are randomly allocated to intervention and control groups and followed up to examine differences in outcomes between the groups.
Reduction in risk	The extent to which a treatment reduces a risk of an outcome, in comparison with patients not receiving the treatment of interest.
Regimens	A pattern of treatment e.g. dose, frequency of a drug.
Respiratory depression	The rate and/or depth of respiration are insufficient to maintain adequate gas exchange in the lungs.
Ribonucleic acid	One of two types of nucleic acid made by cells. It contains information that has been copied from DNA (the other type of nucleic acid). Many forms of ribonucleic acid have functions related to making proteins.
Risk	The probability of an outcome which is given by the number with the outcome divided by the number with AND without the outcome.
Risk of bias	Bias in the reported outcomes of a study may be caused by an inadequacy in the way the study is designed or conducted. For example, if any of the following aspects of the trial were not conducted properly then the trial may be said to have an increased risk of bias: the random allocation of the treatments, allocation concealment, blinding of researchers during invention and measurement of outcomes, missing outcome data, selective outcome reporting.
Risk ratio	The ratio of risks in two treatment groups. In intervention studies, it is the ratio of the risk in the intervention group to the risk in the control group. A risk ratio of one indicates no difference between comparison groups. For undesirable outcomes, a risk ratio that is less than one indicates that the intervention was effective in reducing the risk of that outcome. (Also called relative risk, RR.).
Sample size	The number of units (persons, animals, patients, specified circumstances, etc.) in a population to be studied. The sample size should be big enough to have a high likelihood of detecting a true difference between two groups.
Singleton	A single baby.
Stillbirth	Death in a fetus $\geq$400g or at least 20 weeks' gestation age.
Substantial gross motor dysfunction	The inability to make the purposeful movements of the large muscles that are necessary to complete or master a prescribed task.
Synergistic effect	Interaction between drugs that has a positive effect on an outcome.
Systematic review	A review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research, and to collect and analyse data from the studies that are included in the review. Statistical methods (meta-analysis) may or may not be used to analyse and summarise the results of the included studies.
Therapeutic range	A concentration range that provides efficacy without unacceptable toxicity.
Tocolysis	The inhibition of contractions of the uterus during labour.
Tocolytic	A medication that can inhibit the contractions of the uterus during labour.

Guideline Panel Membership

Members	Expertise	Work affiliation
Chairperson Professor Caroline Crowther*	Maternal Fetal Medicine Specialist	Professor Maternal and Fetal Medicine, Director of the Australian Research Centre for Health of Women and Babies (ARCH), Discipline of Obstetrics and Gynaecology, The University of Adelaide
Ms Philippa Middleton*	Epidemiologist Research Methodologist	Research Leader with ARCH, Discipline of Obstetrics and Gynaecology, The University of Adelaide
Ms Tanya Bubner*	Researcher	Manager of ARCH, Discipline of Obstetrics and Gynaecology, The University of Adelaide
Dr Helena Oakey*	Statistician	Senior Statistician with ARCH, Discipline of Obstetrics and Gynaecology, The University of Adelaide
Ms Mary Paleologos	Administrative Assistant	Administration Assistant with ARCH, Discipline of Obstetrics and Gynaecology, The University of Adelaide
Dr Lisa Askie*	Epidemiologist	Senior Research Fellow/Manager, Australian New Zealand Clinical Trials Registry, NHMRC Clinical Trials Centre, University of Sydney
Professor Jonathan Morris*	Maternal Fetal Medicine Subspecialist	Professor of Obstetrics and Gynaecology, Head of Discipline, Obstetrics, Gynaecology and Neonatology, University of Sydney
Professor Lex Doyle*	Neonatologist Developmental Paediatrician	Professor, Obstetrics and Gynaecology, University of Melbourne
Associate Professor Vicki Flenady*	Epidemiologist Research Methodologist Neonatal Nurse	Mater Mothers' Research Centre, Mater Health Services, University of Queensland
Mr Neil Hotham	Senior Pharmacist Drug Information Specialist	Senior Specialist Drug Information Pharmacist, Women's and Children's Hospital, Adelaide
Ms Allison Rogers	Midwife/SA Perinatal Practice Guidelines	Project Midwife, SA Perinatal Practice Guidelines, Women's and Children's Hospital, Adelaide
Professor Peter Davis*	Neonatologist, Royal Australian College of Physicians (RACP) representative	Consultant Neonatologist, Royal Women's Hospital, University of Melbourne
Professor Lesley McCowan	Maternal Fetal Medicine Subspecialist	Head of Department, Sub-specialist in Maternal Fetal Medicine, Department of Obstetrics and Gynaecology, University of Auckland

Dr Jane Alsweiler	Neonatologist	Senior Lecturer in Paediatrics, University of Auckland
Ms Ruth Martis	Midwife/New Zealand College of Midwives Representative/Lecturer	Lecturer, Christchurch Polytechnic Institute of Technology
Dr Dell Horey	Epidemiologist Consumer representative	Research Fellow, La Trobe University
Ms Rowena Crawford	Consumer representative	Life's Little Treasures Inc.
Ms Sonia Alix	Consumer representative	Liggins Institute, University of Auckland
Associate Professor Susan Walker	Royal Australian and New Zealand College of Obstetrics and Gynaecology (RANZCOG) representative	University of Melbourne
Dr Trudi Mannix	Australian College of Neonatal Nurses (ACNN) Representative	Lecturer, Nursing and Midwifery, Flinders University
Professor David Ellwood	Women's Health Australasia (WHA) representative	Deputy Dean & Professor of Obstetrics & Gynaecology, The Australian National University Medical School, The Canberra Hospital
Ms Sarah McIntyre	Cerebral Palsy Representative	Research Fellow, NSW/ACT CP Register Cerebral Palsy Institute University of Notre Dame Australia

*** Executive panel members**

Summary of Clinical Recommendations, Good Practice Points, Implementation Implications and Research Recommendations

Clinical Recommendations

This set of clinical recommendations needs to be considered as a whole – recommendations should not be applied in isolation.

CLINICAL RECOMMENDATIONS	GRADE	Chapter
In women at risk of early preterm* imminent# birth, use magnesium sulphate for neuroprotection of the fetus, infant and child:	**A**	**4-7**
	B	8
* when gestational age is less than 30 weeks. # when early preterm birth is planned or definitely expected within 24 hours. (When birth is planned, commence magnesium sulphate as close to four hours before birth as possible).	A	9
• intravenously with a 4 gram loading dose (slowly over 20-30 minutes) and 1 gram per hour maintenance dose via intravenous route, with no immediate repeat doses. Continue regimen until birth or for 24 hours, whichever comes first.	C	10
• regardless of plurality (number of babies in utero).	B	11
• regardless of the reason women (at less than 30 weeks' gestation) are considered to be at risk of preterm birth.	B	12
• regardless of parity (number of previous births for the woman).	B	13
• regardless of anticipated mode of birth.	B	14
• whether or not antenatal corticosteroids have been given.	B	15

Good Practice Points

Timing (Chapter 9)

If birth before 30 weeks is planned or expected to occur sooner than four hours (e.g. scheduled caesarean or late presentation to hospital), administer magnesium sulphate to women at risk of preterm birth, as there is still advantage likely from administration within this time.

Urgent delivery (Chapter 10)

In situations where urgent delivery is necessary because of actual or imminent maternal or fetal compromise (e.g. severe fetal distress or antepartum haemorrhage), then birth should not be delayed to administer magnesium sulphate.

Repeat doses (Chapter 10)

In the event that birth does not occur after giving magnesium sulphate for neuroprotection of the infant, and preterm birth (less than 30 weeks' gestation) again appears imminent (planned or definitely expected within 24 hours), a repeat dose of magnesium sulphate may be considered at the discretion of the attending health professional.

Locations of administration of antenatal magnesium sulphate (Chapter 10)

The locations of administration of antenatal magnesium sulphate intravenously to women should be determined by each individual maternity facility.

Monitoring (Chapter 10)

During administration of magnesium sulphate intravenously, women should be regularly assessed as detailed in individual obstetric unit protocols. Resuscitation and ventilatory support should be immediately available, if needed, during administration of magnesium sulphate. Should hypotension or respiratory depression occur prompt medical review is recommended. This may include cessation of magnesium sulphate.

Loading

A minimum assessment should include checking pulse, blood pressure, respiratory rate and patellar reflexes before loading dose, 10 minutes after loading dose infusion has started and at the end of the loading dose infusion (20-30 minutes). The infusion should be stopped if respiratory rate decreases more than 4 breaths per minute below baseline, or is less than 12 breaths per minute; or diastolic blood pressure decreases more than 15 mm Hg below baseline level.

Maintenance

While the maintenance infusion is running, observe for any adverse effects. The minimum assessments should include checking pulse, blood pressure, respiratory rate, patellar reflexes and urine output 4-hourly. Stop infusion if respiratory rate is less than 12 breaths per minute; if patellar reflexes are absent, if hypotension occurs or if urine output is less than 100 mL over 4 hours.

Toxicity

Magnesium toxicity is unlikely with the regimens recommended in these guidelines and serum magnesium concentrations do not need to be routinely measured (RCOG 2006). In women with renal compromise, serum magnesium monitoring is recommended.

Calcium gluconate (1 g (10 mL of 10% solution) slowly via intravenous route over 10 minutes) can be given if there is clinical concern over respiratory depression.

Potential interactions (Chapter 10)

There is a potential theoretical interaction between magnesium sulphate and nifedipine of hypotension and neuromuscular blockade effects, although this is seldom reported in clinical practice (Snyder & Cardwell 1989; Ben-Ami 1994). Regular monitoring of the mother is recommended as detailed in individual obstetric unit protocols. If hypotension occurs, nifedipine and magnesium sulphate administration should cease and the woman reviewed by a medical practitioner.

Implementation Implications

Changes in usual care (Chapter 7)
While intravenous magnesium sulphate administration is standard care to prevent and treat eclampsia, only a few obstetric units in Australia and New Zealand are using antenatal magnesium sulphate for fetal, infant, and child neuroprotection.

Resource implications (Chapter 7)
Although magnesium sulphate is an inexpensive drug, setting up, maintaining and monitoring magnesium sulphate infusions will incur additional staff time. There will also be training needs, but these should be minimal as all units will have experience with magnesium sulphate infusions to treat or prevent eclampsia.

Less than 1.2% of all births occur at before 30 weeks' gestation; around 3528 such births occur in Australia (AIHW 2009) and 640 in New Zealand each year. Up to 10% of these babies will have been exposed in utero to magnesium sulphate as treatment for prevention and treatment of eclampsia. If all other women who gave birth before 30 weeks' gestation were given magnesium sulphate for neuroprotection of the fetus, infant, and child, up to 4104 more women in Australia and New Zealand each year would need additional care and monitoring. (This figure does not include a small number of women at less than 30 weeks' gestation where birth is planned or definitely expected within 24 hours and who do not actually give birth before 30 weeks' gestation).

On the other hand, fewer cases of cerebral palsy will mean substantial savings at the overall health systems and societal level.

Changes in the way care is currently organised (Chapter 7)
It is acknowledged that while all tertiary obstetric units dealing with babies likely to be born at or before 30 weeks will already have established protocols and systems that will enable them to administer magnesium sulphate intravenously to women at risk of preterm birth less than 30 weeks' gestation, appropriate staffing structures may not be in place to enable the safe administration of magnesium sulphate.

The ideal setting for babies to be born before 30 weeks is a tertiary specialist unit. Given that the clinical indication for magnesium sulphate is planned or definitely expected preterm birth before 30 weeks then its use will generally be within tertiary obstetric units. Women threatening to give birth before 30 weeks in other settings, and fulfilling all other guideline criteria, may be eligible to receive magnesium sulphate after consultation with their tertiary obstetric network, depending on the non-tertiary unit's service capability and staffing.

Magnesium sulphate infusions should not be used during antenatal transfer unless resuscitation and ventilator support are immediately available. If a clinical decision is made to transfer a woman who has received magnesium sulphate in another setting to a tertiary obstetric unit, the magnesium sulphate maintenance infusion can be stopped during the transfer.

Barriers to implementation (Chapter 7, 8 and 10)
Barriers to implementation will include finding the extra time and staff required to administer magnesium sulphate to more women. However, as magnesium sulphate infusions, in the regimens

recommended, are already widely practised for treatment of severe pre-eclampsia and eclampsia at these gestational ages, training needs should be minimal as all units will have experience.

Monitoring women after they have received antenatal infusions of magnesium sulphate is usually recommended. Monitoring formed part of the published study methods for two of the included randomised controlled trials (Crowther 2003 and Marret 2006, also see Appendix H.] There is, however, no consensus on what form this monitoring should take. For example the Society of Obstetric Medicine of Australia and New Zealand (SOMANZ) state that obstetric units should determine their own protocols for monitoring outcomes [SOMANZ 2008, also see Appendix H]. As toxicity is unlikely with the regimens recommended in these guidelines, routine monitoring of serum magnesium sulphate concentrations should not be required.

Research Recommendations

These research recommendations have been derived from Panel discussions during the course of developing the Guidelines.

Prevention of Cerebral Palsy
How to prevent cerebral palsy and identifying causes and causal pathways are priority research questions.

Follow up of children in existing trials
Continuing the follow up of children in the existing randomised trials is necessary to elucidate if the benefits from antenatal magnesium sulphate seen in early childhood translate into later benefits.

Audit of antenatal magnesium sulphate use and rates of cerebral palsy
It will be important to monitor the antenatal use of magnesium sulphate for neonatal neuroprotection, ideally through national audit; and to link data to national childhood cerebral palsy registers and databases.

Existing trials
Individual triallists should be approached to provide unpublished data, for subsequent revisions of the Cochrane review '*Magnesium sulphate for women at risk of preterm birth for the neuroprotection of the fetus'* (Doyle 2009), where possible, on:

- optimal timing of magnesium sulphate administration.
- optimal treatment regimens.
- gestational age breakdown or available gestational age subgroups (at trial entry).
- reasons women were considered to be at risk of preterm birth and health outcomes.
- plurality and health outcomes.
- parity and health outcomes.
- mode of birth and health outcomes.
- use of antenatal corticosteroids and health outcomes.

Individual patient meta-analyses
Individual patient meta-analyses through an international collaboration of triallists responsible for the existing randomised trials will permit further exploration of:

- gestational age when magnesium sulphate was administered and health outcomes.
- whether differences in timing of magnesium sulphate administration result in differences in outcomes such as cerebral palsy and combined death and cerebral palsy.
- whether different magnesium sulphate regimens result in different rates of adverse outcomes such as cerebral palsy and combined death and cerebral palsy.
- whether differences in plurality result in different rates of adverse outcomes such as cerebral palsy and combined death and cerebral palsy.

- whether differences in reasons women were considered to be at risk of preterm birth result in different rates of adverse outcomes such as cerebral palsy and combined death and cerebral palsy.
- influence of parity.
- whether mode of birth modifies neurodevelopmental outcomes.
- whether differences in use of antenatal corticosteroids result in different rates of adverse outcomes such as cerebral palsy and combined death and cerebral palsy.

Biomarkers for cerebral palsy

Investigations to identify biomarkers for cerebral palsy in at risk groups to allow a more targeted use of antenatal administration of magnesium sulphate.

Further randomised controlled trials

Further randomised trials are needed, comparing antenatal magnesium sulphate with placebo when given to women at risk of preterm birth at 30 weeks' gestation or more, that assess mortality, cerebral palsy and combined death and cerebral palsy.

Further randomised controlled trials are required specifically comparing:

- different speeds of administering the loading dose of magnesium sulphate to establish if slower loading reduces maternal adverse effects.
- optimal timing of the antenatal administration of magnesium sulphate prior to preterm birth.
- loading dose versus loading dose plus maintenance.
- different loading doses (4 g versus 6 g).
- use of repeat doses of magnesium sulphate.
- treatment of the very preterm infant with magnesium sulphate after birth.

Chapter 1: Need for these Guidelines

It is now 14 years since the publication of a case-control study first described the association of antenatal magnesium sulphate prior to preterm birth and the prevention of cerebral palsy (Nelson 1995). The evidence available on this topic has been growing and has recently reached a translational 'flashpoint'. With the recent publication of the US trial (Rouse 2008), the updated Cochrane review '*Magnesium sulphate for women at risk of preterm birth for the neuroprotection of the fetus'* (Doyle 2009) shows, for the first time, that magnesium sulphate given to women prior to preterm birth can reduce the risk of cerebral palsy. This Cochrane review now contains five trials (including the Australian and New Zealand randomised trial of antenatal magnesium sulphate for neuroprotection of the fetus, funded through the National Health and Medical Research Council (NHMRC) Project Grant 3503267 (Crowther 2003)).

The updated Cochrane review concludes that antenatal magnesium sulphate therapy given to women at risk of preterm birth substantially reduced the risk of cerebral palsy in their child (risk ratio (RR) 0.68 95% confidence interval (CI) 0.54 to 0.87; five trials, 6145 infants).

This is a very important finding, as few interventions have been found to prevent cerebral palsy which can have devastating and long-term consequences. Over 120 children are diagnosed with cerebral palsy in New Zealand each year and over 600 are similarly diagnosed in Australia. About 45% of all cases of cerebral palsy are related to preterm birth. Preventing cerebral palsy and identifying causes and causal pathways have been identified as the lead priority for research by consumers, clinicians and researchers (McIntyre 2009).

The prevention of cerebral palsy fits within the 'Promoting and maintaining good health' National Research Priority; three of the four goals of this Priority are relevant, specifically;

- a healthy start to life;
- ageing well, ageing productively; and
- preventive health.

Aim of the guideline

While it is now clear that magnesium sulphate has a role in reducing the risk of cerebral palsy, the evidence for how and when to use magnesium sulphate is less clear. Colleges (such as the Royal Australian and New Zealand College of Obstetricians and Gynaecologists), societies and individual hospitals and clinicians have requested detailed evidence-based guidance in the form of a national statement.

These ***Antenatal Magnesium Sulphate Prior to Preterm Birth for Neuroprotection of the Fetus, Infant, and Child Guidelines*** specifically address whether the administration of magnesium sulphate to women prior to preterm birth:

- *improves the health outcomes for the fetus, infant and child;*
- *causes adverse outcomes for the women; or the fetus, infant and child;*

- *varies by:*
    - *gestational age magnesium sulphate is given;*
    - *time magnesium sulphate is planned to be given prior to birth;*
    - *regimen (dosing and routes of administration);*
    - *number of babies in utero;*
    - *reason women are considered to be at risk of preterm birth;*
    - *parity of the women;*
    - *mode of birth and interaction with magnesium sulphate;*
    - *combined effect of antenatal corticosteroids and magnesium sulphate.*

Outcomes to be considered:

- Death and any neurological impairment (including cerebral palsy, blindness, deafness, developmental delay) for the fetus/infant/child.
- Harmful effects by the therapy for the woman and the child (maternal respiratory depression, cardiac arrest, hypotension, side effects, and fetal/neonatal side effects.

Our purpose and rationale is to provide practical evidence-based guidance on the best practice for clinical care in the use of magnesium sulphate prior to preterm birth. These guidelines will be relevant for health professionals who care for women at risk of preterm birth and their babies; for pregnant women and their partners and families; and for policy makers in maternity care.

Chapter 2: Summary of Guideline Development Process

A multidisciplinary expert advisory panel (the Panel) was established to oversee the development of these Guidelines (see p.7-8 for a list of members and their roles and affiliations).

The purpose of the Panel was to prepare an evidence-based guideline on best practice for clinical care in the use of antenatal magnesium sulphate prior to preterm birth for the neuroprotection of the fetus, infant and child.

The Guideline was developed according to the requirements of the Australian National Health and Medical Research Council (NHMRC) and the New Zealand Guidelines Group (NZGG) – see appendices A and D.

The Panel formulated a set of critical clinical questions which formed the framework for the Guidelines (these questions are listed in Chapter 1). Each question is addressed in a separate chapter* using the following format:

- a description of the studies comprising the relevant evidence;
- the main results from these studies;
- a summary of the judgements from the evidence statements (see below);
- using judgements to formulate recommendations (and good practice points);
- the implications for implementing the recommendations;
- further research required to address the specific question adequately.

*For Question 1 (Does administration of magnesium sulphate prior to preterm birth improve the health outcomes for the fetus, infant, and child?) these components are included in four chapters (Chapters 4-7).

Summary of timeline:

- 12 Oct 2009 - input sought by email from full panel.
- 16 Oct 2009 - subsequent drafts discussed by teleconference.
- 12 Nov 2009 - face to face meeting in Sydney.
- 12 Dec 2009 - open meeting in Adelaide.
- 19 Dec 2009 to 18 Jan 2010 - public consultation of draft guidelines.
- Feb 2010 - final guideline document.
- March 2010 – draft guidelines released.
- 17 November 2010 – NHMRC approved guidelines.

Updating the Guidelines

One source of new evidence in the future will be an individual patient data (IPD) meta-analysis. Funding has been awarded through a NHMRC Project Grant to commence in 2010 (NHMRC 627228). Therefore we anticipate a major update of these Guidelines in approximately two years using data from the IPD.

Chapter 3: Background

Cerebral palsy and link with preterm birth

Cerebral palsy and cognitive dysfunction are the most frequently occurring neurologic impairments associated with preterm birth (before 37 weeks gestation), and any therapy that can reduce their prevalence would substantially reduce overall neurologic impairments and disabilities among surviving preterm infants. The cost to the Australian community of cerebral palsy including financial cost and lost wellbeing is AUD$3.87 billion per annum. For the individual the financial and lost wellbeing cost per annum is over AUD$115,000 (Access Economics 2008).

Cerebral palsy is a term which includes a number of different diseases or conditions that can arise at any time during brain development. Cerebral palsy can involve a disorder of movement or posture, or both, and a disorder of motor function which is permanent but may change over time (Oxford Register 2001).

Approximately 42% of all cases of cerebral palsy are associated with preterm birth (Australian Cerebral Palsy Register Group 2009) with the rate of cerebral palsy amongst neonatal survivors born at less than 28 weeks gestation up to 30 times higher compared with infants born at term (Stanley 1992).

At present there is no cure for cerebral palsy, which makes effective preventive interventions of paramount importance. Prevention of cerebral palsy has been identified by consumers, clinicians and researchers as a top priority for research by the Cerebral Palsy Institute (McIntyre 2009).

Preterm birth and neurological outcome

Babies born preterm have a higher chance of dying in their first few weeks of life. Preterm infants who survive have greater risk of neurologic impairments, such as cerebral palsy, blindness, deafness, or cognitive dysfunction (either intellectual impairment or developmental delay), and a greater risk of substantial disability as a result of these neurologic impairments (Doyle 2001; Saigal & Doyle 2008). Intraventricular haemorrhage (IVH) is a known risk factor for the later development of cerebral palsy (Kuban 1992). The risk of IVH and periventricular leukomalacia increases the earlier the gestational age at birth (Vermeulen 2001).

The rate of preterm birth is increasing in many countries, with recently reported rates of 12.8% in the United States (National Center for Health Statistics 2009); over 8% in Australia (AIHW 2009) and over 7% in New Zealand (New Zealand Health Information Service 2006), with corresponding increases in the number of babies at risk of death or an adverse neurological outcome.

Biological plausibility for use of magnesium sulphate for fetal and infant neuroprotection

In humans, magnesium sulphate is essential for health through key cellular processes, including glycolysis, oxidative phosphorylation, protein synthesis, DNA and RNA aggregation and maintenance of plasma membrane integrity (Mildvan 1987; McIntosh et al 1989).

Animal studies have shown that magnesium sulphate can provide a neuroprotective effect (McDonald 1990) preventing post-hypoxic brain injury by blocking the excess release of glutamate in the calcium channel. The fetal and newborn brain seems more susceptible to damage from

glutamate release. Consequently, blocking glutamate receptors through agents, such as magnesium sulphate, may reduce the risk of injury in the perinatal period (Espinoza 1991).

Possible role of magnesium sulphate for neuroprotection of the fetus, infant and child

Kuban and colleagues were the first to report that antenatal magnesium sulphate was associated with a reduction in the risk of IVH in babies born with birthweights less than 1500 g (Kuban 1992). A case-control analysis from the California Cerebral Palsy project investigated whether *in utero* exposure to magnesium sulphate was associated with a lower prevalence of cerebral palsy among infants born weighing less than 1500 g (Nelson 1995). Cases were singleton children with cerebral palsy whose birthweight was less than 1500 g. Controls were randomly sampled from live births of less than 1500 g from the same birth populations. Magnesium sulphate given to mothers during labour was associated with a significantly marked reduction in the risk of cerebral palsy (odds ratio 0.14; 95% confidence interval 0.05 to 0.51).

Other observational studies have supported a reduction in cerebral palsy in preterm infants by maternal administration of magnesium sulphate (Hauth 1995; Schendel 1996; Wiswell 1996) or found a reduction in the risk of IVH (Finesmith 1997; Perlman 1994; Wiswell 1996) and perinatal mortality (Grether 1998). However, not all observational studies have reported benefit for antenatal magnesium sulphate for the risk of IVH (Canterino 1999; Kimberlin 1998; Paneth 1997; Weintraub 2001), cerebral palsy (Grether 2000; O'Shea 1998; Paneth 1997) or paediatric mortality (Kimberlin 1998).

Maternal adverse effects and side effects

Magnesium sulphate produces flushing, sweating, and a sensation of warmth by its peripheral vasodilator effects when infused intravenously. Other reported maternal side effects, related to dosage and speed of infusion, include nausea, vomiting, headache, palpitations and, rarely, pulmonary oedema. Administration of magnesium sulphate to concentrations above the recommended therapeutic range can lead to respiratory depression, respiratory arrest, cardiac arrest and death.

Fetal, neonatal and infant adverse effects and side effects

In the neonate, hypermagnesaemia can lead to hyporeflexia, poor sucking, and, rarely, respiratory depression needing mechanical ventilation (Levene 1995; Lipsitz 1971).

Magnesium sulphate use in pregnancy

The focus of these Guidelines is antenatal use of magnesium sulphate for neuroprotection of the fetus, infant and child. The evidence for the effectiveness of magnesium sulphate for this purpose comes from four trials (Crowther 2003; Marret 2006; Mittendorf 2002; Rouse 2008) which have been pooled in the Cochrane systematic review *'Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus'* (Doyle 2009).

Magnesium sulphate has also been used antenatally for:

- ***Tocolysis (to inhibit contractions in threatened preterm labour)***

  In the relevant randomised trials from the Cochrane systematic review *'Magnesium sulphate for preventing preterm birth in threatened preterm labour'*, Crowther 2002 found magnesium sulphate to be ineffective at delaying birth or preventing preterm birth, and its use was

associated with an increased mortality for infants. (Preliminary results for the update of this Cochrane review [currently in draft form] again indicate that magnesium sulphate was ineffective at delaying or preventing preterm birth although no significant differences in fetal, neonatal, infant or total mortality between magnesium sulphate and placebo/no treatment or between magnesium sulphate and other drugs used for tocolysis were seen);

- ***Maintenance therapy for preventing preterm birth after threatened preterm labour***

In the Cochrane systematic review *'Magnesium maintenance therapy for preventing preterm birth after threatened preterm labour'* Crowther 1998 found insufficient evidence of any differences between magnesium sulphate maintenance therapy and either placebo/no treatment, or alternative therapies (ritodrine or terbutaline) to prevent preterm birth after an episode of threatened preterm labour;

- ***Neuroprotection of the mother (to prevent and treat pre-eclampsia)***

The Cochrane systematic review *'Magnesium sulphate and other anticonvulsants for women with pre-eclampsia'* (Duley 2003) found that magnesium sulphate more than halved the risk of eclampsia and probably reduced the risk of maternal death, but did not improve outcomes for the baby in the short term.

Evidence summaries for the tocolytic and maternal neuroprotective use of magnesium sulphate can be found in Appendix E.

Evidence relating to possible harms to the mother or the fetus/infant/child from any antenatal use of magnesium sulphate (compared with placebo or no treatment) will be considered later (see Chapters 5 and 6 and Appendix G).

Chapter 4: Improving Health Outcomes for the Fetus, Infant, and Child (Question 1)

Question 1: Does the administration of magnesium sulphate to women prior to preterm birth improve the health outcomes for the fetus, infant, and child?

Magnesium sulphate is given to pregnant women at risk of preterm birth with the intention of preventing cerebral palsy and other adverse neurodevelopmental outcomes.

As foreshadowed in Chapter 3, the four trials (Crowther 2003, Marret 2006, Mittendorf 2002 (neuroprotective arm only) and Rouse 2008) in the Doyle 2009 Cochrane systematic review *'Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus'* form the evidence base for the effectiveness of antenatal use of magnesium sulphate for fetal, infant or child neuroprotective intent, the focus of these guidelines.

The evidence for potential harms was taken from a wider evidence base – from studies related to fetal, infant and child neuroprotective intent, as well as tocolytic intent and maternal neuroprotective intent (pre-eclampsia). These studies are contained in four Cochrane reviews (Doyle 2009, Duley 2003, Crowther 2002 and Crowther 1998) – see Chapters 5 and 6.

The evidence for effectiveness outlined in this chapter was considered with the evidence for potential harms in Chapter 7, where there is formulation of an overall recommendation about the use of antenatal magnesium sulphate for neuroprotection of the fetus, infant and child.

NEUROPROTECTION (FETUS, INFANT, AND CHILD)

The Doyle 2009 Cochrane review compared magnesium sulphate with placebo or no treatment given to women at risk of preterm birth and included four trials (4446 infants) which addressed infant neuroprotection.

Death and cerebral palsy are competing outcomes as most perinatal deaths or those deaths that occur later before cerebral palsy can be diagnosed. Therefore, the combined outcome of death or cerebral palsy is commonly considered the most clinically relevant outcome for assessing neuroprotection.

In Doyle 2009, the combined outcome of death or cerebral palsy or cerebral palsy alone showed significant reductions where women who were at risk of preterm birth were given magnesium sulphate antenatally with the intent of providing neuroprotection (see Table 1). The review showed that 63 babies (95% confidence interval 44 to 155) need to be treated with magnesium sulphate for one baby to avoid cerebral palsy. The corresponding number needed to treat to benefit (NNTB) for combined death or cerebral palsy was 42 babies (95% confidence interval 24 to 346).

Table 1: Magnesium sulphate vs placebo/no treatment: primary outcomes (Doyle 2009 Cochrane Review)

Primary outcomes	RR (95% CI)	Number of trials; participants
Death or cerebral palsy	**0.85 (0.74 to 0.98)***	four trials; 4446 infants
Death (fetal and later)	0.95 (0.80 to 1.12)	four trials; 4446 infants
Cerebral palsy	**0.71 (0.55 to 0.91)***	four trials; 4446 infants
Any neurological impairment	1.03 (0.87 to 1.21)	one trial; 1255 infants
Death or substantial gross motor dysfunction	0.84 (0.71 to 1.00)	three trials; 4387 infants

**significantly in favour of magnesium sulphate*

See Appendix F.1-3: Evidence tables/graphs

Table 2: Magnesium sulphate vs placebo/no treatment: selected secondary outcomes (Doyle 2009 Cochrane Review)

Secondary outcomes	RR (95% CI)	Number of trials; participants
Neonatal outcomes		
Intraventricular haemorrhage	0.96 (0.86 to 1.08)	four trials; 4552 infants
Severe intraventricular haemorrhage (grade 3/4)	0.83 (0.62 to 1.13)	two trials; 3699 infants
Periventricular leukomalacia	0.93 (0.68 to 1.28)	four trials; 4552 infants
Infant/child outcomes		
Substantial gross motor dysfunction	**0.60 (0.43 to 0.83)***	three trials; 4387 infants
Development delay or intellectual impairment	1.00 (0.91 to 1.09)	three trials; 4387 infants
Major neurological disability	1.14 (0.86 to 1.51)	one trial; 1255 infants
Blindness	0.97 (0.14 to 6.90)	two trials; 1943 infants
Deafness	0.51 (0.05 to 4.96)	two trials; 1943 infants

**significantly in favour of magnesium sulphate*

Chapter 5: Adverse Outcomes for the Women (Question 2)

Question 2: Does the use of magnesium sulphate prior to preterm birth cause adverse outcomes for the women?

Evidence regarding potential maternal harms was extracted from those trials that compare magnesium sulphate with placebo or no treatment in the four Cochrane reviews looking at the various indications for antenatal use of magnesium sulphate (Crowther 1998, Crowther 2002, Doyle 2009 and Duley 2003).

Women given magnesium sulphate were about three times more likely to cease therapy compared with women not given magnesium sulphate therapy (placebo or no treatment), mainly due to flushing (20.4% vs 2.2%), nausea/vomiting (3.2% vs 0.4%) and headaches (0.7% vs 0.3%). Overall cessation of therapy was 7.5% in the magnesium sulphate group compared with 2.7% in the placebo/no treatment groups.

Hypotension (variously defined) and respiratory depression (variously defined) were also significantly elevated among women given magnesium sulphate. Overall hypotension was 2.0% in the magnesium sulphate groups compared to 1.2% in the placebo/no treatment groups. Overall respiratory depression was 1.3% in the magnesium sulphate groups and 0.8% in the placebo/no treatment groups.

In the Cochrane review on preventing eclampsia (Duley 2003), a small but significant absolute increase of 2.5% in the caesarean rate was seen, from 47.2% in the placebo group to 49.7% in the magnesium group (RR 1.05 95% CI 1.01 to 1.10). There was not a significant increase in the caesarean rate in the Doyle 2009 Cochrane Review (48.8% for the magnesium sulphate group and 47.2% for the placebo group).

In very large doses, magnesium sulphate can have toxic, even life-threatening effects for women. This has been documented in case reports (for example McDonnell 2009). Careful monitoring of the woman's magnesium sulphate administration is therefore advised (see Chapter 10).

See Appendix G.1: Evidence tables

Chapter 6: Adverse Outcomes for Fetus, Infant, and Child (Question 3)

Question 3: Does the use of magnesium sulphate prior to preterm birth cause adverse outcomes for the fetus, infant, and child?

Evidence regarding potential harms to the fetus, infant or child was extracted from the trials comparing magnesium sulphate with placebo or no treatment in the four Cochrane reviews looking at the various indications for antenatal use of magnesium sulphate (Crowther 1998, Crowther 2002, Doyle 2009 and Duley 2003).

None of the harms for the fetus, infant or child were significantly increased with antenatal use of magnesium sulphate including total deaths (fetal, neonatal, or infant), intraventricular haemorrhage or necrotising enterocolitis.

See Appendix G.2: Evidence tables

Chapter 7: Summary of Evidence for Questions 1-3

Summary of evidence statement judgements for fetal, infant, and child neuroprotection

The evidence base for using magnesium sulphate as an agent for fetal, infant, and child neuroprotection has low risk of bias. Results between trials are fairly consistent. Benefits were judged to outweigh potential harms and clinical impact considered to be very large, due to the importance of reducing the risk of cerebral palsy.

While evidence was applicable to the context of Australian and New Zealand health care, it had less generalisability in regard to the intended target population (women at risk of preterm birth) as the majority of women in the largest trial had preterm prelabour rupture of membranes (PPROM) when recruited to the trial (and so represented a narrower subset of women at risk of preterm birth).

Overall the body of evidence was considered sufficiently good enough to make the following grade A recommendation:

CLINICAL RECOMMENDATION	GRADE
In women at risk of early preterm* imminent# birth, use magnesium sulphate for neuroprotection of the fetus, infant and child. *see chapter 8 #see chapter 9	A

Appendix F1-3: Evidence statements

IMPLEMENTATION IMPLICATIONS

Changes in usual care

While intravenous magnesium sulphate administration is standard care to prevent and treat eclampsia, only a few obstetric units in Australia and New Zealand are using antenatal magnesium sulphate for fetal, infant, and child neuroprotection.

Resource implications

Although magnesium sulphate is an inexpensive drug, setting up, maintaining and monitoring magnesium sulphate infusions will incur additional staff time. There will also be training needs but these should be minimal as all units will have experience with magnesium sulphate infusion to treat or prevent eclampsia.

Less than 1.2% of all births occur at before 30 weeks' gestation; around 3528 such births occur in Australia (AIHW 2009) and 640 in New Zealand each year. Up to 10% of these babies will have been exposed in utero to magnesium sulphate as treatment for prevention and treatment of eclampsia. If all other women who gave birth before 30 weeks' gestation were given magnesium sulphate for neuroprotection of the fetus, infant, and child, up to 4104 more women in Australia and New Zealand each year would need additional care and monitoring. (This figure does not include a small number of women at less than 30 weeks' gestation where birth is planned or definitely expected within 24 hours and who do not actually give birth before 30 weeks' gestation).

On the other hand, fewer cases of cerebral palsy will mean substantial savings at the overall health systems and societal level.

Changes in the way care is currently organised

It is acknowledged that while all tertiary obstetric units dealing with babies likely to be born at or before 30 weeks will already have established protocols and systems that will enable them to administer magnesium sulphate intravenously to women at risk of preterm birth less than 30 weeks' gestation, appropriate staffing structures may not be in place to enable the safe administration of magnesium sulphate.

The ideal setting for babies to be born before 30 weeks is a tertiary specialist unit. Given that the clinical indication for magnesium sulphate is planned or definitely expected preterm birth before 30 weeks then its use will generally be within tertiary obstetric units. Women threatening to give birth before 30 weeks in other settings, and fulfilling all other guideline criteria, may be eligible to receive magnesium sulphate after consultation with their tertiary obstetric network, depending on the non-tertiary unit's service capability and staffing.

Magnesium sulphate infusions should not be used during antenatal transfer unless resuscitation and ventilator support are immediately available. If a clinical decision is made to transfer a woman who has received magnesium sulphate in another setting to a tertiary obstetric unit, the magnesium sulphate maintenance infusion can be stopped during the transfer.

Barriers to implementation

Barriers to implementation will include finding the extra time and staff required to administer magnesium sulphate to more women. However, as magnesium sulphate infusions, in the regimens recommended, are already widely practised for treatment of severe pre-eclampsia and eclampsia at these gestational ages, training needs should be minimal as all units will have experience.

FURTHER RESEARCH RECOMMENDATIONS AND AUDIT

- Further analyses of the existing trials (such as subgroup analyses and individual patient data meta-analyses) will provide evidence to elucidate optimal timing of magnesium sulphate administration and its optimal regimens (see subsequent chapters).
- A randomised trial comparing different speeds of administering the loading dose of magnesium sulphate would establish if slower loading reduces maternal adverse effects.
- Investigations to identify biomarkers for cerebral palsy in at risk groups to allow a more targeted antenatal administration of magnesium sulphate.
- It will be important to monitor the antenatal use of magnesium sulphate, ideally through national audit; and to link data to national childhood registers and databases.
- School-age outcomes will be available from some studies; results of these studies may lead to modifications of these guidelines.

Chapter 8: Gestational Age (Question 4)

Question 4: Do the improvements for the fetus, infant, and child vary by gestational age?

This chapter summarises the evidence available from the four individual neuroprotective intent trials within the Doyle 2009 Cochrane Review that consider gestational age at trial entry and effect of antenatal magnesium sulphate.

All women in the four trials included in the Doyle 2009 Cochrane review were given magnesium sulphate before 34 weeks' gestation. In Rouse 2008, all women were less than 32 weeks at trial entry with the majority (68% of trial participants) less than 30 weeks gestation (Costantine 2009).

Table 3: Gestational age at trial entry for trials (Doyle 2009 Cochrane Review)

Study	Gestational age
Mittendorf 2002	< 34 weeks at randomisation
Marret 2006	< 33 weeks
Rouse 2008 (32% of trial participants)	31- 32 weeks
Crowther 2003 & Rouse 2008 (68% of trial participants)	< 30 weeks

However the data analyses published in a systematic review by Costantine 2009 did not include all women and so only subgroup analyses for women at different gestational ages are possible at present; women with a gestational age of less than 34 weeks, less than 33 weeks, less than 32 weeks and less than 30 weeks. There is one trial with each subgroup available for each analysis but results are inconclusive due to small sample sizes.

Table 4: Results of primary outcomes by gestational age subgroup (Doyle 2009 Cochrane Review)

Trial	Gestational age	DEATH or CEREBRAL PALSY	CEREBRAL PALSY	DEATH
		RR (95% CI)		
[+]Mittendorf 2002 (n=59)	< 34 weeks	4.83 (0.60 to 38.90)	6.77 (0.37 to 125.65)	1.93 (0.19 to 20.18)
Marret 2006 (n=688)	< 33 weeks	0.80 (0.58 to 1.10)	0.70 (0.41 to 1.19)	0.85 (0.55 to 1.32)
Rouse 2008 (n=2444)	< 32 weeks	0.90 (0.73 to 1.10)	**0.59 (0.40 to 0.85)***	1.13 (0.87 to 1.48)
Crowther 2003 (n=1255)	< 30 weeks	0.82 (0.66 to 1.02)	0.85 (0.55 to 1.31)	0.81 (0.62 to 1.05)
OVERALL	**< 34 weeks**	**0.86 (0.75 to 0.98)***	**0.71 (0.55 to 0.91)***	0.95 (0.80 to 1.12)

[+]*neuroprotective arm*

See Appendix F.4 for evidence tables/graphs

Summary of evidence statement judgements for gestational age subgroup

The subgroup analyses are from trials with low risk of bias, and where results between trials are fairly consistent. While the evidence is applicable to the Australian and New Zealand context, generalisability was reduced as the majority of the women (87%) in the largest trial (Rouse 2008) had PPROM and so represent a limited subset of women at risk of preterm birth.

Overall clinical impact was judged to be very large but since any differences in death and cerebral palsy by gestational age are unclear at present, no particular subgroup was judged by the guideline panel to have any more or less impact than another.

How recommendation was formulated

To minimise the number of women exposed the guideline panel felt it would be prudent, at this stage, to restrict magnesium sulphate administration to the subgroup containing the lowest gestational age (less than 30 weeks) and therefore recommend that magnesium sulphate be given only for neuroprotective intent when women are at risk of preterm birth (less than 30 weeks' gestation).

If magnesium sulphate administration is restricted to women at less than 30 weeks' gestation at risk of preterm birth; this will be a smaller group than those at less than 34 weeks' gestation, which will have a somewhat smaller impact on resource allocations.

See Appendix F.4 for evidence statement

CLINICAL RECOMMENDATION	GRADE
In women at risk of early preterm* imminent# birth, use magnesium sulphate for neuroprotection of the fetus, infant or child: *when gestational age is less than 30 weeks. #see chapter 9	B

IMPLEMENTATION IMPLICATIONS

As for Chapter 7.

FURTHER RESEARCH RECOMMENDATIONS

- Individual triallists should be approached to provide unpublished gestational age breakdowns or be requested to provide available gestational age subgroup analyses.
- Individual patient data meta-analysis by gestational age when magnesium sulphate was administered and health outcomes needs to be conducted.
- Further randomised trials are needed, comparing antenatal magnesium sulphate with placebo when given to women at risk of preterm birth at 30 weeks' gestation or more, that assess mortality, cerebral palsy and combined death and cerebral palsy.

Chapter 9: Timing (Question 5)

Question 5: Do improvements to the fetus, infant, and child vary by time magnesium sulphate is planned to be given prior to preterm birth?

This chapter summarises the evidence available from the four individual randomised neuroprotective intent trials included in the Doyle 2009 Cochrane Review that looked at the time magnesium sulphate was planned to be given prior to preterm birth.

In two of the four neuroprotective intent trials (Crowther 2003 and Marret 2006), magnesium sulphate was given when birth was planned or expected within 24 hours. The median time from randomisation to birth for women in the magnesium sulphate group was 3.7 hours (interquartile range (IQR) 1.4 to 13.8) for Crowther 2003 and 1 hour 38 minutes (IQR 5 minutes to 25 hours and 5 minutes) for Marret 2006. In Rouse 2008, at the time of recruitment to the study only 3% of women were planned or expected to give birth within 24 hours. Although a further 10% were in advanced preterm labour, most (87%) women had PPROM with a median time to birth of 25 hours (IQR 11 to 63 hours) from rupture of membranes. Mittendorf 2002 did not specify the time prior to preterm birth in which it was planned that magnesium sulphate was to be given (although women recruited to the study were in advanced preterm labour with cervical dilatation of more than 4 cm).

Table 5: Timing of magnesium sulphate administration for trials (Doyle 2009 Cochrane Review)

Study	Timing
Crowther 2003 **Marret 2006**	When birth was planned or definitely expected within 24 hours
Rouse 2008	• when birth was planned or expected within 24 hours for indicated preterm birth (3.1% only); • advanced preterm labour, with cervical dilatation between 4 and 8 cm (10.3%); • PPROM 86.7% - median 25 hours, interquartile range 11 to 63 hours from rupture of membranes to birth interval
Mittendorf 2002	Not specified

At present subgroup analyses are unable to provide conclusive results on the optimal timing for the administration of magnesium sulphate prior to anticipated preterm birth.

Table 6: Results of primary outcomes by timing for trials (Doyle 2009 Cochrane Review)

Trial	Timing	DEATH or CEREBRAL PALSY	CEREBRAL PALSY	DEATH
		RR (95% CI)		
Crowther 2003; Marret 2006 (n=1943)	If birth planned or definitely expected within 24 hours	**0.81 (0.68 to 0.97)***	0.79 (0.56 to 1.10)	0.82 (0.66 to 1.03)
Rouse 2008 (n=2444)	Variable	0.90 (0.73 to 1.10)	**0.59 (0.40 to 0.85)***	1.13 (0.87 to 1.48)
Mittendorf 2002 (n=59)	Not specified	4.83 (0.60 to 38.90)	6.77 (0.37 to 125.65)	1.93 (0.19 to 20.18)
OVERALL		**0.86 (0.75 to 0.98)***	**0.71 (0.55 to 0.91)***	0.95 (0.80 to 1.12)

**significantly in favour of magnesium sulphate*

See Appendix F.5: evidence tables/graphs

Summary of evidence statement judgements for timing of magnesium sulphate administration subgroup

The subgroup analyses come from trials with low risk of bias, where the results between trials are fairly consistent. The evidence from the subgroups in which birth was planned or expected within 24 hours (Crowther 2003 and Marret 2006) was judged to be directly generalisable to the target population, and the overall evidence applicable.

Overall clinical impact was judged to be very large but since differences in death and cerebral palsy based on the timing of planned magnesium sulphate administration are unclear at present, no particular subgroup was judged to have any greater or lesser impact than another.

How recommendation was formulated

The subgroup in which preterm birth was planned or definitely expected within 24 hours (Crowther 2003 and Marret 2006) was judged to be most representative of all subgroups included in the intended target groups for this guideline. In addition, this subgroup showed a reduction in death or cerebral palsy (see Table 6), even though it contained only 44% of the total number of women across all four trials. On the other hand, Rouse 2008 (with 56% of the total number of women in the Cochrane review) individually showed a benefit for cerebral palsy with magnesium sulphate (see table 6 above).

In a small side study of Crowther 2003, Smith 2003 found that antenatal infusions enabled prompt transfer of magnesium sulphate to the mother (within 30 minutes) and that neonatal magnesium sulphate concentrations remained elevated to 24 hours. This indicates that magnesium sulphate crosses the placenta to the fetus promptly after commencing the infusion.

Based on this evidence, the guideline panel recommended that magnesium sulphate be administered when early preterm birth is planned or definitely expected within 24 hours. (When birth is planned, commence magnesium sulphate as close to four hours before birth as possible).

see Appendix F.5: evidence statement

CLINICAL RECOMMENDATION	GRADE
In women at risk of early preterm* imminent[#] birth, use magnesium sulphate for neuroprotection of the fetus, infant or child: [#]when early preterm birth is planned or definitely expected within 24 hours. (When birth is planned, commence magnesium sulphate as close to four hours before birth as possible). *see chapter 8	A

GOOD PRACTICE POINT

If birth before 30 weeks is planned or expected to occur sooner than four hours (e.g. scheduled caesarean or late presentation to hospital), administer magnesium sulphate to women at risk of preterm birth, as there is still advantage likely from administration within this time.

IMPLEMENTATION IMPLICATIONS

As for chapter 7.

FURTHER RESEARCH RECOMMENDATIONS

- Individual triallists should be approached to provide unpublished optimal timing of magnesium sulphate administration
- Individual patient data meta-analysis can be used to explore whether differences in timing of magnesium sulphate administration result in different rates of adverse outcomes such as cerebral palsy and combined death and cerebral palsy.
- Further randomised trials evaluating the optimal timing of the antenatal administration of magnesium sulphate prior to preterm birth are warranted.

Chapter 10: Regimens (Question 6)

Question 6: Do improvements to the fetus, infant, and child vary by regimens?

This chapter summarises the evidence of the four individual neuroprotective intent trials in the Doyle 2009 Cochrane Review for regimens used to administer magnesium sulphate.

In these trials, the loading doses of magnesium sulphate given were either 4 grams or 6 grams.

Two trials did not use a maintenance dose (Mittendorf 2002 and Marret 2006) and two trials gave maintenance doses of either 1 gram per hour (Crowther 2003) or 2 grams per hour (Rouse 2008). No repeat dosing was given in three of the four trials (Mittendorf 2002; Crowther 2003 and Marret 2006). All trials used intravenous magnesium sulphate.

Table 7: Regimens of trials (Doyle 2009 Cochrane Review)

Study	Loading Dose	Maintenance Dose	Repeat dosing	Route	Actual regimen given (in magnesium group)
Marret 2006 (PREMAG)	4 g (over 30 mins)	none	none	IV	**91% (259/286) given full dose** 2% (7/286) given partial dose only 7% (20/286) not given magnesium sulphate
Mittendorf 2002 (MagNET)	4 g bolus	none	none	IV	Not reported
Crowther 2003 (ACTOMgSO$_4$)	4 g (over 20 mins)	1 g/hour; until birth or up to 24 hours, whichever was first	none	IV	**91% (484/535) given full loading dose** 7% (38/535) given partial loading dose 84% (451/535) started maintenance dose 2% (13/535) women not given magnesium sulphate
Rouse 2008 (BEAM)	6 g (over 20-30 mins)	2 g/hour; stopped if birth had not occurred in 12 hours and was no longer considered imminent	If contractions recurred, infusion was resumed at 2 g/hour; if at least 6 hours had passed since the discontinuation of magnesium, another loading dose was given	IV	**91% (996/1,096) given magnesium sulphate for 3 h or more** 8% (82/1,096) given magnesium sulphate 3 h before birth 2% (18/1,096) not given magnesium sulphate (42.2% given repeat dose)

There was a significant reduction in the combined outcome of death or cerebral palsy; and of cerebral palsy across all trials (RR 0.85; 95% CI 0.74 to 0.98 and RR 0.71; 95% CI 0.52 to 0.97; 4446 infants). Rouse 2008, which was considerably larger than the other trials, significantly contributed to the finding of the overall reduction in cerebral palsy (RR 0.59; 95% CI 0.40 to 0.85; 2444 infants).

Table 8: Results of primary outcomes by regimen for trials (Doyle 2009 Cochrane Review)

Trial	Regimen	DEATH OR CEREBRAL PALSY RR (95% CI)	CEREBRAL PALSY	DEATH
Marret 2006; Mittendorf 2002 (n=747)	4 g (no maintenance); Marret 2006 (over 30 mins); Mittendorf 2002 (bolus)	1.45 (0.27 to 7.72)	1.37 (0.18 to 10.70)	0.88 (0.57 to 1.35)
Crowther 2003 (n=1255)	4 g (over 20 mins) plus 1 g/hour maintenance	0.82 (0.66 to 1.02)	0.85 (0.55 to 1.31)	0.81 (0.62 to 1.05)
Rouse 2008 (n=2444)	6 g (over 20-30 mins) plus 2 g/hour maintenance	0.90 (0.73 to 1.10)	**0.59 (0.40 to 0.85)***	1.13 (0.87 to 1.48)
OVERALL (n=4446)		**0.85 (0.74 to 0.98)***	**0.71 (0.52 to 0.97)***	0.95 (0.80 to 1.12)

**significantly in favour of magnesium sulphate*

see Appendix F.6: evidence tables/graphs

Summary of evidence statement judgements for regimens

The evidence base for regimens used to administer magnesium sulphate to women at risk of preterm birth for neuroprotection of their fetus, infant or child was judged to have a low risk of bias despite some unexplained inconsistency between Marret 2006 and Mittendorf 2002 in subgroups. For the combined outcome of death and cerebral palsy; and the outcome of cerebral palsy alone, in the 4 g no maintenance subgroups, the effect was in opposite directions in the two trials (in favour of magnesium sulphate in Marret, in favour of no magnesium sulphate in Mittendorf, with neither result statistically significant).

The evidence was judged by the guideline panel to be both generalisable and applicable to the Australian and New Zealand healthcare context.

Overall the clinical impact was judged to be very large, however, since differences in death and cerebral palsy by regimen are unclear at present, no particular regimen subgroup was judged to have any greater or lesser impact than another.

How the recommendation was formulated

Although the trial with higher loading dose with repeat treatment permitted (Rouse 2008) was the only study to show statistical significance on its own (RR of cerebral palsy 0.59 95% CI 0.40 to 0.85), it was unclear whether this was due to a dose effect or due to the size of the trial, (which was the largest in the meta-analysis and therefore had more power to detect differences). However, the case for a dose effect is weakened by the lack of a significant finding for the combined outcome of death or cerebral palsy (RR 0.90 95% CI 0.73 to 1.10).

Because of this uncertainty, the guideline panel felt it prudent to restrict magnesium sulphate administration to the lowest loading dose (4 g) used with a maintenance dose (again based on the lowest maintenance dose of 1 g/hour). Therefore the guideline panel recommends that magnesium sulphate should only be given for neuroprotection as a 4 g loading dose slowly over 20-30 minutes with 1 gram per hour maintenance dose and with no immediate repeat doses, via intravenous route. This should be continued up until birth or within 24 hours, whichever comes first.

The loading regimen of 4 g magnesium sulphate is identical to loading doses commonly used throughout Australia, New Zealand and elsewhere to treat women with pre-eclampsia (see Appendix H). The maintenance dose of 1 g/hr of magnesium sulphate is consistent with maintenance doses commonly used throughout Australia and New Zealand to treat women with pre-eclampsia and eclampsia (see Appendix H).

There is considerable variation in the method of giving the loading doses (by either infusion pump or syringe pump). A time period of 20-30 minutes for infusion of a 4 g loading dose is recommended for women with pre-eclampsia (see Appendix H).

Appendix F. 6: Evidence tables/graphs

CLINICAL RECOMMENDATION	GRADE
In women at risk of early preterm* imminent# birth, use magnesium sulphate for neuroprotection of the fetus, infant or child: intravenously with a 4 gram loading dose (slowly over 20-30 minutes) and 1 gram per hour maintenance dose via intravenous route, with no immediate repeat doses. Continue regimen up until birth or for 24 hours, whichever comes first. *see chapter 8 #see chapter 9	C

GOOD PRACTICE POINTS

Urgent delivery

In situations where urgent delivery is necessary because of actual or imminent maternal or fetal compromise (e.g. severe fetal distress or antepartum haemorrhage), then birth should not be delayed to administer magnesium sulphate.

Repeat doses

In the event that birth does not occur after giving magnesium sulphate for neuroprotection of the infant, and preterm birth (less than 30 weeks' gestation) again appears imminent (planned or definitely expected within 24 hours), a repeat dose of magnesium sulphate may be considered at the discretion of the attending health professional.

Locations of administration of antenatal magnesium sulphate (Chapter 10)

The locations of administration of antenatal magnesium sulphate intravenously to women should be determined by each individual maternity facility.

Monitoring

During administration of magnesium sulphate intravenously, women should be regularly assessed as detailed in individual obstetric unit protocols. Resuscitation and ventilatory support should be immediately available, if needed, during administration of magnesium sulphate. Should hypotension or respiratory depression occur prompt medical review is recommended. This may include cessation of magnesium sulphate.

Loading

A minimum assessment should include checking pulse, blood pressure, respiratory rate and patellar reflexes before loading dose, 10 minutes after loading dose infusion has started and at the end of the loading dose infusion (20-30 minutes). The infusion should be stopped if respiratory rate decreases more than 4 breaths per minute below baseline, or is less than 12 breaths per minute; or diastolic blood pressure decreases more than 15 mm Hg below baseline level (Crowther 2003).

Maintenance

While the maintenance infusion is running, observe for any adverse effects. The minimum assessments should include checking pulse, blood pressure, respiratory rate, patellar reflexes and urine output 4-hourly. Stop infusion if respiratory rate is less than 12 breaths per minute; if patellar reflexes are absent, if hypotension occurs or if urine output is less than 100 mLs over 4 hours.

Toxicity

Magnesium toxicity is unlikely with the regimens recommended in these guidelines and serum magnesium concentrations do not need to be routinely measured (RCOG 2006). In women with renal compromise, serum magnesium monitoring is recommended.

Calcium gluconate (1 gram (10 mL of 10% solution) slowly via intravenous route over 10 minutes) can be given if there is clinical concern over respiratory depression.

Potential interactions (Chapter 10)

There is a potential theoretical interaction between magnesium sulphate and nifedipine of hypotension and neuromuscular blockade effects (Snyder & Cardwell 1989; Ben-Ami 1994), although this is seldom reported in clinical practice. Regular monitoring of the woman is recommended as detailed in individual obstetric unit protocols. If hypotension occurs, nifedipine and magnesium sulphate should cease and the woman reviewed by a medical practitioner.

IMPLEMENTATION IMPLICATIONS

Australian and New Zealand clinicians are less likely to be comfortable using loading doses higher than 4 gram.

Monitoring women after they have been given antenatal infusions of magnesium sulphate is usually recommended. Monitoring formed part of the published study methods for two of the included randomised controlled trials (Crowther 2003 and Marret 2006) – see Appendix H. There is, however, no consensus on what form this monitoring should take. For example the Society of Obstetric Medicine of Australia and New Zealand (SOMANZ) state that obstetric units should determine their own protocols for monitoring outcomes (SOMANZ 2008 [also see Appendix H]). As toxicity is unlikely with the regimens recommended in these guidelines, routine monitoring of serum magnesium sulphate concentrations should not be required.

FURTHER RESEARCH RECOMMENDATIONS

- Individual triallists should be approached to provide unpublished optimal treatment regimens.
- Individual patient data meta-analysis can be used to explore whether different magnesium sulphate regimens result in different rates of adverse outcomes such as cerebral palsy and combined death and cerebral palsy.
- Further randomised trials of regimens are required, specifically comparing:
    - loading dose versus loading dose plus maintenance
    - different loading doses (4 gram versus 6 gram)
    - use of repeat doses of magnesium sulphate.

Chapter 11: Number of Babies in Utero (Question 7)

Question 7: Do improvements to the fetus, infant, and child vary by number of babies in utero?

This chapter summarises the evidence from the four individual neuroprotective intent trials within the Doyle 2009 Cochrane review for the number of babies in utero.

All four trials included twins; two trials also included higher order multiple gestations (Crowther 2003 and Marret 2006). Only Crowther 2003 and Rouse 2008 reported death separately as an outcome for single and multiple pregnancies and only Crowther 2003 reported cerebral palsy outcomes separately for these groups.

Table 9: Plurality of trials (Doyle 2009 Cochrane Review)

Study	Single	Twin	Higher order	Reported separately
Crowther 2003	Yes	Yes	Yes (triplet+quad)	Single vs multiple
Rouse 2008	Yes	Yes	No	Single vs twin^{++}
Marret 2006	Yes	Yes	Yes (triplet)	No
Mittendorf 2002	Yes	Yes	No	No

Table 10: Results of primary outcomes by plurality for trials (Doyle 2009 Cochrane Review)

Number of babies in utero	DEATH or CEREBRAL PALSY	CEREBRAL PALSY	DEATH
		RR (95% CI)	
Multiple	0.73 (0.50 to 1.08) Crowther 2003	0.52 (0.21 to 1.25) Crowther 2003	0.90 (0.63 to 1.31) Crowther 2003, Rouse 2008
Single	0.86 (0.67 to 1.11) Crowther 2003	1.01 (0.61 to 1.68) Crowther 2003	0.96 (0.68 to 1.37) Crowther 2003, Rouse 2008
Multiple and single	*0.88 (0.74 to 1.05) Marret 2006, Mittendorf 2002, Rouse 2008*	***0.65 (0.48 to 0.88)**** *Marret 2006, Mittendorf 2002, Rouse 2008*	*0.88 (0.57 to 1.35) Marret 2006, Mittendorf 2002*
OVERALL	**0.86 (0.75 to 0.98)***	**0.71 (0.55 to 0.91)***	0.94 (0.79 to 1.12)

$^{++}$Rouse 2008 reported only moderate to severe cerebral palsy, (not all cerebral palsy) so plurality data from Rouse can only be reported for the outcome of death.

Appendix F.7: Evidence tables/graphs

Summary of evidence statement judgements for number of babies in utero subgroup of infant neuroprotection

The subgroup analyses come from trials with low risk of bias, and results between trials are fairly consistent. While evidence is applicable, generalisability to the Australian and New Zealand context was reduced since the majority of the women in the largest trial had PPROM (and therefore represented a narrower subset of women at risk of preterm birth).

Overall clinical impact was judged to be very large, but since any differences in death and cerebral palsy by number of babies in utero is unclear at present, no particular subgroup was judged to have any greater or lesser impact than another.

The guideline panel therefore recommends that magnesium sulphate be used regardless of plurality.

Appendix F.7: Evidence statements

CLINICAL RECOMMENDATION	GRADE
In women at risk of early preterm* imminent# birth, use magnesium sulphate for neuroprotection of the fetus, infant or child: regardless of plurality (number of babies in utero). *see chapter 8 #see chapter 9	B

IMPLEMENTATION IMPLICATIONS

As for Chapter 7.

FURTHER RESEARCH RECOMMENDATIONS

- If triallists collected data on plurality, these data should be obtained and aggregate analyses conducted.
- Individual patient data meta-analysis can be used to explore whether differences in plurality result in different rates of adverse outcomes such as cerebral palsy and combined death and cerebral palsy.

Chapter 12: Reasons Women (at less than 30 weeks gestation) Considered at Risk of Preterm Birth (Question 8)

Question 8: Do improvements to the fetus, infant, and child vary by reason women (at less than 30 weeks gestation) considered to be at risk of preterm birth?

At this stage there is insufficient evidence to identify the reasons women were considered at risk of preterm birth and included in studies relating to the administration of magnesium sulphate.

See Appendix F.8

CLINICAL RECOMMENDATION	GRADE
In women at risk of early preterm* imminent# birth, use magnesium sulphate for neuroprotection of the fetus, infant or child: regardless of reason women considered (at less than 30 weeks' gestation) to be at risk of preterm birth. *see chapter 8 #see chapter 9	B

IMPLEMENTATION IMPLICATIONS

As for chapter 7.

FURTHER RESEARCH RECOMMENDATIONS

- If triallists collected data on reasons women were considered to be at risk of preterm birth, these data should be obtained and aggregate analyses conducted.
- Individual patient data meta-analysis can be used to explore whether differences in reasons women were considered to be at risk of preterm birth result in different rates of adverse outcomes such as cerebral palsy and combined death and cerebral palsy.

Chapter 13: Parity (Question 9)

Question 9: Do improvements to the fetus, infant, and child vary by parity of women?

Parity of women was not reported in any of the trials included in the Doyle 2009 Cochrane review.

At this stage there is insufficient evidence to identify whether parity is a significant factor in the use of magnesium sulphate.

See Appendix F.9

CLINICAL RECOMMENDATION	GRADE
In women at risk of early preterm* imminent# birth, use magnesium sulphate for neuroprotection of the fetus, infant or child: regardless of parity (number of previous births for the woman). *see chapter 8 #see chapter 9	B

IMPLEMENTATION IMPLICATIONS

As for Chapter 7.

FURTHER RESEARCH RECOMMENDATIONS

- If triallists collected data on parity, these data should be obtained and aggregate analyses conducted.
- It may be possible to elucidate any influence of parity through individual patient data meta-analysis.

Chapter 14: Mode of Birth (Question 10)

Question 10: Do improvements to the fetus, infant, and child vary by mode of birth?

This chapter summarises the evidence from the four individual neuroprotective intent trials within the Doyle 2009 Cochrane review for mode of birth.

Three of the four trials (Crowther 2003, Marret 2006 and Rouse 2008) reported mode of birth (caesarean section and vaginal birth), but not outcomes for the child by mode of birth.

Mode of birth as an outcome

Overall there was no significant difference in mode of birth between women given magnesium sulphate and those not given magnesium sulphate. When the three trials are pooled, the results are non-significant, ranging from a 7% decrease to a 7% increase in the number of caesarean sections (RR 1.00 95% CI 0.93 to 1.07).

At present there is insufficient evidence to show whether the use of magnesium sulphate has any influence on the mode of birth.

See Appendix F:10

Table 11: Results of primary outcomes by mode of birth for trials (Doyle 2009 Cochrane Review)

Trial	Caesarean Section	Vaginal Birth
	RR (95% CI)	
Crowther 2003 (n=1062 women)	0.98 (0.88 to 1.10)	1.02 (0.90 to 1.17)
Marret 2006 (n=564 women)	1.17 (0.95 to 1.46)	0.91 (0.80 to 1.03)
Rouse 2008 (n=2241 women)	0.97 (0.88 to 1.08)	1.02 (0.95 to 1.09)
OVERALL (n=3867)	1.00 (0.93 to 1.07)	1.00 (0.95 to 1.06)

Mode of birth as an effect modifier

It is possible that the neuroprotective effect of antenatal magnesium sulphate may be modified by mode of birth. Elective caesarean section has been shown to be associated with reduced neonatal encephalopathy (Badawi 1998) and there is some suggestion in the literature that caesarean section may be associated with improved survival and improved neurodevelopmental outcomes for extremely low birthweight infants (Wilson-Costello 2007).

CLINICAL RECOMMENDATION	GRADE
In women at risk of early preterm* imminent# birth, use magnesium sulphate for neuroprotection of the fetus, infant or child: regardless of anticipated mode of birth. *see chapter 8 #see chapter 9	B

IMPLEMENTATION IMPLICATIONS

As for Chapter 7.

FURTHER RESEARCH RECOMMENDATIONS

Any modifying effect of mode of birth on neurodevelopmental outcomes could be explored in the trials included in the Doyle 2009 Cochrane review through a four-way comparison of:

- caesarean births in the magnesium sulphate groups
- caesarean births in the placebo/no treatment groups
- vaginal births in the magnesium sulphate groups
- vaginal births in the placebo/no treatment groups.

Chapter 15: Effect of Antenatal Corticosteroids (Question 11)

Question 11: Do improvements to the fetus, infant, and child vary by combined effect of antenatal corticosteroids and magnesium sulphate?

Table 12: Results of primary outcomes by corticosteroid use for trials (Doyle 2009 Cochrane Review)

Trial	High use of antenatal corticosteroids
Crowther 2003	yes
Rouse 2008	yes
Marret 2006	yes
Mittendorf 2002	unknown

At this stage there is insufficient evidence to identify any effect on outcomes when antenatal corticosteroids have been used.

See Appendix F:11

CLINICAL RECOMMENDATION	GRADE
In women at risk of early preterm* imminent# birth, use magnesium sulphate for neuroprotection of the fetus, infant or child: whether or not antenatal corticosteroids have been given. *see chapter 8 #see chapter 9	B

IMPLEMENTATION IMPLICATIONS

As for Chapter 7.

FURTHER RESEARCH RECOMMENDATIONS

- Further data on antenatal corticosteroid use should be obtained from individual triallists and aggregate analyses conducted.
- Individual patient data meta-analysis can be used to explore whether differences in use of antenatal corticosteroids result in different rates of adverse outcomes such as cerebral palsy and combined death and cerebral palsy.

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Appendix A: Process and Methods

Overview of the guideline development process

There was a recognised urgent need for guidelines on the use of magnesium sulphate for neuroprotection to assist clinical decision making. Since there were no known existing guidelines suitable for adaptation, a group of experts in their fields met on 17 September 2009 at the University of Adelaide to discuss developing guidelines. Present at the meeting were Professor Caroline Crowther, Ms Philippa Middleton, Professor Peter Davis, Associate Professor Vicki Flenady, Dr Lisa Askie, Dr Helena Oakey, Dr Neil Hotham, Dr Dell Horey and Dr Jane Alsweiler. At this meeting the group discussed the establishment of a multidisciplinary expert advisory panel to oversee the development of the guidelines, defined the Panel's purpose, identified the clinical questions and harms that needed to be considered and established a process for developing the guidelines.

Establishing the Expert Advisory Panel

A multidisciplinary panel was established to oversee the development of the guidelines. Representation was invited from:

- Health professionals in the fields of maternal fetal medicine, obstetrics, midwifery, neonatology and neonatal nursing;
- Relevant allied health practitioners e.g. pharmacist;
- Research methodology experts including epidemiologists and a biostatistician;
- Consumer representatives;
- Representatives from professional colleges and bodies (RANZCOG; ACM; NZCOM; RACP; ACNN; and WHA).

Purpose of the Panel

The purpose of the *Antenatal Magnesium Sulphate Prior to Preterm Birth for Neuroprotection of the Fetus, Infant, and Child Guideline Development Panel* was to prepare a guideline on best practice for clinical care on the use of magnesium sulphate prior to preterm birth. The guidelines are relevant for health professionals who care for women at risk of preterm birth and their babies, pregnant women and their partners, and policy makers in maternity care.

Clinical Questions Defined

Does the administration of magnesium sulphate to women prior to preterm birth:

- Improve the health outcomes for the fetus/infant/child?
- Cause adverse outcomes for the women?
- Cause adverse outcomes for the fetus/infant/child?
- Do any improvements for the fetus/infant/child vary by:
    - Gestational age magnesium sulphate given?
    - Time magnesium sulphate planned to be given prior to birth?
    - Dose regimen planned?
    - Number of babies in-utero?
    - Reason women considered at risk of preterm birth (preterm labour, preterm prelabour rupture of the membranes, antepartum haemorrhage, pre-eclampsia, fetal compromise; maternal factors)?

- Parity of the women?
- Mode of birth?
- Use of antenatal corticosteroids?

Draft Health Outcomes Considered for the Guidelines:

- Death and neurosensory disability (including cerebral palsy, blindness, deafness, developmental delay) for the fetus, infant, and child.
- Harmful effects by the therapy for the woman and the child (maternal respiratory depression, cardiac arrest, hypotension, side effects, and fetal/neonatal side effects.
- Resources needed and economic component.

Literature Review Process

It was agreed to follow NHMRC and NZGG guideline processes. There was a systematic identification and synthesis of the best available scientific evidence. Evidence for effectiveness included systematic reviews and randomised trials assessing outcomes of antenatal magnesium sulphate for fetal neuroprotection. In addition, the substantial randomised literature for the use of magnesium sulphate during pregnancy was assessed for evidence about harms of antenatal magnesium use for mother and baby. Evidence statements (assessing evidence base, consistency, clinical impact, generalisability, applicability and draft recommendations) were prepared, and then discussed by the panel, for each of the clinical questions.

Summary of timeline:

- 12 Oct 2009 – input sought by email from full panel.
- 16 Oct 2009 – subsequent drafts discussed by teleconference.
- 12 Nov 2009 – face to face meeting in Sydney.
- 19 Dec 2009 – 18 Jan 2010: public consultation of draft guidelines.
- 12 Dec 2009 – open meeting in Adelaide.
- Jan/Feb 2010 – final guideline document.
- March 2010 – draft guidelines released.
- 17 November 2010 – NHMRC approved guidelines.

Appointment of the Panel

On 16 October 2009 the Guideline Panel met via teleconference. Prior to the meeting Panel members were required to declare their conflict of interest (see p. 52). At the meeting the purpose of the Panel was established, defined clinical questions were discuss and approved, the NHMRC evidence statements process used to address these questions was explained and the ongoing process for developing the guidelines was established.

Development of the Guidelines

Synthesis of new and existing evidence

The Cochrane Library was searched for relevant Cochrane reviews, other systematic reviews and RCTs (last searched August 2008). PubMed was last searched in August 2008. References of retrieved articles were checked for potentially relevant studies.

Developing recommendations

The Guideline recommendations for each clinical question were developed using procedures outlined in the *"NHMRC additional levels of evidence and grades for recommendations for developers of guidelines: Stage 2 consultation 2008 – 2010"* (available from the NHMRC website). Each recommendation was assigned a grade for 'A' to 'D'. 'A' refers to a recommendation based on a body of evidence that can be trusted to guide practice. 'B' refers to a recommendation based on a body of evidence that can be trusted to guide practice in most situations. Grade 'C' means that the body of evidence provides some support for the recommendation, but care should be taken in its application. Grade 'D' means that the body of evidence is weak and the recommendation should be applied with caution. Each recommendation was assigned a grade taking into account the volume, consistency, generalisability, applicability and clinical impact of the body of evidence supporting each recommendation. The standardised evidence statement form used to formulate and grade the recommendations can be found in Appendix B.

Panel Member Input

Panel members provided input into the draft guideline document on an ongoing basis via email. The executive group of the Panel met face to face on 12 November 2009 to consider the comments received from the Panel and to consolidate the draft document. At this meeting the additional clinical question 'mode of birth' was identified.

On 12 December 2009 a workshop was held in Adelaide attended by the Panel members and other participants with an interest in magnesium sulphate guidelines. The purpose of the meeting was to provide an overview of the evidence surrounding the use of magnesium sulphate for neuroprotection, the need for the guidelines, the guideline development process and draft recommendations, allow participants to provide input into the implementation implications, good practice points, audit process and further research needed.

Public Consultation Process

The draft Guideline document was released for public consultation in December 2009, published through The Australian national newspaper and made available on the Australian Research Centre for Health of Women and Babies (ARCH) website. Public consultation closed on 18 January 2010.

Response to feedback and completion of final guideline document

Material provided through the public consultation process was incorporated into the Guideline document. A summary of the public consultation comments and Panel member responses are provided in Appendix I.

Declarations of competing interest of the guideline panel members

Professor Caroline Crowther

- Chief Investigator for the Australian Collaborative Trial of Magnesium Sulphate (ACTOMgSO_4) funded through the National Health and Medical Research Council (NHMRC) Project Grant 3503267.
- Co-author for the Cochrane Review 'Magnesium sulphate for preventing preterm birth in threatened preterm labour'.
- Co-author for the Cochrane Review 'Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus'.
- Co-author for the Cochrane Review 'Magnesium maintenance therapy for preventing preterm birth after threatened preterm labour'.

- Co-author on updates of other Cochrane Reviews assessing antenatal use of magnesium sulphate.

Professor Lex Doyle

- Co-author for the Cochrane Review 'Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus'.
- Co-author for the Cochrane Review 'Magnesium sulphate for preventing preterm birth in threatened preterm labour'.
- Investigator for the ACTOMgSO_4 trial.
- Co-author on updates of other Cochrane Reviews assessing antenatal use of magnesium sulphate.

Professor Lesley McCowan

- Assisted in the coordination of the ACTOMgSO_4 trial in New Zealand.

Ms Philippa Middleton

- Co-author for the Cochrane Review 'Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus'.
- Co-author on updates of other Cochrane Reviews assessing antenatal use of magnesium sulphate.

Appendix B: How to use the NHMRC Evidence Statement Form

Step 1 — Rate each of the five components

Applying evidence in real clinical situations is not usually straightforward. Consequently guideline developers find that the body of evidence supporting a recommendation rarely consists of entirely one rating for all the important components (outlined above). For example, a body of evidence may contain a large number of studies with a low risk of bias and consistent findings, but which are not directly applicable to the target population or Australian healthcare context and have only a limited clinical impact. Alternatively, a body of evidence may only consist of one or two randomised trials with small sample sizes that have a moderate risk of bias but have a very large clinical impact and are directly applicable to the Australian healthcare context and target population. The NHMRC evidence grading system is designed to allow for this mixture of components, while still reflecting the overall body of evidence supporting a guideline recommendation.

The components described above should be rated according to the matrix shown in Table 1. Enter the results into the NHMRC Evidence Statement Form (see Appendix C) along with any further notes relevant to the discussions for each component.

Table 1: Body of evidence matrix

Component	A	B	C	D
	Excellent	**Good**	**Satisfactory**	**Poor**
Evidence base[1]	one or more level I studies with a low risk of bias or several level II studies with a low risk of bias	one or two level II studies with a low risk of bias or a SR/several level III studies with a low risk of bias	one or two level III studies with a low risk of bias, or level I or II studies with a moderate risk of bias	level IV studies, or level I to III studies/SRs with a high risk of bias
Consistency[2]	all studies consistent	most studies consistent and inconsistency may be explained	some inconsistency reflecting genuine uncertainty around clinical question	evidence is inconsistent
Clinical impact	very large	substantial	moderate	slight or restricted
Generalisability	population/s studied in body of evidence are the same as the target population for the guideline	population/s studied in the body of evidence are similar to the target population for the guideline	population/s studied in body of evidence differ to target population for guideline but it is clinically sensible to apply this evidence to target population[3]	population/s studied in body of evidence differ to target population and hard to judge whether it is sensible to generalise to target population
Applicability	directly applicable to Australian healthcare context	applicable to Australian healthcare context with few caveats	probably applicable to Australian healthcare context with some caveats	not applicable to Australian healthcare context

SR = systematic review; several = more than two studies

[1] Level of evidence determined from the NHMRC evidence hierarchy – Table 3, Part B

[2] If there is only one study, rank this component as 'not applicable'.

[3] For example, results in adults that are clinically sensible to apply to children OR psychosocial outcomes for one cancer that may be applicable to patients with another cancer

The Evidence Statement Form also provides space to enter any other relevant factors that were taken into account by the guideline developers when judging the body of evidence and developing the wording of the recommendation.

Step 2 — Prepare an evidence statement matrix

In the 'Evidence statement matrix ' section of the form, summarise the guideline developers' synthesis of the evidence relating to each component at the right hand side of the form, and fill in the evidence matrix at the left hand side of the form. Each recommendation should be accompanied by this matrix as well as the overall grade given to the recommendation (see Step 3). Developers should indicate dissenting opinions or other relevant issues in the space provided under the evidence matrix.

Step 3 — Formulate a recommendation based on the body of evidence

Develop wording for the recommendation. This should address the specific clinical question and ideally be written as an action statement. The wording of the recommendation should reflect the strength of the body of evidence. Words such as 'must' or 'should' are used when the evidence underpinning the recommendation is strong, and words such as 'might' or 'could' are used when the evidence base is weaker.

Step 4 — Determine the grade for the recommendation

Determine the overall grade of the recommendation based on a summation of the rating for each individual component of the body of evidence. **A recommendation cannot be graded A or B unless the evidence base and consistency of the evidence are both rated A or B.**

NHMRC overall grades of recommendation are intended to indicate the strength of the body of evidence underpinning the recommendation. This should assist users of the clinical practice guidelines to make appropriate and informed clinical judgments. Grade A or B recommendations are generally based on a body of evidence that can be trusted to guide clinical practice, whereas Grades C or D recommendations must be applied carefully to individual clinical and organisational circumstances and should be interpreted with care (see Table 2).

Table 2: Definition of NHMRC grades of recommendations

Grade of recommendation	Description
A	Body of evidence can be trusted to guide practice
B	Body of evidence can be trusted to guide practice in most situations
C	Body of evidence provides some support for recommendation(s) but care should be taken in its application
D	Body of evidence is weak and recommendation must be applied with caution

Implementing guideline recommendations

How the guidelines will be implemented should be considered at the time that the guideline recommendations are being formulated. Guidelines require an implementation plan that ensures appropriate roll out, supports and evaluation of guideline effectiveness in improving practice, and guideline uptake. The Evidence Statement Form asks developers to consider four questions related to the implementation of each recommendation:

- Will this recommendation result in changes in usual care?
- Are there any resource implications associated with implementing this recommendation?
- Will the implementation of this recommendation require changes in the way care is currently organised?
- Are the guideline development group aware of any barriers to the implementation of this recommendation?

Appendix C: NHMRC Evidence Statement Form

(If rating is not completely clear, use the space next to each criteria to note how the group came to a judgment).

Key question(s):		**Evidence table ref:**
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted

4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*		
Component	Rating	Description
1. Evidence base		
2. Consistency		
3. Clinical impact		
4. Generalisability		
5. Applicability		

Indicate any dissenting opinions

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

UNRESOLVED ISSUES *If needed, keep note of specific issues that arise when each recommendation is formulated and that require follow-up.*

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	YES
	NO
Are there any resource implications associated with implementing this recommendation?	YES
	NO
Will the implementation of this recommendation require changes in the way care is currently organised?	YES
	NO
Are the guideline development group aware of any barriers to the implementation of this recommendation?	YES
	NO

Appendix D: New Zealand Processes

The NZ guiding principles for guideline developers are detailed in the "Handbook for the Preparation of Explicit Evidence-Based Clinical Practice Guidelines" (NZGG 2001).

Appendix E: Tocolysis Intent and Maternal Neuroprotective Intent

TOCOLYSIS

a) Crowther 2002 compared magnesium sulphate with no magnesium sulphate (either placebo or an alternative tocolytic drug) for initial (acute) tocolysis in women thought to be in preterm labour. This Cochrane review included 23 trials (with over 2000 women). The last search was conducted in May 2002.

Magnesium sulphate was found to be **ineffective** at either delaying birth or preventing preterm birth, and its use was associated with increased mortality for infants (of the 24 deaths (18 in the magnesium group and 10 in the placebo group), all but two were neonates or infants).

Cochrane review of magnesium sulphate for tocolysis (Crowther 2002)

TOCOLYSIS	RR (95% CI)	Number of trials, participants
Birth within 48 hours of tocolysis	0.85 (0.58 to 1.25)	11 trials, 881 women
Preterm birth (< 37 weeks)	0.91 (0.75 to 1.11)	6 trials, 424 women
Perinatal mortality	2.82 (1.20 to 6.62)	7 trials, 727 infants

b) Crowther 1998 compared magnesium sulphate with no magnesium sulphate (either a placebo or an alternative drug) used for maintenance in women who already had been given some medication to stop early labour. The Cochrane review included three trials (303 women, 322 infants). The last search for this review was conducted in August 2002.

No differences in the incidence of preterm birth or perinatal mortality were seen when magnesium sulphate maintenance therapy was compared with either a placebo, or no treatment, or alternative therapies (ritodrine or terbutaline).

Cochrane review of magnesium sulphate for maintenance of tocolysis (Crowther 1998)

TOCOLYSIS (MAINTENANCE)	RR (95% CI)	Number of trials, participants
Preterm birth < 37 weeks (magnesium v placebo/no treatment)	0.85 (0.47 to 1.51)	1 trial, 50 infants
Preterm birth < 37 weeks (magnesium v ritodrine or terbutaline)	0.98 (0.56 to 1.72)	2 trials, 100 infants
Perinatal mortality (magnesium v placebo/no treatment)	5.00 (0.25 to 99.16)	1 trial, 50 infants
Perinatal mortality (magnesium v ritodrine or terbutaline)	5.00 (0.25 to 99.16)	1 trial, 50 infants

Summary of evidence statement judgements for tocolysis

The evidence base for tocolysis was of poor to moderate quality (high to moderate risk of bias), with some inconsistency between the results of different trials. Tocolysis with magnesium sulphate was judged to have a substantial negative impact on outcomes, in particular, increased infant mortality. The evidence was judged to be both generalisable and applicable.

NEUROPROTECTION (MOTHER) – PRE-ECLAMPSIA

Magnesium sulphate is given to pregnant women with the intention of preventing eclampsia.

Duley 2003 compared magnesium sulphate with placebo or no anticonvulsant for preventing eclampsia in women with pre-eclampsia. This Cochrane review included 11,444 women (six trials) and 9961 infants (three trials). The last search was conducted in November 2002.

Duley 2003 found that while magnesium sulphate more than halved the risk of eclampsia, and probably reduced the risk of maternal death, the review did not demonstrate effects on improved infant outcomes. However, there was no overall difference in the risk of stillbirth or neonatal death (RR 1.04, 95% CI 0.93 to 1.15) or other infant outcomes. This was also true for the subset of unpublished outcome data provided by the trial investigators for the Doyle 2009 Cochrane review.

Summary of evidence statement judgements for maternal neuroprotection

The evidence base for maternal neuroprotection (preventing pre-eclampsia) with magnesium sulphate has a mixed risk of bias and results are fairly consistent between trials. The impact on fetal and infant outcomes was judged to be negligible. While the evidence may be applicable, it has lower generalisability as most women in the largest trial were from low or middle income countries.

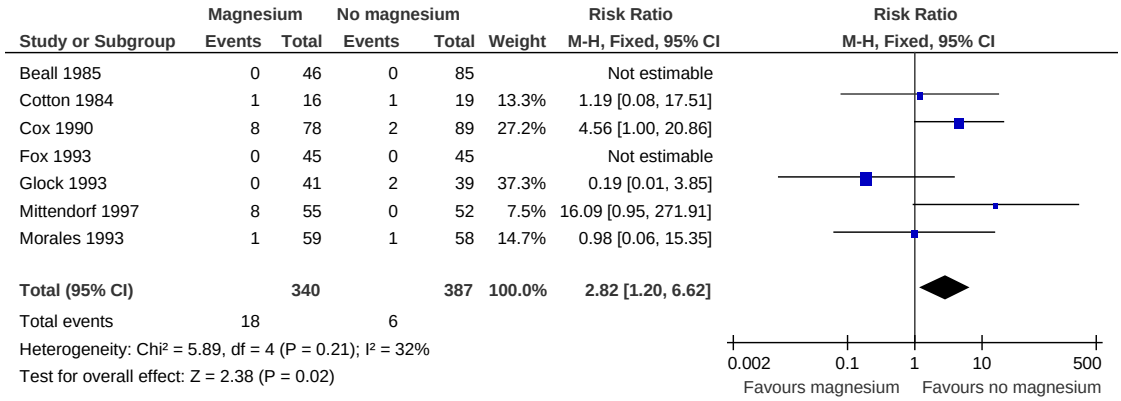
Q1-Q3: Effectiveness Summary for Cochrane Reviews

Tocolysis

Crowther 2002

This Cochrane review included 23 trials (with over 2000 women). Magnesium sulphate was ineffective at delaying birth or preventing preterm birth, and its use is associated with an increased mortality for the infant.

DEATH



Study or Subgroup	Magnesium Events	Magnesium Total	No magnesium Events	No magnesium Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Beall 1985	0	46	0	85		Not estimable
Cotton 1984	1	16	1	19	13.3%	1.19 [0.08, 17.51]
Cox 1990	8	78	2	89	27.2%	4.56 [1.00, 20.86]
Fox 1993	0	45	0	45		Not estimable
Glock 1993	0	41	2	39	37.3%	0.19 [0.01, 3.85]
Mittendorf 1997	8	55	0	52	7.5%	16.09 [0.95, 271.91]
Morales 1993	1	59	1	58	14.7%	0.98 [0.06, 15.35]
Total (95% CI)		**340**		**387**	**100.0%**	**2.82 [1.20, 6.62]**
Total events	18		6			

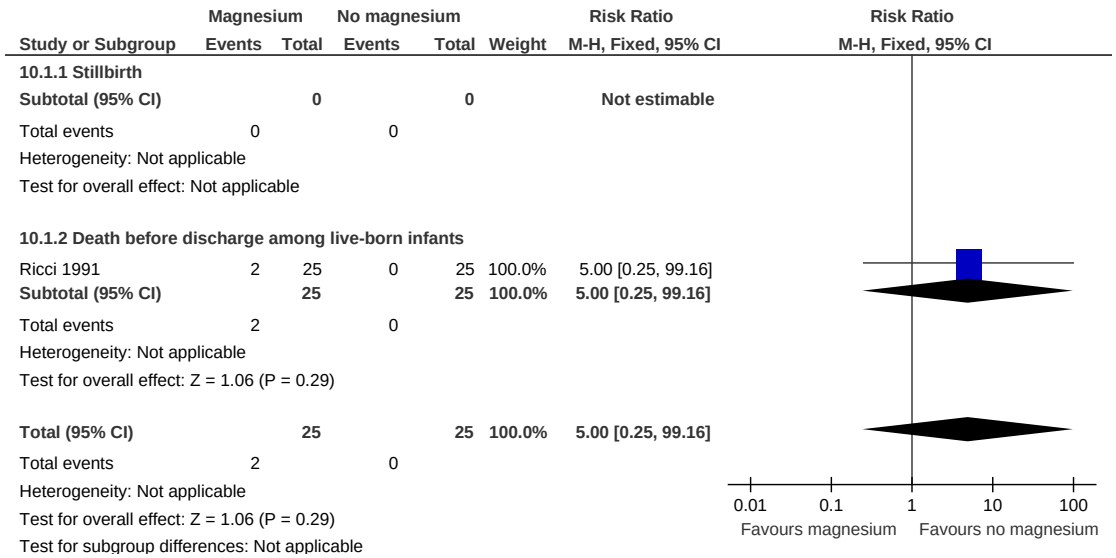
Heterogeneity: Chi² = 5.89, df = 4 (P = 0.21); I² = 32%

Test for overall effect: Z = 2.38 (P = 0.02)

Crowther 1998

This Cochrane review included three trials (303 women) and no differences in the incidence of preterm birth or perinatal mortality were seen when magnesium sulphate maintenance therapy was compared with placebo or no treatment (2 trials (n=183 women); or alternative therapies (ritodrine or terbutaline).

DEATH

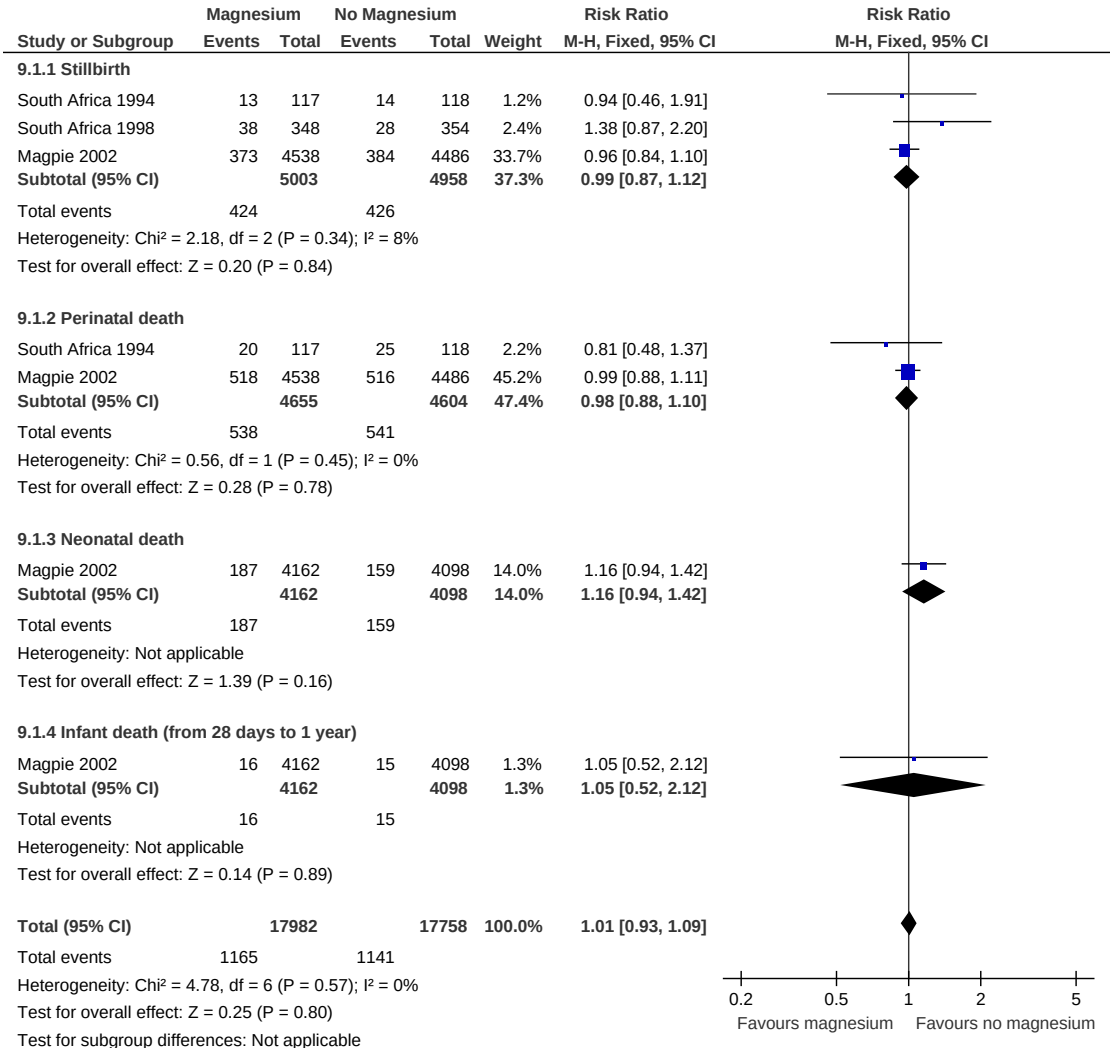


Study or Subgroup	Magnesium Events	Magnesium Total	No magnesium Events	No magnesium Total	Weight	Risk Ratio M-H, Fixed, 95% CI
10.1.1 Stillbirth						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
10.1.2 Death before discharge among live-born infants						
Ricci 1991	2	25	0	25	100.0%	5.00 [0.25, 99.16]
Subtotal (95% CI)		**25**		**25**	**100.0%**	**5.00 [0.25, 99.16]**
Total events	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.06 (P = 0.29)						
Total (95% CI)		**25**		**25**	**100.0%**	**5.00 [0.25, 99.16]**
Total events	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.06 (P = 0.29)						
Test for subgroup differences: Not applicable						

Duley 2003

This Cochrane review compared magnesium sulphate with placebo or no anticonvulsant for preventing eclampsia in women with pre-eclampsia. This review included 11,444 women (six trials) and 9961 infants (three trials) and found that magnesium sulphate more than halves the risk of eclampsia, and probably reduces the risk of maternal death. It does not influence short-term outcomes for the baby.

DEATH



Appendix F: Evidence Statements and Tables – Questions 1 to 11

Q1 – Q3: Effectiveness Summary For Cochrane Reviews

NHMRC Evidence Statement

Key question(s): **Q1: Does the administration of magnesium sulphate to women prior to preterm birth improve health outcomes for the fetus/infant/child?** **Q2: Does the use of magnesium sulphate prior to preterm birth cause adverse outcome for women?** **Q3: Does the use of magnesium sulphate prior to preterm birth cause adverse outcome for the fetus/infant/child?**	
1. Evidence base	
NEUROPROTECTIVE INTENT Four RCTs (level ll intervention), generally with a low risk of bias, included in a systematic review (level I).	A (One or more Level I studies with a low risk of bias or several Level ll studies with low risk of bias)
2. Consistency	
There was some inconsistency between studies, which can probably mostly be explained (different regimens used in each of the four studies).	B (Most studies consistent and inconsistency can be explained)
3. Clinical Impact	
Neuroprotection and prevention of cerebral palsy in this vulnerable preterm population will have a very large potential impact. The number of women needed to be treated to benefit one baby by avoiding cerebral palsy is 63 (95% confidence interval 44 to 155). Women given magnesium sulphate were about three times more likely to cease therapy compared with women not given magnesium therapy mainly due to flushing, nausea/vomiting and headaches. Hypotension and respiratory depression were also increased with magnesium use. No harms for the fetus, infant or child were significantly increased with antenatal use of magnesium.	A (very large)
4. Generalisability	
One neuroprotective trial was conducted in Australia and New Zealand and most of the other trials had populations and settings directly generalisable to the target population (Australian women at risk of preterm birth); women in the large Rouse trial represented a narrower population (87% with PPROM).	B (Evidence directly generalisable to target population with some caveats)
5. Applicability	
Magnesium sulphate is already available in Australian and New Zealand maternity settings and therefore this evidence is directly applicable to the Australian health care context.	A (Evidence directly applicable to Australian healthcare context)
EVIDENCE STATEMENT MATRIX	
Component	**Rating**
Evidence base	A
Consistency	B
Clinical impact	A
Generalisability	B

Applicability	A
RECOMMENDATION	
In women at risk of early preterm* imminent# birth, use magnesium sulphate for neuroprotection of the fetus, infant and child: *when gestational age is less than 30 weeks. #when very preterm birth is planned or definitely expected within 24 hours. (When birth is planned, commence magnesium sulphate as close to four hours before birth as possible).	A
UNRESOLVED ISSUES	
See subsequent chapters	
IMPLEMENTATION OF RECOMMENDATION	
Will this recommendation result in changes in usual care? Partially – some obstetric settings are already using magnesium sulphate for this indication.	YES
Are there any resource implications associated with implementing this recommendation? Yes, setting up, maintaining and monitoring magnesium infusions will incur extra staff time. (On the other hand, at an overall societal and health systems level, fewer cases of cerebral palsy will mean cost savings).	YES
Will the implementation of this recommendation require changes in the way care is currently organised? Partially, midwifery/nursing staff will require extra time to manage the magnesium infusions.	YES
Are the guideline development group aware of any barriers to the implementation of this recommendation? Yes, as above – extra time required, plus additional task in the busy and perhaps fraught setting of a preterm birth.	YES

Appendix F: Evidence Tables and Graphs: Q1-3: OVERALL

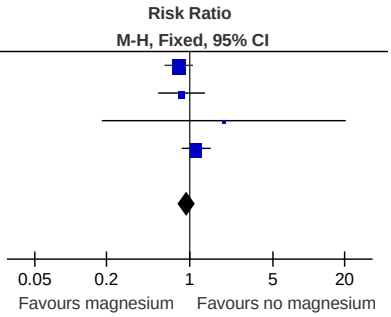
Doyle 2009

DEATH

Study or Subgroup	Magnesium Events	Total	No magnesium Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Crowther 2003	87	629	107	626	44.6%	0.81 [0.62, 1.05]
Marret 2006	34	352	38	336	16.2%	0.85 [0.55, 1.32]
Mittendorf 2002	2	30	1	29	0.4%	1.93 [0.19, 20.18]
Rouse 2008	103	1188	96	1256	38.8%	1.13 [0.87, 1.48]
Total (95% CI)		**2199**		**2247**	**100.0%**	**0.95 [0.80, 1.12]**
Total events	226		242			

Heterogeneity: Chi² = 3.73, df = 3 (P = 0.29); I² = 20%

Test for overall effect: Z = 0.62 (P = 0.53)

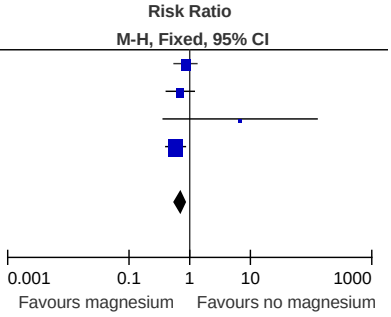


CEREBRAL PALSY

Study or Subgroup	Magnesium Events	Total	No magnesium Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Crowther 2003	36	629	42	626	29.0%	0.85 [0.55, 1.31]
Marret 2006	22	352	30	336	21.1%	0.70 [0.41, 1.19]
Mittendorf 2002	3	30	0	29	0.3%	6.77 [0.37, 125.65]
Rouse 2008	41	1188	74	1256	49.5%	0.59 [0.40, 0.85]
Total (95% CI)		**2199**		**2247**	**100.0%**	**0.71 [0.55, 0.91]**
Total events	102		146			

Heterogeneity: Chi² = 4.01, df = 3 (P = 0.26); I² = 25%

Test for overall effect: Z = 2.74 (P = 0.006)

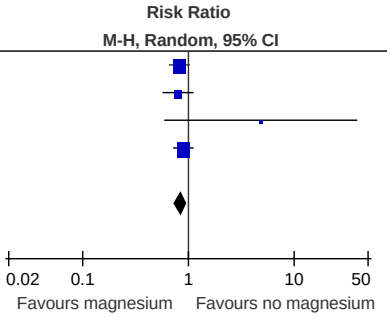


DEATH OR CEREBRAL PALSY

Study or Subgroup	Magnesium Events	Total	No magnesium Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Crowther 2003	123	629	149	626	39.9%	0.82 [0.66, 1.02]
Marret 2006	56	352	67	336	18.2%	0.80 [0.58, 1.10]
Mittendorf 2002	5	30	1	29	0.5%	4.83 [0.60, 38.90]
Rouse 2008	144	1188	170	1256	41.4%	0.90 [0.73, 1.10]
Total (95% CI)		**2199**		**2247**	**100.0%**	**0.85 [0.74, 0.98]**
Total events	328		387			

Heterogeneity: Tau² = 0.00; Chi² = 3.17, df = 3 (P = 0.37); I² = 5%

Test for overall effect: Z = 2.21 (P = 0.03)



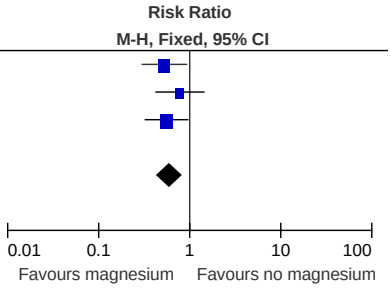
F: Q1-3: OVERALL

SUBSTANTIAL GROSS MOTOR DYSFUNCTION

Study or Subgroup	Magnesium Events	Total	No magnesium Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Crowther 2003	18	629	34	626	36.4%	0.53 [0.30, 0.92]
Marret 2006	18	352	22	336	24.1%	0.78 [0.43, 1.43]
Rouse 2008	20	1188	38	1256	39.5%	0.56 [0.33, 0.95]
Total (95% CI)		**2169**		**2218**	**100.0%**	**0.60 [0.43, 0.83]**
Total events	56		94			

Heterogeneity: Chi² = 1.01, df = 2 (P = 0.60); I² = 0%

Test for overall effect: Z = 3.08 (P = 0.002)

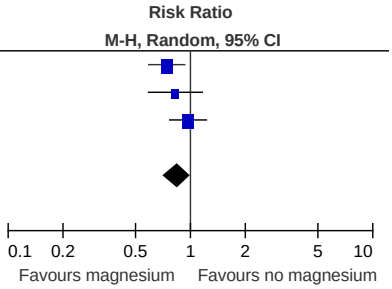


DEATH OR SUBSTANTIAL MOTOR DYSFUNCTION

Study or Subgroup	Magnesium Events	Total	No magnesium Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Crowther 2003	105	629	141	626	39.8%	0.74 [0.59, 0.93]
Marret 2006	52	352	60	336	21.4%	0.83 [0.59, 1.16]
Rouse 2008	123	1188	134	1256	38.8%	0.97 [0.77, 1.22]
Total (95% CI)		**2169**		**2218**	**100.0%**	**0.84 [0.71, 1.00]**
Total events	280		335			

Heterogeneity: Tau² = 0.01; Chi² = 2.67, df = 2 (P = 0.26); I² = 25%

Test for overall effect: Z = 1.95 (P = 0.05)

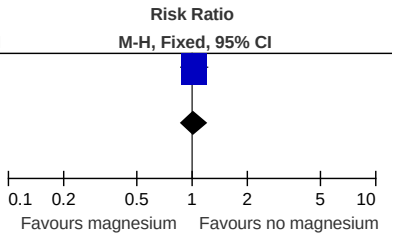


ANY NEUROLOGICAL IMPAIRMENT

Study or Subgroup	Magnesium Events	Total	No magnesium Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Crowther 2003	193	629	187	626	100.0%	1.03 [0.87, 1.21]
Total (95% CI)		**629**		**626**	**100.0%**	**1.03 [0.87, 1.21]**
Total events	193		187			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.31 (P = 0.75)

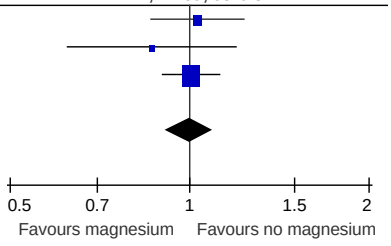


DEVELOPMENT DELAY OR INTELLECTUAL IMPAIRMENT

Study or Subgroup	Magnesium Events	Total	No magnesium Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Crowther 2003	176	629	170	626	26.2%	1.03 [0.86, 1.23]
Marret 2006	57	352	63	336	9.9%	0.86 [0.62, 1.20]
Rouse 2008	406	1188	427	1256	63.9%	1.01 [0.90, 1.12]
Total (95% CI)		**2169**		**2218**	**100.0%**	**1.00 [0.91, 1.09]**
Total events	639		660			

Heterogeneity: Chi² = 0.90, df = 2 (P = 0.64); I² = 0%

Test for overall effect: Z = 0.05 (P = 0.96)



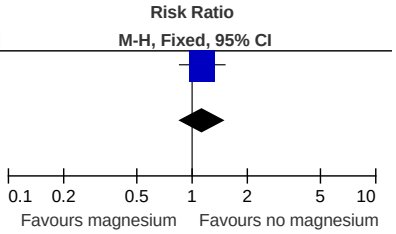
F: Q1-3: OVERALL

MAJOR NEUROLOGICAL DISABILITY

Study or Subgroup	Magnesium Events	Total	No magnesium Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Crowther 2003	89	629	78	626	100.0%	1.14 [0.86, 1.51]
Total (95% CI)		**629**		**626**	**100.0%**	**1.14 [0.86, 1.51]**
Total events	89		78			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.88 (P = 0.38)

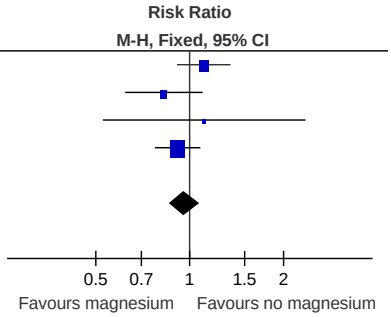


INTRAVENTRICULAR HAEMORRHAGE

Study or Subgroup	Magnesium Events	Total	No magnesium Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Crowther 2003	165	629	148	626	30.4%	1.11 [0.92, 1.34]
Marret 2006	71	352	82	336	17.2%	0.83 [0.62, 1.09]
Mittendorf 2002	13	85	11	80	2.3%	1.11 [0.53, 2.34]
Rouse 2008	218	1188	252	1256	50.1%	0.91 [0.78, 1.08]
Total (95% CI)		**2254**		**2298**	**100.0%**	**0.96 [0.86, 1.08]**
Total events	467		493			

Heterogeneity: Chi² = 3.75, df = 3 (P = 0.29); I² = 20%

Test for overall effect: Z = 0.65 (P = 0.51)

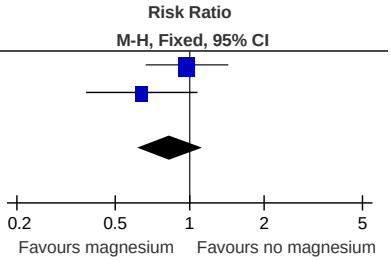


INTRAVENTRICULAR HAEMORRHAGE (grade 3/4)

Study or Subgroup	Magnesium Events	Total	No magnesium Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Crowther 2003	49	629	50	626	57.6%	0.98 [0.67, 1.42]
Rouse 2008	23	1188	38	1256	42.4%	0.64 [0.38, 1.07]
Total (95% CI)		**1817**		**1882**	**100.0%**	**0.83 [0.62, 1.13]**
Total events	72		88			

Heterogeneity: Chi² = 1.69, df = 1 (P = 0.19); I² = 41%

Test for overall effect: Z = 1.18 (P = 0.24)

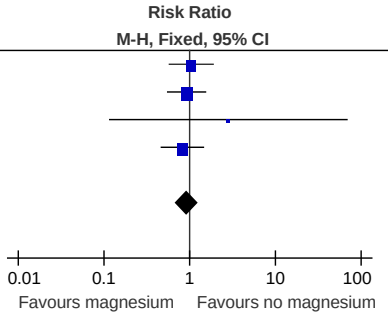


PERIVENTRICULAR LEUKOMALACIA

Study or Subgroup	Magnesium Events	Total	No magnesium Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Crowther 2003	22	629	21	626	27.5%	1.04 [0.58, 1.88]
Marret 2006	27	352	28	336	37.5%	0.92 [0.55, 1.53]
Mittendorf 2002	1	85	0	80	0.7%	2.83 [0.12, 68.37]
Rouse 2008	21	1188	27	1256	34.3%	0.82 [0.47, 1.45]
Total (95% CI)		**2254**		**2298**	**100.0%**	**0.93 [0.68, 1.28]**
Total events	71		76			

Heterogeneity: Chi² = 0.80, df = 3 (P = 0.85); I² = 0%

Test for overall effect: Z = 0.43 (P = 0.67)



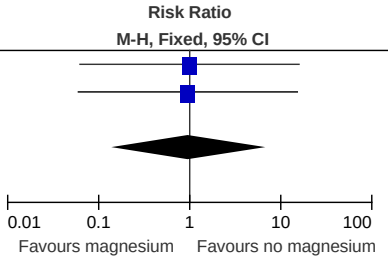
F: Q1-3: OVERALL

BLINDNESS

Study or Subgroup	Magnesium Events	Magnesium Total	No magnesium Events	No magnesium Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Crowther 2003	1	629	1	626	49.5%	1.00 [0.06, 15.88]
Marret 2006	1	352	1	336	50.5%	0.95 [0.06, 15.20]
Total (95% CI)		**981**		**962**	**100.0%**	**0.97 [0.14, 6.90]**
Total events	2		2			

Heterogeneity: Chi² = 0.00, df = 1 (P = 0.98); I² = 0%

Test for overall effect: Z = 0.03 (P = 0.98)

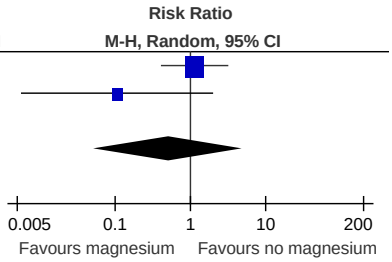


DEAFNESS

Study or Subgroup	Magnesium Events	Magnesium Total	No magnesium Events	No magnesium Total	Weight	Risk Ratio M-H, Random, 95% CI
Crowther 2003	8	629	7	626	66.2%	1.14 [0.41, 3.12]
Marret 2006	0	352	4	336	33.8%	0.11 [0.01, 1.96]
Total (95% CI)		**981**		**962**	**100.0%**	**0.51 [0.05, 4.96]**
Total events	8		11			

Heterogeneity: Tau² = 1.77; Chi² = 2.42, df = 1 (P = 0.12); I² = 59%

Test for overall effect: Z = 0.58 (P = 0.56)



Q4: Gestational Age

NHMRC Evidence Statement

Key question(s): **Q4: Do improvements to the fetus/infant/child vary by gestational age magnesium sulphate given?**	
1. Evidence base	
Subgroup analysis from 4 RCTs with low risk of bias; therefore the comparisons by gestational age are non-randomised comparisons (level III).	B (Several Level lll studies with low risk of bias)
2. Consistency	
	B (Most studies consistent and inconsistency can be explained)
3. Clinical Impact	
Overall impact is very large.	A (overall)
4. Generalisability	
As for overall; women in the large Rouse trial represented a narrower population (87% with PPROM).	B (Evidence directly generalisable to target population with some caveats)
5. Applicability	
As for overall	A (Evidence directly applicable to Australian healthcare context)

Other factors

In the absence of being able to distinguish different levels of clinical impact between the present gestational age subgroups, the choices are to:

a) make no recommendation regarding gestational age;
b) make a recommendation that magnesium sulphate can be given up to 34 weeks;
c) make a recommendation that magnesium sulphate be only given to women less than 32 weeks;
d) make a recommendation that magnesium sulphate be only given to women less than 30 weeks gestation.

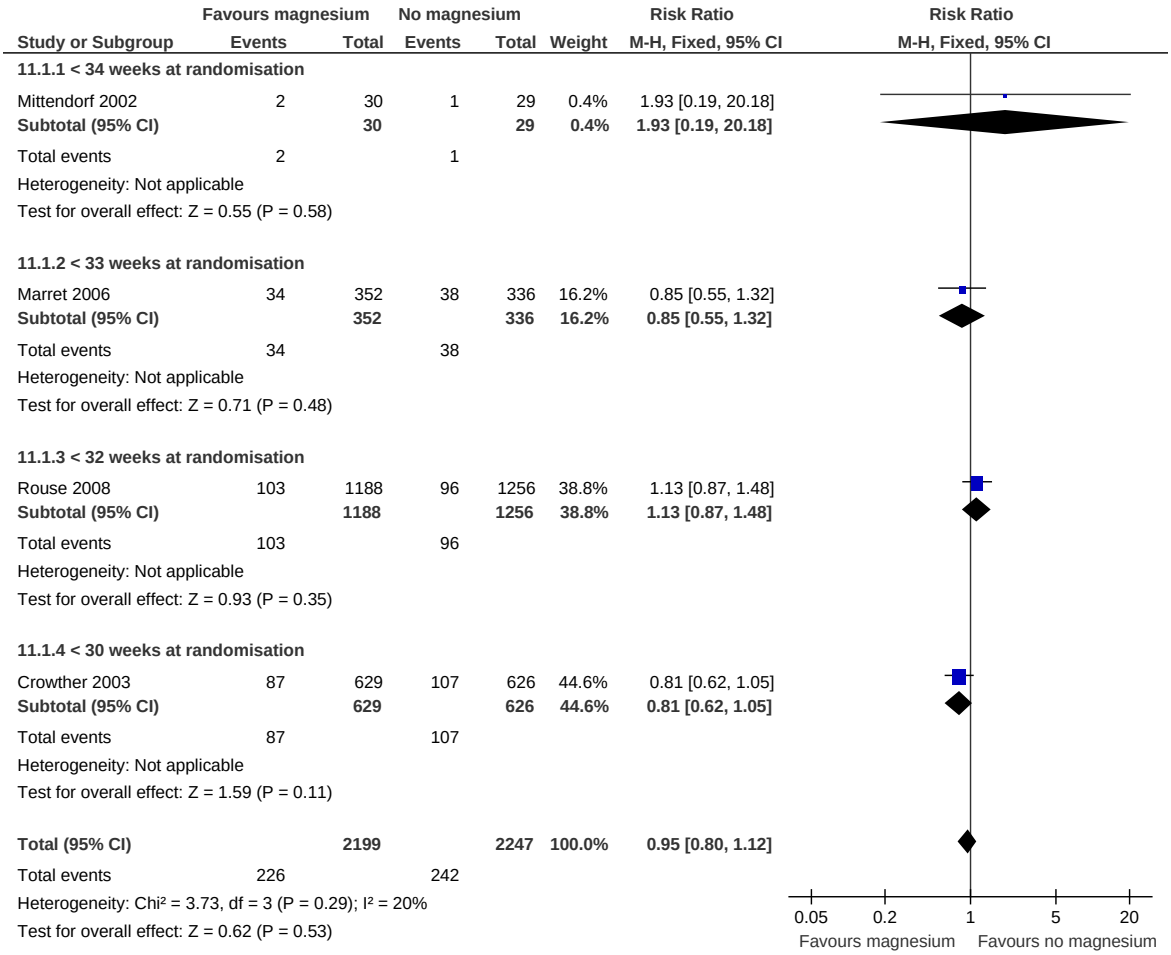
EVIDENCE STATEMENT MATRIX	
Component	**Rating**
Evidence base	B
Consistency	B
Clinical impact	A (overall)
Generalisability	B
Applicability	A

RECOMMENDATION	
• **Magnesium sulphate be only given to women less than 30 weeks gestation.**	**B**
UNRESOLVED ISSUES	
Some of the trials have stratified by gestational age but have not published these analyses. Individual patient data meta-analyses by gestational age are needed.	
IMPLEMENTATION OF RECOMMENDATION	
Will this recommendation result in changes in usual care?	YES
Are there any resource implications associated with implementing this recommendation?	YES
Will the implementation of this recommendation require changes in the way care is currently organised?	YES
Are the guideline development group aware of any barriers to the implementation of this recommendation?	YES

Appendix F 4: Evidence Table and Graphs: GESTATIONAL AGE

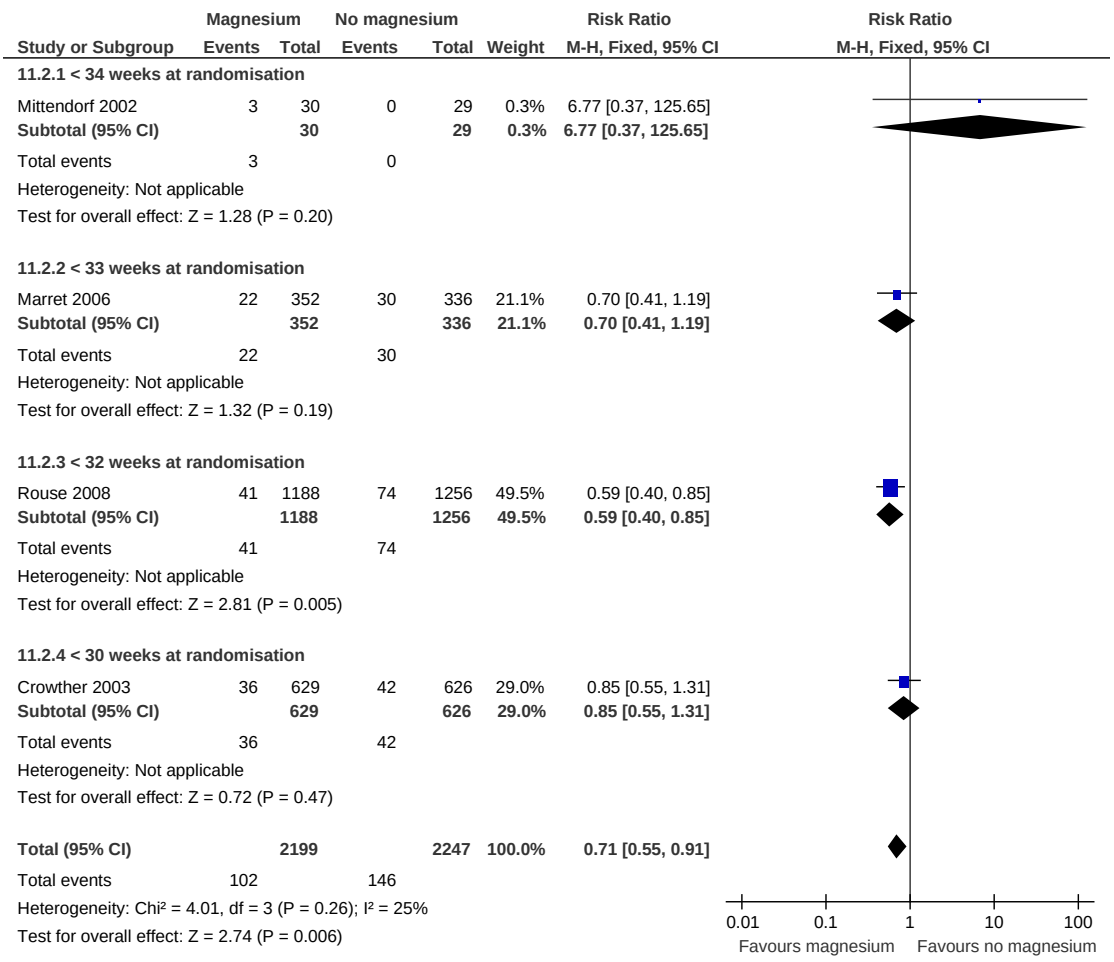
Study	Gestational age
Mittendorf 2002	< 34 weeks at randomisation
Marret 2006	< 33 weeks
Rouse 2008	< 32 weeks
Crowther 2003	< 30 weeks

DEATH



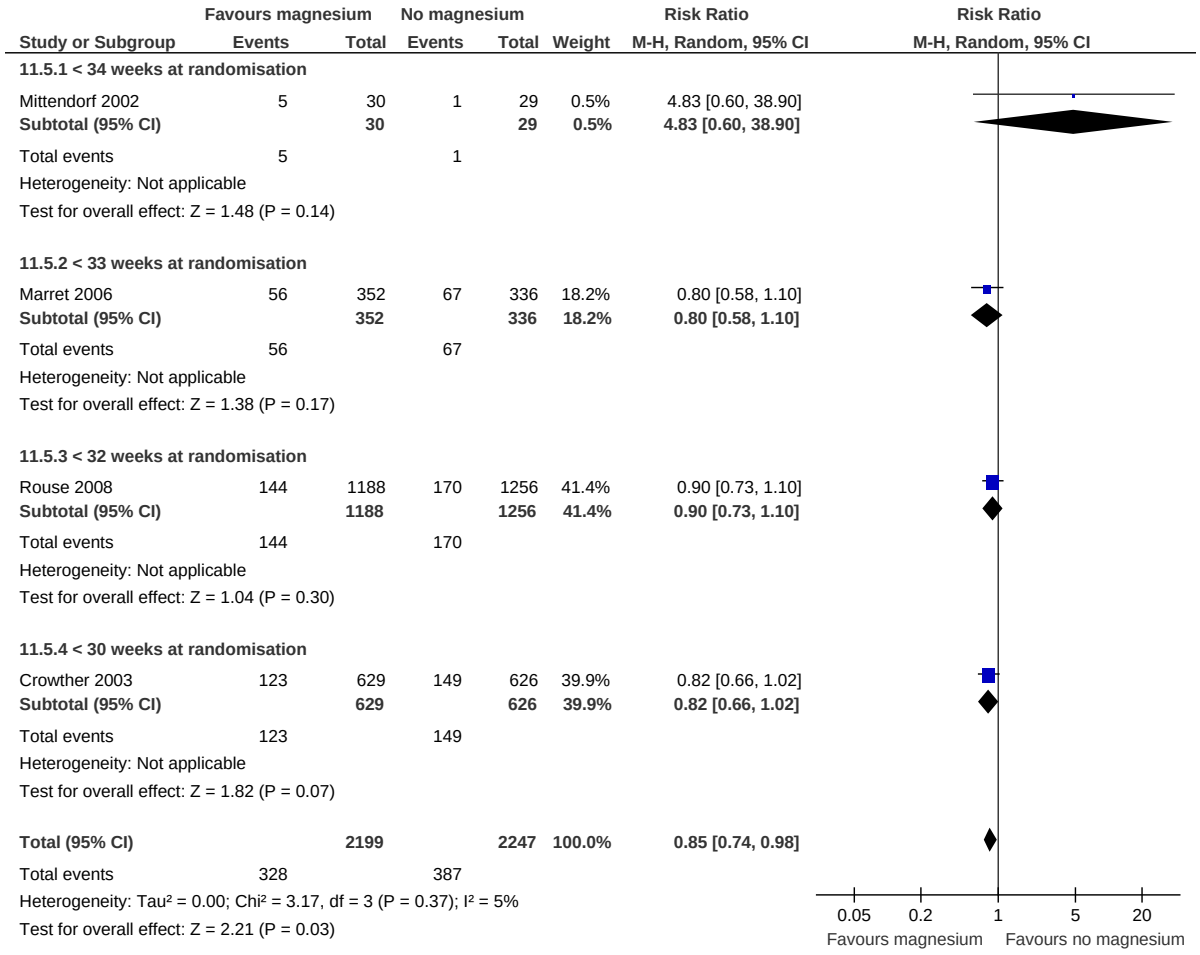
F 4: GESTATIONAL AGE

CEREBRAL PALSY



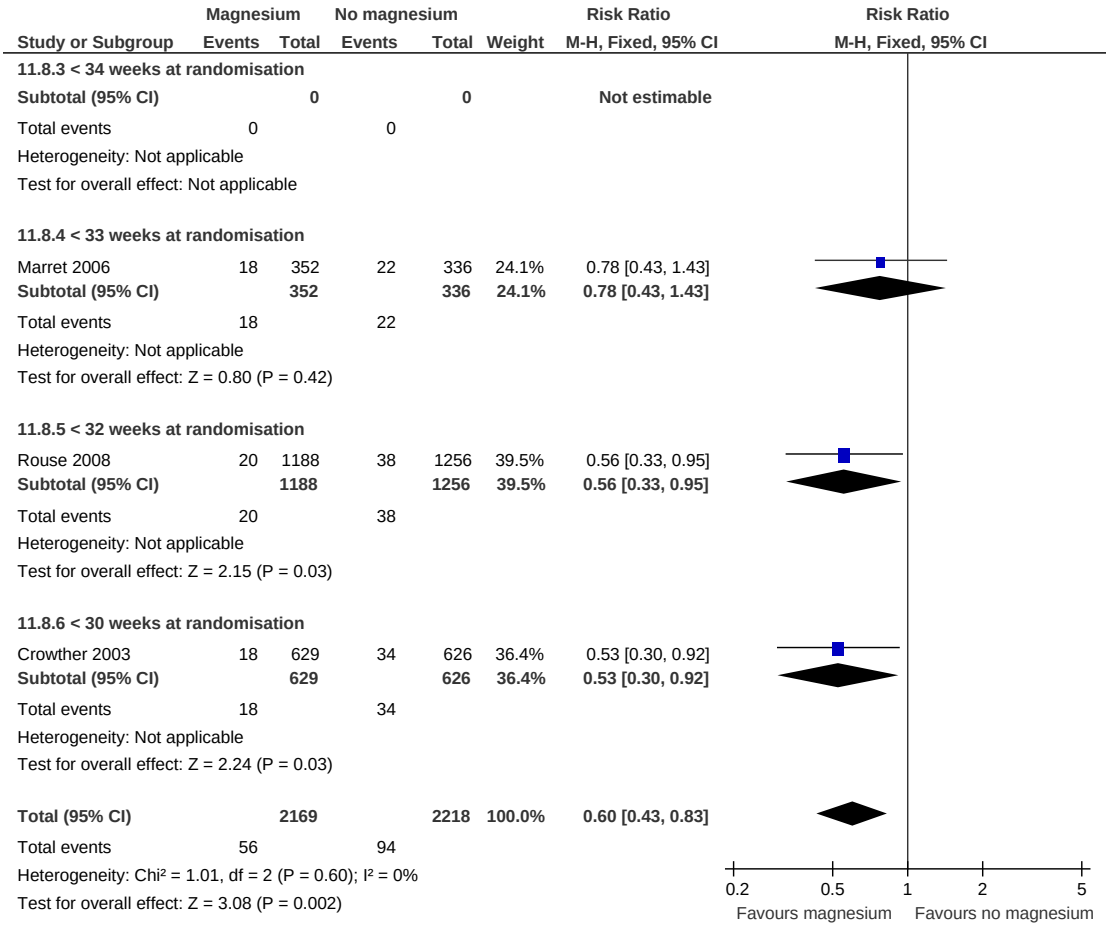
F 4: GESTATIONAL AGE

DEATH OR CEREBRAL PALSY



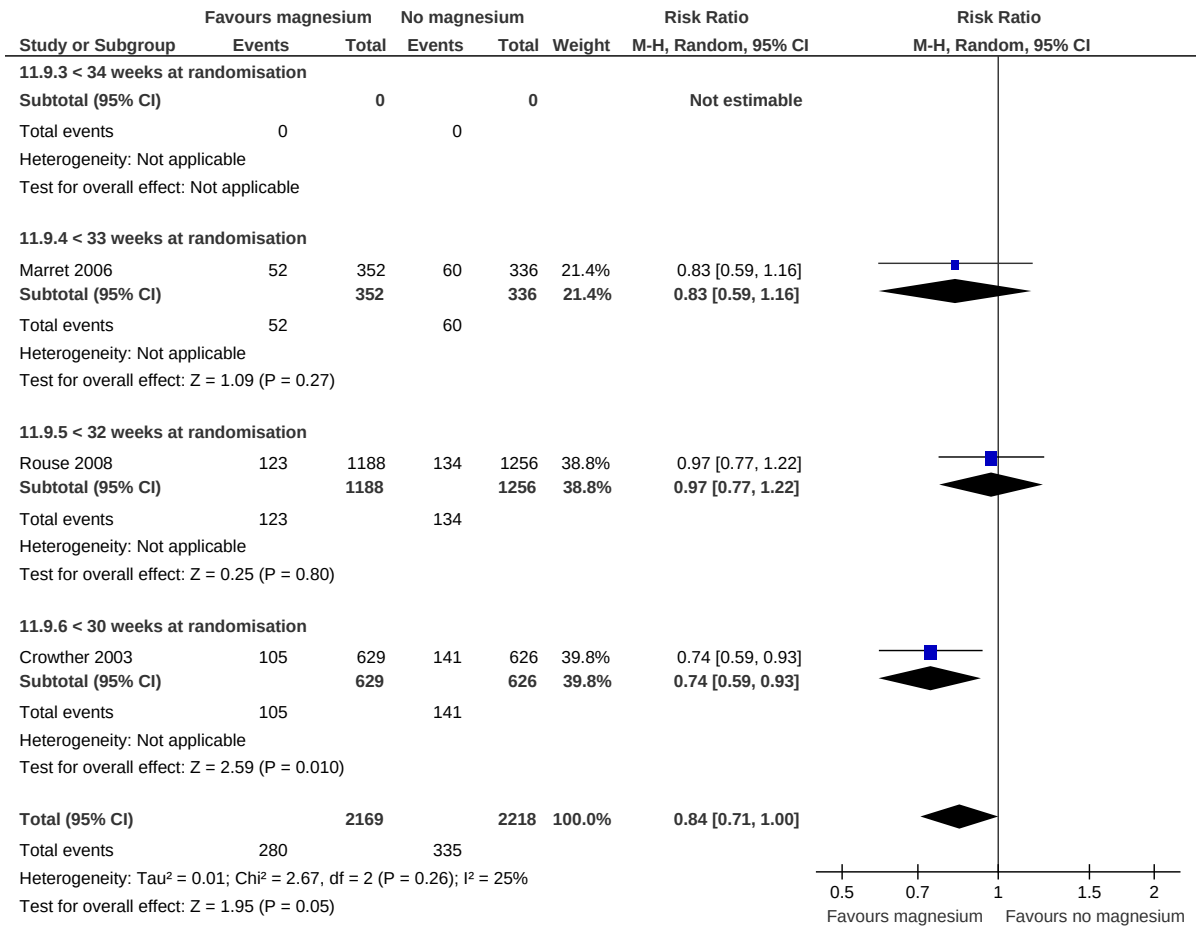
F 4: GESTATIONAL AGE

SUBSTANTIAL GROSS MOTOR DYSFUNCTION



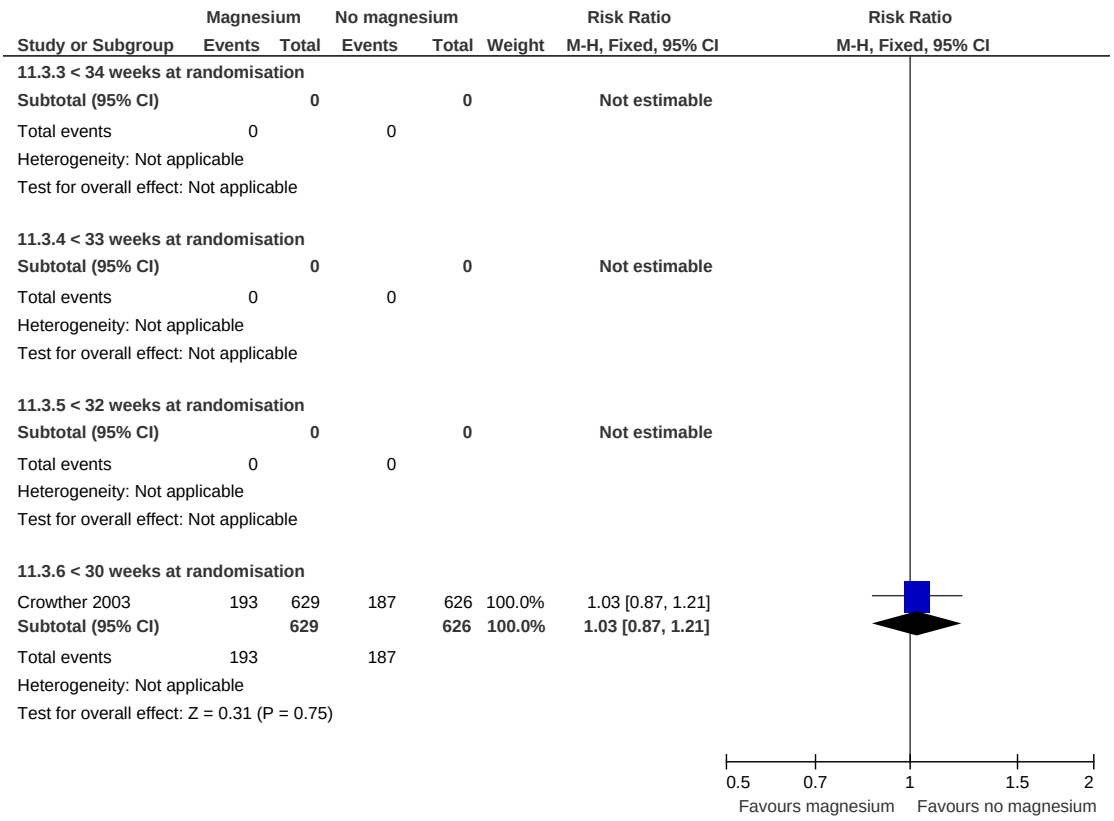
F 4: GESTATIONAL AGE

DEATH OR SUBSTANTIAL MOTOR DYSFUNCTION



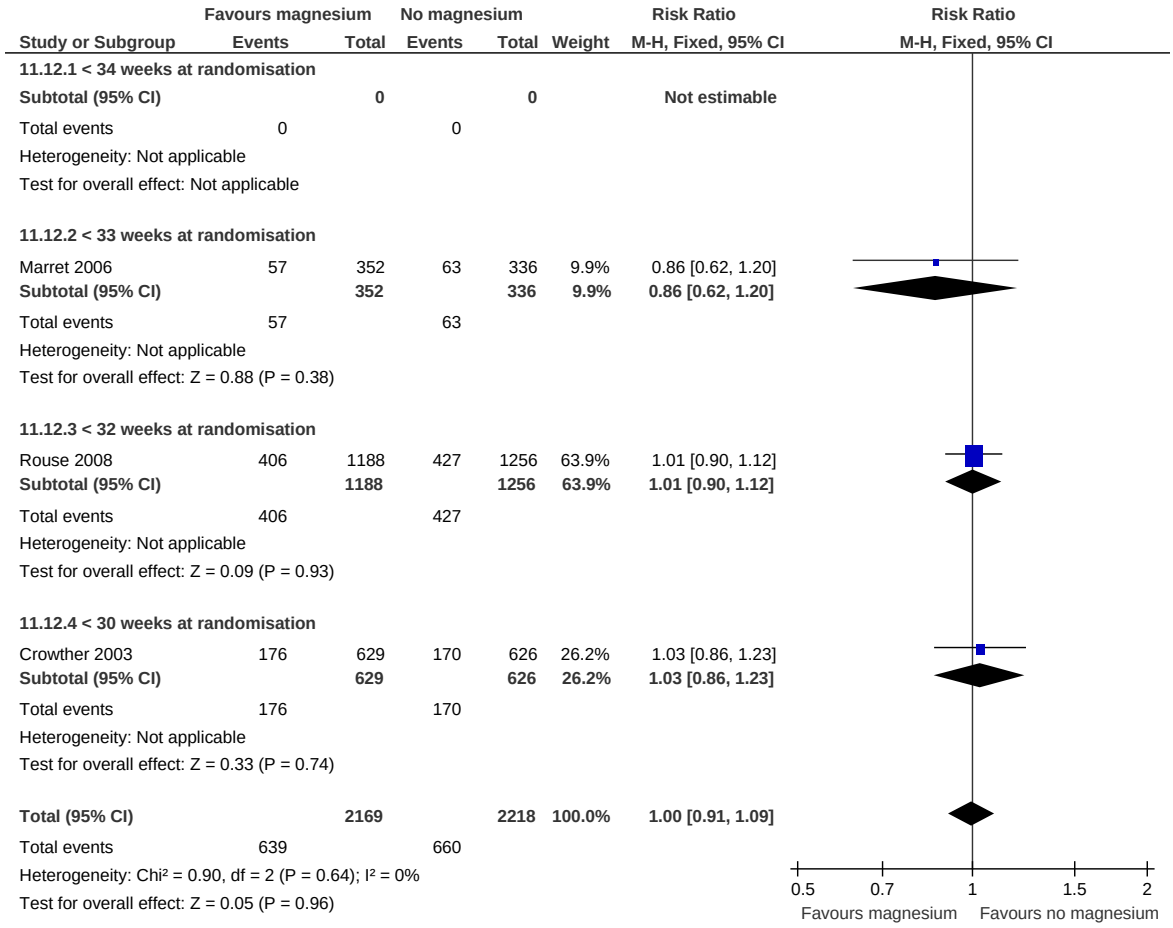
F 4: GESTATIONAL AGE

ANY NEUROLOGICAL IMPAIRMENT



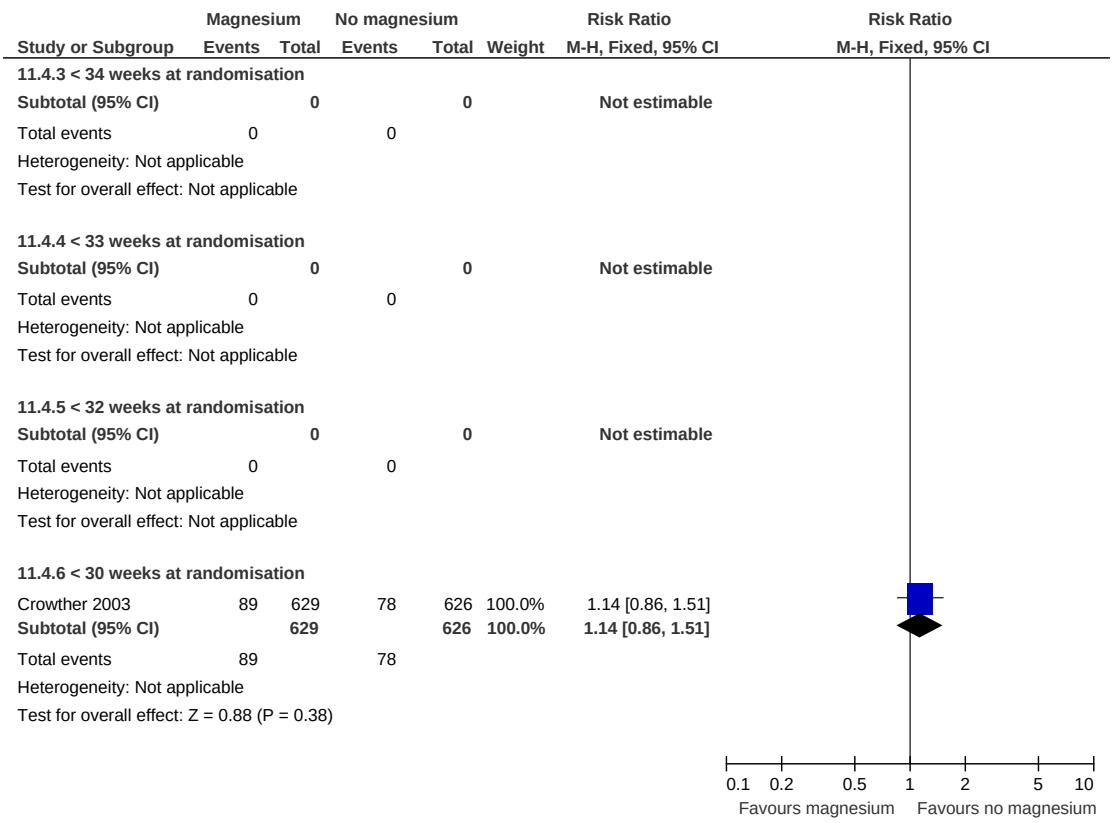
F 4: GESTATIONAL AGE

DEVELOPMENT DELAY OR INTELLECTUAL IMPAIRMENT



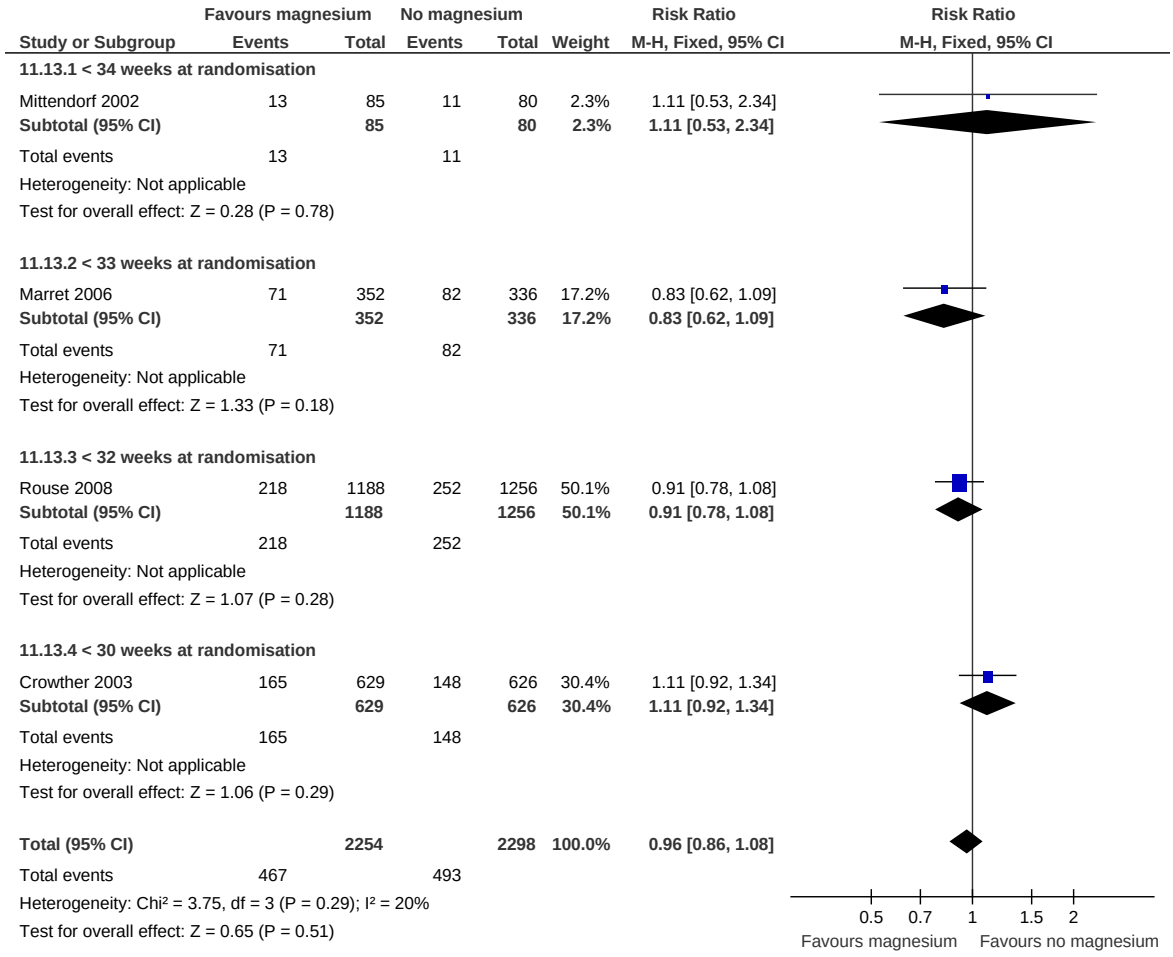
F 4: GESTATIONAL AGE

MAJOR NEUROLOGICAL DISABILITY



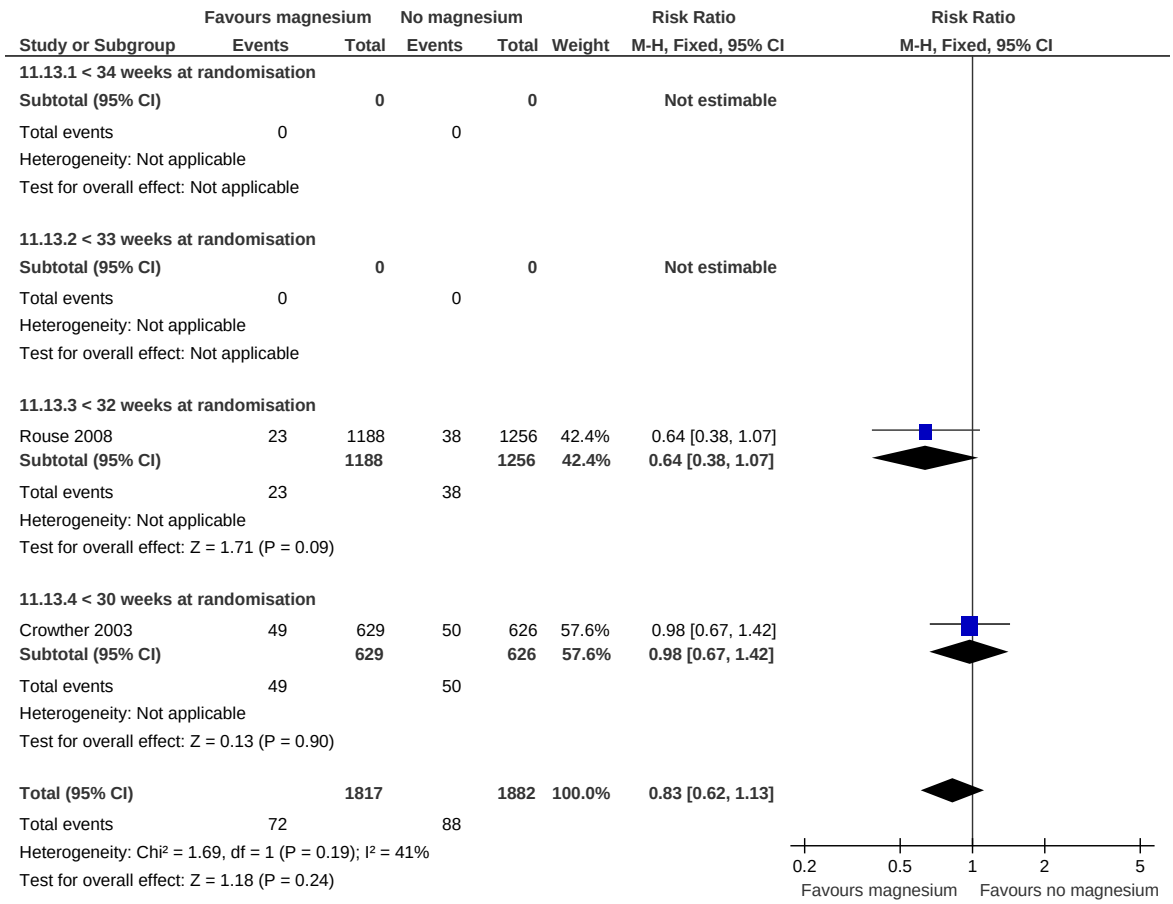
F 4: GESTATIONAL AGE

INTRAVENTRICULAR HAEMORRHAGE



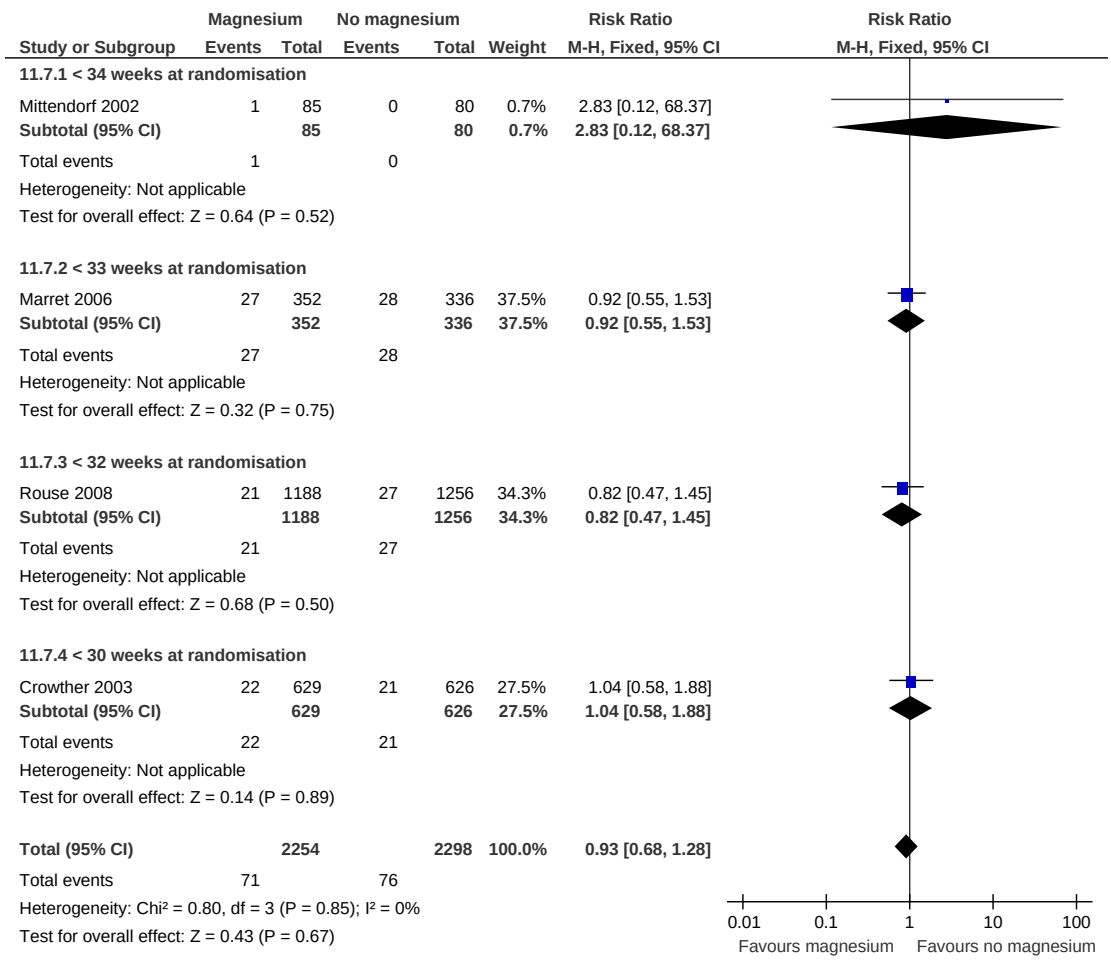
F 4: GESTATIONAL AGE

INTRAVENTRICULAR HAEMORRHAGE (grade 3/4)



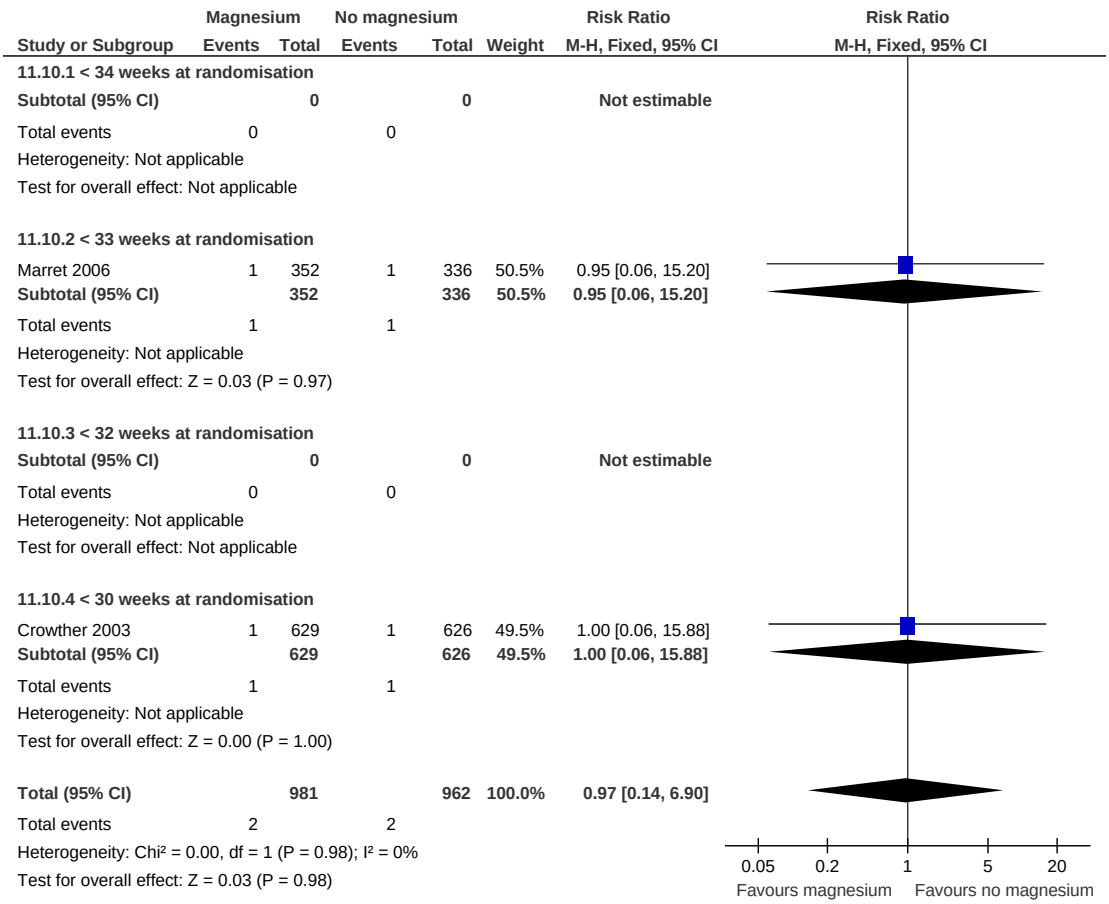
F 4: GESTATIONAL AGE

PERIVENTRICULAR LEUKOMALACIA



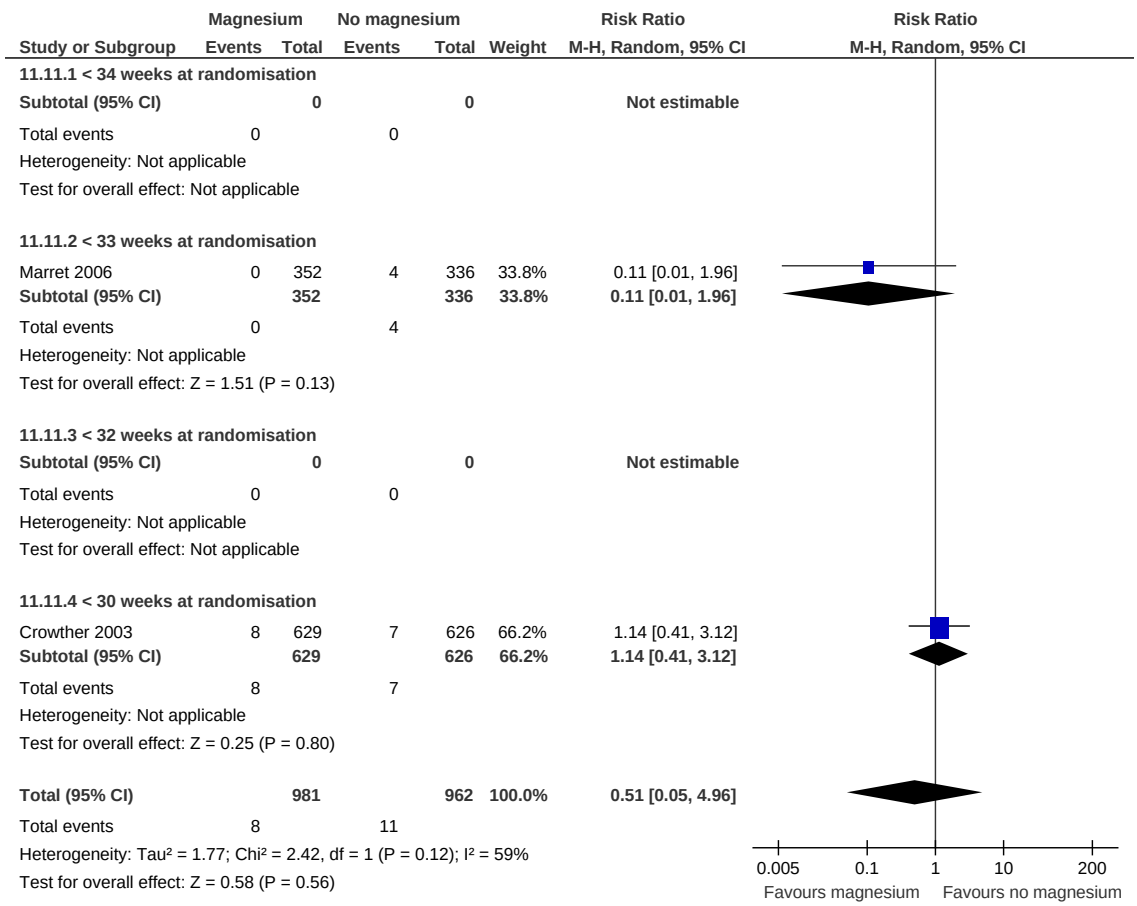
F 4: GESTATIONAL AGE

BLINDNESS



F 4: GESTATIONAL AGE

DEAFNESS



Q5: Time Magnesium Sulphate Planned To Be Given Prior To Preterm Birth

NHMRC Evidence Statement

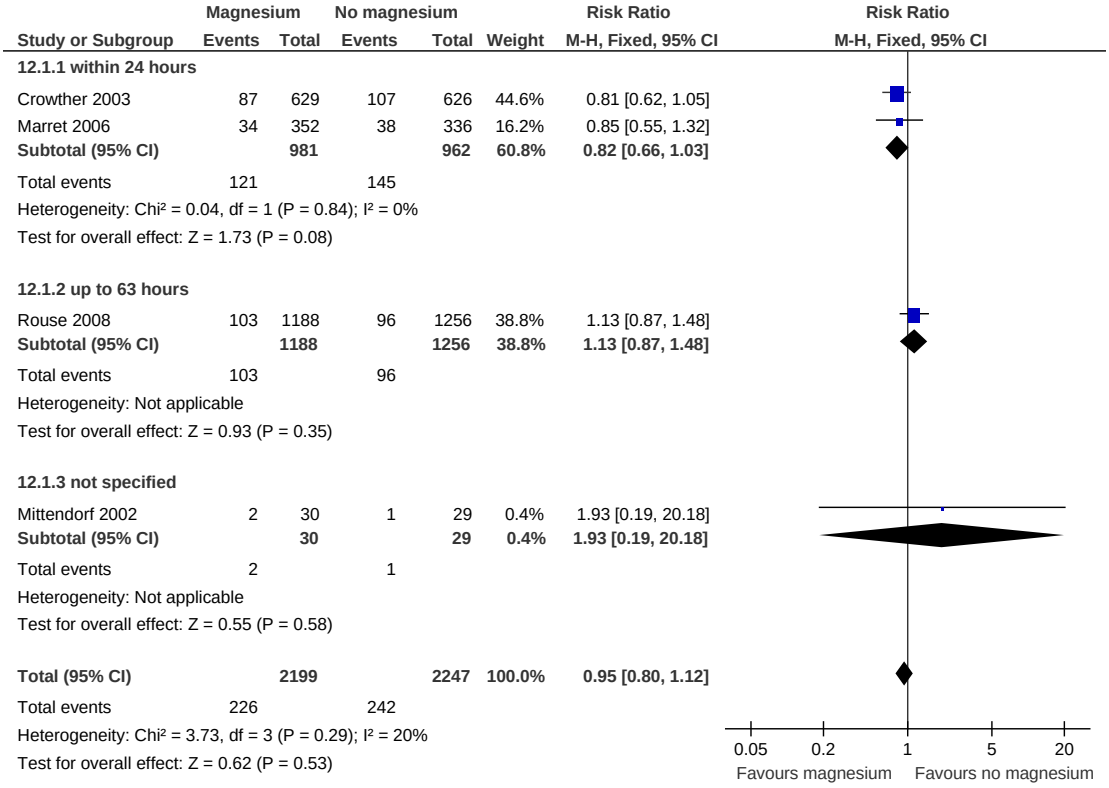
Key question(s): **Q5: Do improvements to the fetus/infant/child vary by time magnesium sulphate planned to be given prior to preterm birth?**	
1. Evidence base	
Subgroup analysis from four RCTs with low risk of bias; therefore some of the comparisons by time magnesium is planned are non-randomised comparisons (level III).	B (Several Level II and lll studies with low risk of bias)
2. Consistency	
	B (Most studies consistent and inconsistency can be explained)
3. Clinical Impact	
Overall impact is very large	A (overall)
4. Generalisability	
B overall; but A for the birth planned within 24 hours subgroup	A (Evidence directly generalisable to target population with some caveats)
5. Applicability	
As for overall	A (Evidence directly applicable to Australian healthcare context)
Other factors In the absence of being able to assess clinical impact, the choices are: a) To make no recommendation regarding the timing of administration of magnesium; b) To make a recommendation that magnesium sulphate be only given to women where birth is planned or expected within 24 hours; c) To make a recommendation that magnesium sulphate be given where birth is definitely expected within 24 hours, ideally within 4 hours of a planned birth.	
EVIDENCE STATEMENT MATRIX	
Component	**Rating**
Evidence base	B
Consistency	B
Clinical impact	A (overall)
Generalisability	A
Applicability	A

RECOMMENDATION	
• In women at risk of early preterm* imminent# birth, use magnesium sulphate for neuroprotection of the fetus, infant and child: ○ When early preterm birth is planned or definitely expected within 24 hours. (When birth is planned, commence magnesium sulphate as close to four hours before birth as possible). *when gestational age is less than 30 weeks #when early preterm birth is planned or definitely expected within 24 hours.	A
UNRESOLVED ISSUES	
Need to try to get more detailed timings from trials. Individual patient data meta-analysis needed.	
IMPLEMENTATION OF RECOMMENDATION	
Will this recommendation result in changes in usual care?	YES
Are there any resource implications associated with implementing this recommendation?	YES
Will the implementation of this recommendation require changes in the way care is currently organised?	YES
Are the guideline development group aware of any barriers to the implementation of this recommendation?	YES

Appendix F 5: Evidence table and Graphs: TIMING

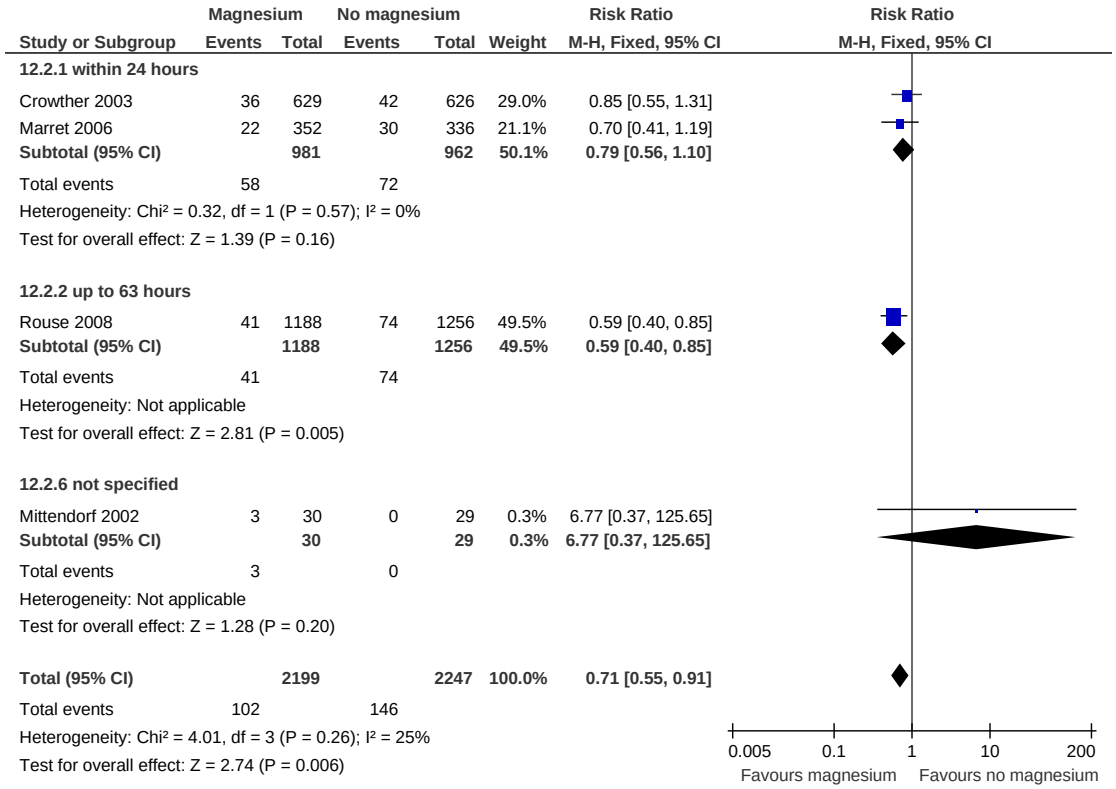
Study	Timing
Crowther 2003, Marret 2006	Where birth was planned or expected within 24 hours
Rouse 2008	Where birth was planned or expected within 24 hours for indicated preterm birth (3.1% only); otherwise advanced preterm labour, with cervical dilatation between 4 and 8 cm (10.3%); PPROM 86.7% - median 25 hours, interquartile range 11 to 63 hours from rupture)
Mittendorf 2002	Not specified

DEATH

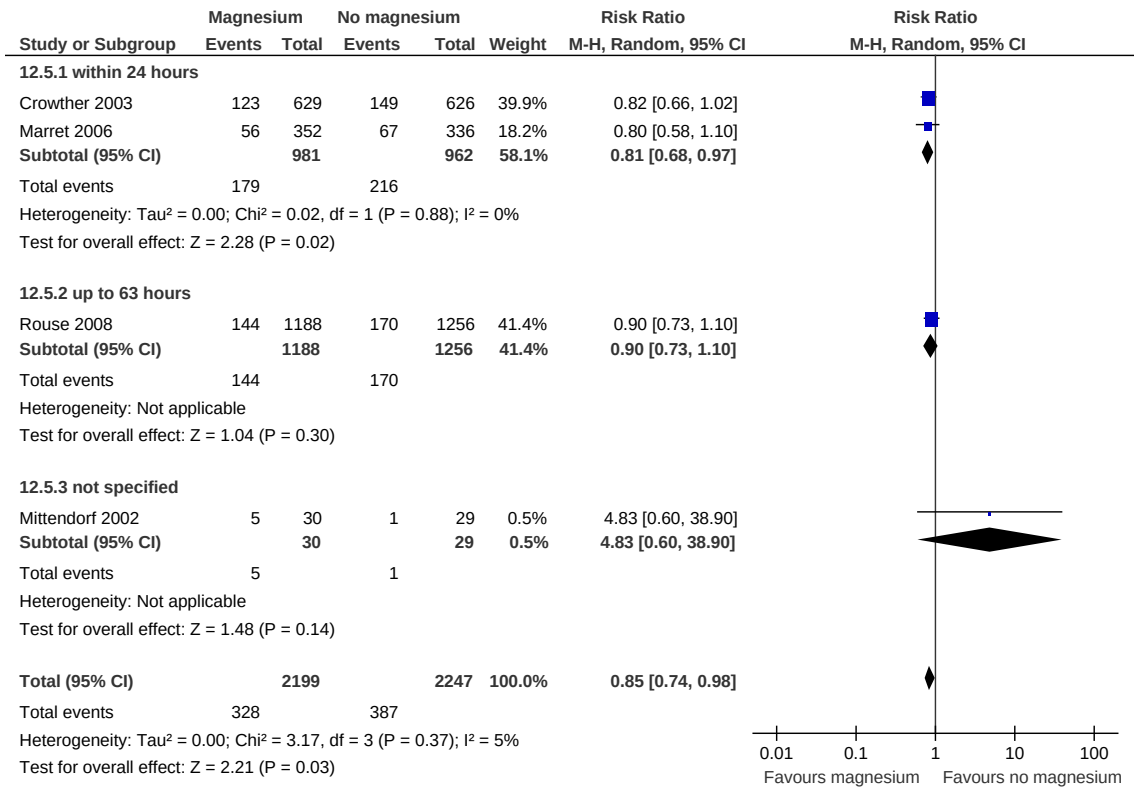


F 5: TIMING

CEREBRAL PALSY

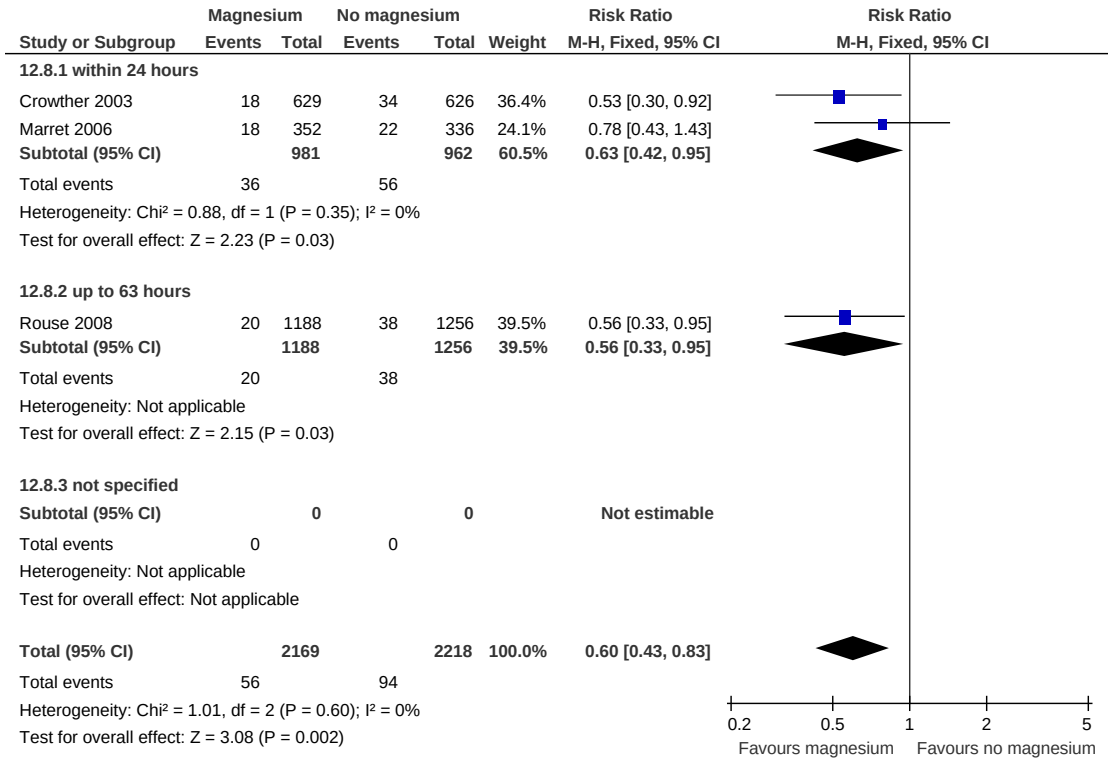


DEATH OR CEREBRAL PALSY

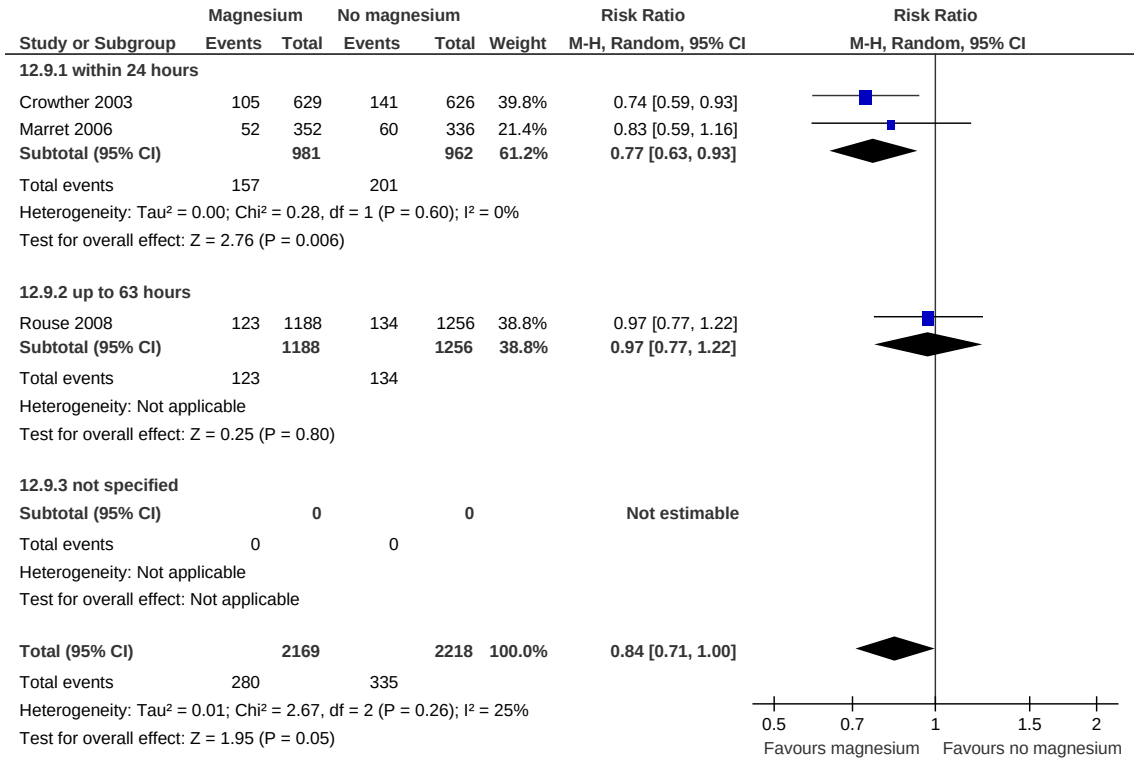


F 5: TIMING

SUBSTANTIAL GROSS MOTOR DYSFUNCTION

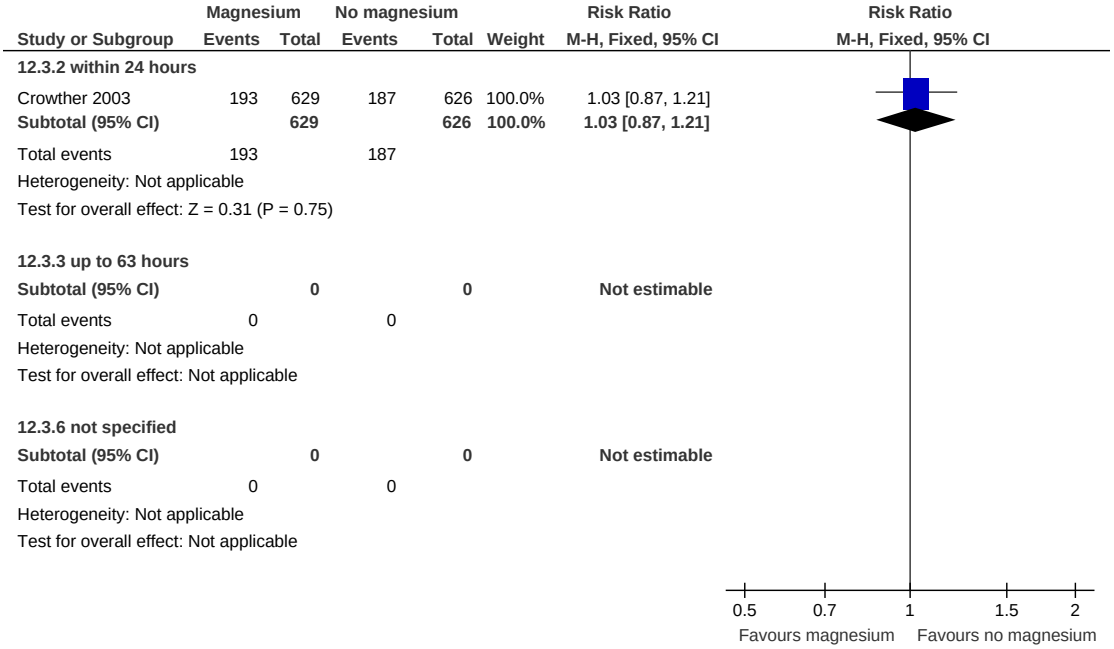


DEATH OR SUBSTANTIAL MOTOR DYSFUNCTION

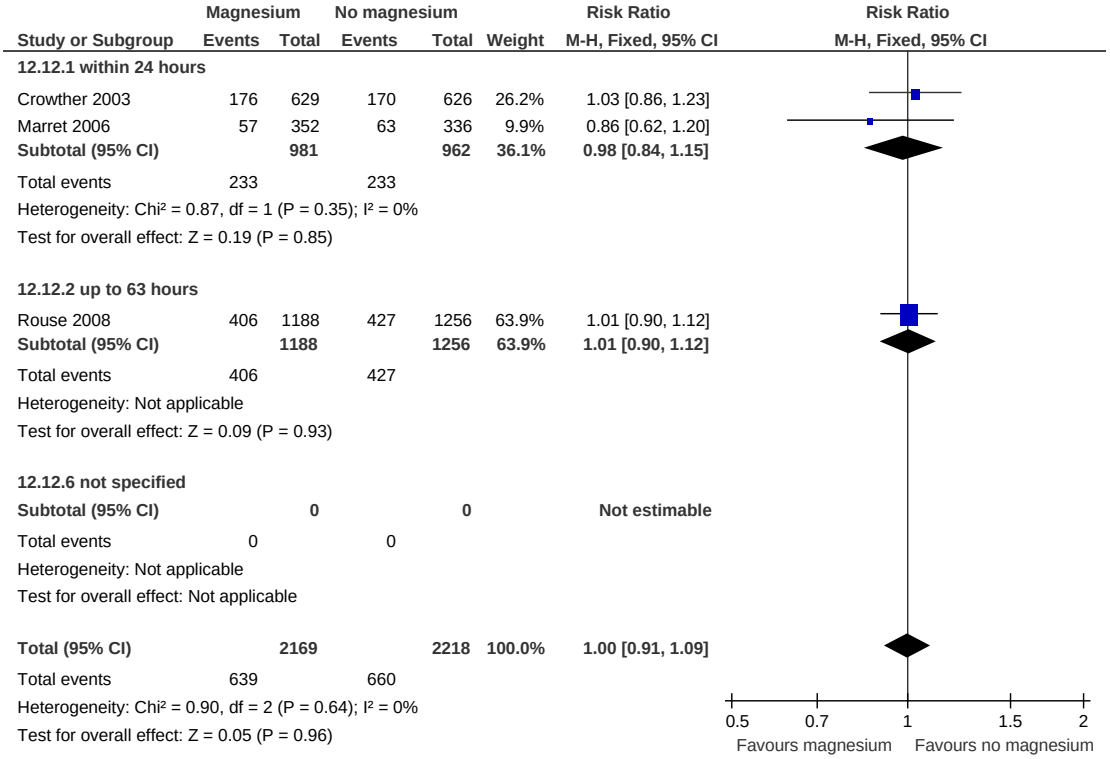


F 5: TIMING

ANY NEUROLOGICAL IMPAIRMENT

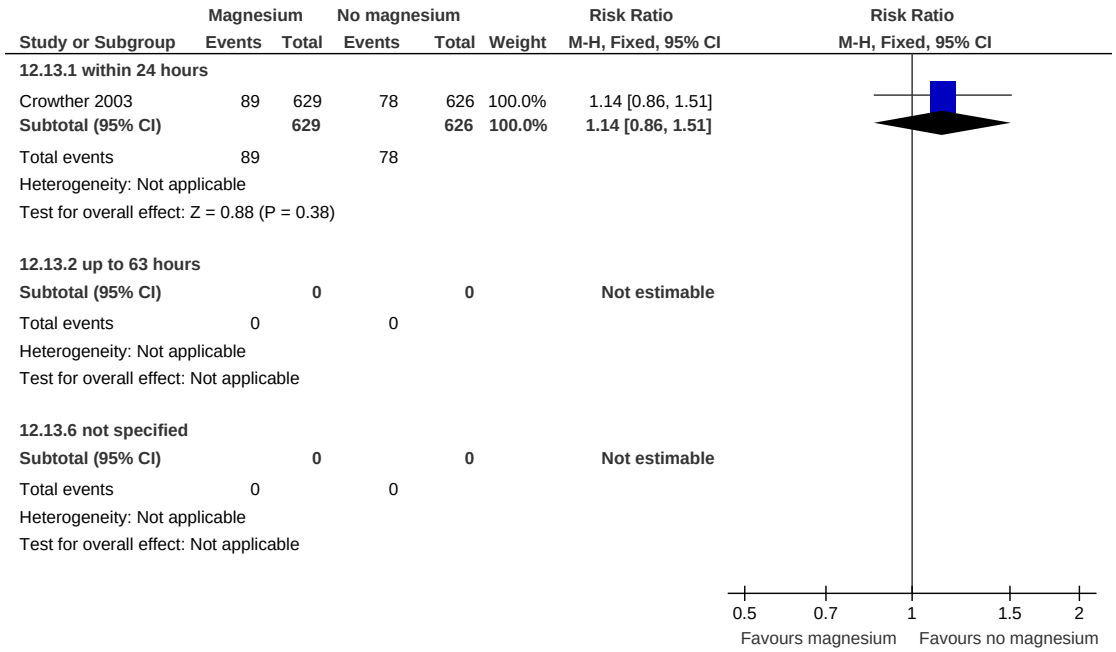


DEVELOPMENT DELAY OR INTELLECTUAL IMPAIRMENT

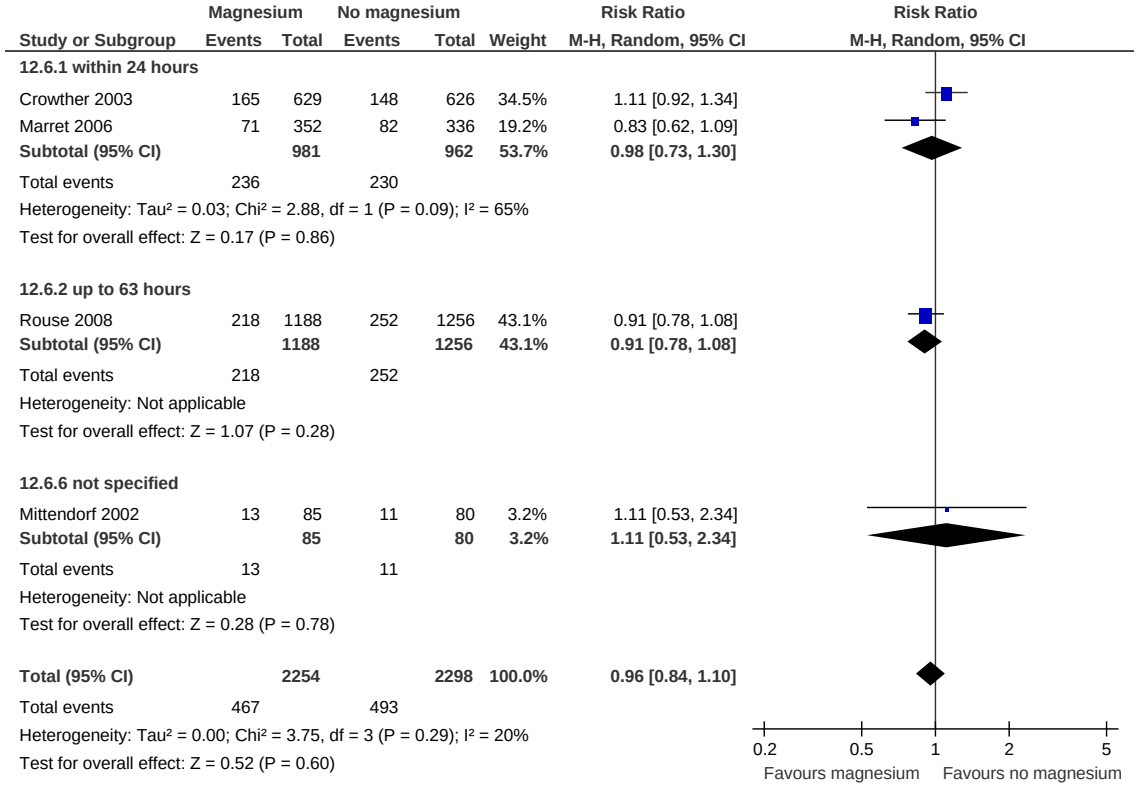


F 5: TIMING

MAJOR NEUROLOGICAL DISABILITY

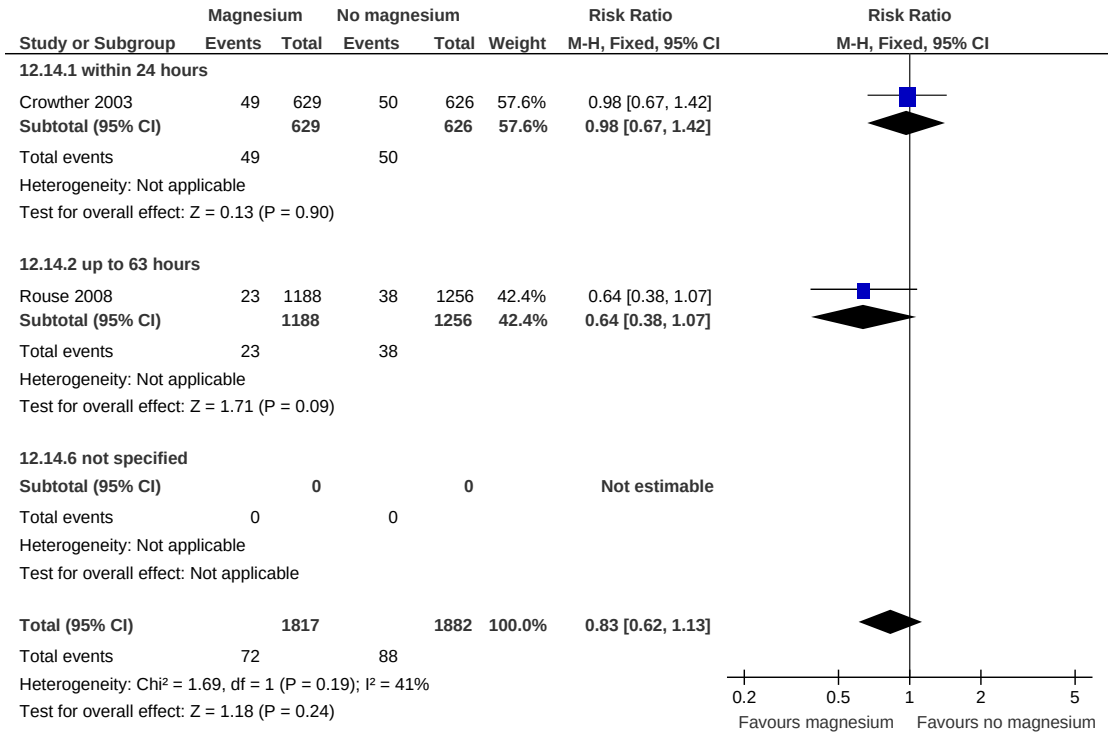


INTRAVENTRICULAR HAEMORRHAGE

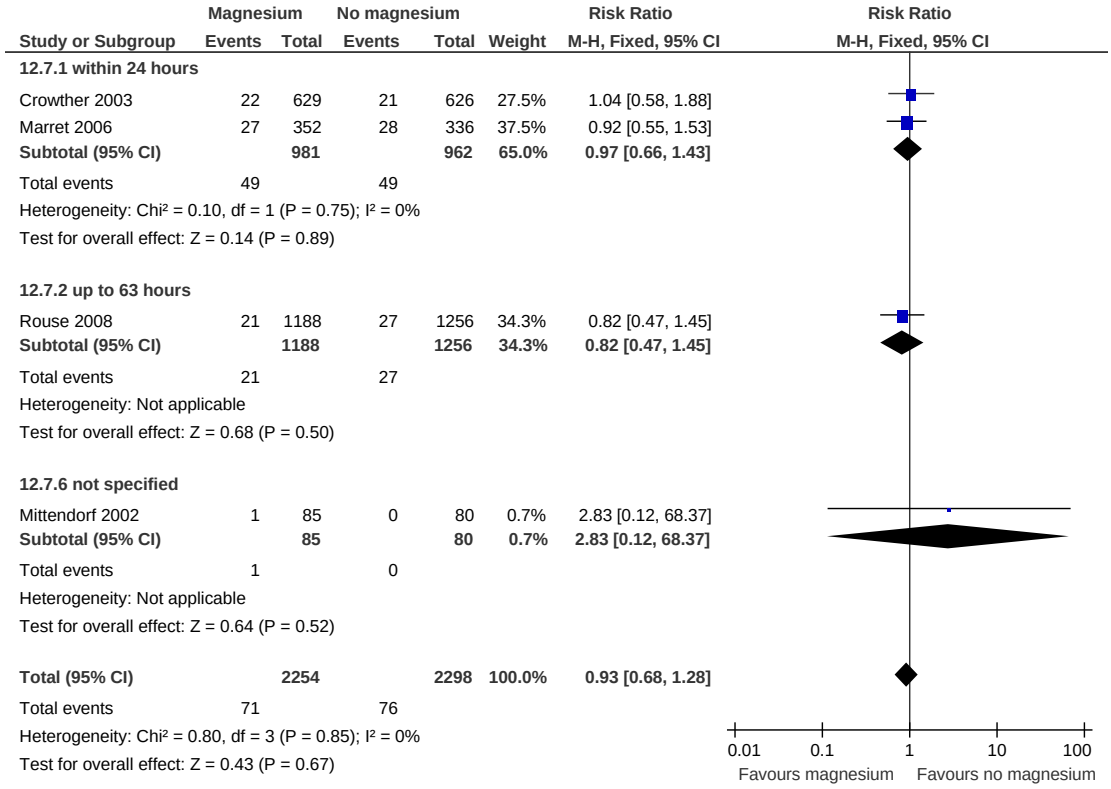


F 5: TIMING

INTRAVENTRICULAR HAEMORRHAGE (grade 3/4)



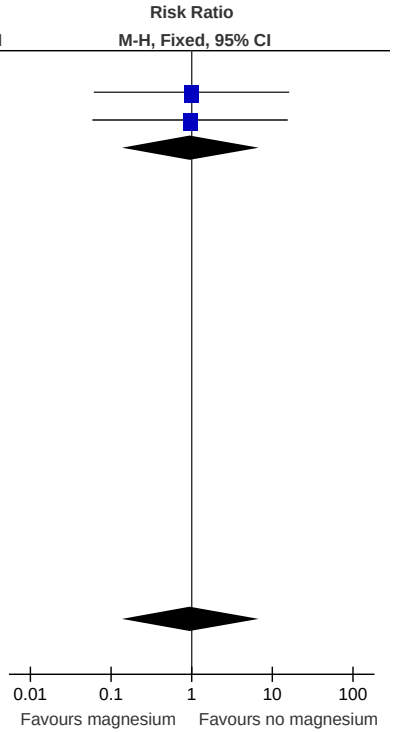
PERIVENTRICULAR LEUKOMALACIA



F 5: TIMING

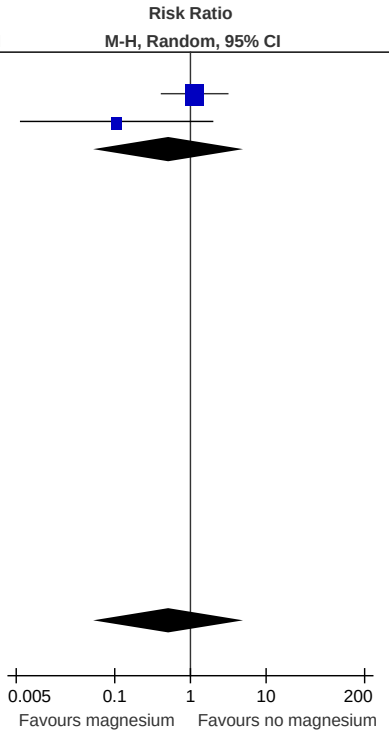
BLINDNESS

Study or Subgroup	Magnesium Events	Total	No magnesium Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
12.10.1 within 24 hours						
Crowther 2003	1	629	1	626	49.5%	1.00 [0.06, 15.88]
Marret 2006	1	352	1	336	50.5%	0.95 [0.06, 15.20]
Subtotal (95% CI)		**981**		**962**	**100.0%**	**0.97 [0.14, 6.90]**
Total events	2		2			
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.98); I² = 0%						
Test for overall effect: Z = 0.03 (P = 0.98)						
12.10.2 up to 63 hours						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
12.10.6 not specified						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**981**		**962**	**100.0%**	**0.97 [0.14, 6.90]**
Total events	2		2			
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.98); I² = 0%						
Test for overall effect: Z = 0.03 (P = 0.98)						



DEAFNESS

Study or Subgroup	Magnesium Events	Total	No magnesium Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
12.11.1 within 24 hours						
Crowther 2003	8	629	7	626	66.2%	1.14 [0.41, 3.12]
Marret 2006	0	352	4	336	33.8%	0.11 [0.01, 1.96]
Subtotal (95% CI)		**981**		**962**	**100.0%**	**0.51 [0.05, 4.96]**
Total events	8		11			
Heterogeneity: Tau² = 1.77; Chi² = 2.42, df = 1 (P = 0.12); I² = 59%						
Test for overall effect: Z = 0.58 (P = 0.56)						
12.11.2 up to 63 hours						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
12.11.6 not specified						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**981**		**962**	**100.0%**	**0.51 [0.05, 4.96]**
Total events	8		11			
Heterogeneity: Tau² = 1.77; Chi² = 2.42, df = 1 (P = 0.12); I² = 59%						
Test for overall effect: Z = 0.58 (P = 0.56)						



Q6: Regimens

NHMRC Evidence Statement

Key question(s): **Q6: Do improvements to the fetus/infant/child vary by regimens?**	
1. Evidence base	
Subgroup analysis from 4 RCTs; therefore the comparisons by regimens are non-randomised comparisons (level III).	B (Several Level lll studies with low risk of bias)
2. Consistency	
Unable to explain inconsistent results between Marret (2006) and Mittendorf (2002) for combined death and cerebral palsy; and cerebral palsy.	C (Some inconsistency, reflecting genuine uncertainty around question)
3. Clinical Impact	
	A (overall)
4. Generalisability	
As for overall.	B (Evidence directly generalisable to target population with some caveats)
5. Applicability	
Australian and NZ clinicians may not be as comfortable with a 6 g loading dose and 2 g/hr maintenance dose.	A (Evidence directly applicable to Australian healthcare context)
Other factors In the absence of being able to assess clinical impact, the choices are: a) To make no recommendation regarding magnesium regimens b) To recommend that magnesium be given from 4 g to 6 g as loading dose and from 1 g to 2 g/hour as a maintenance dose; with repeat doses possible with IV route c) To make a cautious recommendation that magnesium sulphate be only given as a 4 g loading dose (over 20 minutes) and 1 g/hour maintenance dose with no repeat doses with IV route (up until birth or 24 hours whichever comes first).	
EVIDENCE STATEMENT MATRIX	
Component	**Rating**
Evidence base	B
Consistency	C
Clinical impact	A (overall)
Generalisability	B
Applicability	A

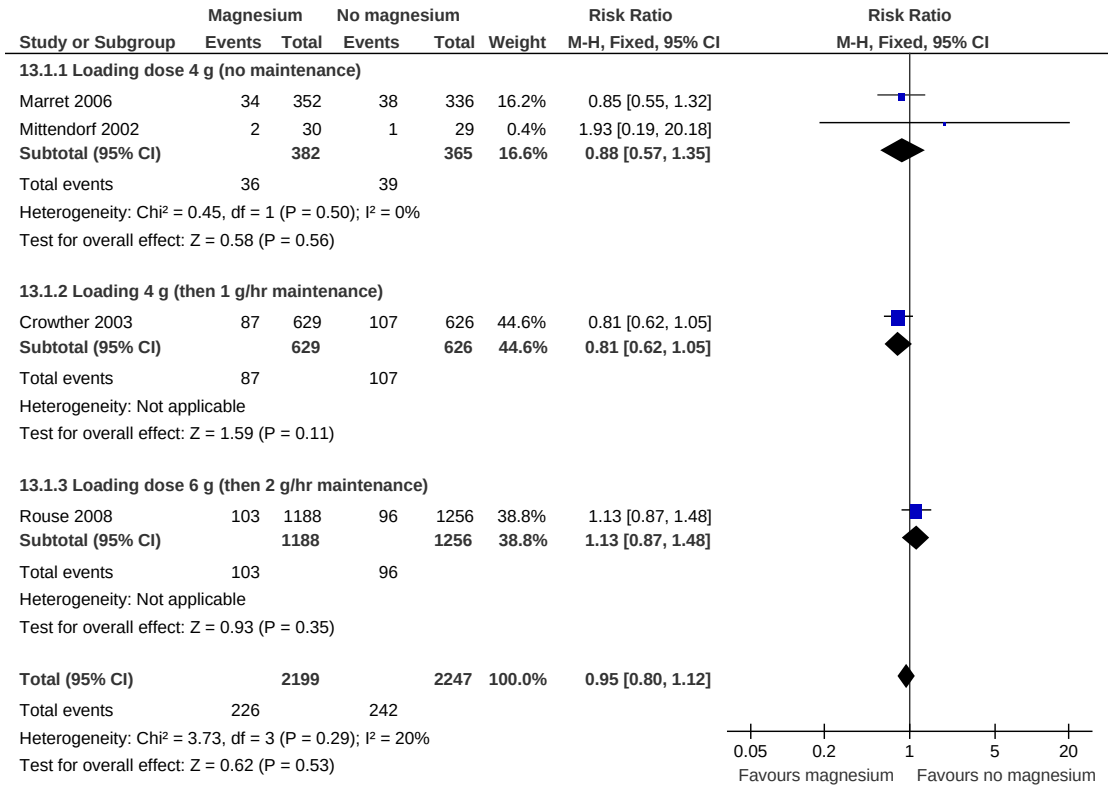
RECOMMENDATION	
• Magnesium sulphate be given intravenously with a 4 gram loading dose (slowly over 20-30 minutes) and 1 gram per hour maintenance dose via intravenous route, with no immediate repeat doses. Continue regimen up until birth or 24 hours whichever comes first.	C
UNRESOLVED ISSUES	
IMPLEMENTATION OF RECOMMENDATION	
Will this recommendation result in changes in usual care?	YES
Are there any resource implications associated with implementing this recommendation?	YES
Will the implementation of this recommendation require changes in the way care is currently organised?	YES
Are the guideline development group aware of any barriers to the implementation of this recommendation?	YES

Appendix F 6: Evidence Table and Graphs: REGIMENS

Study	Loading dose	Maintenance dose	Repeat dosing	Route
Marret 2006	4 g	none	none	IV
Mittendorf 2002	4 g	none	none	IV
Crowther 2003	4 g	1 g/hr	none	IV
Rouse 2008	6 g	2 g/hr	42.2% received repeat dose	IV

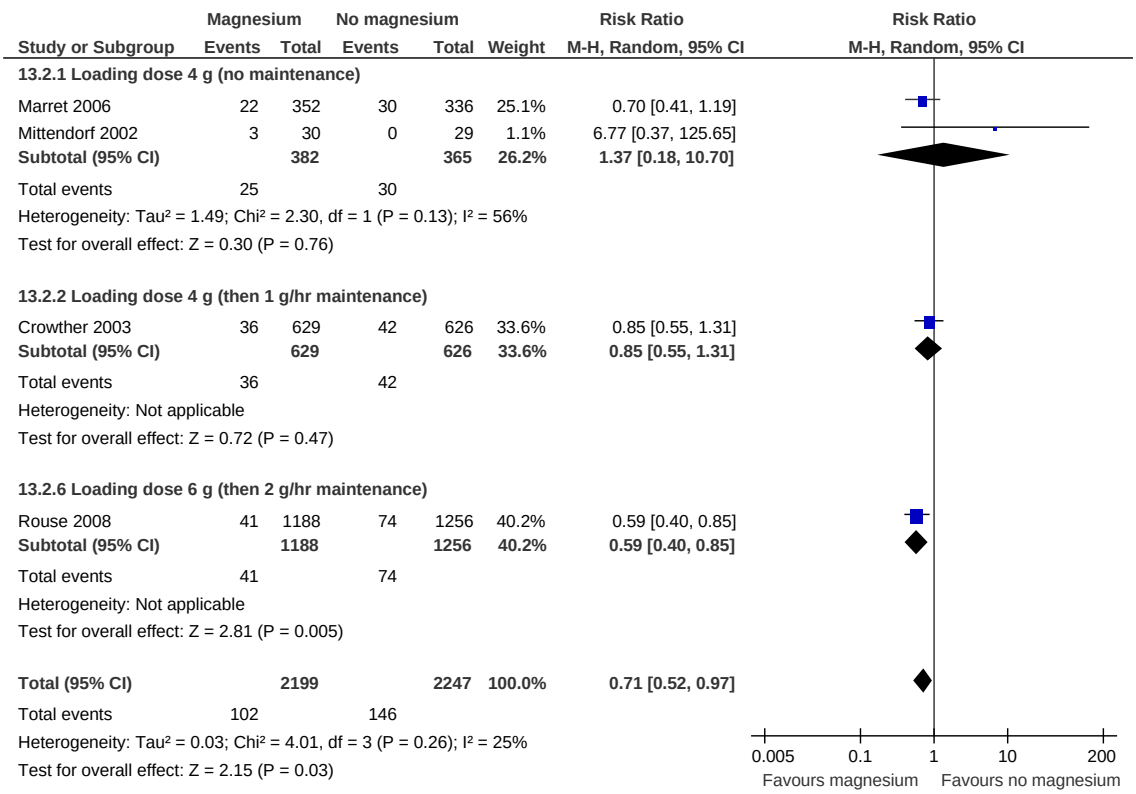
IV= Intravenous

DEATH

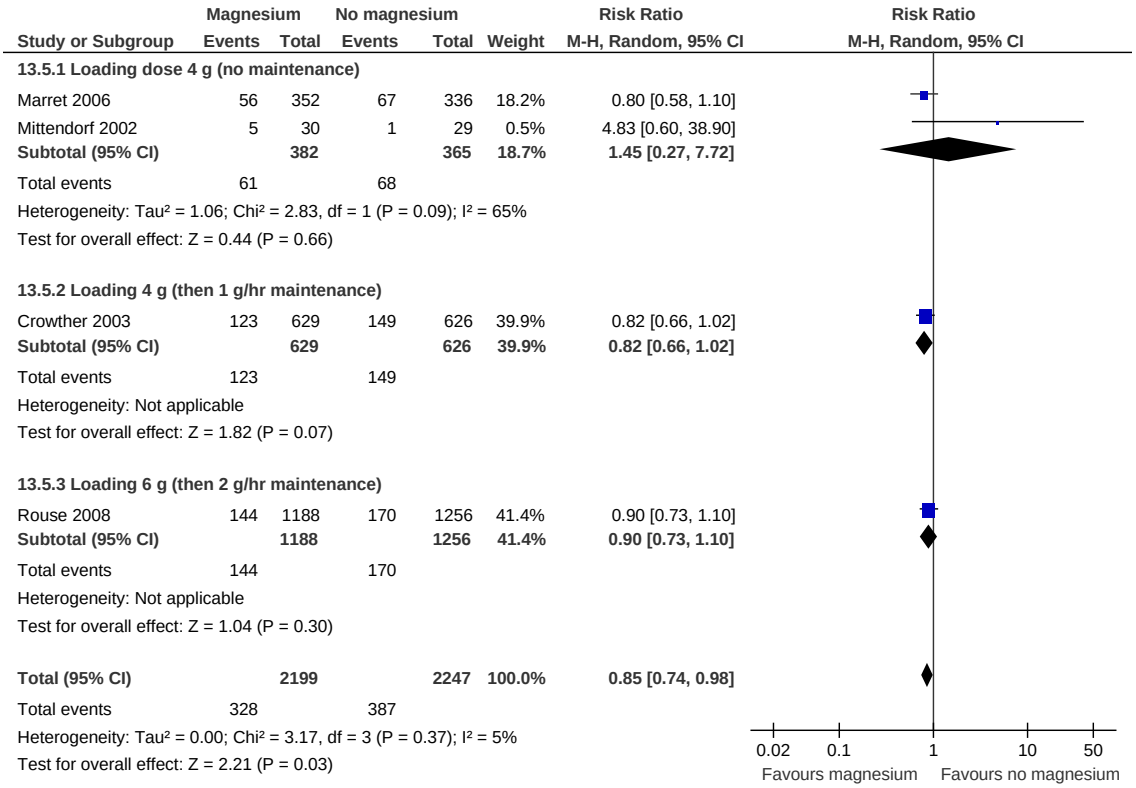


F 6: REGIMENS

CEREBRAL PALSY

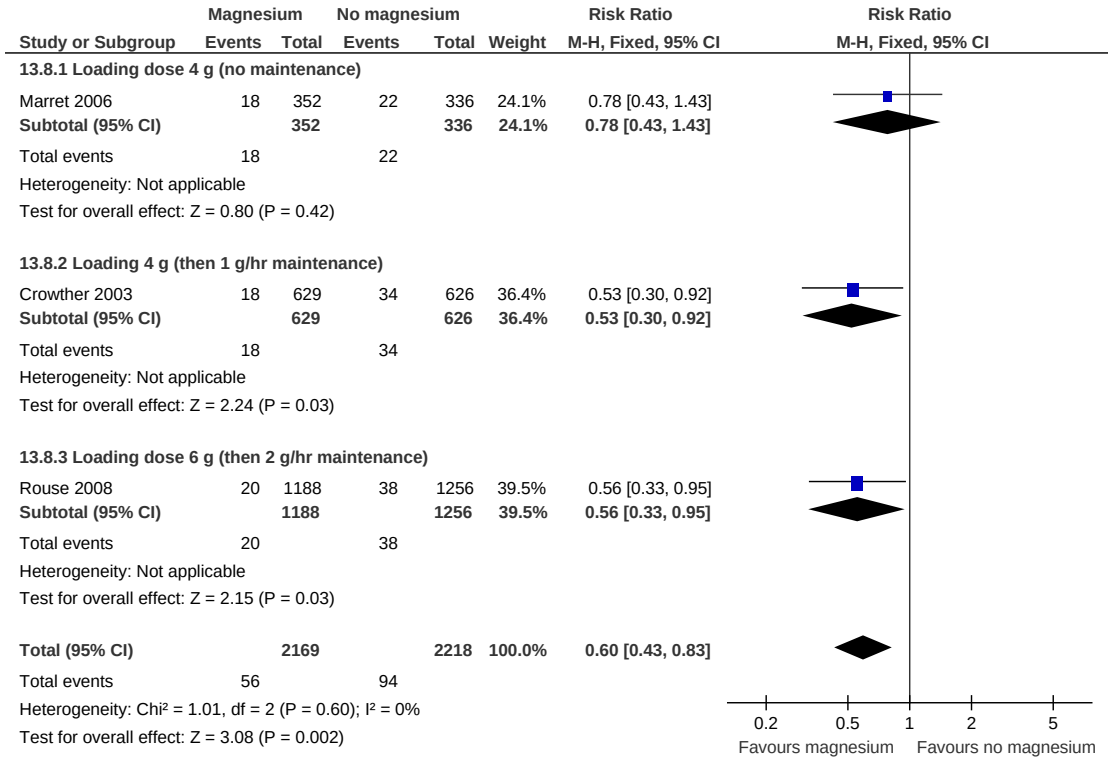


DEATH OR CEREBRAL PALSY

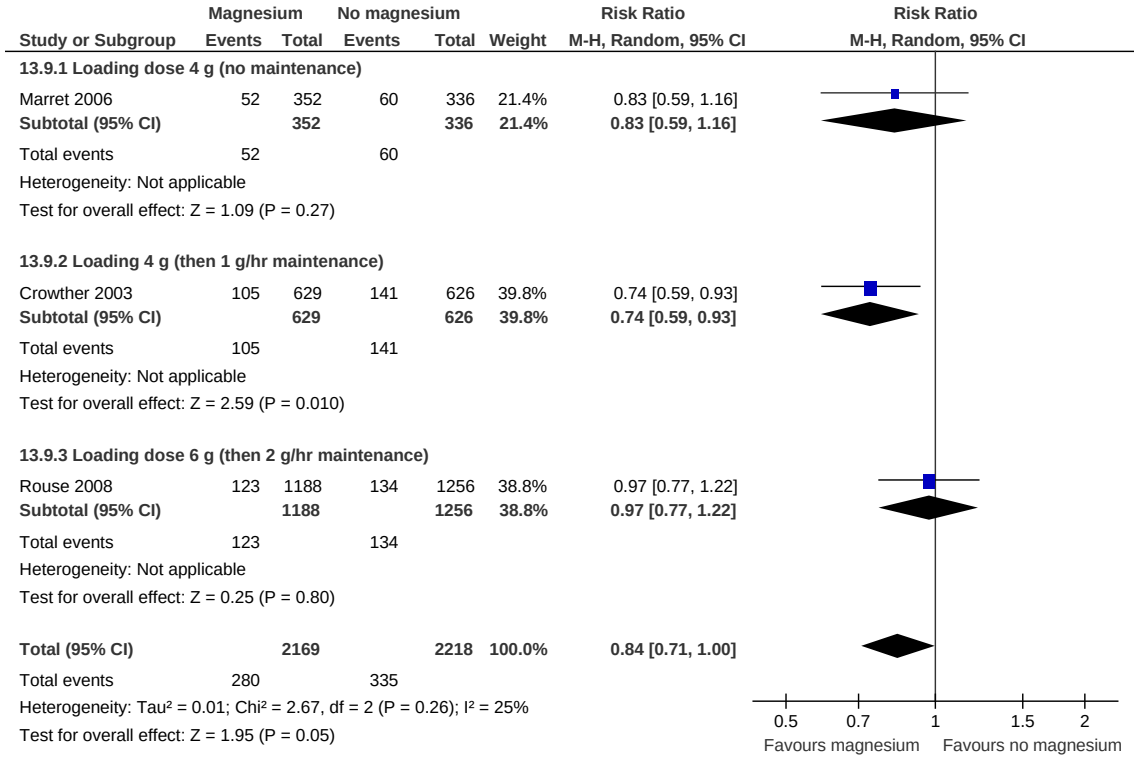


F 6: REGIMENS

SUBSTANTIAL GROSS MOTOR DYSFUNCTION

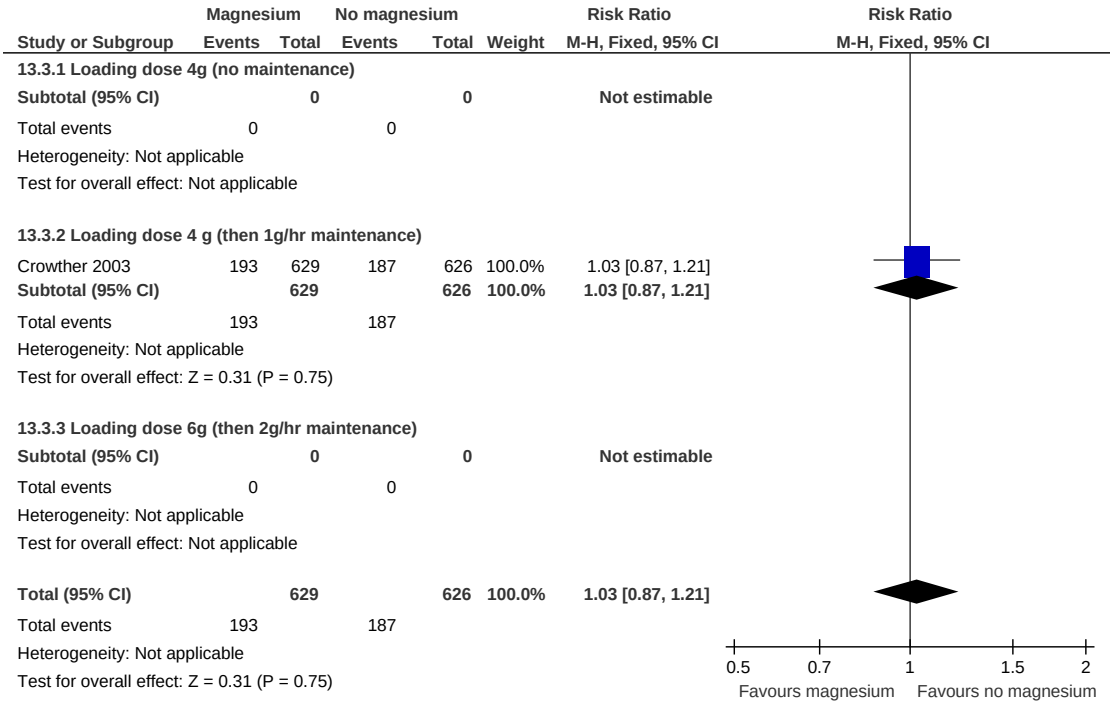


DEATH OR SUBSTANTIAL MOTOR DYSFUNCTION

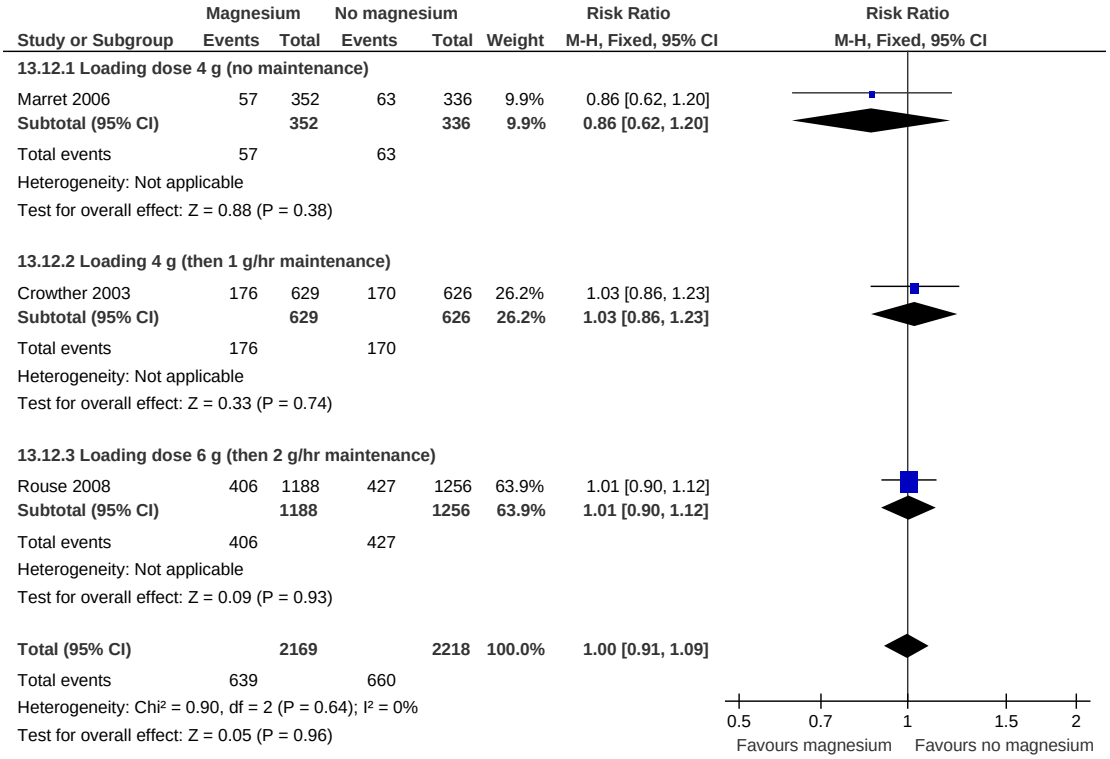


F 6: REGIMENS

ANY NEUROLOGICAL IMPAIRMENT

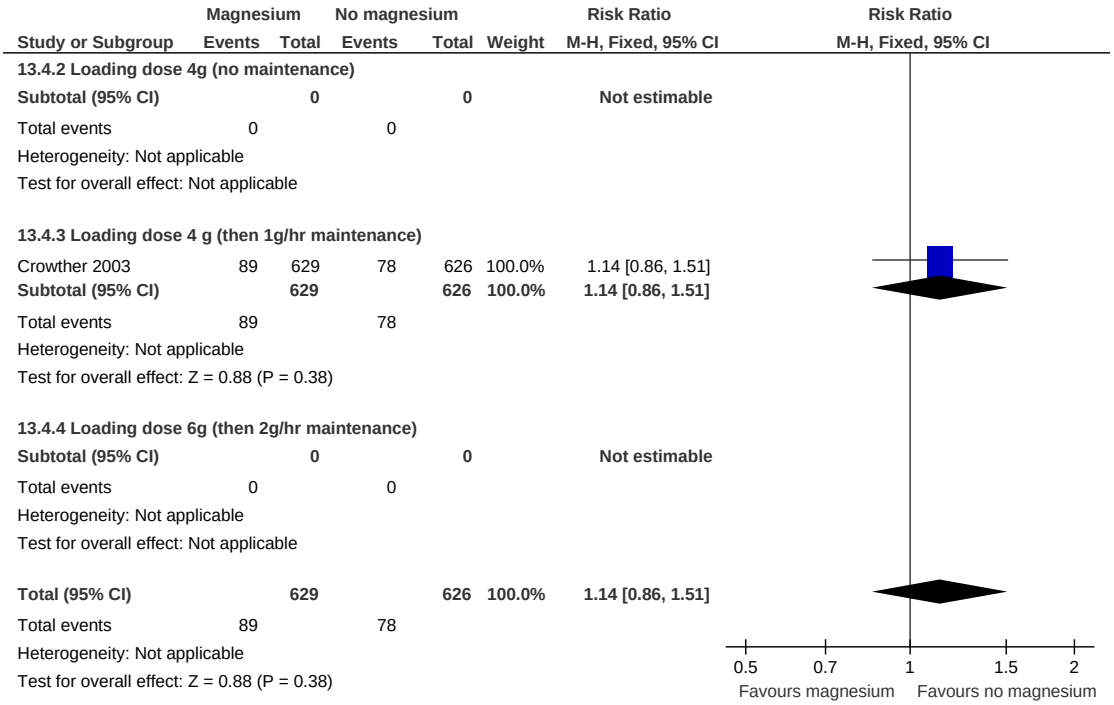


DEVELOPMENT DELAY OR INTELLECTUAL IMPAIRMENT

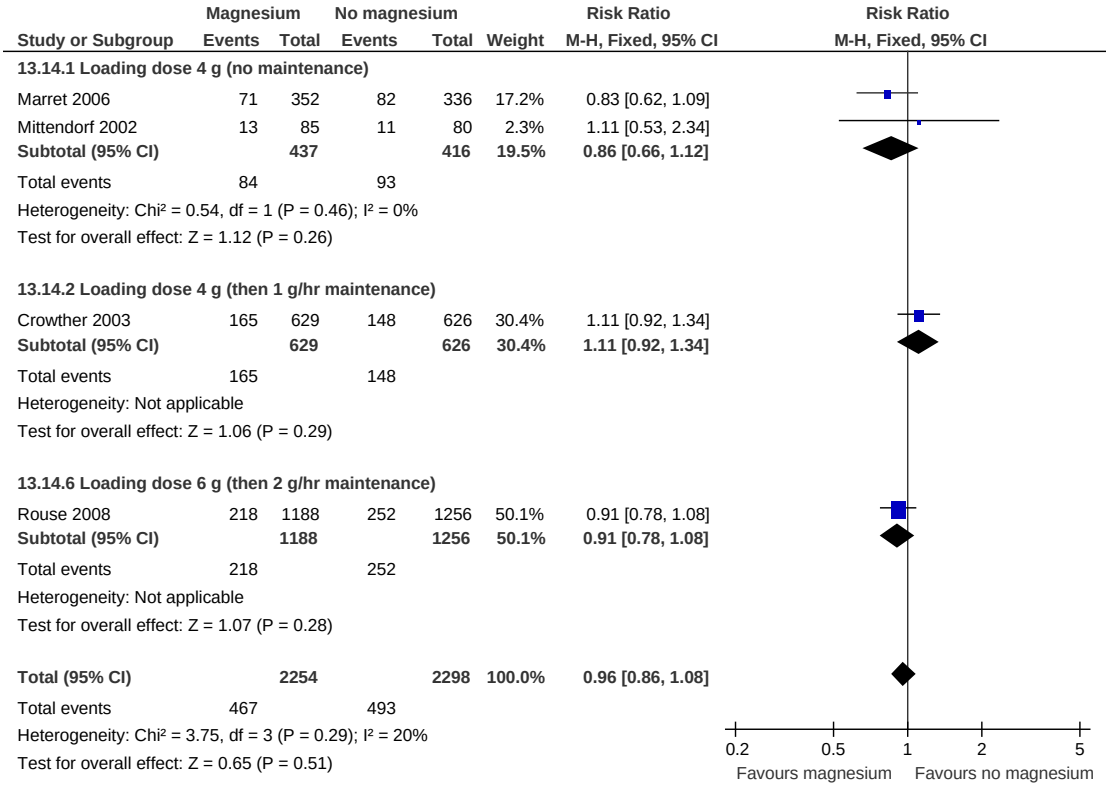


F 6: REGIMENS

MAJOR NEUROLOGICAL DISABILITY

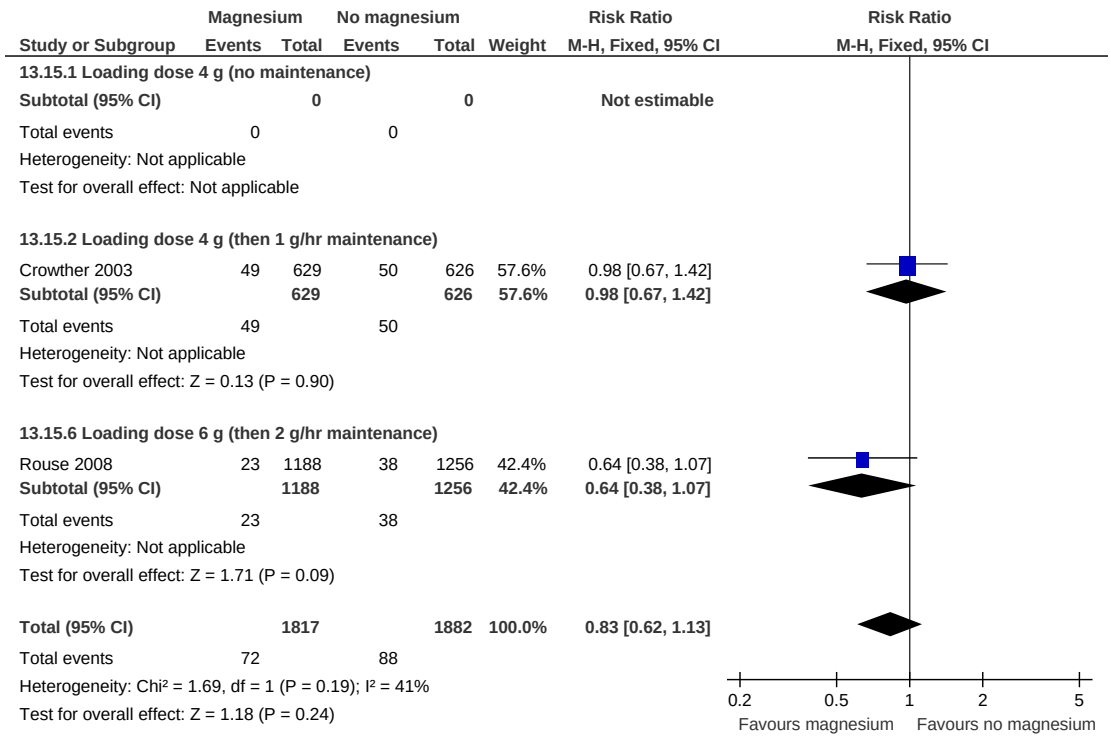


INTRAVENTRICULAR HAEMORRHAGE

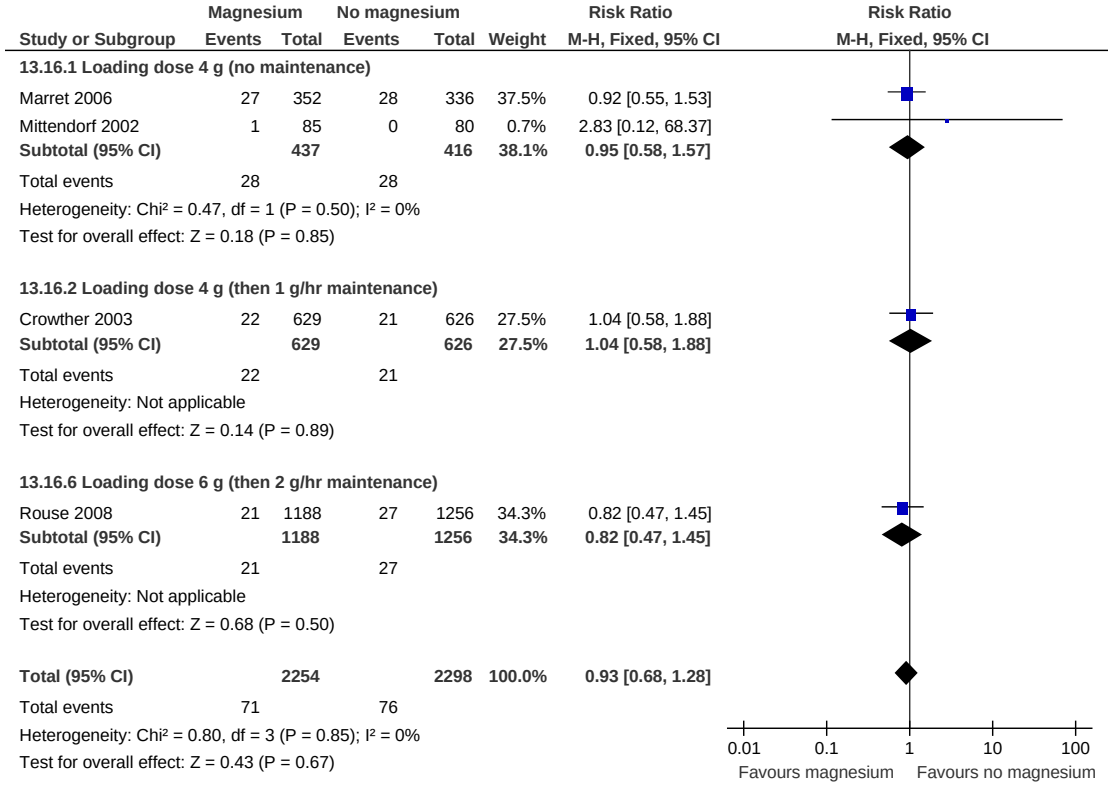


F 6: REGIMENS

INTRAVENTRICULAR HAEMORRHAGE (grade 3/4)

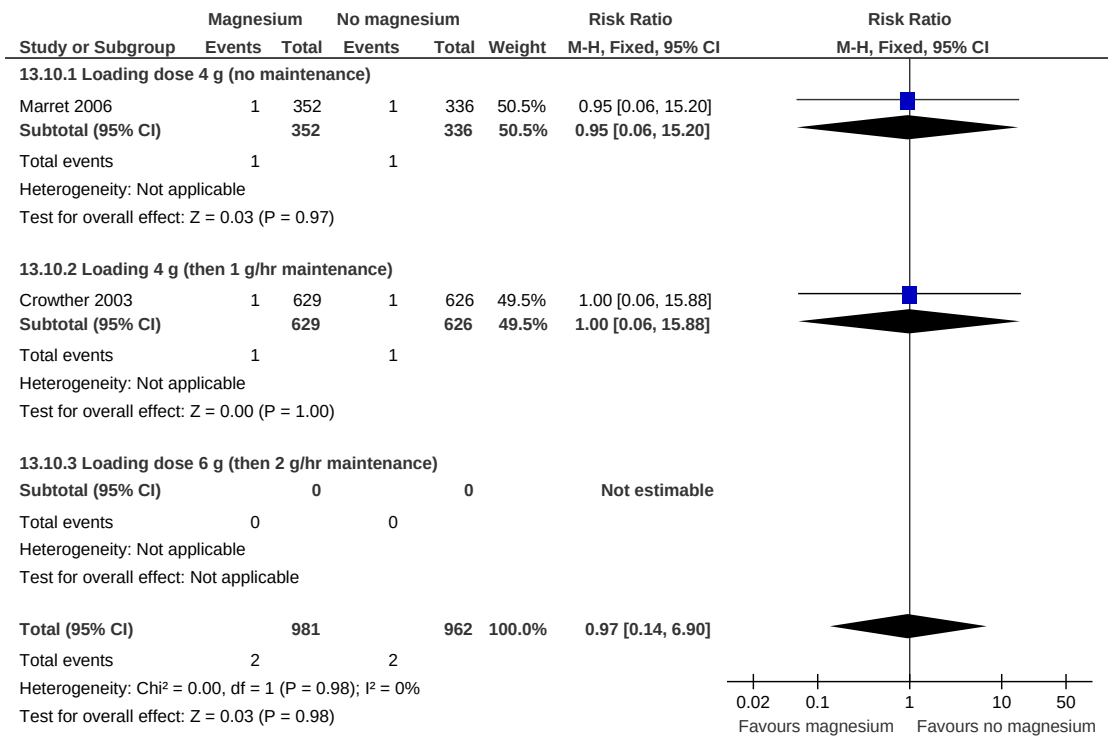


PERIVENTRICULAR LEUKOMALACIA

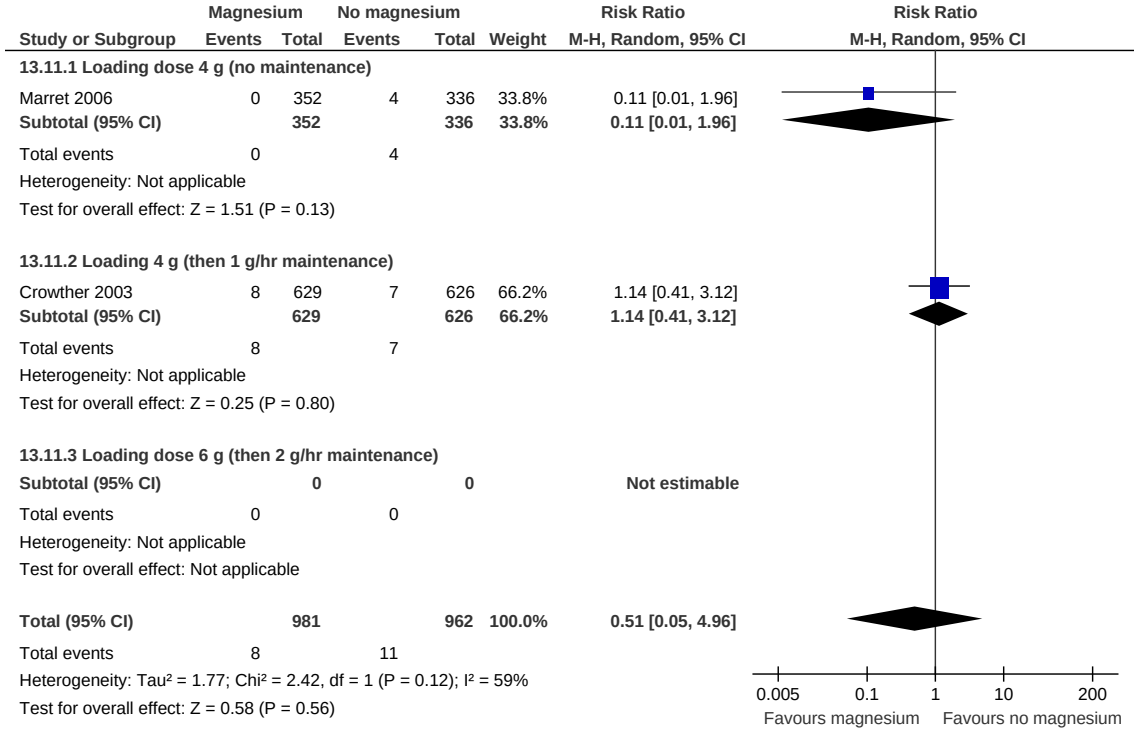


F 6: REGIMENS

BLINDNESS



DEAFNESS



Q7: Number of babies in utero

NHMRC Evidence Statement

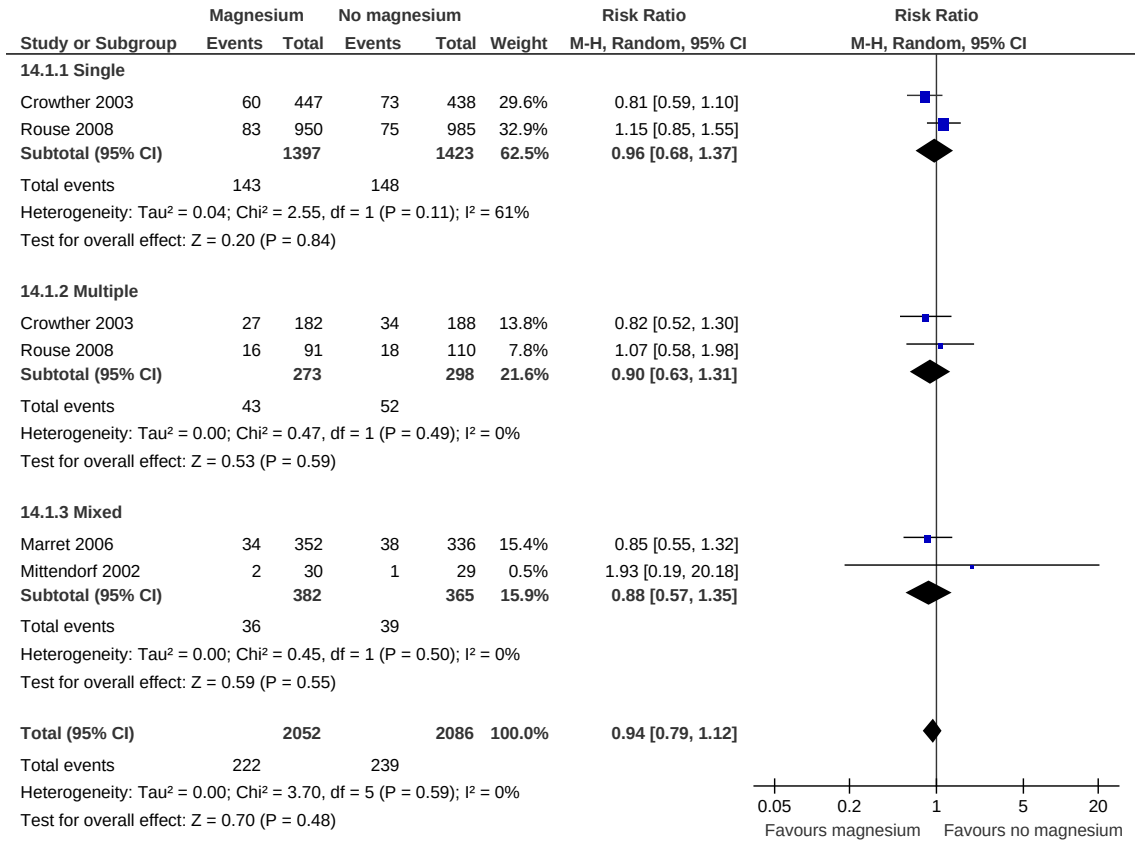
Key question(s): **Q7: Do improvements to the fetus/infant/child vary by number of babies in utero?**	
1. Evidence base	
Subgroup analysis from 4 RCTs; therefore the comparisons by the number of babies in utero are non-randomised comparisons (level III).	B (Several Level lll studies with low risk of bias)
2. Consistency	
	B (Most studies consistent and inconsistency can be explained)
3. Clinical Impact	
Very large	A (overall)
4. Generalisability	
As for overall.	B (Evidence directly generalisable to target population with some caveats)
5. Applicability	
No evidence to suggest that benefit is specific to either single or multiple (up to 4) babies in utero	A (Evidence directly applicable to Australian healthcare context)
Other factors In the absence of being able to assess clinical impact, the choices are: a) To make no recommendation regarding magnesium regimens; b) To make a cautious recommendation that magnesium sulphate be given to women with up to 4 babies in utero; c) To make a recommendation that magnesium sulphate be given to women regardless of plurality.	
EVIDENCE STATEMENT MATRIX	
Component	**Rating**
Evidence base	B
Consistency	B
Clinical impact	A (overall)
Generalisability	B
Applicability	A

RECOMMENDATION	
• Magnesium sulphate be given to women regardless of plurality.	B
UNRESOLVED ISSUES	
Individual patient data meta-analysis needed.	
IMPLEMENTATION OF RECOMMENDATION	
Will this recommendation result in changes in usual care?	YES
Are there any resource implications associated with implementing this recommendation?	YES
Will the implementation of this recommendation require changes in the way care is currently organised?	YES
Are the guideline development group aware of any barriers to the implementation of this recommendation?	YES

F 7: Evidence Tables and Graphs: NUMBER OF BABIES IN UTERO

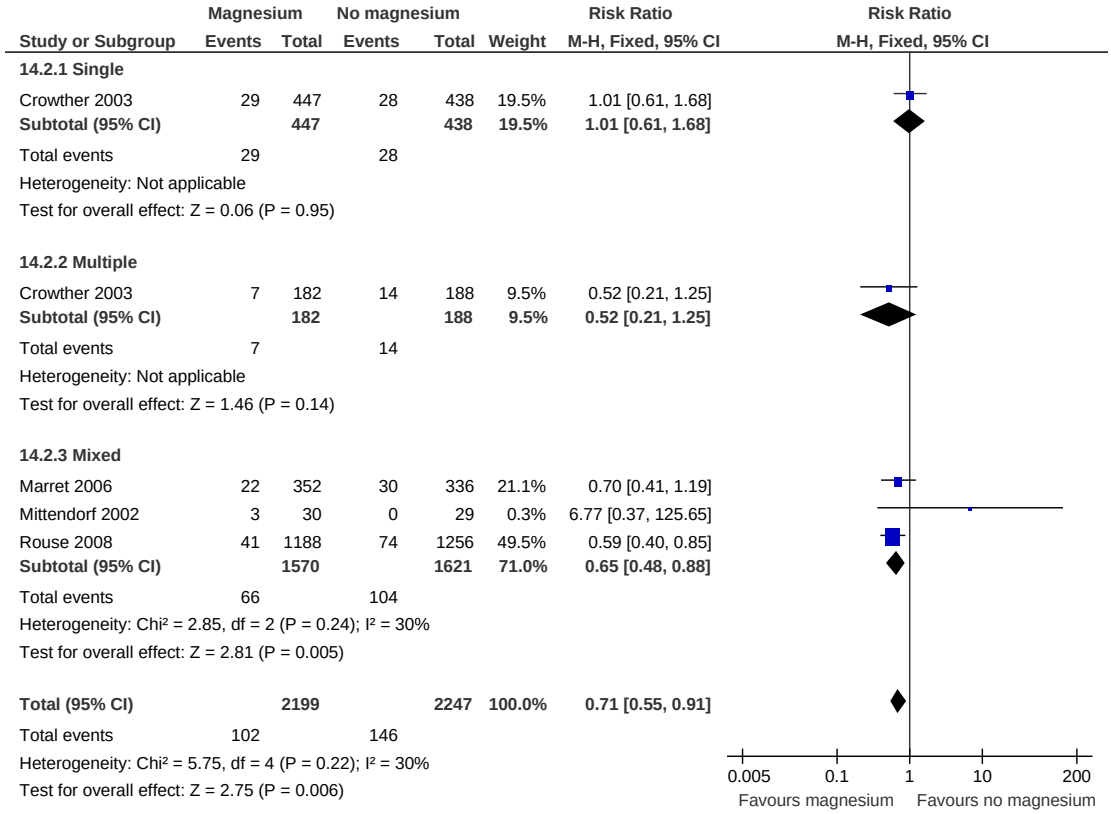
Study	Single	Twin	Higher order	Reported separately
Crowther 2003	Yes	Yes	Yes (triplet+quad)	Single vs multiple
Rouse 2008	Yes	Yes	No	Single vs twin
Marret 2006	Yes	Yes	Yes (triplet)	No
Mittendorf 2002	Yes	Yes	No	No

DEATH

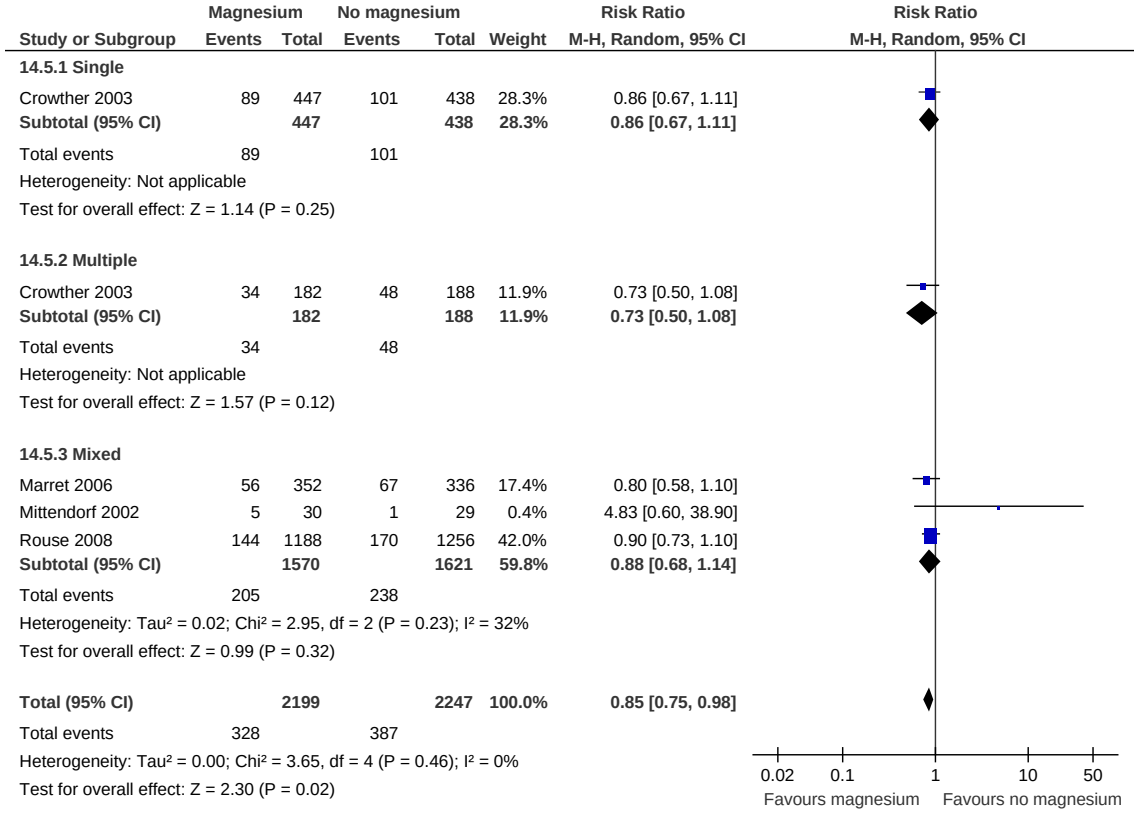


F 7: NUMBER OF BABIES IN UTERO

CEREBRAL PALSY

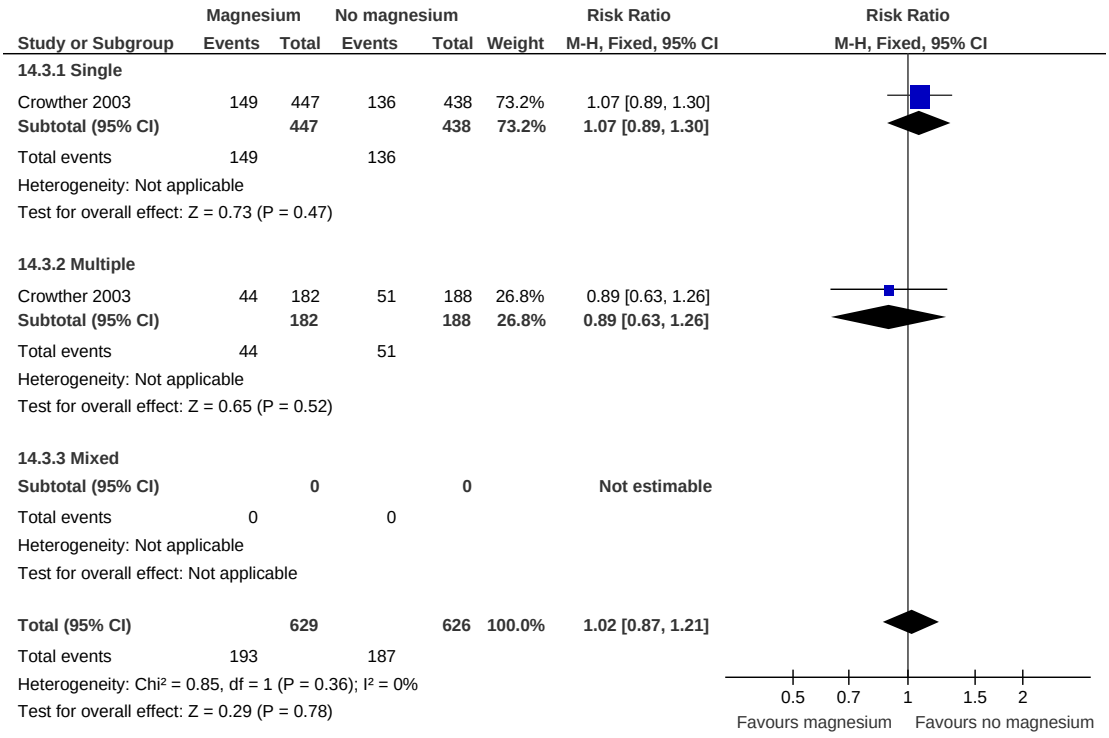


DEATH OR CEREBRAL PALSY

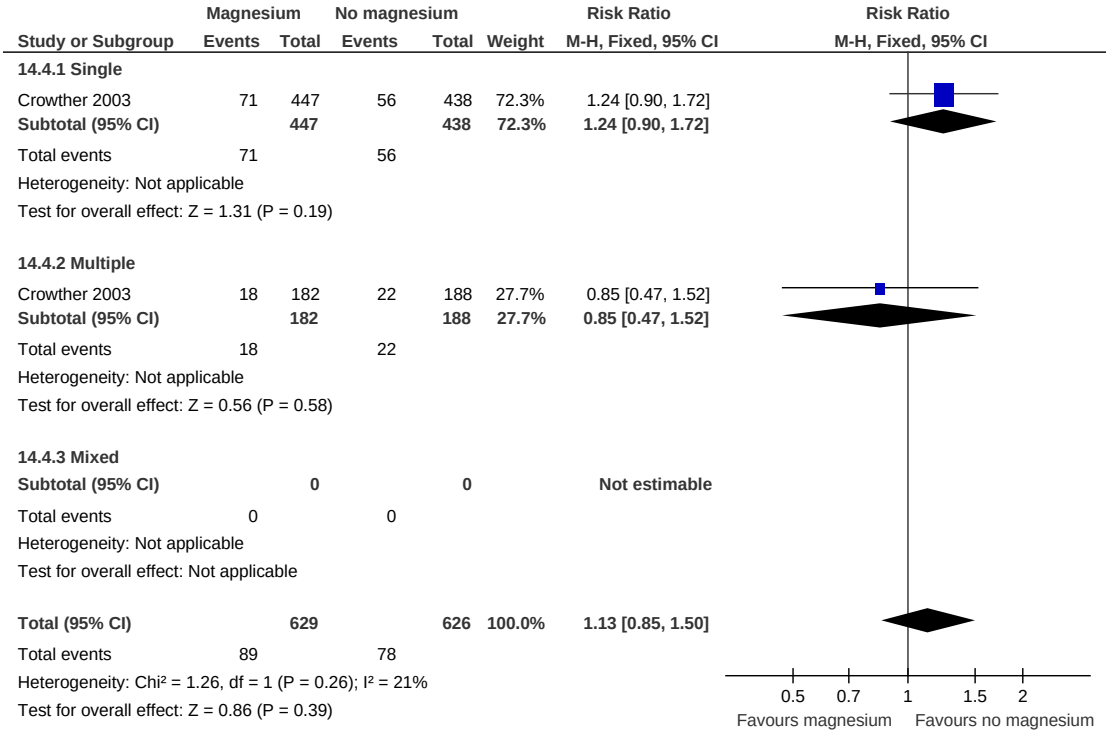


F 7: NUMBER OF BABIES IN UTERO

ANY NEUROLOGICAL IMPAIRMENT



MAJOR NEUROLOGICAL DISABILITY



Q8: Reason for treatment

NHMRC Evidence Statement

Key question(s): **Q8: Do improvements to the fetus/infant/child vary by reason women considered (at less than 30 weeks gestation) to be at risk of preterm birth?**	
1. Evidence base	
Subgroup analysis from 4 RCTs; therefore the comparisons by time magnesium is planned are non-randomised comparisons (level III).	B (Several Level lll studies with low risk of bias)
2. Consistency	
	B (Most studies consistent and inconsistency can be explained)
3. Clinical Impact	
Very large	A (overall)
4. Generalisability	
As for overall.	B (Evidence directly generalisable to target population with some caveats)
5. Applicability	
As for overall.	A (Evidence directly applicable to Australian healthcare context)
Other factors In the absence of being able to assess clinical impact, the choices are: a) To make no recommendation regarding reason for treatment with magnesium sulphate; b) To recommend that magnesium be given to all women regardless of whether reason for treatment is PROM, preterm labour or preterm birth; c) To make a cautious recommendation that magnesium sulphate be only given to women at risk of preterm birth within 24 hours.	
EVIDENCE STATEMENT MATRIX	
Component	**Rating**
Evidence base	B
Consistency	B
Clinical impact	A (overall)
Generalisability	B
Applicability	A

RECOMMENDATION	
• Magnesium sulphate be given regardless of reason women considered (at less than 30 weeks' gestation) to be at risk of preterm birth.	B
UNRESOLVED ISSUES	
Individual patient data meta-analysis needed	
IMPLEMENTATION OF RECOMMENDATION	
Will this recommendation result in changes in usual care?	YES
Are there any resource implications associated with implementing this recommendation?	YES
Will the implementation of this recommendation require changes in the way care is currently organised?	YES
Are the guideline development group aware of any barriers to the implementation of this recommendation?	YES

Q9: Parity Of Women

NHMRC Evidence Statement

Key question(s): **Q9: Do improvements to the fetus/infant/child vary by parity of women?**	
1. Evidence base	
Subgroup analysis from 4 RCTs; therefore the comparisons by parity of women are non-randomised comparisons (level III).	B (Several Level lll studies with low risk of bias)
2. Consistency	
	B (Most studies consistent and inconsistency can be explained)
3. Clinical Impact	
Very large	A (overall)
4. Generalisability	
As for overall.	B (Evidence directly generalisable to target population with some caveats)
5. Applicability	
As for overall.	A (Evidence directly applicable to Australian healthcare context)
Other factors In the absence of being able to assess clinical impact, the choices are: a) To make no recommendation regarding giving magnesium sulphate to women based on parity; b) To recommend that magnesium sulphate be given to all women regardless of parity.	
EVIDENCE STATEMENT MATRIX	
Component	**Rating**
Evidence base	B
Consistency	B
Clinical impact	A (overall)
Generalisability	B
Applicability	A

RECOMMENDATION	
• Magnesium sulphate be given to all women regardless of parity (number of previous births for the woman).	B
UNRESOLVED ISSUES	
Individual patient data meta-analysis needed	
IMPLEMENTATION OF RECOMMENDATION	
Will this recommendation result in changes in usual care?	YES
Are there any resource implications associated with implementing this recommendation?	YES
Will the implementation of this recommendation require changes in the way care is currently organised?	YES
Are the guideline development group aware of any barriers to the implementation of this recommendation?	YES

Q10: Mode Of Birth

NHMRC Evidence Statement

Key question(s): **Q10: Do improvements to the fetus/infant/child vary by mode of birth?**	
1. Evidence base	
Subgroup analysis from 4 RCTs; therefore the comparisons by time magnesium is planned are non-randomised comparisons (level III).	B (Several Level lll studies with low risk of bias)
2. Consistency	
	B (Most studies consistent and inconsistency can be explained)
3. Clinical Impact	
Very large	A (overall)
4. Generalisability	
As for overall.	B (Evidence directly generalisable to target population with some caveats)
5. Applicability	
As for overall.	A (Evidence directly applicable to Australian healthcare context)
Other factors In the absence of being able to assess clinical impact, the choices are: a) To make no recommendation regarding giving magnesium sulphate to women based on mode of birth; b) To recommend that magnesium sulphate be given to all women regardless of mode of birth.	
EVIDENCE STATEMENT MATRIX	
Component	**Rating**
Evidence base	B
Consistency	B
Clinical impact	A (overall)
Generalisability	B
Applicability	A

RECOMMENDATION	
• Magnesium sulphate be given to all women regardless of mode of birth.	B
UNRESOLVED ISSUES	
Individual patient data meta-analysis needed.	
IMPLEMENTATION OF RECOMMENDATION	
Will this recommendation result in changes in usual care?	YES
Are there any resource implications associated with implementing this recommendation?	YES
Will the implementation of this recommendation require changes in the way care is currently organised?	YES
Are the guideline development group aware of any barriers to the implementation of this recommendation?	YES

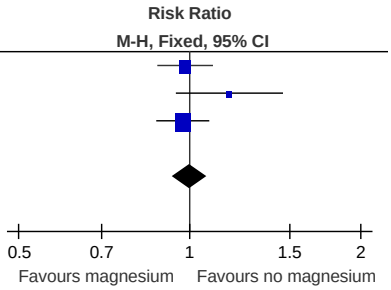
Appendix F 10: Evidence Table and Graphs: MODE OF BIRTH

Study	Caesarean Section	Vaginal Birth
Crowther 2003	Yes	Yes
Rouse 2008	Yes	Yes
Marret 2006	Yes	Yes
Mittendorf 2002	No	No

CAESAREAN SECTION

	Magnesium		No magnesium			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Crowther 2003	289	535	290	527	35.3%	0.98 [0.88, 1.10]
Marret 2006	116	286	96	278	11.8%	1.17 [0.95, 1.46]
Rouse 2008	417	1096	448	1145	52.9%	0.97 [0.88, 1.08]
Total (95% CI)		**1917**		**1950**	**100.0%**	**1.00 [0.93, 1.07]**
Total events	822		834			

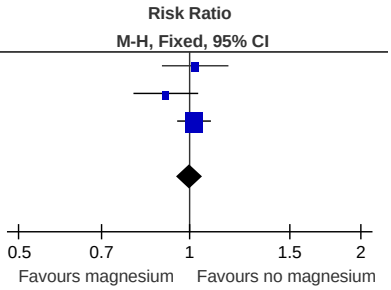
Heterogeneity: Chi² = 2.55, df = 2 (P = 0.28); I² = 22%
Test for overall effect: Z = 0.01 (P = 0.99)



VAGINAL BIRTH

	Magnesium		No magnesium			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Crowther 2003	246	535	237	527	21.6%	1.02 [0.90, 1.17]
Marret 2006	170	286	182	278	16.7%	0.91 [0.80, 1.03]
Rouse 2008	679	1096	697	1145	61.7%	1.02 [0.95, 1.09]
Total (95% CI)		**1917**		**1950**	**100.0%**	**1.00 [0.95, 1.06]**
Total events	1095		1116			

Heterogeneity: Chi² = 2.56, df = 2 (P = 0.28); I² = 22%
Test for overall effect: Z = 0.01 (P = 0.99)



Q11: Combined Effect Of Antenatal Corticosteroids

NHMRC Evidence Statement

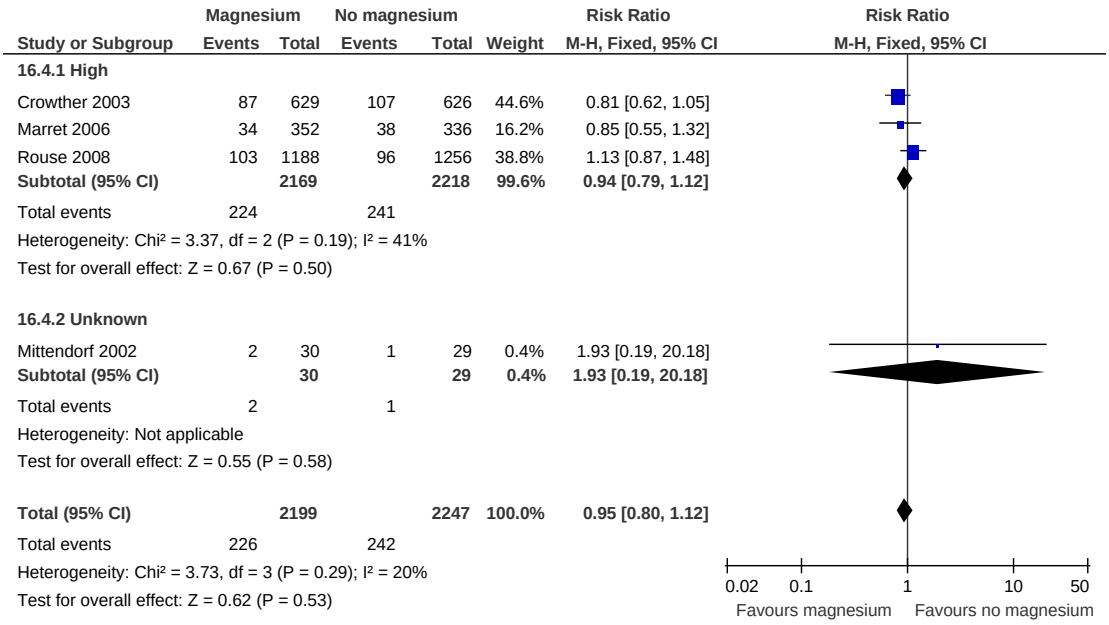
Key question(s): **Q11: Do improvements to the fetus/infant/child vary by combined effect of antenatal corticosteroids and magnesium sulphate?**	
1. Evidence base	
Subgroup analysis from 4 RCTs; therefore the comparisons by time magnesium is planned are non-randomised comparisons (level III).	B (Several Level lll studies with low risk of bias)
2. Consistency	
	B (Most studies consistent and inconsistency can be explained)
3. Clinical Impact	
Very large	A (overall)
4. Generalisability	
As for overall.	B (Evidence directly generalisable to target population with some caveats)
5. Applicability	
As for overall.	A (Evidence directly applicable to Australian healthcare context)
Other factors In the absence of being able to assess clinical impact, the choices are: a) To make no recommendation regarding giving magnesium sulphate to women receiving antenatal corticosteroids; b) To recommend that magnesium sulphate be given to all women whether or not antenatal corticosteroids have been given.	
EVIDENCE STATEMENT MATRIX	
Component	**Rating**
Evidence base	B
Consistency	B
Clinical impact	A (overall)
Generalisability	B
Applicability	A

RECOMMENDATION	
• Magnesium sulphate be given to all women whether or not antenatal corticosteroids have been given.	B
UNRESOLVED ISSUES	
Individual patient data meta-analysis needed	
IMPLEMENTATION OF RECOMMENDATION	
Will this recommendation result in changes in usual care?	YES
Are there any resource implications associated with implementing this recommendation?	YES
Will the implementation of this recommendation require changes in the way care is currently organised?	YES
Are the guideline development group aware of any barriers to the implementation of this recommendation?	YES

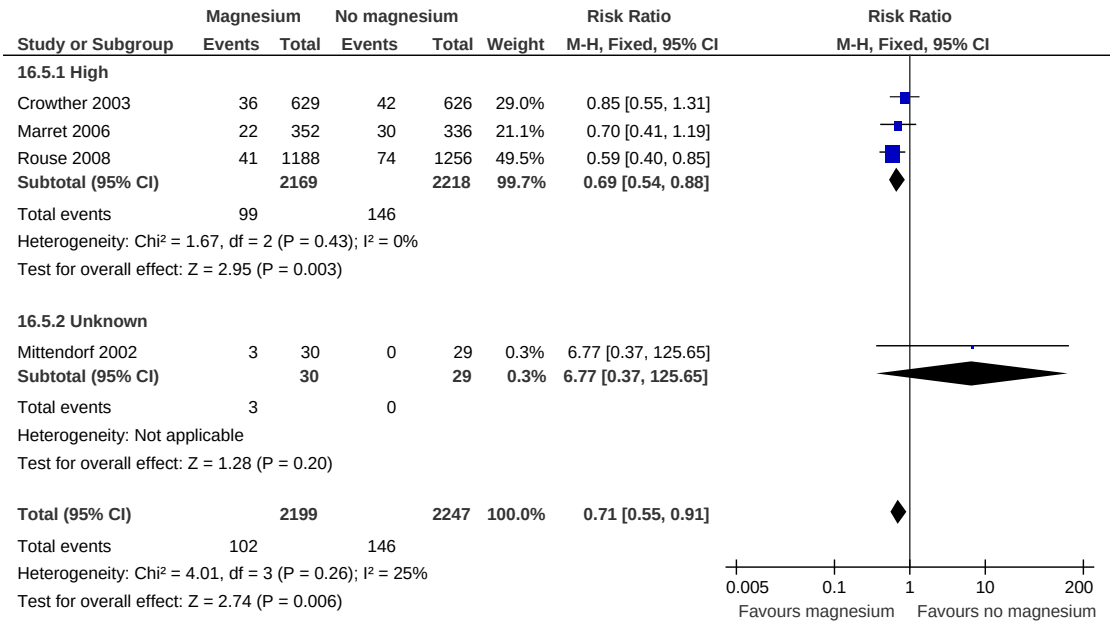
Appendix F 11: Evidence Table and Graphs: COMBINED EFFECT OF ANTENATAL CORTICOSTEROIDS

Study	High use of antenatal corticosteroids
Crowther 2003	yes
Rouse 2008	yes
Marret 2006	yes
Mittendorf 2002	unknown

DEATH

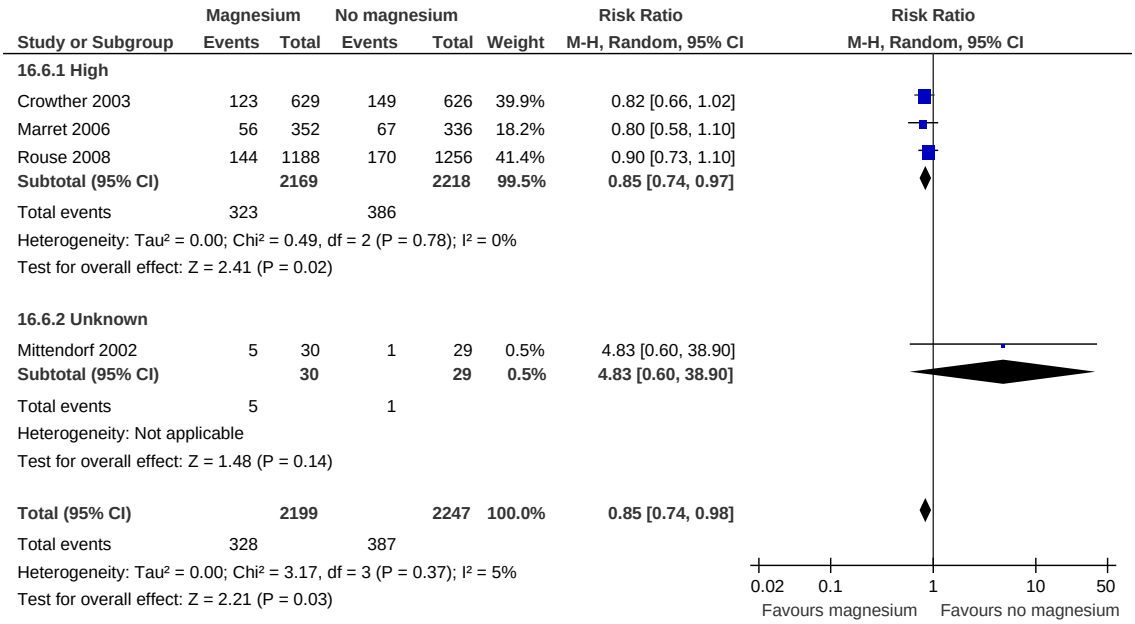


CEREBRAL PALSY



F 11: COMBINED EFFECT OF ANTENATAL CORTICOSTEROIDS

DEATH OR CEREBRAL PALSY



Appendix G: Harms – Maternal; and Fetus, Infant, and Child

Maternal Harms

Effect (95% CI)	No of trials	No of women	Trial references	Source
CESSATION OF MATERNAL THERAPY				
RR 3.12 (2.35 to 4.15)	**2**	**3,293**	**Crowther 2003; Rouse 2008**	**Doyle 2009 (CR)**
	181/1631 (11.1%) vs 59/1672 (3.5%)			
RR 1.59 (0.57 to 4.41)	4	310	Cotton 1984; Cox 1990; Fox 1993; Ma 1992;	Crowther 2002 (CR)
	8/151 (5.3%) vs 7/159 (4.4%)			
RR 2.69 (2.18 to 3.31)	**1**	**10,110**	**Magpie 2002**	**Magpie 2002**
	317/4999 (6.3%) vs 118/4993 (2.4%)			
Not reported in any trials				Crowther 1998 (CR)
HYPOTENSION				
RR 1.90 (1.11 to 3.26)	**1**	**9,992**	**Magpie 2002**	**Duley 2003 (CR)**
RR 1.51 (1.09 to 2.09)	**2**	**1,626**	**Crowther 2003; Marret 2006**	**Doyle 2009 (CR)**
RR 3.16 (0.13 to 76.30)	1	156	Cox 1990	Crowther 2002 (CR)
Overall RR 1.63 (1.23 to 2.15)	**119/5896 (2.0%) vs 72/5828 (1.2%)**			
Not reported in any trials				Crowther 1998 (CR)
RESPIRATORY DEPRESSION OR OTHER RESPIRATORY PROBLEM				
RR 1.98 (1.24 to 3.15)	**2**	**10,667**	**Magpie 2002; South Africa 1998**	**Duley 2003 (CR)**
RR 1.31 (0.83 to 2.07)	2	3,303	Crowther 2003; Rouse 2008	Doyle 2009 (CR)
Overall RR 1.62 (1.17 to 2.24)	**93/6975 (1.3%) vs 57/7005 (0.8%)**			
RESPIRATORY ARREST				
RR 1.02 (0.06 to 16.25)	4	5,411	Crowther 2003; Magpie 2006; Marret 2006; Rouse 2008	Doyle 2009 (CR)
RR 3.16 (0.13 to 76.30)	1	156	Cox 1990	Crowther 2002 (CR)
RR 2.50 (0.49 to 12.88)	1	10,110	Magpie 2002	Duley 2003 (CR)
TENDON REFLEXES (absent or reduced)				
RR 1.00 (0.70 to 1.42)	2	10,667	Magpie 2002; South Africa 1998	Duley 2003 (CR)
TACHYCARDIA				
RR 0.0 (0.0 to 0.0)	1	35	Cotton 1984	Crowther 2002 (CR)
RR 1.53 (1.03 to 2.29)	**1**	**1,062**	**Crowther 2003**	**Doyle 2009 (CR)**
RR 1.05 (0.15 to 7.21)	1	133	Rust 1996	Crowther 1998 (CR)
CARDIAC ARREST				
RR 0.34 (0.04 to 3.26)	4	5,411	Crowther 2003; Magpie 2006; Marret 2006; Rouse 2008	Doyle 2009 (CR)
RR 0.80 (0.21 to 2.98)	1	10,110	Magpie 2002	Duley 2003 (CR)
CAESAREAN				
RR 1.05 (1.01 to 1.10)	**6**	**10,108**	**Magpie 2002; South Africa 1994; South Africa 1998; Taiwan 1995; Memphis 1997; Tennessee 2001**	**Duley 2003 (CR)**
	2528/5082 (49.7%) vs 2370/5026 (47.2%)			
RR 1.07 (0.62 to 1.83)	3	281	Cotton 1984; Cox 1990; Fox 1993	Crowther 2002 (CR)
RR 1.00 (0.93 to 1.07)	3	2,323	Crowther 2003; Marret 2006; Rouse 2008	Doyle 2009 (CR)
MORTALITY				
RR 0.32 (0.01 to 7.92)	3	2,323	Crowther 2003; Marret 2006;	Doyle 2009 (CR)

			Rouse 2008	
RR 0.54 (0.26 to 1.10)	2	10,795	Magpie 2002; South Africa 1998	Duley 2003 (CR)
ADMISSION TO ICU				
RR 0.89 (0.54 to 1.47)	2	2,606	Crowther 2003; Magpie 2006 (part)	Doyle 2009 (CR)
HOSPITAL STAY (days)				
MD 0.17 (-0.18 to 0.53)	2	2,606	Crowther 2003; Magpie 2006 (part)	Doyle 2009 (CR)
POSTPARTUM HAEMORRHAGE				
RR 0.87 (0.67 to 1.12)	2	1,626	Crowther 2003; Marret 2006	Doyle 2009 (CR)
RR 0.96 (0.88 to 1.05)	2	8,909	Magpie 2002; Memphis 1997	Duley 2003 (CR)
ANY SIDE EFFECTS				
RR 1.88 (1.11 to 3.20)	**1**	**133**	**Rust 1996**	**Crowther 1998 (CR)**
RR 5.26 (4.59 to 6.03)	**1**	**9,992**	**Magpie 2002**	**Duley 2003 (CR)**
	1201/4999 (24.0%) vs 228/4993 (4.6%)			
FLUSHING				
RR 9.38 (7.74 to 11.37)	**2**	**10,127**	**Magpie 2002; Memphis 1997**	**Duley 2003 (CR)**
NAUSEA/VOMITING				
RR 8.88 (5.46 to 14.43)	**1**	**9,992**	**Magpie 2002**	**Duley 2003 (CR)**
RR 0.73 (0.30 to 1.81) nausea only	1	133	Rust 1996	Crowther 1998 (CR)
RR 0.42 (0.08 to 2.08) vomiting only	1	133	Rust 1996	Crowther 1998 (CR)
DIARRHOEA				
RR 7.67 (2.41 to 24.41)	**1**	**133**	**Rust 1996**	**Crowther 1998 CR)**
ABDOMINAL PAIN				
RR 0.0 (0.0 to 0.0)	0	0	0	Crowther 1998 (CR)
CHEST PAIN				
RR 0.0 (0.0 to 0.0)	0	0	0	Crowther 1998 (CR)
STROKE				
RR 0.50 (0.13 to 2.00)	1	10,110	Magpie 2002	Duley 2003 (CR)
GIVEN CALCIUM GLUCONATE				
RR 1.35 (0.63 to 2.88)	2	10,795	Magpie 2002; South Africa 1998	Duley 2003 (CR)
SLURRED SPEECH				
RR 3.04 (0.13 to 73.42)	1	135	Memphis 1997	Duley 2003 (CR)
MUSCLE WEAKNESS				
RR 11.99 (5.22 to 27.54)	**1**	**9,992**	**Magpie 2002**	**Duley 2003 (CR)**
DIZZINESS				
RR 3.70 (1.84 to 7.42)	**1**	**9,992**	**Magpie 2002**	**Duley 2003 (CR)**
DROWSINESS/CONFUSION				
RR 2.22 (1.01 to 4.87)	**1**	**9,992**	**Magpie 2002**	**Duley 2003 (CR)**
HEADACHE				
RR 2.12 (1.19 to 3.76)	**1**	**9,992**	**Magpie 2002**	**Duley 2003 (CR)**
PROBLEM AT INJECTION SITE (INTRAMUSCULAR OR INTRAVENOUS)				
RR 1.78 (1.52 to 2.08)	**1**	**9,992**	**Magpie 2002**	**Duley 2003 (CR)**
INDUCTION OF LABOUR				
RR 0.99 (0.94 to 1.04)	1	8,774	Magpie 2002	Duley 2003 (CR)
BLOOD TRANSFUSION				
RR 0.91 (0.77 to 1.09)	1	8,774	Magpie 2002	Duley 2003 (CR)

RR = risk ratio: MD = mean difference

Fetus, Infant and Child

Effect (95% CI)	No of trials	No of women /infants	Trial references	Source
FETAL DEATHS				
RR 5.70 (0.28 to 116.87)	3	277	Cotton 1984; Cox 1990; Fox 1993	Crowther 2002 (CR)
RR 0.78 (0.42 to 1.46)	4	4,446	Crowther 2003; Marret 2006 Mittendorf 2002 (neuroprotective); Rouse 2008	Doyle 2009 (CR)
RR 0.99 (0.87 to 1.12)	3	9,961	Magpie 2002; South Africa 1998 South Africa 1994	Duley 2003 (CR)
NEONATAL AND INFANT DEATHS				
RR 1.16 (0.94 to 1.42)	1	9,270	Magpie 2002	Duley 2003 (CR)
TOTAL DEATHS (FETAL, NEONATAL AND INFANT)				
RR 1.74 (0.63 to 4.77)	3	292	Cotton 1984; Cox 1990; Fox 1993	Crowther 2002 (CR)
RR 0.95 (0.80 to 1.12)	4	4,446	Crowther 2003; Marret 2006; Mittendorf 2002; Rouse 2008	Doyle 2009 (CR)
RR 5.00 (0.25 to 99.16)	1	50	Ricci 1991	Crowther 1998 (CR)
ASSISTED VENTILATION				
RR 1.17 (0.61 to 2.24)	1	165	Cox 1990	Crowther 2002 (CR)
NECROTISING ENTEROCOLITIS (NEC)				
RR 1.19 (0.33 to 4.29)	3	289	Cotton 1984; Cox 1990; Fox 1993	Crowther 2002 (CR)
ADMISSION TO NEONATAL ICU/SCN				
RR 0.49 (0.18 to 1.32)	1	165	Cox 1990	Crowther 2002 (CR)
RR 1.57 (0.76 to 3.24)	1	133	Rust 1996	Crowther 1998 (CR)
RR 1.01 (0.96 to 1.06)	1	8,260	Magpie 2002	Duley 2003 (CR)
APGAR SCORE <7 at 5 MINUTES				
RR 1.03 (0.90 to 1.18)	3	4,387	Crowther 2003 Marret 2006 Rouse 2008	Doyle 2009 (CR)
RR 1.02 (0.85 to 1.22)	1	8,260	Magpie 2002	Duley 2003 (CR)
NEONATAL CONVULSIONS				
RR 0.80 (0.56 to 1.13)	3	4,387	Crowther 2003 Marret 2006 Rouse 2008	Doyle 2009 (CR)
NEONATAL HYPOTONIA				
RR 1.02 (0.77 to 1.36)	1	2,444	Rouse 2008	Doyle 2009 (CR)
CHRONIC LUNG DISEASE (oxygen at 36 days)				
RR 1.12 (0.95 to 1.32)	2	1,943	Crowther 2003 Marret 2006	Doyle 2009 (CR)
CHRONIC LUNG DISEASE (oxygen at 28 days)				
RR 1.07 (0.94 to 1.22)	1	1,255	Crowther 2003	Doyle 2009 (CR)
INTRAVENTRICULAR HAEMORRHAGE TOTAL				
RR 0.86 (0.28 to 2.62)	3	289	Cotton 1984 Cox 1990 Fox 1993	Crowther 2002 (CR)
RR 3.00 (0.13 to 70.30)	1	50	Ricci 1991	Crowther 1998 (CR)
RR 0.96 (0.86 to 1.08)	4	4,552	Crowther 2003 Marret 2006 Mittendorf 2002 Rouse 2008	Doyle 2009 (CR)
INTRAVENTRICULAR HAEMORRHAGE (SEVERE GRADES 3 & 4)				

RR 0.0	1	90	Fox 1993	Crowther 2002 (CR)
RR 0.83 (0.62 to 1.13)	2	3699	Crowther 2003 Rouse 2008	Doyle 2009 (CR)
INTRAVENTRICULAR HAEMORRAGE (SEVERE GRADES 3 & 4) OR PVL				
RR 0.0	1	90	Fox 1993	Crowther 2002 (CR)
PERIVENTRICULAR LEUKOMALACIA				
RR 0.0	1	90	Fox 1993	Crowther 2002 (CR)
RR 0.93 (0.68 to 1.28)	4	4,552	Crowther 2003 Marret 2006 Mittendorf 2002 Rouse 2008	Doyle 2009 (CR)
NEONATAL LENGTH OF STAY				
MD 1.18 (-0.46 to 2.82) days	2	180	Ricci 1991 Rust 1996	Crowther 1998 (CR)
RR 1.02 (0.93 to 1.11) (> 7 days)	1	8,260	Magpie 2002	Duley 2003 (CR)

Appendix H: Additional Information about Regimens and Monitoring for giving Magnesium Sulphate to Prevent Eclampsia from Clinical Practice Guidelines and Management Protocols

Condition

The Society of Obstetric Medicine of Australia and New Zealand (SOMANZ) recommend magnesium sulphate as the drug of choice for prophylaxis against eclampsia for women with preeclampsia. The World Health Organization (WHO), Royal College of Obstetricians and Gynaecologists (RCOG) and Society of Obstetricians and Gynaecologists of Canada (SOGC) give more cautious recommendations, indicating that treatment with magnesium sulphate is recommended in severe pre-eclampsia. SOGC qualifies this by indicating that magnesium sulphate may be given for women with non-severe preeclampsia. SOGC does not give any guidelines on recommended dosage regimens. RCOG indicates that in cases of less severe disease the decision is less clear and will depend on an individual case assessment. The New South Wales Department of Health is more conservative indicating it is appropriate for use for seizure prophylaxis in a woman who has already had an eclamptic seizure and indicates that the efficacy is less certain for use as a seizure prophylaxis in a woman with severe pre-eclampsia who is at risk of eclampsia (Table H1).

Loading Dose

A loading dose of 4 g of magnesium sulphate is recommended by all those guidelines that specified doses. Administration recommendations for the loading dose vary when administered by infusion pumps, with both the volume and time of administration differing. However, the syringe pump administration recommendations are similar. RCOG and SOMANZ do not give any recommendation for the administration of the loading dose in either the infusion or syringe pump. SOMANZ indicate that it is appropriate that obstetric units determine their own protocols. The Royal Women's Hospital (Victoria) guidelines do not give any recommendation for the administration of the loading dose by infusion pump (Table H2).

Maintenance dose

Most of the guidelines consulted who specified doses recommend 1 g of magnesium sulphate per hour as a maintenance dose. SOMANZ is the exception with 1-2 g of magnesium sulphate per hour recommended as a maintenance dose. All guidelines who specified doses recommend a maintenance period of 24 hrs either after birth and/or 24 hrs after last seizure. RCOG and SOMANZ do not give any recommendation for the administration of the maintenance dose in either the infusion or syringe pump. SOMANZ indicate that it is appropriate that obstetric units determine their own protocols. In addition, the South Australian guidelines recommend a total daily dose not exceeding 30-40 g of magnesium sulphate (Table H3).

Monitoring

SOMANZ recommend monitoring of serum levels of magnesium sulphate, however they indicate that it is appropriate that obstetric units determine their own protocols for monitoring outcomes. RCOG recommend 'regular assessment' but give no indication of timing. The Royal Women's Hospital (Victoria) guidelines recommend monitoring for 4 hrs following the discontinuation of the magnesium infusion (Tables H4 and H5).

Table H.1: Magnesium sulphate recommendation for condition

Guidelines	Condition
NSW	Seizure prophylaxis in a woman with severe pre-eclampsia who is at risk of eclampsia (although efficacy for this is less certain). Seizure prophylaxis in a woman who has already had an eclamptic seizure.
The Royal Women's Hosp, VIC	Women with preeclampsia for whom there concern about the risk of eclampsia. Management of an eclamptic seizure.
SA	Pre-eclampsia to prevent eclampsia (prophylaxis). For eclamptic seizures.
RCOG	Consider for severe pre-eclampsia where there is concern about risk of eclampsia. Women with less severe pre-eclampsia, the decision to use $MgSO_4$ is less clear and depends on the individual case. Eclampsia for seizures.
SOMANZ	Preeclampsia (prevention of eclampsia). For eclamptic seizures.
WHO	To prevent seizure in a woman with severe pre-eclampsia. Prevention and treatment of eclampsia.
SOGC	Eclampsia. Women with severe pre-eclampsia to prevent eclampsia (prophylaxis). Consider for women with non-severe pre-eclampsia.

Table H.2 Recommended intravenous (IV) loading dose of magnesium sulphate for treating pre-eclampsia and eclampsia

Guidelines	Condition (see Table H.1 for details)	Dosage in Grams (g)	Infusion by infusion pump			Infusion by syringe pump			Other
			Volume	*$MgSO_4$ Solution concentration*	*Time*	*Volume*	*$MgSO_4$ Solution concentration*	*Time*	
NSW	Pre-eclampsia/ Eclampsia	4 g	108 mL	add 8 mL of 50% soln to 100 mL saline	20-30 min	8 mL	9 mL of 50% soln, prime line with 1 mL	15 min	
The Royal Women's Hosp, VIC	Pre-eclampsia	4 g				8 mL	50% soln	15 min	
	Eclampsia	4 g				8 mL	50% soln	5 min to 10 min	
SA	Pre-eclampsia	4 g	20 mL	40 mL 50% soln in 60 mL saline	20 min	8 mL	50% soln	20 min	
	Eclampsia	4 g	20 mL	40 mL 50% soln in 60 mL saline	10 min	8 mL	50% soln	10 min	
RCOG	Eclampsia	4 g			5-10 min				IV by infusion pump
SOMANZ	Eclampsia	4 g			10-15 min				IV infusion (no details of type)
WHO	Pre-eclampsia/ Eclampsia	4 g							IV infusion (20% solution) over 5 min

If blank then this indicates no information for this variable

If separate regimens were given for the different conditions then these are stated, if not stated separately, only one regimen was given for both conditions.

soln=solution

SCOG gives no recommendations on volume or concentration

Table H.3 Recommended intravenous (IV)* maintenance dose of magnesium sulphate for the treatment of pre-eclampsia and eclampsia

Guideline	Condition (see Table H.1 for details)	Dosage in grams (g)	Timing	Infusion by infusion pump		Infusion by syringe pump		Other	Time period for continuing maintenance dose
				Volume Per hour	*$MgSO_4$ Solution concentration*	*Volume Per hour*	*$MgSO_4$ Solution concentration*		
NSW	Pre-eclampsia / Eclampsia	1 g	per hour	40 mL	add 20 mL of $MgSO_4$ 50% soln to 380 mL saline	2 mL	50 mL of 50% soln, prime line with 1 mL		At least 24 hrs
The Royal Women's Hosp, VIC	Pre-eclampsia / Eclampsia	1 g	per hour			2 mL	50 mL of 50% soln		At least 24 hrs after birth
SA	Pre-eclampsia / Eclampsia	1 g	per hour	5 mL	20% soln (40 mL 50% soln in 60 mL saline)	2 mL	50% soln		For 24 hrs after last seizure and 24 hr after birth
RCOG	Eclampsia	1 g	per hour						Later of 24 hrs after last seizure or 24 hrs after birth Unless clinical reason for continuing
SOMANZ	Eclampsia	1-2 g	per hour					IV infusion (no details of type)	For 24 hrs after last seizure

SCOG gives no recommendations on volume or concentration

*WHO recommends intramuscular maintenance

If blank then this indicates no information for this variable

Table H.4 Recommended prenatal maternal monitoring during loading dose (if separately documented): indications for stopping treatment and time interval between monitoring with magnesium sulphate for pre-eclampsia and eclampsia

Guideline	Maternal blood Pressure	Respiratory Rate	Pulse	Urine output	Patellar reflexes	Serum $MgSO_4$	Serum Creatinine	Other
NSW					Check after completion of loading dose			Close observation and assessment required for duration of infusion.
The Royal Women's Hosp, VIC	5min (x4 readings)		5min (x4 readings)		Check after completion of loading dose			Observe for development of side effects

SOGC, WHO, SOMANZ, RCOG and SA do not give any separate recommendations for maternal monitoring during treatment

Table H.5 Recommended prenatal maternal monitoring during maintenance dosage: time interval between monitoring and indications for review or stopping treatment with magnesium sulphate for pre-eclampsia and eclampsia

Guideline	Maternal blood Pressure	Respiratory Rate	Pulse	Urine output	Serum creatinine	Patellar reflexes	Serum $MgSO_4$	Other
NSW	1-2 hr	1-2 hr, stop if <10 breaths per min	1-2 hr	1-2 hr, Stop if <30 mL for 3 consecutive hrs		2 hrs, Stop if absent	At 1 hr after commencing infusion then as clinically indicated	Where woman's condition is unstable increase frequency of observation
The Royal Women's Hosp, VIC	0.5 hr	0.5 hr should be ≥16 per min, review if <12 per min	0.5 hr	1 hr urine, 4 hrs urinary protein Review if <100 mL urine in 4 hrs		1 hr, Review if absent	6 hrs or Request if any of respiratory, urine or reflexes are under review or further seizures or renal impairment.	2 hr temperature **ECG monitoring and anaesthetist aware of woman's medical condition
SA	1hr	1 hr, stop if <10-12 breaths per min		insert indwelling catheter and monitor 1hrly, if <100 ml over 4 hrs check serum $MgSO_4$	6 hrs, if >100mmol/L check serum $MgSO_4$	Minimum 4 hourly, stop if absent	Test 6 hrly if serum creatinine >100 mmol/L or urine <100 mL over 4 hrs	1hr Pulse SpO2 oximeter **ECG monitoring and anaesthetist on site
SOMANZ	YES	YES		YES		YES	YES	Oxygen saturation
RCOG		If respiratory rate depression (no details) give calcium gluconate 1 g over 10 min		Stop if <20 mL/hr		Stop if absent	"Magnesium toxicity is unlikely with these regimens and levels do not need to be routinely measured"	
WHO		Stop or delay if <16 per min		Stop or delay if output is less than 30 mL per hr over preceding 4 hrs		Stop or delay if absent		

**** for eclamptic seizures only**

Table H.6 Antidote for magnesium sulphate toxicity

Guidelines	Antidote
NSW	Calcium chloride or calcium gluconate (10 mL of 10% solution) by slow intravenous injection over 3 minutes.
The Royal Women's Hosp, VIC	Calcium gluconate (10 mL of 10% solution over 10 minutes) by slow intravenous injection. The patient requires ECG monitoring during and after administration because of the potential for cardiac arrhythmias. Resuscitation and ventilator support should be available during and after administration of both magnesium sulphate and calcium gluconate.
SA	Call for medical assistance, administer oxygen at 8-12 litres, stop infusion, monitor vital signs. Administer Calcium gluconate (10% solution), 10 mL, slowly, IV check electrolytes, creatinine, magnesium sulphate concentrations.
RCOG	Calcium gluconate 1 g (10 mL) over 10min can be given if concern over respiratory depression.
WHO	Give calcium gluconate 1 g (10 mL of 10% soln) IV slowly over 10 min until respirations satisfactory. Assist ventilation using mask and bag, anaesthetic apparatus or intubation.

SOMANZ and SOGC do not give recommendations of antidote

Table H.7 Details of magnesium sulphate concentrations and effects (taken from The Royal Women's Hospital, VIC guidelines)

Magnesium sulphate concentrations (mmol/L)	Effects
0.8-1.0	Normal plasma concentrations
1.7-3.5	**Therapeutic range**
2.5-5.0	ECG changes (P-Q interval prolongation, widen QRS complex)
4.0-5.0	Reduction in deep tendon reflexes
>5.0	Loss of deep tendon reflexes
>7.5	Sinoatrial and atrioventricular blockade. Respiratory paralysis and CNS depression
>12	Cardiac arrest

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Education material for teachers of midwifery. Midwifery education modules -2nd edition. Managing eclampsia. World Health Organization (WHO).

Maternity care in South Australia. Perinatal practice guidelines. Section 6 chapter 96. Magnesium sulphate infusion regimen. 26th Oct 2009.

Recommended loading dose of magnesium sulphate from trials

Trial	Arm of trial	Dosage in Grams (g)	Infusion				Other details
			Volume	$MgSO_4$ solution concentration	time	type	
Rouse 2008		6 g			20-30 min	IV infusion	
Crowther 2003		4 g	8 mL	16 mmol of 0.5% $MgSO_4$ soln	20 min	IV infusion	
Marret 2006		4 g	40 mL	0.1g/mL $MgSO_4$ soln	30 min	IV infusion	Single dose
Mittendorf 2002	Tocolytic	4 g				IV infusion	
	Neuroprotective	4 g					Single dose

If blank then this indicates no information for this variable

Recommended maintenance dose of magnesium sulphate from trials

Trial	Arm of trial	Dosage in Grams (g)	Infusion				Other details
			Volume	$MgSO_4$ solution concentration	time	type	
Rouse 2008		2 g			Per hr	IV infusion	
Crowther 2003		1 g	2 mL	0.5% $MgSO_4$ soln	Per hr	IV infusion	
Marret 2006							No maintenance dose given
Mittendorf 2002	Tocolytic	2-3 g			Per hr	IV infusion	
	Neuroprotective						No maintenance dose given

If blank then this indicates no information for this variable

Recommended prenatal maternal monitoring during magnesium sulphate dosage for fetal, infant and child neuroprotection

Trial	Monitoring	Cease treatment
Rouse 2008	No details	Discontinue if birth had not occurred after 12 hrs and no longer considered imminent
Crowther 2003	Pulse rate, blood pressure, respiratory rate monitored throughout infusion and any maternal adverse events recorded	Stop if respiratory rate decreases more than 4/min below baseline, diastolic blood pressure decreases more than 15mmHg below baseline
Marret 2006	Pulse rate, blood pressure, respiratory rate, tendon reflex and any maternal adverse effects recorded throughout infusion	Stopped at anaesthetist discretion
Mittendorf 2002	Pulse rate, blood pressure/respiratory rate monitored throughout infusion and maternal side effects recorded	Stop if respiratory rate drops below 16/min or if blood pressure drops more than 15mm Hg below baseline

Appendix I: Public consultation comments and Panel responses

	Comment Received	Response/Justification
1	**Patient information sheets** Information sheets and/or leaflets be designed and provided which will provide clear and comprehensive information and explanation of the treatment and range of side effects so that women are able to make an informed decision.	Information sheets relevant for consumers will be prepared and disseminated after the main guideline documents have been finalised.
2	**Information and education for midwives.** A comprehensive strategy be considered to ensure that midwives can access information and education regarding the administration of magnesium sulphate during the antenatal period for women at high risk of pre term labour.	The clinical practice guidelines provide guidance on administration of magnesium sulphate during the antenatal period and will be readily available for use by midwives in their practice. In addition we expect that individual centres will already have individual obstetric unit protocols or develop more detailed local protocols based on the Guidelines.
3	**Patient care during administration of magnesium sulphate.** During administration of magnesium sulphate the woman should receive one on one midwifery care in the birthing suite of a facility (not in an antenatal or postnatal ward).	When magnesium sulphate is administered the recommended monitoring under good practice points should be available. We expect that each maternity health facility will have their own protocols regarding models of care.
4	**Audit and follow up.** Long term audit and follow up of the women and babies who have received magnesium sulphate prior to 30 weeks' gestation to ensure benefit.	Agree. The Guidelines recommend an audit process (page 14).
5	**Further research.** Further research is prioritised to studying the impact for women of administration of magnesium sulphate.	Agree. The priority research recommendations are given within the guidelines (page 14) and these focus on outcomes for women and their babies.
6	**Monitoring recommendations.** Minimum standards of observations to include: a. monitoring of oxygen saturation;	a. The Panel consider that monitoring oxygen saturation is not required as a minimum standard – respiratory rate is reduced by magnesium sulphate serum concentrations above the therapeutic range and therefore is an appropriate minimum observation for respiratory depression. Recording respiratory rate has been a standard monitoring requirement for using magnesium sulphate for

	b. reflexes prior to loading dose to gain baseline reflex responses; c. temperature; and d. continuous fetal heart monitoring	pre-eclampsia. b. This has been added to baseline assessment within the Guidelines. c. The flushing experienced by women with a magnesium sulphate infusion is not related to a temperature rise. Routine temperature monitoring is therefore not required. d. The method and frequency of monitoring the fetal heart should be determined by the underlying clinical condition of the woman and her fetus.
7	**Gestation at which magnesium sulphate is administered.** Evidence supports a likely benefit in the large group of infants born between 30.0 and 33.6 weeks' gestation. We would consider 32 weeks' gestation as a compromise position.	The Panel decided that current evidence to support this wider interpretation is not strong enough for National Clinical Guidelines therefore the recommendations are not open to all gestational ages at this point in time. Further research of higher gestational ages through RCTs and individual patient data (IPD) meta-analysis is needed and in planning stages.
8	**Timing of magnesium sulphate administration.** The clinical recommendation and relevant good practices points should be combined to achieve greater clarity and consistency.	The clinical recommendation and good practice points each deal with a different clinical scenario; time to give magnesium sulphate prior to planned birth time; severe fetal and maternal compromise; and birth expected within 4 hours. The Panel considered that the clinical recommendation should stand alone and be supported by separate good practice points.
9	**Loading dose regimen for magnesium sulphate.** Clinical recommendation is confusing.	The Panel consider that a statement about no immediate repeat doses is important and appropriate to include within the clinical recommendation.
10	**Repeat magnesium sulphate at a later gestation if birth does not occur when magnesium sulphate first administered.** Giving discretion to the 'attending health professional'.	As evidence about need for repeat doses is presently unclear no firm recommendation can be given. The decision needs to be at the discretion of the attending health professional.
11	**Nifedipine administration.** The interaction between magnesium sulphate and nifedipine in relation to hypotension.	We have included additional information about hypotension in monitoring under good practice points.