ANTENATAL CORTICOSTEROIDS GIVEN TO WOMEN PRIOR TO BIRTH TO IMPROVE FETAL, INFANT, CHILD AND ADULT HEALTH

NEW ZEALAND AND AUSTRALIAN CLINICAL PRACTICE GUIDELINES 2015

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Disclaimer

These guidelines are a general guide to appropriate practice to be used subject to the health practitioners clinical judgement and the individual womans' 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.

Endorsement:

Endorsement for these Clinical Practice Guidelines has been received from The Perinatal Society of Australia and New Zealand, The Perinatal Society of Australia and New Zealand – Consumer Group, New Zealand College of Midwives, Neonatal Nurses College of Aotearoa, Australian College of Neonatal Nurses and The Royal Australasian College of Physicians.

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Summary of clinical recommendations

Use of a single course of antenatal corticosteroids for women at risk of preterm birth

Clinical recommendation	Strength of recommendation		Chapter
	NHMRC	GRADE	
In a woman at risk of early preterm,* imminent# birth use a single course of antenatal corticosteroids.$	A	STRONG	3 to 5
*when gestational age is 34 weeks' and 6 days or less.	Practice point		12
#when preterm birth is planned or expected within the next seven days, even if birth is likely within 24 hours.	A	STRONG	11
$regardless of the reason the woman is considered at risk of preterm birth.%	Practice point		14
The optimal time to administer antenatal corticosteroids is when preterm birth is planned or expected within the next 48 hours.	Practice Point		11
Where appropriate, estimate the risk of preterm birth by considering the use of adjunct prediction tests including fetal fibronectin and assessment of cervical length.	Practice point		14.11 and 14.12
Where appropriate, monitor for signs of puerperal sepsis when antenatal corticosteroids have been given.	Practice point		14
As corticosteroid use: **Either:** Betamethasone 24 mg in divided doses, completed between 12 and 36 hours.	A	STRONG	10
*Administer Celestone® Chronodose®,** as two intramuscular doses of 11.4 mg, 24 hours apart.*	Practice point		9 to 10
Or: Dexamethasone 24 mg in divided doses completed between 24 and 40 hours.	A	STRONG	10
Administer dexamethasone phosphate## intramuscularly, in four doses of 6 mg, 12 hours apart.	Practice point		9 to 10

% history of previous preterm birth with additional risk factor(s) for preterm birth; preterm labour; preterm prelabour repture of membranes; chorioamnionitis; antepartum haemorrhage; multiple pregnancy (twins and higher order) with additional risk factor(s)for preterm birth; diabetes mellitus or gestational diabetes; systemic infection; pregnancy associated hypertension or pre-eclampsia; intrauterine growth restriction / fetal compromise; ultrasound evidence of cervical shortening/funnelling; positive results of fetal fibronectin test; medically indicated preterm birth.

** Celestone® Chronodose® Injection, available in New Zealand and Australia, is a sterile aqueous suspension containing betamethasone sodium phosphate and betamethasone acetate. A single dose provided in 2 mL of Celestone Chronodose Injection contains betamethasone 11.4 mg, as betamethasone sodium phosphate 7.8 mg (in solution) and betamethasone acetate 6 mg (in suspension) in an aqueous vehicle containing sodium phosphate, sodium phosphate monobasic, disodium edetate, benzalkonium chloride and water for injection.

##Dexamethasone phosphate is available as a 4 mg/mL injection which contains 4.37 mg dexamethasone sodium phosphate, in addition propylene glycol, disodium edetate, sodium hydroxide and water for injection. The preparation in New Zealand is Dexamethasone-Hameln and in Australia is Dexamethasone Sodium Phosphate - Hospira Australia Pty Ltd.

Use of repeat antenatal corticosteroids for women at risk of preterm birth

Clinical recommendation	Strength of recommendation		Chapter
	NHMRC	GRADE	
Use repeat antenatal corticosteroids in women at risk of early preterm,[*] imminent[#] birth following a single course of antenatal corticosteroids.[^$]	A	STRONG	6 to 8
[*]when gestational age is 32 weeks' and 6 days or less.	Practice point		12
[#] when preterm birth is planned or expected within the next seven days, even if birth is likely within 24 hours.	A	STRONG	11
[^]not less than seven days following a single course of antenatal corticosteroids.	A	STRONG	11
[$]regardless of the reason the woman is considered at risk of preterm birth.[%]	Practice point		14
The clinical decision to use a repeat dose should be based on an assessment of ongoing risk for preterm birth.	Practice point		10
Where appropriate, estimate the risk of preterm birth by considering the use of adjunct prediction tests including fetal fibronectin and assessment of cervical length.	Practice point		14.11 and 14.12
Where appropriate, monitor for signs of puerperal sepsis when antenatal corticosteroids have been given.	Practice point		14
As repeat antenatal corticosteroid use: **Either: A single repeat dose** of 12 mg betamethasone.	A	STRONG	10 and 11
Administer Celestone® Chronodose®[**] 11.4 mg, intramuscularly as one dose.	Practice point		10
After this dose, if the woman has not given birth seven or more days and less than 14 days from administration of a previous repeat dose and is still considered to be at risk of preterm birth within the next seven days a further, single, repeat dose of Celestone® Chronodose®[**] 11.4 mg can be administered.	A	STRONG	10
Use up to a maximum of three, single, repeat doses only.	Practice point		10
Or: A single repeat course of 24 mg betamethasone in divided doses completed within 24 hours. Do not give any further repeat courses.	A A	STRONG STRONG	10 and 11 10 and 11
Administer Celestone® Chronodose®[**] 11.4 mg, as two intramuscular doses, 24 hours apart.	Practice point		10
If betamethasone is not available use dexamethasone.	Practice point		9

[%] history of previous preterm birth with additional risk factor(s) for preterm birth; preterm labour; preterm prelabour repture of membranes; chorioamnionitis; antepartum haemorrhage; multiple pregnancy (twins and higher order) with additional risk factor(s)for preterm birth; diabetes mellitus or gestational diabetes; systemic infection; pregnancy associated hypertension or pre-eclampsia; intrauterine growth restriction / fetal compromise; ultrasound evidence of cervical shortening/funnelling; positive results of fetal fibronectin test; medically indicated preterm birth.

** Celestone® Chronodose® Injection (the only currently registered product in New Zealand) is a sterile aqueous suspension containing betamethasone sodium phosphate and betamethasone acetate. A single dose provided in 2 mL of Celestone Chronodose Injection contains betamethasone 11.4 mg, as betamethasone sodium phosphate 7.8 mg (in solution) and betamethasone acetate 6 mg (in suspension) in an aqueous vehicle containing sodium phosphate, sodium phosphate monobasic, disodium edetate, benzalkonium chloride and water for injection.

##Dexamethasone phosphate is available as a 4 mg/mL injection which contains 4.37 mg dexamethasone sodium phosphate, in addition propylene glycol, disodium edetate, sodium hydroxide and water for injection. The preparation in New Zealand is Dexamethasone-Hameln and in Australia is Dexamethasone Sodium Phosphate - Hospira Australia Pty Ltd.

Use of antenatal corticosteroids for fetal lung maturation prior to elective caesarean section at term

Clinical recommendations	Strength of recommendation		Chapter
	NHMRC	GRADE	
For elective caesarean section at term, where possible, plan at ≥39 weeks' gestation.	Practice point		13
Use antenatal corticosteroids 48 hours prior to caesarean birth planned beyond 34 weeks' and 6 days gestation if there is known fetal lung immaturity.	Practice point		13

Use of antenatal corticosteroids for fetal lung maturation given to women with diabetes in pregnancy or gestational diabetes:

At risk of preterm birth

Clinical recommendations	Strength of recommendation		Chapter
	NHMRC	GRADE	
Use a single course of antenatal corticosteroids for women with diabetes in pregnancy or gestational diabetes at risk of preterm birth	Practice point		14.7
Repeat antenatal corticosteroids for a woman with diabetes in pregnancy or gestational diabetes at risk of preterm birth.	Practice point		14.7
Where appropriate, monitor women with diabetes in pregnancy or gestational diabetes at risk of preterm birth for signs of puerperal sepsis when antenatal corticosteroids have been given.	Practice point		14.7
Women with diabetes in pregnancy or gestational diabetes at risk of preterm birth and receiving antenatal corticosteroids will require blood glucose monitoring and management of any hyperglycaemia.	Practice Point		14.7
Where appropriate, estimate the risk of preterm birth by considering the use of adjunct prediction tests including fetal fibronectin and assessment of cervical length.	Practice Point		14.7

At term

Clinical recommendations	Strength of recommendation		Chapter
	NHMRC	GRADE	
There is insufficient evidence currently to make a recommendation for the use of antenatal corticosteroids at term (≥37 weeks' gestation) for women with diabetes in pregnancy.	Practice point		15
Use antenatal corticosteroids 48 hours prior to caesarean birth planned beyond 34 weeks' and 6 days gestation in women with diabetes in pregnancy or with gestational diabetes if there is known fetal lung immaturity.	Practice point		15
If antenatal corticosteroids are used, monitor maternal blood glucose concentrations and treat if elevated.	Practice point		15

Use of antenatal corticosteroids in women with a multiple pregnanacy (twins and higher order)

With additional risk factor(s) for preterm birth

Clinical recommendations	Strength of recommendation		Chapter
	NHMRC	GRADE	
Use a single course of antenatal corticosteroids for women with a multiple pregnancy at risk of preterm birth.	Practice point		14.6
Repeat antenatal corticosteroids for a woman with a multiple pregnancy at risk of preterm birth.	Practice point		14.6
Where appropriate, estimate the risk of preterm birth by considering the use of adjunct prediction tests including fetal fibronectin and assessment of cervical length.	Practice point		14.6
Where appropriate, monitor women with a multiple pregnancy at risk of preterm birth for signs of puerperal sepsis when antenatal corticosteroids have been given.	Practice point		14.6

With no additional risk factor(s) for preterm birth (prophylactic)

Clinical recommendations	Strength of recommendation		Chapter
	NHMRC	GRADE	
Do not use a single course of antenatal corticosteroids in women with a multiple pregnancy where there is no other identified risk of preterm birth.	Practice point		14.6
Do not use repeat antenatal corticosteroids in women with a multiple pregnancy where there is no other identified risk of preterm birth.	Practice point		14.6

Summary of research recommendations

Use of a single course of antenatal corticosteroids for women at risk of preterm birth.

Research recommendations:	Chapter(s)
There is a need to better assess the impact, if any, of *in utero* exposure to a single course of antenatal corticosteroids on: • the hypothalamic-pituitary adrenal axis of the infant, child and adult; • the glucose-insulin axis in childhood; • the later risk of the infant developing diabetes in adulthood.	**3 to 5**
Future research that investigates the use of a single course of antenatal corticosteroids should include • outcomes on maternal quality of life; • report on the risk factors for preterm birth of the included participants; • an assessment of the degree and health impact, if any, of changes in maternal blood glucose control.	**3 to 5** **14**
Randomised trials are needed to: • compare betamethasone and dexamethasone to assess the effect on the short term and long term outcomes for the infant; • investigate the optimal timing for antenatal corticosteroids where preterm birth is planned (e.g. maternal medical indications or fetal compromise) and women can be randomised to administration of antenatal corticosteroids at different time intervals prior to birth; • investigate the neonatal benefits of antenatal corticosteroids administered to women at less than 24 weeks' gestation; • investigate if smaller doses are needed at lower gestational ages; • investigate the neonatal benefits of antenatal corticosteroids administered late preterm (34 weeks' and 6 days to <37 weeks' gestation); • review the effect of a single course of antenatal corticosteroids on women with systemic infection at risk of preterm birth; • evaluate the use of antenatal corticosteroids in settings where a single course of prophylactic antenatal corticosteroids is being used for women with a multiple pregnancy and no other identified risk of preterm birth.	**9** **11** **12** **12** **12** **14** **14**
To maximise benefit and minimise harm to the mother and infant there is a need to establish: • the minimally effective dose per course of both betamethasone and dexamethasone; • the optimal timing interval per course between doses for both betamethasone and dexamethasone; • the optimal number of doses per course for betamethasone; • the optimal number of doses per course for dexamethasone. • establish the haemodynamic effects of antenatal corticosteroids on the growth restricted fetus. • establish the optimal timing of birth following administration of antenatal corticosteroids to women with a fetus with intrauterine growth restriction.	**10** **14**

Repeat antenatal corticosteroids for women at risk of preterm birth

Research recommendations:	Chapter(s)
There is a need to better assess the impact, if any, of *in utero* exposure to repeat antenatal corticosteroids on: Physiological outcomes: • the glucose-insulin axis in childhood, • hypothalamic-pituitary adrenal axis, • bone mass, • body size and body composition, • neurosensory impairments, • respiratory function. Health outcomes: • cardiovascular disease, • metabolic disease, • diabetes, • psychological health, • the later risk of developing diabetes in adulthood. Social outcomes: • educational attainment, • behaviour, • cognitive ability.	**6 to 8**
Any future research to investigate the effects of treatment with repeat antenatal corticosteroids should: • include outcomes for maternal quality of life. • report on the risk factors for preterm birth of the included participants. • assess the degree and health impact of changes in maternal blood glucose control.	**6 to 8** **14**
Randomised trials are needed to: • evaluate dexamethasone as the repeat antenatal corticosteroid; • compare the use of different timing of administration of repeat antenatal corticosteroids prior to preterm birth where preterm birth is definitely expected or planned; • investigate the effects of repeat antenatal corticosteroids in women ≥32 weeks' and 6 days gestation; • investigate if antenatal corticosteroids should be repeated in women at risk of preterm birth who had antenatal corticosteroids 7 days previously and then present with chorioamnionitis; • assess the impact, if any, of repeat antenatal corticosteroids in women with systemic infection at risk of preterm birth; • evaluate in settings where repeat prophylactic antenatal corticosteroids are being used for women with a multiple pregnancy and no other identified risk of preterm birth.	**9** **11** **12** **14** **14** **14**
Conduct an individual patient data meta-analysis to explore key outcomes.	**11**
Further research is required to explore betamethasone and dexamethasone as the repeat antenatal corticosteroid for: • the optimal dose • the optimal number of dose(s) in a course • the optimal interval between courses • the effect of multiple repeat doses/courses.	**10**
Establish the best management of women with diabetes in pregnancy given repeat antenatal corticosteroids.	**14**
Conduct a decision analysis / economic analysis for antenatal corticosteroids	**16**

Use of antenatal corticosteroids for fetal lung maturation prior to elective caesarean section at term

Research recommendation:	Refer to Chapter
Randomised trials are needed to investigate the neonatal effects and childhood disability rates when antenatal corticosteroids are administered to women prior to planned caesarean section at term gestation (≥37 weeks') where their infants are at increased risk of neonatal respiratory disease.	13

Use of antenatal corticosteroids for fetal lung maturation given to women with diabetes in pregnancy at term

Research recommendation:	Refer to Chapter
Randomised trials are needed to investigate the effects, if any, of using antenatal corticosteroids at term gestation (≥37 weeks') in women with diabetes in pregnancy.	15

Glossary of terms

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.
Apgar score	A measure of the physical condition of a newborn infant at one and five minutes after birth. The score is obtained by adding points (2, 1 or 0) for heart rate, respiratory effort, muscle tone, response to stimulation, and skin colouration. A score of ten represents best condition.
Applicability	The degree to which a body of evidence is relevant to a particular health care context.
Clinical impact	Measure of potential benefit from application of the guideline to a population.
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.
Course	A series of doses administered over a designated period
Developmental delay	Any significant lag in a child's physical, cognitive, behavioural, emotional or social development, in comparison with the norms.
Dose	A quantity of medicine taken at a specific time point
Eclampsia	Seizures (convulsions) in a pregnant woman related to hypertensive disease in pregnancy.
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.
Gestational age	The period of time between last menstrual period and birth.
Harms	Adverse effects
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 a persons' ability to perform.
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.
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 neonatal period which is the first four weeks after birth.
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 anindividuals' speech, motor skills, vision, memory, hearing, muscle actions and learning abilities.
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.

Periventricular leucomalacia	A form of brain injury characterised by the death of white matter near the cerebral ventricles in the newborn 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.
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' gestation.
Preterm labour	Labour before 37 weeks of gestation.
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 treatments. P-values will depend on study size; large studies can detect small differences for example.
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 such as dose or frequency of a drug.
Respiratory distress syndrome	Respiratory distress usually in preterm babies, caused by developmental insufficiency of surfactant production and structural immaturity of the lungs.
Respiratory distress	The presence of cyanosis, grunting, inspiratory stridor, nasal flaring and tachypnoea.
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 intervention 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 ≥400 g or at least 20 weeks' gestational age.
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.
Transient tachypnoea of the newborn	Tachypnoea (fast breathing) immediately or within two hours of birth along with other signs of respiratory distress. Usually resolves in 24 to 48 hours.

Chapter 1: Need for these Clinical Practice Guidelines, summary of the development process and key clinical questions

A single course of antenatal corticosteroids has a major role in reducing death and major morbidity in babies born preterm (Lawn 2012, Roberts 2006). The evidence is less clear as to what, when, how and to whom to give antenatal corticosteroids. There is variation in the uptake of the evidence for the use of repeat courses of antenatal corticosteroids (Spencer 2014) and uncertainty about the use of antenatal corticosteroids in women with specific obstetric complications (Bonanno 2012). Advice in the form of these bi-national Clinical Practice Guidelines (New Zealand and Australia) provides evidence-based recommendations to guide decision-making in clinical practice and highlights areas requiring further research.

Aims of these Clinical Practice Guidelines

To prepare evidence-based Clinical Practice Guidelines on the use of antenatal corticosteroids given to women prior to birth to improve fetal, infant and child and adult health.

Target audience

The purpose and rationale is to provide practical, evidence-based guidance on best practice for clinical care in the use of antenatal corticosteroids targeted to the following audiences:

- health professionals caring for pregnant women, where the baby is at increased risk of respiratory distress syndrome due to factors such as preterm birth;
- health professionals caring for the infants and children born following administration of antenatal corticosteroids;
- pregnant women and their partners; and
- policy makers in maternity care.

Scope of the Clinical Practice Guidelines

The scope of these Clinical Practice Guidelines is to examine the evidence for giving a woman at risk of preterm birth (<37 weeks' gestation) a single course and/or repeat antenatal corticosteroids prior to preterm birth, for the purpose of improving health outcomes of their baby.

The scope includes the use of antenatal corticosteroids for women at term gestation (37 weeks' gestation or more) where the baby is at increased risk of respiratory distress syndrome; including women having an elective caesarean section for any indication; and women with a diagnosis of diabetes or gestational diabetes.

Summary of the development process

Clinical Practice Guidelines Panel

A multidisciplinary expert advisory Clinical Practice Guidelines Panel was established to oversee the development of these antenatal corticosteroid Clinical Practice Guidelines (Appendix A). The purpose of the Clinical Practice Guidelines Panel was to prepare evidence based guidelines on the best practice for clinical care in the use of antenatal corticosteroids for improving fetal, infant child and adult health. Declared conflicts of interest can be referred to in (Appendix A).

The Executive Group comprised Professor Caroline Crowther, Dr Julie Brown, Dr Jane Alsweiler and Ms Philippa Middleton who guided the overall preparation of the guidelines. The Management Group consisted of the Executive Group and Tineke Crawford, Dr Elaine Fyfe and Dr Emma McGoldrick who identified and synthesised the evidence presented in these guidelines.

These Clinical Practice Guidelines were developed using procedures recommended by the Australian National Health and Medical Research Council (NHMRC 1998) and the former New Zealand Guideline Group (New Zealand Guidelines Group 2012).

Key clinical questions for these Clinical Practice Guidelines

The Clinical Practice Guidelines Panel developed a set of clinical questions to be addressed:

The use of antenatal corticosteroids for women at risk of preterm birth (≤37 weeks' gestation):

- What are the short and long term benefits and harms of a single course of antenatal corticosteroids for the mother fetus, infant, child and adult prior to preterm birth?
- For a woman at risk of preterm birth, who has received a single course of antenatal corticosteroids and is at ongoing risk of preterm birth, what are the short and long term benefits and harms of a repeat dose(s) of antenatal corticosteroids for the mother, fetus, infant, child and adult?
- What is the safety for the mother, fetus, infant, child, adult of administering a single course or a repeat dose(s) of antenatal corticosteroids to women with the following risk factors for preterm birth:
    a) history of a previous preterm birth
    b) preterm labour
    c) preterm prelabour rupture of membranes
    d) chorioamnionitis
    e) an antepartum haemorrhage
    f) a multiple pregnancy (twins and higher order)
    g) diabetes mellitus or gestational diabetes
    h) a medically indicated preterm birth
    i) systemic infection
    j) pregnancy associated hypertension or pre-eclampsia
    k) intrauterine growth restriction/fetal compromise
    l) ultrasound evidence of cervical shortening/funnelling
    m) fetal fibronectin test results

Type of antenatal corticosteroids to use

- Do benefits or harms in the mother, fetus, infant, child and adult vary by whether betamethasone or dexamethasone is administered as a single course of antenatal corticosteroids?
- Do benefits or harms in the mother, fetus, infant, child and adult vary by whether betamethasone or dexamethasone is administered as the repeat dose(s) of antenatal corticosteroids?

Drug regimens and timing of administration of antenatal corticosteroids

- What is the most effective dose, number of doses in a course and optimal interval between doses when using a single course of antenatal corticosteroids?
- What is the most effective dose, number of doses in a course and optimal interval between courses for repeat antenatal corticosteroids?
- Is a single repeat dose/course (or rescue dose/course) more effective than multiple repeat dose(s)/courses?
- What is the optimal time prior to preterm birth to administer a single course of antenatal corticosteroids?
- What is the optimal time prior to preterm birth to administer a repeat dose(s) of antenatal corticosteroids?
- What is the optimal timing between a first course of antenatal corticosteroids and initiating a repeat dose(s)?
- At what gestational ages is a single course of antenatal corticosteroids effective?
- At what gestational ages is a repeat dose(s) of antenatal corticosteroids effective?

Use of antenatal corticosteroids at term gestation

- What are the benefits and harms for the mother, fetus, infant, child and adult of administering antenatal corticosteroids for fetal lung maturation to women planning an elective caesarean section at term (37 weeks' gestation or more)?
- What are the benefits and harms for the mother, fetus, infant, child and adult of administering antenatal corticosteroids for fetal lung maturation to women with diabetes mellitus or gestational diabetes at term (37 weeks' gestation or more)?

Key clinical outcomes for these Clinical Practice Guidelines

The Clinical Practice Guidelines Panel developed a comprehensive list of relevant maternal, fetal, child and adult clinical outcomes and health resource utilisation outcomes for use in these guidelines. The primary outcomes and secondary outcomes are listed below. Most of these outcomes were from key Cochrane systematic reviews listed in Appendix B.

Primary maternal outcomes for these Clinical Practice Guidelines

- Maternal infection requiring treatment including:
  - Chorioamnionitis
  - Puerperal sepsis
  - Pyrexia after trial entry requiring antibiotics
  - Intrapartum fever requiring antibiotics
  - Postnatal pyrexia requiring antibiotics
- Quality of life

Primary fetal, neonatal and infant outcomes for these Clinical Practice Guidelines

- Fetal, neonatal or later death
- Respiratory distress syndrome
- Composite serious outcome (may include fetal, neonatal or later death, severe respiratory distress, severe intraventricular haemorrhage (Grade 3 or 4), chronic lung disease, necrotising enterocolitis, retinopathy of prematurity, cystic periventricular leukomalacia, patent ductus arteriosus, neonatal encephalopathy)

Primary infant as a child outcomes for these Clinical Practice Guidelines

- Neurosensory disability (composite of impairments: cerebral palsy, visual impairment, hearing impairment, developmental delay)
- Survival free of neurosensory disability
- Survival free of metabolic disease

Primary infant as an adult outcomes for these Clinical Practice Guidelines

- Neurosensory disability (composite of impairments: cerebral palsy, visual impairment, hearing impairment, intellectual impairment)
- Survival free of neurosensory disability
- Survival free of metabolic disease

Secondary maternal outcomes for these Clinical Practice Guidelines

- Mortality
- Hypertension
- Mode of birth
- Postpartum haemorrhage
- Breastfeeding at hospital discharge
- Breastfeeding at 6 months postnatally
- Postnatal depression symptoms
- Mental anxiety
- Adverse effects of antenatal corticosteroid therapy (including gastrointestinal upset, glucose intolerance, insomnia, pain at injection site, bruising at injection site, infection at injection site, weight gain, Cushing syndrome)
- Gestational diabetes mellitus diagnosis after antenatal corticosteroid treatment
- Insulin use after antenatal corticosteroid treatment

Additional maternal outcomes for women with diabetes and gestational diabetes:

- Use of insulin or an increase in insulin use after antenatal corticosteroid treatment
- Elevated glycated haemoglobin (HbA1c) postpartum
- Elevated fasting plasma glucose
- Change in glycaemic control after antenatal corticosteroid treatment
- Hospital admission for glucose control
- Maternal hyperglycaemia
- Maternal hypoglycaemia

Secondary fetal, neonatal and infant outcomes for these Clinical Practice Guidelines

Other respiratory morbidity outcomes:

- Interval between antenatal corticosteroid exposure and birth
- Transient tachypnoea of the neonate (term)
- Use and duration of respiratory support

- Use and duration of oxygen supplementation
- Use of surfactant
- Pulmonary hypertension
- Chronic lung disease
- Air leak syndrome
- Inotropic support
- Use of nitric oxide for respiratory support

Other infant morbidity outcomes for these Clinical Practice Guidelines:

- Intraventricular haemorrhage (any grade)
- Severe intraventricular haemorrhage (Grade 3 or 4)
- Cystic periventricular leukomalacia/white matter injury
- Neonatal encephalopathy in term babies
- Necrotising enterocolitis
- Retinopathy of prematurity
- Patent ductus arteriosus (defined as requiring treatment)
- Neonatal blood pressure (including hypertension, hypotension)
- Hypoglycaemia requiring treatment
- Hyperglycaemia requiring treatment
- Gestational age at birth
- Apgar score <7 at 5 minutes
- Early neonatal infection (<48 hours)
- Late neonatal infection (≥48 hours)
- Use of post-natal corticosteroids
- Hypothalamic Pituitary Adrenal axis suppression

Neonatal anthropometry:

- Birthweight
- Birth length
- Birth head circumference
- z scores at birth for weight, height, length, head circumference
- Small for gestational age
- Placental weight
- Anthropometry at hospital discharge for weight, height, length, head circumference (including z scores)

Infant as a child secondary outcomes for these Clinical Practice Guidelines

- Total mortality
- Cerebral palsy
- Cognitive ability
- Learning disability
- Developmental delay, Intelligence Quotient
- Visual impairment
- Hearing impairment
- Child behaviour
- Educational attainment
- Anthropometry
- Respiratory disease/lung function
- Insulin sensitivity
- Hypothalamic Pituitary Adrenal suppression
- Diabetes

- Blood pressure
- Age at puberty

Infant as an adult secondary outcomes for these Clinical Practice Guidelines

- Total mortality
- Cerebral palsy
- Cognitive ability
- Learning disability
- Intelligence Quotient
- Visual impairment
- Hearing impairment
- Educational attainment
- Anthropometry
- Respiratory disease/lung function
- Insulin sensitivity
- Hypothalamic Pituitary Adrenal suppression
- Diabetes
- Cardiovascular disease
- Age at puberty

Health services outcomes for pregnancy, birth and postnatally for these Clinical Practice Guidelines

- Length of antenatal hospitalisation for the women
- Length of postnatal hospitalisation for the women
- Maternal admission to intensive care
- Baby admission to neonatal intensive care
- Length of stay in neonatal intensive care
- Length of neonatal hospitalisation

Format of guideline

Each chapter within these guidelines follows the same format:

- Description of the evidence for use of antenatal corticosteroids.
- Summary of the judgements of the evidence. Jjudgements are used to formulate the clinical practice recommendations and practice points. Research recommendations are made if there is a lack of high quality evidence to answer the clinical question developed by the Clinical Practice Guideline Panel.

Research methods used in these guidelines

The methods used to identify the evidence are summarised below and given in detail in Appendix C. A systematic literature search of multiple electronic databases was undertaken up to October 2012 and repeated again in September 2014 (Roberts CPG version 2015; Crowther CPG version 2015; Brownfoot CPG version 2015; Sotiriadis CPG version 2015). Appendix C details the search strategy. The population included women of any gestation who had received antenatal corticosteroids (any type, dose or regimen) for fetal lung maturation.

Where possible the evidence presented in these Clinical Practice Guidelines is based on the gold standard of systematic reviews and randomised controlled trials. Quality of included studies was assessed using adapted NHMRC methods (NHMRC 1998) and GRADE methods (http://www.gradeworkinggroup.org/ accessed 23/07/2014).

Summaries of evidence for each question were produced (Appendix M).

Summary of timeline

29th November 2012	First Panel meeting in Auckland, New Zealand.
15th September 2014	Second Panel meeting in Auckland, New Zealand.
20th October 2014	Third Panel meeting/teleconference to confirm clinical recommendations, research recommendations and practice points.
January – February 2015	Consultation period and endorsement by stakeholders.
April 2015	Release of these Clinical Practice Guidelines at The Perinatal Society of Australia and New Zealand Annual Conference.

Updating the guidelines

These guidelines will be reviewed in three years' time and updated as required.

Chapter 2: Background

Preterm birth - the burden of disease

A working paper prepared for the United Nations Commission on Life-Saving Commodities for Women and Children (Born too Soon) (Lawn 2012) reported that worldwide 10 percent of all babies are born preterm and globally over one million babies will die each year as a consequence of being born preterm. Respiratory distress syndrome is the most common complication due to lung immaturity. Preterm birth is acknowledged as the second most common cause of childhood deaths after pneumonia. Consequences extend beyond the immediate newborn period and many of the children who survive have long term disability and increased risk of chronic disease in adulthood (Saigal 2008).

Reducing the burden of preterm birth - Antenatal corticosteroid therapy - Current uncertainties

Single course of antenatal corticosteroids - neonatal benefits

Having established the major beneficial effect of antenatal corticosteroids on lung maturation in a sheep model (Liggins 1969), Professor Liggins and Dr Howie initiated the first randomised controlled trial in humans of betamethasone for the prevention of respiratory distress syndrome in Auckland, New Zealand (Liggins 1972).

The first systematic review of the evidence on the use of a single course of antenatal corticosteroids included 12 randomised controlled trials and showed that antenatal corticosteroids given prior to preterm birth were highly effective in preventing neonatal mortality, respiratory distress syndrome and reducing the risk of intraventricular haemorrhage (Crowley 1990).

A single course of antenatal corticosteroids prior to preterm birth has now become a standard, prophylactic treatment against respiratory distress syndrome. However, the evidence for benefit in a woman at risk of preterm birth with specific obstetric risk factors remains unclear. These include women with pregnancy associated hypertension syndromes, diabetes in pregnancy (including type 1 and type 2 diabetes and gestational diabetes), a multiple pregnancy, preterm labour and preterm prelabour rupture of membranes. The minimal effective dose and optimal timing of administration of antenatal corticosteroids prior to birth is unclear (Roberts 2006).

Repeat courses of antenatal corticosteroids - benefits and harms

No evidence of benefit in decreased respiratory distress syndrome or neonatal mortality has been observed when infants are born seven days or more following exposure to a single course of antenatal corticosteroids compared with no antenatal corticosteroid exposure (Roberts 2006). Supplementary data from the Liggins and Howie randomised trial (Liggins 1972) raised concerns about reduced birthweight if birth had not occurred after seven days of treatment in the infants exposed to a single course of antenatal corticosteroid treatment compared with no exposure (Roberts 2006).

Subsequent meta-analyses of randomised controlled trials assessing the use of repeat antenatal corticosteroids found benefit in repeat dose(s) of antenatal corticosteroids to women at risk of preterm birth more than seven days after the initial course of corticosteroids (Crowther 2011). There remains ongoing uncertainty about the potential adverse effects on long term child and adulthood outcomes (Crowther 2011, Roberts 2006).

Which antenatal corticosteroid is best?

Despite the widespread use of antenatal corticosteroids prior to preterm birth (ANZNN 2014), globally there is wide variation in clinical practice for the type of corticosteroid used, the dose and frequency given, and on the route of administration (Aleman 2013, Baud 1999, Brownfoot 2013, Cosmi 2004,

Erickson 2001, Hui 2007, Jobe 2004, Lee 2006, Parant 2008, Pattanittum 2008, Saengwaree 2005, Spencer 2014). Both betamethasone and dexamethasone are used as antenatal corticosteroids in clinical practice in New Zealand and Australia with betamethasone the most commonly used (Quinlivan 1998, Spencer 2014). The optimal type of corticosteroid to use for antenatal treatment remains unclear. There are currently few published data from randomised trials on the long term effects of betamethasone compared directly with dexamethasone (Brownfoot 2013).

Antenatal corticosteroids prior to elective caesarean section close to term gestation

The use of antenatal corticosteroids prior to elective caesarean section, at gestations close to term, to reduce the risk of infant respiratory distress syndrome is an area of on-going debate. There is minimal high quality evidence (Ahmed 2014, Stutchfield 2005) and ongoing concerns about administration of a drug with short-term benefit but potentially long-term harm for the infant, child or adult (Aiken 2014, Hansen 2008, Steer 2005, Stutchfield 2013).

Use of antenatal corticosteroids in women with diabetes and gestational diabetes

There is debate as to whether antenatal corticosteroids should be given to women with diabetes and gestational diabetes. Infants of these women have increased risk of respiratory distress syndrome but antenatal corticosteroid administration has been associated with elevated maternal blood glucose concentrations (Kaushal 2003).

Mode of administration, dosage and timing prior to birth

The optimal route of administration of betamethasone and dexamethasone is uncertain. Both betamethasone and dexamethasone may be administered as intramuscular and intravenous injections.

- Intramuscular preparations of betamethasone reported include Celestone® Soluspan® (betamethasone 6 mg as 3 mg/ml betamethasone sodium phosphate, and 3 mg/ml betamethasone acetate) and Celestone® Chronodose® (betamethasone 5.7 mg, as betamethasone sodium phosphate 3.9 mg/ml and betamethasone acetate 3 mg/ml).
- Dexamethasone is most commonly administered in the form of dexamethasone sodium phosphate.

Betamethasone has been given intra-amniotically and dexamethasone can be given orally (Brownfoot 2013).

There is uncertainty about the optimal dose of corticosteroids to use, what constitutes a course, timing of use prior to birth and frequency of administration between doses and/or courses (Brownfoot 2013).

Antenatal corticosteroids - Removing uncertainties by assessing the evidence

The focus of these Clinical Practice Guidelines is the preparation of evidence based guidelines on the use of antenatal corticosteroids given prior to birth for improving fetal, infant, child and adult health. The evidence for effectiveness and harm comes from 49 randomised controlled trials. The majority of this evidence is synthesised within four relevant Cochrane systematic reviews:

1. **"Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth." (Roberts 2006) (21 randomised controlled trials, 3885 women and 4269 infants).**
   The literature search was updated to assist with these Clinical Practice Guidelines. A further five trials (584 women and 584 infants) were included in the systematic review prepared for these Clinical Practice Guidelines (Roberts CPG version 2015) (26 trials, 4469 women and 4853 infants). See Appendix D, Appendix E and Appendix F.
2. **"Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes." (Crowther 2011) (10 randomised controlled trials, 4733 women and 5700 infants).**
   The literature search was updated to assist with these Clinical Practice Guidelines. Three conference abstracts reporting follow-up of the Crowther (2006) trial and one paper reporting follow-up of the Murphy (2008) trial were included in the systematic review prepared for these Clinical Practice Guidelines (Crowther CPG version 2015). See Appendix G, Appendix H and Appendix I.
3. **"Different corticosteroids and regimens for accelerating fetal lung maturation for women at risk of preterm birth." (Brownfoot 2013) (12 randomised controlled trials, 1159 women and 1218 infants).**
   The literature search for this review was updated for these Clinical Practice Guidelines (Brownfoot CPG version 2015). One trial comparing different doses and timing of administration was added (one trials including 121 women).
4. **"Corticosteroids for preventing neonatal respiratory morbidity after elective caesarean section at term." (Sotiriadis 2009) (1 randomised controlled trial, 943 women and 942 infants).**
   The literature search was updated to assist with these Clinical Practice Guidelines. One additional trial including 452 women and 452 infants was included in the systematic review prepared for these Clinical Practice Guidelines (Sotiriadis CPG version 2015).

Given the key clinical questions developed by the Clinical Practice Guidelines Panel to be answered and the seminal importance of the evidence from the four systematic reviews for these Clinical Practice Guidelines a summary is provided below. Information includes: inclusion criteria, primary outcomes, geographical location, timing of trials, antenatal corticosteroid regimen, risk of bias and outcomes reported (maternal, infant, infant as a child, infant as an adult).

1. "Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth"

This systematic review was updated for these Clinical Practice Guidelines using the Roberts (2006) Cochrane systematic review protocol and the data reported hereafter are based on these updated data and are referred to as Roberts CPG version 2015.

Eligibility for inclusion in Roberts (2006) Cochrane systematic review (population and intervention)

The Cochrane systematic review '*Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth'* (Roberts 2006) included randomised controlled trials that recruited women prior to anticipated preterm birth (elective, or following spontaneous labour), regardless of other co-morbidity. Women could have a multiple or singleton pregnancy. The interventions reported in the trials compared a single course of antenatal corticosteroid (betamethasone, dexamethasone, or hydrocortisone) with placebo, or with no treatment.

Eligibility criteria for inclusion and exclusion for each trial including the five additional trials included in the systematic review prepared for these Clinical Practice Guidelines are detailed in Appendix J.

Primary outcomes for the Roberts (2006) Cochrane systematic review

Primary maternal outcomes

- death;
- chorioamnionitis;
- puerperal sepsis.

Primary fetal/ neonatal outcomes

- perinatal death;
- respiratory distress syndrome;
- moderate/severe respiratory distress syndrome;
- chronic lung disease;
- intraventricular haemorrhage;
- severe intraventricular haemorrhage;
- birthweight.

Primary child and child as an adult outcomes were

- death;
- neurodevelopmental disability.

Description of trials included in the Roberts CPG version 2015 systematic review

The Roberts (2006) Cochrane systematic review included 21 trials (3885 women and 4269 infants) (Amorim 1999, Block 1977, Cararach 1991, Carlan 1991, Collaborative Group on Antenatal Steroid Therapy 1981, Dexiprom 1999, Doran 1980, Fekih 2002, Gamsu 1989, Garite 1992, Kari 1994, Lewis 1996, Liggins 1972, Morales 1989, Nelson 1985, Parsons 1988, Qublan 2001, Schutte 1980, Silver 1996, Taeusch 1979, Teramo 1980).

The updated literature search conducted for these Clinical Practice Guidelines identified five additional randomised trials (584 women and 584 infants) (Balci 2010, Shanks 2010, Porto 2011, Goodner 1979, Lopez 1989).

A total of twenty-six randomised controlled trials were included in the Roberts CPG version 2015 systematic review. There were data available for 4469 women and 4853 infants.

Geographical location of where these trials were conducted

Twelve trials were conducted in the USA (Block 1977, Carlan 1991, Collaborative Group on Antenatal Steroid Therapy 1981, Garite 1992, Goodner 1979, Lewis 1996, Morales 1989, Nelson 1985, Parsons 1988, Shanks 2010, Silver 1996, Taeusch 1979). Two trials were conducted in Finland (Kari 1994, Teramo 1980) and in Brazil (Amorim 1999, Porto 2011) and one trial from each of the following countries Colombia (Lopez 1989), Spain (Cararach 1991), South Africa (Dexiprom 1999), Turkey (Balci 2010), Canada (Doran 1980), Tunisia (Fekih 2002) United Kingdom (Gamsu 1989), New Zealand (Liggins 1972), Jordan (Qublan 2001), and The Netherlands (Schutte 1980).

Era of conduct of these trials

Seven trials completed recruitment mainly in the 1970s (1845 women and 2086 infants), seven trials completed recruitment mainly in the 1980s (1140 women and 1213 infants), nine trials completed recruitment mainly in the 1990s (1032 women and 1102 infants), and three trials completed recruitment after 2000 (452 women and 452 infants).

Antenatal corticosteroid regimens utilised within these trials

One trial (Cararach 1991) did not specify the corticosteroid used or the dose administered.

Betamethasone:

Nineteen trials (3028 women and 3289 infants) used betamethasone as the antenatal corticosteroid. The Nelson (1985) trial used two different regimens. The different regimens used in the trials included:

- 2 x 12 mg betamethasone 24 hours apart was used in twelve trials (Amorim 1999, Block 1977, Carlan 1991, Fekih 2002, Garite 1992, Lewis 1996, Liggins 1972, Lopez 1989, Morales 1989, Porto 2011, Shanks 2010, Teramo 1980);
- 2 x 14 mg over 2 consecutive days was used in one trial (Schutte 1980);
- 1 x 12 mg was used in one trial (Balci 2010);
- 4 x 4 mg 12 hours apart was used in one trial (Doran 1980);
- 6 x 4 mg 8 hours apart was used in one trial (Gamsu 1989);
- 2 x 6 mg 12 hours apart was used in one trial (Nelson 1985);
- 2 x 12 mg 12 hours apart was used in two trials (Nelson 1985, Parsons 1988);
- One trial used betamethasone but did not specify the regimen (Goodner 1979).

Dexamethasone:

Seven trials (1391 women and 1514 infants) used dexamethasone as the antenatal corticosteroid. Several different regimens were used:

- 4 x 6 mg 12 hours apart was used in three trials (Kari 1994, Qublan 2001, Shanks 2010);
- 6 x 4 mg 8 hours apart was used in one trial (Taeusch 1979);
- 2 x 12 mg 24 hours apart was used in one trial (Dexiprom 1999);
- 4 x 5 mg 12 hours apart was used in two trials (Collaborative Group on Antenatal Steroid Therapy 1981, Silver 1996);

Use of weekly repeat courses of antenatal corticosteroids

Eight of the 26 trials included in the Roberts CPG version 2015 systematic review allowed use of weekly repeat courses of study medication in their trial protocols (821 women and 848 infants) (Amorim 1999, Carlan 1991, Garite 1992, Lewis 1996, Morales 1989, Parsons 1988, Qublan 2001, Silver 1996). None of these trials reported data by number of doses of antenatal corticosteroids received or proportion of participants who received more than one course of antenatal corticosteroids. Separate analysis of primary outcomes for those studies allowing use of a single course of study medication and those studies allowing weekly repeat courses of study medication was conducted *post hoc* in the Roberts (2006) review.

Risk of bias of trials included in Roberts CPG version 2015 systematic review

Risk of bias for the included trials (selection bias, performance and detection bias, attrition bias, reporting bias, other bias) is shown in **Table 1**. There was inadequate detail provided to be able to judge the risk of selection bias (randomisation and allocation concealment) in more than half of the trials and overall risk of bias is judged as unclear. Eleven of 26 trials did not blind participants or personnel and risk of bias is considered to be high. Outcome data was adequately reported (low risk of bias) in 15 of 26 trials, although long term follow-up has only been reported in two of 26 trials. Overall selective reporting was considered to be of low risk of bias.

Selection bias

- Eleven of the 26 trials used computer-generated or random number-generated randomisation sequences (Amorim 1999, Balci 2010, Block 1977, Dexiprom 1999, Garite 1992, Lewis 1996, Liggins 1972, Nelson 1985, Porto 2011, Qublan 2001, Silver 1996), permuted blocks were used by two trials (Kari 1994, Lewis 1996).
- The remaining trials did not describe the method of sequence generation in sufficient detail to enable a judgement of risk of bias to be made.
- Eight trials were considered to be at low risk of bias for allocation concealment as they used coded drug boxes or vials in order to conceal the randomisation sequence or study treatment (Amorim 1999, Block 1977, Dexiprom 1999, Doran 1980, Liggins 1972, Porto 2011, Schutte 1980, Silver 1996).
- One trial was assessed as having a high risk of bias due to a sealed envelope containing the identity of the contents being attached to each vial "to be opened only in case of an emergency" (Collaborative Group on Antenatal Steroid Therapy 1981).
- Two trials were assessed as unclear risk due to insufficient information provided to confirm the boxes were sequentially numbered (Taeusch 1979, Teramo 1980).
- Six trials used sealed envelopes, only one of which used opaque envelopes (Lewis 1996) and was assessed as low risk of bias. The remaining five studies did not specify if the envelopes were opaque and were therefore assessed as having an unclear risk of bias for allocation concealment (Balci 2010, Garite 1992, Morales 1989, Nelson 1985, Shanks 2010).
- The remaining trials did not include any details on the method of allocation concealment.

Performance and detection bias (blinding)

- Fifteen of the 26 included trials were placebo controlled (Amorim 1999, Block 1977, Collaborative Group on Antenatal Steroid Therapy 1981, Dexiprom 1999, Doran 1980, Gamsu 1989, Garite 1992, Goodner 1979, Kari 1994, Liggins 1972, Porto 2011, Schutte 1980, Silver 1996, Taeusch 1979, Teramo 1980).
- The remaining 11 trials were not blinded as they used expectant management in the control arm (Balci 2010, Cararach 1991, Carlan 1991, Fekih 2002, Lewis 1996, Lopez 1989, Morales 1989, Nelson 1985, Parsons 1988, Qublan 2001, Shanks 2010).

Incomplete outcome data (attrition bias)

- For maternal, fetal and neonatal outcomes, intention-to-treat analysis was possible in ten of the 26 included trials (Balci 2010, Cararach 1991, Doran 1980, Gamsu 1989, Kari 1994, Liggins 1972, Nelson 1985, Parsons 1988, Qublan 2001, Teramo 1980). In the remaining 15 trials losses to follow up were generally small and less than 5%. No details for attrition were provided by (Goodner 1979).
- In the trial conducted by Silver (1996) 49 of 124 (40%) women initially recruited who remained undelivered after 29 weeks were not included in the trial report or therefore the systematic review.

- Only two of the 26 trials have followed participants into childhood and adulthood (Liggins 1972, Schutte 1980). Liggins (1972) reported outcome data for 18% of children at ages 4 to 6 years (31 in the treatment arm and 23 in the control arm) and 44% of adults at age 30 years (219 in the treatment arm and 193 in the control arm). Schutte (1980) reported outcome data for 12% children in the follow-up study at ages 10 to 12 years (4 in the treatment arm and 8 in the control arm) and 21% adults in the follow-up study at age 20 years (10 in the treatment arm and 11 in the control arm).

Selective reporting (reporting bias)

- The study protocol was unavailable in all of the included trials and all pre-specified outcomes for the individual trials appear to have been reported in 20 of the 26 trials (Amorim 1999, Block 1977, Collaborative Group on Antenatal Steroid Therapy 1981, Dexiprom 1999, Doran 1980, Fekih 2002, Gamsu 1989, Garite 1992, Kari 1994, Lewis 1996, Liggins 1972, Lopez 1989, Morales 1989, Nelson 1985, Parsons 1988, Porto 2011, Schutte 1980, Silver 1996, Taeusch 1979, Teramo 1980).
- Three studies were only available in abstract form and were not published as full text articles (Cararach 1991, Carlan 1991, Goodner 1979).
- One trial reported on maternal outcomes that were not pre-specified (Balci 2010).
- One trial pre-specified respiratory distress syndrome as an outcome but did not report the data (Shanks 2010).
- One trial only reported on respiratory distress syndrome and no other maternal or neonatal outcomes (Goodner 1979).
- One trial only reported on maternal outcomes (Shanks 2010).

Outcomes reported in the included trials in the Roberts CPG version 2015 systematic review

Maternal outcomes

Eighteen of the 26 randomised controlled trials comparing a single course of antenatal corticosteroids with no antenatal corticosteroids reported maternal outcomes for 3111 women (Amorim 1999, Balci 2010, Carlan 1991, Dexiprom 1999, Fekih 2002, Garite 1992, Kari 1994, Lewis 1996, Liggins 1972, Lopez 1989, Morales 1989, Nelson 1985, Porto 2011, Qublan 2001, Schutte 1980, Shanks 2010, Silver 1996, Taeusch 1979) (**Table 2**).

Fetal and neonatal outcomes

Twenty-five of the 26 randomised controlled trials comparing a single course of antenatal corticosteroids with no antenatal corticosteroids reported fetal and neonatal outcomes for 4793 infants (Amorim 1999, Balci 2010, Block 1977, Cararach 1991, Carlan 1991, Collaborative Group on Antenatal Steroid Therapy 1981, Dexiprom 1999, Doran 1980, Fekih 2002, Gamsu 1989, Garite 1992, Goodner 1979, Kari 1994, Lewis 1996, Liggins 1972, Lopez 1989, Morales 1989, Nelson 1985, Parsons 1988, Porto 2011, Qublan 2001, Schutte 1980, Shanks 2010, Silver 1996, Taeusch 1979, Teramo 1980) (**Table 2**).

Childhood outcomes

Only five of the 26 randomised trials comparing a single course of antenatal corticosteroids with no antenatal corticosteroids have reported childhood outcomes, with data available for 933 children (Amorim 1999, Collaborative Group on Antenatal Steroid Therapy 1981, Kari 1994, Liggins 1972, Schutte 1980) (**Table 2**).

Child as adult outcomes

Only two of the 26 randomised trials comparing a single course of antenatal corticosteroids with no antenatal corticosteroids have reported adult outcomes, with data available for 545 adults (Liggins 1972, Schutte 1980) (**Table 2**).

Table 1: Risk of bias of included trials in the Roberts CPG version 2015 systematic review

Author (Year)	Random sequence generation	Allocation concealment	Blinding of participants/ personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Amorim (1999)							
Balci (2010)							
Block (1977)							
Cararach (1991)							
Carlan (1991)							
Collaborative (1981)							
Dexiprom (1999)							
Doran (1980)							
Fekih (2002)							
Gamsu (1989)							
Garite (1992)							
Goodner (1979)							
Kari (1994)							
Lewis (1996)							
Liggins (1972)							
Lopez (1989)							
Morales (1989)							
Nelson (1985)							
Parsons (1988)							
Porto (2011)							
Qublan (2001)							
Schutte (1980)							
Shanks (2010)							
Silver (1996)							
Taeusch (1979)							
Teramo (1980)							

Low risk of bias	Unclear risk of bias	High risk of bias

Table 2: Twenty-six randomised trials reporting on health outcomes following administration of a single course/dose of antenatal corticosteroids#

Author (Year)	Country	Intervention (number of women/infants)	Control (number of women/ infants)	Outcomes reported			
				Maternal	Neonatal	Child	Adult
Amorim (1999)	Brazil	2 x 12 mg betamethasone (Celestone®) 24 hours apart^ (n=110 mothers and infants).	Placebo (n=110 mothers and infants)	√	√	√	X
Balci (2010)	Turkey	1 x 12 mg betamethasone (Celestone®) (n=50 mothers and infants)	No treatment (n=50 mothers and infants)	√	√	X	X
Block (1977)	USA	2 x 12 mg betamethasone (Celestone® Soluspan®) 24 hours apart (n=60 infants)	Placebo (normal saline) (n=54 infants)	X	√	X	X
Cararach (1991)	Spain	Type and dose not specified (n=12 infants)	Expectant management (n=6 infants)	X	√	X	X
Carlan (1991)	USA	2 x 12 mg betamethasone (type not specified) 24 hours apart^ (n=13 mothers and infants).	Expectant management (n=11 mothers and infants)	√	√	X	X
Collaborative (1981)	USA	4 x 5 mg dexamethasone phosphate 12 hours apart (n=378 infants)	Placebo (n=379 infants)	X	√	√	X
Dexiprom (1999)	South Africa	2 x 12 mg dexamethasone (no further details) 24 hours apart (n=102 mothers, 105 infants)	Placebo (n=102 mothers, 103 infants)	√	√	X	X
Doran (1980)	Canada	4 x 3 mg betamethasone acetate and 3mg betamethasone sodium phosphate 12 hourly (n=81 infants)	Placebo (n=63 infants)	X	√	X	X
Fekih (2002)	Tunisia	2 x 12 mg betamethasone (Celestone® Chronodose®) 24 hours apart (n=59 mothers, 63 infants)	Expectant management (n=59 mothers, 68 infants)	√	√	X	X
Gamsu (1989)	UK	6 x 4 mg betamethasone phosphate 8 hourly (n=131 infants)	Placebo (n=137 infants)	X	√	X	X
Garite (1992)	USA	2 x 6 mg betamethasone acetate and 6 mg betamethasone phosphate (Celestone®) 24 hours apart^ (n=37 mothers, 40 infants)	Placebo (n=39 mothers, 42 infants)	√	√	X	X
Goodner (1979)	USA	Betamethasone (no further details) (n=45 infants)	Placebo (saline) (n=47 infants)	X	√	X	X
Kari (1994)	Finland	4 x 6 mg dexamethasone sodium phosphate (Oradexon) 12 hours apart (n=77 mothers, 95 infants)	Placebo (n=80 mothers, 95 infants)	√	√	√	X
Lewis (1996)	USA	2 x 12 mg betamethasone (no further details) 24 hours apart^ (n=39 mothers and infants)	Expectant management (n=40 mothers and infants)	√	√	X	X
Liggins (1972)[$$]	New Zealand	2 x 6 mg betamethasone phosphate and 6 mg betamethasone acetate 24 hours apart (no further details). After the first 717 women had enrolled the treatment intervention was doubled to 2 x 12 mg betamethasone phosphate and 12 mg betamethasone acetate 24 hours apart (n=560 mothers, 601 infants)	6 mg cortisone acetate (n=582 mothers, 617 infants)	√	√	√	√
Lopez (1989)	Colombia	2 x 12 mg betamethasone (no further details) 12 hours apart (n=20 mothers and infants)	No treatment (n=20 mothers and infants)	√	√	X	X

Author (Year)	Country	Intervention	Control	Outcomes reported			
Morales (1989)	USA	Expectant management plus 2 x 12 mg betamethasone (Celestone®) 24 hours apart^ (n=87 mothers and infants)	Expectant management (n=78 mothers and infants)	√	√	X	X
Nelson (1985)	USA	2 x 6 mg or 12 mg betamethasone (Celestone® Soluspan®) 12 hours apart, birth 24 to 48 hours after PPROM and after 24 hours of corticosteroid therapy (n=22 mothers and infants)	Delivery 24 to 48 hours after PPROM (n=22 mothers and infants)	√	√	X	X
Parsons (1988)	USA	2 x 12 mg betamethasone (no further details) 12 hours apart^ (n=23 infants)	Expectant management (n=22 infants)	X	√	X	X
Porto (2011)	Brazil	2 x 12 mg betamethasone (as 3mg betamethasone acetate and 3.9 mg disodium phosphate) 24 hours apart (n=163 mothers and infants)	Placebo (n=157 mothers and infants)	√	√	X	X
Qublan (2001)	Jordan	4 x 6 mg dexamethasone (no further details) 12 hours apart^ (n=72 mothers and infants)	Expectant management (n=67 mothers and infants)	√	√	X	X
Schutte (1980)	Holland	2 x 8 mg betamethasone phosphate and 6 mg betamethasone acetate (no further details) 24 hours apart (n=50 mothers, 65 infants)	Placebo (n=51 mothers, 58 infants)	√	√	√	√
Shanks (2010)	USA	2 x 12 mg betamethasone (no further details) 24 hours apart, or 4 x 6 mg dexamethasone (no further details) 12 hours apart (n=13 mothers)	No treatment (n=19 mothers)	√	X	X	X
Silver (1996)	USA	4 x 5 mg dexamethasone (no further details) 12 hours apart^ (n=39 mothers, 54 infants)	Placebo (n=36 mothers, 42 infants)	√	√	X	X
Taeusch (1979)	USA	6 x 4 mg dexamethasone phosphate (Decadron) 8 hours apart (n=39 mothers, 54 infants)	Placebo (n=36 mothers, 42 infants)	√	√	X	X
Teramo (1980)	Finland	2 x 12 mg betamethasone (Celestone®) 24 hours apart (n=38 infants)	Placebo (n=42 infants)	X	√	X	X

* Source Roberts CPG version 2015

#All antenatal corticosteroids were administered intramuscularly,

^ weekly repeat courses permitted in trial protocol,

PPROM preterm pre-labour rupture of membranes,

√ reported,

X not reported

$$Additional data were provided by the authors for inclusion in the Roberts (2006) systematic review.

2. *'Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes'* (Crowther 2011)

Eligibility for inclusion in Crowther (2011) Cochrane systematic review (population and intervention)

The Cochrane systematic review *Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes* (Crowther 2011) included randomised controlled trials that recruited women who had already received a single course of antenatal corticosteroid seven or more days previously and were still considered to be at risk of preterm birth. The interventions reported in the trials compared a repeat dose(s) of antenatal corticosteroids (betamethasone, dexamethasone with or without additional placebo administration). Eligibility criteria for inclusion and exclusion in each trial are detailed in Appendix K.

Primary outcomes for repeat doses of prenatal corticosteroids, Crowther (2011) systematic review

Primary maternal outcomes

- chorioamnionitis;
- puerperal sepsis.

Primary fetal/ neonatal outcomes

- respiratory distress syndrome;
- severe lung disease;
- composite serious outcome (however defined by authors);
- birthweight;
- fetal, neonatal or later death;
- chronic lung disease;
- intraventricular haemorrhage.

Primary child and child as adult outcomes

- total deaths;
- survival free of any disability;
- survival free of major disability ;
- disability at childhood or adult follow-up (developmental delay or intellectual impairment, blindness, deafness, or cerebral palsy after 18 months of age);
- composite serious outcome;
- major sensorineural disability in adulthood (defined as any of legal blindness, sensorineural deafness requiring hearing aids, moderate or severe cerebral palsy, or developmental delay or intellectual impairment (defined as developmental quotient or intelligence quotient less than two standard deviations below mean)).

Description of trials included in the Crowther (2011) Cochrane systematic review and the Crowther CPG version 2015 systematic review

Ten randomised controlled trials were included in the Crowther (2011) systematic review. There were data available for 4733 women and 5700 infants (Aghajafari 2002, Crowther 2006, Garite 2009, Guinn 2001, Mazumder 2008, McEvoy 2002, McEvoy 2010, Murphy 2008, Peltoniemi 2007, Wapner 2006).

The updated literature search for these Clinical Practice Guidelines (Crowther CPG version 2015) found no new randomised trials but did identify follow-up data for the Crowther (2006) trial (Crowther 2011b, McKinlay 2015, McKinlay 2013ab) and the Murphy (2008) trial (Asztelos 2013).

Geographical location of where these trials were conducted
Five of the 10 trials were conducted in the USA (Garite 2009, Guinn 2001, McEvoy 2002, McEvoy 2010, Wapner 2006); one each in Canada (Aghajafari 2002), India (Mazumder 2008) and Finland (Peltoniemi 2007); one in Australia and New Zealand (Crowther 2006); and one multicentre trial recruited from 20 countries (Murphy 2008).

Era of conduct of these trials
All ten trials were conducted between 2000 and 2010.

Repeat antenatal corticosteroid regimen utilised in these trials
All ten trials used betamethasone as the repeat antenatal corticosteroid following completion of a single course of antenatal corticosteroids (**Table 3**). The most commonly used regimen was betamethasone 2 x 12 mg, 24 hours apart.

Seven trials administered the first repeat dose(s) of antenatal betamethasone when the woman remained undelivered ≥7 days following the single course of antenatal corticosteroids with continued risk of preterm birth (Aghajafari 2002, Crowther 2006, Guinn 2001, Mazumder 2008, McEvoy 2002, Peltoniemi 2007, Wapner 2007). Three trials administered the first repeat dose(s) of antenatal betamethasone when the woman remained undelivered ≥14 days following the single course of antenatal corticosteroids with continued risk of preterm birth (Garite 2009, McEvoy 2010, Murphy 2008).

Two trials (Garite 2009, Peltoniemi 2007) did not allow any further repeat doses/courses in their trial protocol. The remaining eight trials did allow for further repeat doses/courses if the woman was still at continued risk of preterm birth.

Undelivered ≥7 days following single course of antenatal corticosteroids with continued risk of preterm birth

- 2 x 12 mg (Celestone® Soluspan®), 24 hours apart. Weekly repeat course until 33 weeks' and 6 days gestation or birth (Aghajafari 2002);
- 1 x 11.4 mg (Celestone® Chronodose). Weekly repeat dose until <32 weeks' gestation or birth (Crowther 2006);
- 2 x 12 mg (brand of betamethasone not specified) 24 hours apart. Weekly repeat course until 34 weeks' gestation or birth (Guinn 2001);
- 2 x 12 mg (brand of betamethasone not specified) 24 hours apart. Weekly repeat course until 33 weeks' and 6 days gestation or birth (Mazumder 2008);
- 2 x 12 mg (Celestone® Soluspan®), 24 hours apart. Weekly repeat course up to 34 weeks' gestation (McEvoy 2002);
- 1 x 12 mg (brand of betamethasone not specified) dose up to 34 weeks' gestation (Peltoniemi 2007);
- 2 x 12 mg (as 6 mg betamethasone sodium phosphate and 6 mg betamethasone acetate, brand not specified) 24 hours apart. Weekly repeat course up to 33 weeks' and 6 days gestation or birth (Wapner 2006).

Undelivered ≥14 days following single course of antenatal corticosteroids with continued risk of preterm birth

- 2 x 12 mg (brand of betamethasone not specified) 24 hours apart. No further repeat course (Garite 2009);
- 2 x 12 mg (Celestone® Soluspan®), 24 hours apart. Weekly repeat course up to 34 weeks' gestation (McEvoy 2010);

- 2 x 12 mg (Celestone® Soluspan®), 24 hours apart. Repeat course every 14 days until 33 weeks' gestation or birth (Murphy 2008).

Risk of bias of trials included in Crowther (2011) Cochrane systematic review

The risk of bias of the included trials (selection bias, performance and detection bias, attrition bias, reporting bias, other bias) is shown in **Table 4**. Overall the trials included in the Crowther (2011) Cochrane systematic review were considered to be at low risk of bias.

Selection bias

Eight of the 10 included trials had adequate sequence generation (Aghajafari 2002, Crowther 2006, Garite 2009, Guinn 2001, Mazumder 2008, McEvoy 2002, McEvoy 2010, Wapner 2006).

- Three trials used computer generated randomisation (Aghajafari 2002, Garite 2009, Guinn 2001).
- One trial used a website-generated random number list (Mazumder 2008).
- One trial used centralised telephone randomisation (Crowther 2006).
- Two trials used random number tables (no details) (McEvoy 2002, McEvoy 2010).
- One trial used centralised randomisation (Wapner 2006).

Two trials provided insufficient evidence to determine if adequate sequence generation had been performed (Murphy 2008, Peltoniemi 2007).

All 10 trials reported adequate allocation concealment.

- Six trials maintained allocation concealment through a centralised pharmacist on each site (Aghajafari 2002, Garite 2009, Guinn 2001, McEvoy 2002, McEvoy 2010, Wapner 2006).
- Two trials used a central telephone randomisation service for study number and then treatment pack allocation (Crowther 2006, Murphy 2008).
- Two trials used sequentially numbered opaque sealed envelopes (Mazumder 2008, Peltoniemi 2007).

Blinding (performance bias and detection bias)

A placebo was used in all the trials, except (Mazumder 2008).

Incomplete outcome data (attrition bias)

All 10 trials provided data on women and children up to the time of primary hospital discharge after birth.

- Four trials reported no losses to follow-up to primary hospital discharge (Aghajafari 2002, Crowther 2006, McEvoy 2002, Peltoniemi 2007).
- In the remaining six trials losses to follow-up to primary hospital discharge were less than 4% (Garite 2009, Guinn 2001, Mazumder 2008, McEvoy 2010, Murphy 2008, Wapner 2006).
- Five trials reported some follow-up data in early childhood (Crowther 2006, Mazumder 2008, Murphy 2008, Peltoniemi 2007, Wapner 2006). There were no data available for survival free of major neurosensory disability at two years' corrected age follow-up in 86/1146 (7.5%) of those alive at randomisation in the Crowther (2006) trial. In the Murphy (2008) trial 201/2305 (8.9%) children alive at randomisation had no data for the primary outcome of death or the presence of neurologic impairment at 18 to 24 months corrected age. Data from 56/315 (18%) of children were unavailable at two to three years of age for the primary outcome of survival without severe

neurological, cognitive or sensory impairment in the Peltoniemi (2007) trial. In the Wapner (2006) trial 108/594 (18%) did not have childhood follow-up. Interim data on follow-up at 6 months of age was not reported for (32/76) 42% of survivors (Mazumder 2008).

Selective reporting (reporting bias)

There was no evidence of selective reporting for nine of the 10 trials. There was insufficient detail to make a judgement for Mazumder (2008). The only outcome that was reported by number of repeat corticosteroid courses in the Wapner (2006) trial was body size.

Outcomes reported in the included trials

Maternal outcomes

Eight of the 10 trials reported on maternal outcomes for 4615 women (Aghajafari 2002, Crowther 2006, Garite 2009, Guinn 2001, McEvoy 2002, Murphy 2008, Peltoniemi 2007, Wapner 2006). No maternal outcomes were reported by Mazumder (2008) or McEvoy (2010).

Fetal and neonatal outcomes

All 10 trials reported on fetal and neonatal outcomes (Aghajafari 2002, Crowther 2006, Garite 2009, Guinn 2001, Mazumder 2008, McEvoy 2002, McEvoy 2010, Murphy 2008, Peltoniemi 2007, Wapner 2006).

Childhood outcomes

Six of the 10 randomised controlled trials comparing a repeat course with a single course of antenatal corticosteroids reported early childhood outcomes (up to 2 years) for 3939 children (Aghajafari 2002, Asztalos 2013, Crowther 2011b, Mazumder 2008, Peltoniemi 2007, Wapner 2006).

Two trials identified in the Crowther CPG version 2015 systematic review reported data for later childhood outcomes (up to 8 years) for 2676 children (Crowther 2006, Murphy 2008).

Child as adult outcomes:

None of the participants have currently reached adulthood so there are no data reported to date.

Table 3: Ten randomised trials reporting health outcomes following administration of a repeat course/dose of antenatal corticosteroids in women at recurrent or continued risk of preterm birth*#

Author, Year	Country	Pre-intervention treatment for both intervention and control group	Intervention if at risk of preterm birth after first course	Control	Outcomes reported			
					Maternal	Neonatal	Child	Adult
Aghajafari (2002)	Canada	2 x 12 mg betamethasone (Celestone® Soluspan®), 12 or 24 hourly; or 4 x 5-6 mg dexamethasone (brand not specified),12 hourly	Undelivered 7 or more days following initial course, and at continued risk of preterm birth (timeframe not specified) 2 x 12 mg betamethasone (Celestone® Soluspan® 6 mg betamethasone sodium phosphate and 6 mg betamethasone acetate), 24 hours apart given weekly until 33 weeks' gestation or birth (n=6 mothers and 9 infants)	Weekly placebo 2 x 24 hours apart (n=6 mothers and 7 infants)	√	√	√	N/A
Crowther (2006)	Australia and New Zealand	11.4 mg betamethasone (Celestone® Chronodose®)	Undelivered 7 or more days following initial course and at continued risk of preterm birth 11.4 mg betamethasone (Celestone® Chronodose® betamethasone 5.7mg as betamethasone sodium phosphate 3.9 mg in solution and betamethasone acetate 3mg in suspension) repeated weekly if at risk of preterm birth within the next 7 days and still <32 weeks' gestation (n=489 mothers and 568 infants)	Saline (as per intervention protocol) (n=493 mothers and 578 infants)	√	√	√	N/A
Garite (2009)	USA	2 x 12 mg betamethasone (brand not specified) 24 hours apart ≥14 days	Undelivered at least 14 days following initial course, and at continued risk of preterm birth in the next 7 days. Single course 2 x 12 mg betamethasone (brand not specified) 24 hours apart (n=223 mothers and 289 infants). *Betamethasone became temporarily unavailable in some centres and was replaced with dexamethasone 4 x 6 mg, 12 hourly. (31 women received dexamethasone and 30 women received an equivalent placebo).*	Saline 2 x 24 hours apart (n=214 mothers and 288 infants)	√	√	X	N/A
Guinn (2002)	USA	2 x 12 mg betamethasone (brand not specified), 24 hours apart; or 4 x 6 mg dexamethasone (brand not specified), given at 12 hourly	Undelivered one week following initial course and remains at high risk of preterm delivery. Weekly courses of 2 x 12 mg betamethasone (brand not specified) 24 hours apart until 34 weeks' gestation or birth (n=256 mothers and 256 infants)	Weekly placebo (n=246 mothers and 246 infants)	√	√	X	N/A
Mazumder (2008)	India	2 x 12 mg betamethasone (brand not specified)	Undelivered 7 days after initial course. Betamethasone (brand not stated) 2 x 12 mg 24 hours apart, repeated every 7 days until birth or the end of the 33rd week of gestation (n=38 infants)	Expectant management (n=38 infants)	X	√	X	N/A
McEvoy	USA	2 x 12 mg betamethasone	Undelivered one week after initial course.	Placebo (n=19	√	√	X	N/A

(2002)		(Celestone® Soluspan®) 24 hours apart	2 x 12 mg betamethasone (Celestone® Soluspan® 6 mg betamethasone sodium phosphate and 6 mg betamethasone acetate) 24 hours apart (n=18 mothers and 18 infants) up to 34 weeks' gestation	mothers and 19 infants)				
McEvoy (2010)	USA	2 x 12 mg betamethasone (Celestone® Soluspan®) 24 hours apart	Undelivered at least 14 days following initial course (93% received betamethasone). 2 x 12 mg betamethasone (Celestone® Soluspan® 6 mg betamethasone sodium phosphate and 6 mg betamethasone acetate) 24 hours apart up to 34 weeks' gestation (n=56 infants)	2 doses of placebo (25mg cortisone acetate, an inactive steroid) (n=56 infants)	X	√	X	N/A
Murphy (2008)	Multicentre (20 countries)	2 x 12 mg betamethasone (Celestone® Soluspan®), 24 hours apart	Undelivered 14-21 days after an initial course and continued high risk of preterm birth. 2 x 12 mg betamethasone (Celestone® Soluspan® 6 mg betamethasone sodium phosphate and 6 mg betamethasone acetate) 24 hours apart. If remained at risk of preterm birth continued to receive 2 x 12 mg betamethasone 24 hours apart, every 14 days until 33 weeks' gestation or birth, (n=935 mothers and 1164 infants)	Placebo injection (aluminium monostearate) (n=918 mothers and 1140 infants)	√	√	√	N/A
Peltoniemi (2007)	Finland	A single course of betamethasone (brand not specified)	Undelivered 7 or more days after initial course, and elective delivery or very high risk of spontaneous delivery within 48 hours. A repeat single dose of betamethasone (brand not specified) 12 mg up to 34 weeks' gestation (n=125 mothers and 159 infants)	A single dose of saline (n=124 mothers and 167 infants)	√	√	√	N/A
Wapner (2006)	USA	A single course of betamethasone/ dexamethasone 2 x betamethasone 12 mg 24 hours apart (as 6 mg betamethasone sodium phosphate and 6 mg betamethasone acetate)	Undelivered 7 to 10 days after initial course and high risk of spontaneous preterm birth or diagnosis of placenta praevia or chronic abruption. 2 x 12 mg betamethasone (as 6 mg betamethasone sodium phosphate and 6 mg betamethasone acetate, brand not stated) 24 hours apart repeated weekly if still at risk of preterm birth up to 33 weeks' and 6 days gestation (n=252 mothers and 296 infants)	Placebo (no details) (n=243 mothers and 294 infants)	√	√	√	N/A

*Source: Crowther (2011),

#all administered intramuscularly as betamethasone

N/A not applicable as none of the infants exposed have reached adulthood yet and no data are currently reported,

√ reported

X not reported

Table 4: Risk of bias of included trials in the Crowther (2011) Cochrane review

Author (Year)	Random sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective reporting	Other bias
Aghajafari (2002)						
Crowther (2006)						
Garite (2009)						
Guinn (2002)						
Mazumder (2008)						
McEvoy (2002)						
McEvoy (2010)						
Murphy (2008)						
Peltoniemi (2007)						
Wapner (2006)						

Low risk of bias	Unclear risk of bias	High risk of bias

3. "Different corticosteroids and regimens for accelerating fetal lung maturation for women at risk of preterm birth" (Brownfoot 2013)

Eligibility for inclusion in the Brownfoot (2013) Cochrane systematic review (population and intervention)

The Cochrane systematic review '*Different corticosteroids and regimens for accelerating fetal lung maturation for women at risk of preterm birth'* (Brownfoot 2013) included randomised controlled trials that recruited women at risk of preterm birth (spontaneous preterm labour, preterm prelabour rupture of membranes or elective preterm birth). Women with a multiple or singleton pregnancy were eligible.

The interventions reported in the trials compared different types of antenatal corticosteroid and different doses, frequency, timing and route of administration of antenatal corticosteroids. Eligibility criteria for inclusion and exclusion for each trial are detailed in Appendix L.

Primary outcomes for the Brownfoot (2013) systematic review

Primary maternal outcomes

- death;
- chorioamnionitis;
- puerperal sepsis.

Primary fetal/ neonatal outcomes

- perinatal death;
- respiratory distress syndrome;
- intraventricular haemorrhage.

Primary child and child as an adult outcomes were

- death;
- neurodevelopmental disability.

Description of trials included in the Brownfoot (2013) Cochrane systematic review and the Brownfoot CPG version 2015

The Brownfoot (2013) Cochrane systematic review included 10 relevant trials directly comparing one antenatal corticosteroid with another antenatal corticosteroid and reported health outcomes for 1159 women and 1218 infants (Chen 2005, Danesh 2012, Elimian 2007, Magee 1997, Mulder 1997, Mushkat 2001, Rotmensch 1999, Senat 1998, Subtil 2003, Urban 2005) (**Table 5**).

Two trials directly compared different doses or timing of antenatal corticosteroids. The Brownfoot (2013) Cochrane systematic review included one trial (Khandelwal, 2012) and the updated literature search, Brownfoot CPG version 2015, identified one additional trial (Romejko-Wolniewicz 2013) (**Table 5**).

Geographical location of where these trials were conducted

Two of the trials were conducted in France (Senat 1998, Subtil 2003), two in Israel (Mushkat 2001, Rotmensch 1999), two in the USA (Elimian 2007, Khandelwal, 2012), two in Poland (Urban 2005, Romejko-Wolniewicz 2013) and one each in Taiwan (Chen 2005), UK (Magee 1997), Netherlands (Mulder 1997), and Iran (Danesh 2012).

Era of conduct of these trials

Four trials were conducted in the 1990's (Magee 1997, Mulder 1997, Rotmensch 1999, Senat 1998) and the remainder were conducted after 2000 (Chen 2005, Danesh 2012, Elimian 2007, Khandelwal, 2012; Mushkat 2001, Romejko-Wolniewicz 2013, Subtil 2003, Urban 2005).

Antenatal corticosteroid regimen utilised within these trials

A number of different drug regimens were used (**Table 5**):

- 24 mg betamethasone (12 mg, two doses, 24 hourly) and 24 mg dexamethasone (6 mg, four doses, 12 hourly in six trials (Chen 2005, Danesh 2012, Elimian 2007, Rotmensch 1999, Subtil 2003, Urban 2005);
- 24 mg betamethasone (12 mg, two doses, 12 hourly) and 24 mg dexamethasone (12 mg, two doses, 12 hourly) in two trials (Magee 1997, Mushkat 2001);
- 24 mg betamethasone (6 mg, four doses, 12 hourly) and 16 mg dexamethasone (4 mg, four doses, 12 hourly) in one trial (Senat 1998);
- 24 mg betamethasone (12 mg, two doses, 24 hourly) and 24 mg dexamethasone (12 mg, two doses, 12 hourly) in one trial (Mulder 1997).

In the trials that compared doses or timing of administration of antenatal corticosteroids:

- Khandelwal (2012) directly compared 2 doses of 12 mg of betamethasone 12 hours apart (24 mg completed in 12 hours) with 2 doses of 12 mg of betamethasone 24 hours apart (24 mg completed in 24 hours) (no details on type of betamethasone used).
- Romejko-Wolniewicz (2013) compared 6 doses of 4 mg of betamethasone 8 hours apart (24 mg completed in 30 hours) with 2 doses of 12 mg of betamethasone 24 hours apart (24 mg completed in 24 hours) (no details of type of betamethasone provided).

Risk of bias of trials included in Brownfoot (2013) Cochrane systematic review and Brownfoot CPG version 2015

The risk of bias of the included trials (selection bias, performance and detection bias, attrition bias, reporting bias, other bias) is shown in **Table 6**. Overall there was low risk of bias for methods of randomisation, however there was less detail provided for allocation concealment and therefore this was considered to be unclear risk of bias overall. Four of the 12 trials provided adequate information to determine blinding of participants and personnel. Overall incomplete outcome data and selective reporting were considered to be unclear risk of bias due to lack of detail.

Selection bias

- Five of the 12 trials had adequate allocation concealment (Danesh 2012, Elimian 2007, Khandelwal 2012, Magee 1997, Urban 2005).
- Three of the 12 trials (Rotmensch 1999, Senat 1998, Subtil 2003) had adequate methods of randomisation but the methods of allocation concealment were unclear.
- One trial was quasi-randomised and considered to be at high risk for selection bias (Mushkat 2001).
- Three trials did not provide sufficient details to judge random sequence allocation or allocation concealment and the risk of bias was judged to be unclear (Chen 2005, Mulder 1997, Romejko-Wolniewicz, 2013).

Performance and detection bias (blinding)

- Three of the 12 trials reported blinding of clinicians and participants (Elimian 2007, Magee 1997, Mushkat 2001).
- Four of the 12 trials did not provide any details on blinding of women or researchers (Chen 2005, Mulder 1997, Rotmensch 1999, Urban 2005).
- In five of the 12 trials there was no evidence of blinding (or blinding was not considered to be possible) (Danesh 2012, Khandelwal 2012, Romejko-Wolniewicz, 2013, Senat 1998, Subtil 2003). Outcome assessors were blinded in Khandelwal 2012.

Incomplete outcome data (attrition bias)

- Four of the 12 trials had a low risk of bias for attrition (Danesh 2012, Khandelwal 2012, Senat 1998, Urban 2005).
- Losses to follow up were not clearly reported by Romejko-Wolniewicz (2013) and Rotmensch (1999), and not reported by Mushkat (2001).
- One trial (Elimian 2007) reported no losses to follow-up, however less than 60% of the infants were assessed for intraventricular haemorrhage and periventricular leukomalacia.
- Two trials reported losses to follow-up in excess of 50% at the end of follow-up for some of the biophysical parameters (Magee 1997, Subtil 2003).
- One trial excluded 16% of the women with no details provided on the reasons for exclusion and was considered to be at high risk of attrition bias (Chen 2005).

Selective reporting (reporting bias)

- There was no indication of selective reporting in three of the 12 trials (Elimian 2007, Khandelwal 2012, Subtil 2003).
- One trial did not fully report outcomes that had been pre-specified in the methods section of the original paper (Mushkat 2001).
- For the remaining eight trials, the trial protocol had not been viewed and no judgement could be made as to whether all pre-specified outcomes for the individual trials had been reported.

Outcomes reported in the included trials

Maternal outcomes

Khandelwal 2012 reported on maternal fever and maternal postpartum length of stay. None of the other 11 trials reported on any of the primary or secondary maternal outcomes for the systematic review (**Table 5**).

Fetal and neonatal outcomes

Fetal and or neonatal outcomes were reported by all 12 of the trials (Chen 2005, Danesh 2012, Elimian 2007, Khandelwal 2012, Magee 1997, Mulder 1997, Mushkat 2001, Romejko-Wolniewicz 2013, Rotmensch 1999, Senat 1998, Subtil 2003, Urban 2005) (**Table 5**).

Childhood outcomes and child as adult outcomes

Only one of the 12 trials reported on childhood follow-up (Subtil 2003). Twelve children of the 105 (11%) randomised infants were followed up at 18 months of age (Subtil 2003). Outcomes for the child as an adult were not reported in any of the trials included in the review (**Table 5**).

Table 5: Randomised trials comparing dexamethasone and betamethasone as the antenatal corticosteroid in women at risk of preterm birth*#

				Outcomes reported			
Author/year	Country	Betamethasone (number of women/infants)	Dexamethasone or other comparison (number of women/infants)	Maternal	Neonatal	Child	Adult
Chen (2005)	Taiwan	Betamethasone 2 x 12 mg 24 hourly (brand not specified) (n=81 infants)^	Dexamethasone 4x 6 mg (brand not specified) 12 hourly (n=76 infants)^	X	√	X	X
Danesh (2012)	Iran	Betamethasone sodium (Exir Pharmaceutical Lab., Tehran, Iran) 2 x 12 mg 24 hourly (n=120 women, 120 infants)	Dexamethasone phosphate (Iranhormone Pharmaceutical Lab., Tehran, Iran) 4x 6 mg 12 hourly (n=120 women, 120 infants)	X	√	X	X
Elimian (2007)	USA	Betamethasone (Celestone® Soluspan®), 2 x 12 mg 24 hourly (n= 150 women, 181 infants)	Dexamethasone sodium phosphate (Baxter Healthcare) 4x 6 mg 12 hourly (n=149 women, 178 infants)	X	√	X	X
Khandelwal (2012)	USA	Betamethasone (brand not specified) 2 x 12mg 12 hourly (n=161 women, 180 infants)	Betamethasone (brand not specified) 2 x 12mg 24 hourly (n=67 women, 80 infants)	√	√	X	X
Magee (1997)	UK	Betamethasone (brand not specified) 2 x 12 mg 24 hourly (n=29 women, 29 infants)	Dexamethasone (brand not specified) 2 x 12 mg, 12 hourly (n=29 women, 29 infants)	X	√	X	X
Mulder (1997)	Netherlands	Betamethasone Celestone® Chronodose®) 2 x 12 mg 24 hourly (n=26 women, 26 infants)	Dexamethasone (brand not specified) 2 x 12 mg, 12 hourly (n=24 women, 24 infants)	X	√	X	X
Mushkat (2001)	Israel	Betamethasone (brand not specified) 2 x 12 mg (betamethasone sodium 12 mg and betamethasone acetate 12 mg) 12 hourly (n=17 women, 17 infants)	Dexamethasone (brand not specified) 2 x 12 mg, 12 hourly (n=16 women, 16 infants)	X	√	X	X
Romejo-Wolniewicz (2013)	Poland	Betamethasone (brand not specified)6 x 4mg 8 hourly (n=45 women)	Betamethasone (brand not specified) 2 x 12mg24 hourly (n=76 women)	X	√	X	X
Rotmensch (1999)	Israel & Italy	Betamethasone (Bentalan®) 2 x 12 mg 24 hourly (n=22 women, 22 infants)	Dexamethasone (Decadron®) 2 x 12 mg, 24 hourly (n=24 women, 24 infants)	X	√	X	X
Senat (1998)	France	Betamethasone (Celestone® Chronodose®) 4 x 3 mg (3 mg betamethasone sodium and 3 mg betamethasone acetate) 12 hourly (n=42 women, 53 infants)	Dexamethasone acetate (Soludecadron®) 4 x 4 mg, 12 hourly (n= 40 women, 44 infants)	X	√	X	X
Subtil (2003)	France	Betamethasone acetate and phosphate (Celestone® Chronodose®) 2 x 12 mg, 24 hourly (n=35 women, 35 infants); Betamethasone phosphate (Celestone®) 4 x 6 mg 12 hourly (n=36 women, 36 infants)	Dexamethasone phosphate (Soludecadron®) 4 x 6 mg, 12 hourly (n=36 women, 36 infants)	X	√	√	X
Urban (2005)	Poland	Betamethasone (Diprophos®) 2x 12 mg 24 hourly (n=33 women, 33 infants)	Dexamethasone (Dexaven®) 4x 6 mg 12 hourly (n=34 women, 34 infants)	X	√	X	X

* Source Brownfoot CPG version 2015; #all antenatal corticosteroids administered intramuscularly

^ Chen (2005) analysed data for 140 women of 168 randomised. There are no details to the number allocated to each group and no primary maternal outcomes were reported.

√ reported, X not reported

Table 6: Risk of bias of included trials comparing regimens of antenatal corticosteorids in the Brownfoot CPG version 2015 systematic review

Author (Year)	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Chen (2005)							
Danesh (2012)							
Elimian (2007)							
Khandelwal (2012)							
Magee (1997)							
Mulder (1997)							
Mushkat (2001)							
Romejo-Wolniewicz (2013)							
Rotmensch (1999)							
Senat (1998)							
Subtil (2003)							
Urban (2005)							

Low risk of bias	Unclear risk of bias	High risk of bias

4. '*Corticosteroids for preventing neonatal respiratory morbidity after elective caesarean section at term'* (Sotiriadis, 2009).

Eligibility for inclusion in Sotiriadis (2009) Cochrane systematic review (population and intervention)

The Cochrane systematic review '*Corticosteroids for preventing neonatal respiratory morbidity after elective caesarean section at term'* (Sotiriadis 2009) included only randomised or quasi-randomised controlled trials that recruited women prior to elective caesarean section at term (37 weeks' and 0 days gestation). Women were eligible if they had a twin or a singleton pregnancy. Higher order multiple pregnancies were excluded due to low prevalence and the unlikelihood of reaching term gestation. The interventions reported in eligible trials could compare a prophylactic course of antenatal corticosteroid (betamethasone, dexamethasone, or hydrocortisone) with placebo, or with no treatment.

Primary outcomes for the Sotiriadis (2009) Cochrane systematic review

Primary maternal outcomes:

There were no pre-specified primary maternal outcomes.

Primary fetal/ neonatal outcomes

- respiratory distress syndrome;
- transient tachypnoea of the newborn;
- admission to neonatal special care or intensive care for respiratory morbidity;
- need for mechanical ventilation.

Primary child and child as an adult outcomes

There were no pre-specified child and child as an adult outcomes.

Description of trials included in the Sotiriadis CPG version 2015 systematic review

One randomised controlled trial was included in the Sotiriadis (2009) Cochrane systematic review. There were data available for 943 women and 942 infants (Stutchfield 2005). A follow-up of Stutchfield (2005) for children age 8 to 15 years was identified in the Sotiriadis CPG version 2015 systematic review (Stutchfield 2013). The Sotiriadis CPG version 2015 systematic review also identified one additional trial (Ahmed 2014) including 452 women and 452 infants.

Geographical location of where the trial was conducted

The Stutchfield (2005) trial was conducted in the United Kingdom. The Ahmed (2014) trial was conducted in Egypt.

Era of conduct of the trial

The Stutchfield trial was conducted in 2005 and the Ahmed trial was conducted in 2014.

Antenatal corticosteroid regimen utilised within the trial

The intervention used by Stutchfield (2005) was betamethasone 2 x 12 mg 24 hours apart compared with standard care. No details are provided in the review or in the original paper as to the type of betamethasone administered.

The Ahmed (2014) trial used a total dose of 24 mg dexamethasone (2 doses of 12 mg dexamethasone) completed in 24 hours compared with no antenatal corticosteroids.

Risk of bias of trials included in the Sotiriadis CPG version 2015 systematic review

The risk of bias of the included trials (selection bias, performance and detection bias, attrition bias, reporting bias, other bias) is shown in **Table 6**. There was low risk of bias for methods of randomisation and allocation concealment in one trial and insufficient information to make a judgement for the second trial. None of the participants were blinded (high risk of bias) although outcome assessors were blinded in both trials. Overall incomplete outcome data and selective reporting were considered to be of high risk of bias in one trial and low risk of bias in the second trial. The risk of bias for selective reporting was unclear in both trials. The overall risk of bias is unclear.

Selection bias

- Randomisation - Stutchfield (2005) used a random number generator; Ahmed (2014) provided no details for randomisation.
- Allocation concealment - Stutchfield (2005) used centralised allocation; Ahmed (2014) provided no details for allocation concealment.

Performance and detection bias (blinding):

- Blinding - neither Stutchfield (2005) nor Ahmed (2014) used a placebo and there was no blinding of participants; both Stutchfield (2005) and Ahmed (2014) blinded outcome assessors to the allocation of participants.

Incomplete outcome data (attrition bias)

- Stutchfield (2005) randomised 998 women and analysed 942 women (7% loss in treatment, 4% in controls; 17% protocol violations and losses to follow-up). Of the 56 (6%) women who were excluded; 20 had a twin pregnancy and 7 women gave birth before 37 weeks. There is no information on the remaining 29 women. One hundred and twenty three women were not treated per protocol; 51 had an emergency caesarean section, 24 had a normal birth, 26 did not receive antenatal corticosteroids and the remaining 32 deviated from the dosing regimen, did not have proper documentation or withdrew. Childhood follow-up by questionnaire was completed in 407 of the 799 children who were contacted (51%) (Stutchfield 2013).
- Ahmed (2014) randomised and analysed 452 women. There were no details on protocol violations, if any. No follow-up after hospital discharge has been reported.

Selective reporting:

- Stutchfield (2005) did not pre-specify maternal outcomes but did report on side effects; Ahmed (2014) did not pre-specify or report on maternal outcomes. Infant outcomes pre-specified were respiratory distress syndrome, transient tachypnoea of the newborn, admission to neonatal intensive care but then also reported on duration of neonatal intensive care stay, Apgar scores and mortality. No long term follow-up was reported.

Other bias

- Stutchfield (2005) calculated a sample size of 1100 women based on a reduction in admission to special care baby units for respiratory distress (998 women were randomised). There were no details of sample size calculation reported in the Ahmed (2014) trial.

Table 7: Risk of bias of trials using antenatal corticosteroids prior to elective caesarean section at term

Author (Year)	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Stutchfield (2005)							
Ahmed (2014)							

Low risk of bias	Unclear risk of bias	High risk of bias

Outcomes reported in the included trials

Maternal outcomes

There were no primary maternal health outcomes from the systematic review reported in the Stutchfield (2005) trial, which only reported on maternal side effects although these were not pre-specified. The Ahmed (2014) trials did not pre-specify or report on any maternal outcomes.

Fetal and neonatal outcomes

Both the Stutchfield (2005) and the Ahmed (2014) trials reported on neonatal outcomes.

Childhood outcomes

Stutchfield (2013) reported on follow-up of 862 children from the four largest recruiting centres in the trial, this was 92% of the original study. Of these, 824 (96%) were traced and 799 (93%) were successfully contacted. Only 51% (407/799) completed and returned the questionnaire. No childhood outcomes were reported in the Ahmed (2014) trial.

Child as adult outcomes

There were no outcomes reported for the child as an adult in either the Stutchfield (2005) or Ahmed (2014) trials.

Chapter 3: Benefits and harms of a single course of antenatal corticosteroids for the mother at risk of preterm birth

What are the short and long term benefits and harms of a single course of antenatal corticosteroids for the mother at risk of preterm birth?

The following evidence is based on the Roberts CPG version 2015 systematic review which updated the Roberts (2006) Cochrane systematic review. Evidence is taken from 26 randomised controlled trials (4469 women and 4853 infants) comparing a single course of antenatal corticosteroids with no antenatal corticosteroids where there was a risk for preterm birth. Details of all maternal outcomes can be found in Appendix D.

Maternal primary outcomes for these Clinical Practice Guidelines:

Maternal infection - There were no differences in the risks of maternal infection morbidity outcomes (including chorioamnionitis, puerperal sepsis, pyrexia after trial entry, intrapartum pyrexia or postnatal pyrexia requiring antibiotic treatment) between women treated with a single course of antenatal steroids compared with women who had no antenatal corticosteroids (**Table 8**).

Other primary maternal outcomes for these Clinical Practice Guidelines - No trials included in the Roberts CPG version 2015 systematic review reported data for maternal quality of life.

Table 8: Maternal infection in women treated with a single course of antenatal steroids compared with no treatment*

Outcome	Risk ratio (RR) (95% Confidence Interval)	Number of trials	Trials contributing data	Number of women
Chorioamnionitis	RR 0.90 (0.69 to 1.17)	13	Amorim 1999; Carlan 1991; Dexiprom 1999; Fekih 2002; Garite 1992; Kari 1994; Lewis 1996; Liggins 1972; Lopez 1989; Morales 1989; Qublan 2001; Schutte 1980; Silver 1996	2525
Puerperal sepsis	RR 1.35 (0.93 to 1.95)	8	Amorim 1999; Dexiprom 1999; Garite 1992; Lewis 1996; Qublan 2001; Schutte 1980; Silver 1996; Taeusch 1979	1003
Pyrexia after trial entry^	RR 1.11 (0.74 to 1.67)	4	Amorim 1999; Nelson 1985; Schutte 1980; Taeusch 1979	481
Intrapartum pyrexia^	RR 0.60 (0.15 to 2.49)	2	Amorim 1999; Schutte 1980	319
Postnatal pyrexia^	RR 0.92 (0.64 to 1.33)	5	Amorim 1999; Collaborative 1981; Dexiprom 1999; Fekih 2002; Schutte 1980	1323

* Source Roberts CPG version 2015; ^ requiring treatment with antibiotics

Maternal secondary outcomes for these Clinical Practice Guidelines:

Mortality - Maternal mortality was reported in three trials (Amorim 1999, Dexiprom 1999, Schutte 1980). There were no differences in maternal mortality between women treated with a single course of antenatal corticosteroids and those who had no antenatal corticosteroids (RR 0.98, 95%CI 0.06 to 15.5, 3 trials, n=365 women).

Hypertension - One trial reported on the outcome of hypertension. There were no differences in hypertension between women treated with a single course of antenatal corticosteroids and those who had no antenatal corticosteroids (RR 1.00, 95%CI 0.36 to 2.76, 1 trial, n=220 women).

Health service use - Admission to intensive care was reported in two trials (Amorim 1999, Schutte 1980). There were no differences in maternal admission to intensive care between women treated with a single course of antenatal corticosteroids and those not treated (RR 0.74, 95%CI 0.26 to 2.05, 2 trials, n=319 women).

One trial of women with severe pre-eclampsia (Amorim 1999) found no difference in the mean length of antenatal hospitalisation (MD 0.50, 95%CI -1.40 to 2.40, n=218 women) or in the mean length of postnatal hospitalisation (MD 0.00, 95%CI -1.72 to 1.72, n=218 women) between women who had been treated with a single course of antenatal corticosteroids and those not treated.

Adverse effects of antenatal corticosteroid therapy - (including gastrointestinal upset, glucose intolerance, insomnia, pain at injection site, bruising at injection site, infection at injection site, weight gain, Cushing syndrome). Four trials reported no adverse effects (no details provided) associated with the use of antenatal corticosteroids (Balci 2010, Porto 2011, Schutte 1980, Shanks 2010).

Glucose intolerance - Only one of 26 trials, which randomised women with severe pre-eclampsia, reported on glucose intolerance (Amorim 1999). Glucose tolerance was assessed ≥72 hours after the first dose of antenatal corticosteroids using a 100 g, 3 hour oral glucose tolerance test (Fasting plasma glucose ≥5.8 mmol/L; 1 hour ≥10.6 mmol/L; 2 hour ≥9.2 mmol/L; 3 hour ≥8.1 mmol/L with two or more abnormal results required for diagnosis (O'Sullivan 1964)). Glucose tolerance was only reported in a subset of those randomised (123 of 200; 62%). There was a significant increase in the rate of glucose intolerance between women with severe pre-eclampsia who had been treated with a single course of antenatal corticosteroids and those who had not been treated (RR 2.71, 95%CI 1.14 to 6.46, 1 trial, n=123 women). Caution is advised in interpreting these results due to the incomplete reporting of all women randomised and evidence of imprecision (wide confidence intervals).

There is clearly a paucity of relevant randomised trial evidence about the impact of antenatal corticosteroid use on maternal glucose tolerance. Further research is needed to assess the health impact, if any, of changes in maternal blood glucose control after administration of a single course of antenatal corticosteroids.

Other maternal secondary outcomes for the Clinical Practice Guidelines -

- *No data were reported in the included trials* for any of the other clinical practice guidelines secondary outcomes for the mother that included mode of birth, postpartum haemorrhage, breastfeeding at hospital discharge/6 months postnatally, postnatal depression symptoms, anxiety, maternal hyperglycaemia, maternal hypoglycaemia, glycated haemoglobin A1c, changes in glycaemic control after administration of antenatal corticosteroids or insulin use after trial entry.

Chapter 4: Benefits and harms of a single course of antenatal corticosteroids for the infant prior to preterm birth

What are the short and long term fetal, infant, child and adult benefits and harms of a single course of antenatal corticosteroids prior to preterm birth?

The following evidence is based on the Roberts CPG version 2015 systematic review which updated the Roberts (2006) Cochrane systematic review. Evidence is taken from 26 randomised controlled trials (4469 women and 4853 infants) comparing a single course of antenatal corticosteroids with no antenatal corticosteroids where there was a risk for preterm birth. Details of all infant outcomes can be found in Appendix E and childhood and adulthood outcomes in Appendix F. For these Clinical Practice Guidelines we calculated the absolute risk and the number needed to treat, where reported.

Infant primary outcomes for these Clinical Practice Guidelines:

Fetal, neonatal or later death - Deaths were reported in 21 of the 26 trials in the Roberts CPG version 2015 systematic review (**Table 9**).

Perinatal death - Treatment with a single course of antenatal corticosteroids significantly reduced the risk of perinatal death compared with no exposure to antenatal corticosteroids (RR 0.72, 95%CI 0.58 to 0.89; 13 trials, n=3627 infants) using a random effects model.

- The absolute risk reduction was -4% (95%CI -7% to -2%). The number of women needing treatment with a single course of antenatal corticosteroids to prevent one perinatal death was 23 (95%CI 15 to 50).

Fetal death - No difference was seen between exposure to a single course of antenatal corticosteroids and no exposure for the risk of fetal death (RR 0.98, 95%CI 0.73 to 1.30; 13 trials, n=3627 infants).

Neonatal death - Treatment with a single course of antenatal corticosteroids significantly reduced the risk of neonatal death compared with no exposure to antenatal corticosteroids (RR 0.68, 95%CI 0.58 to 0.80; 21 trials, n=4408).

- The absolute risk reduction was -4% (95%CI -6% to -3%). The number of women needing to be treated with a single course of antenatal corticosteroids to prevent one neonatal death was 22 (95%CI 16 to 38).

Respiratory distress syndrome - Twenty-five of the 26 trials reported on respiratory distress syndrome. A single course of antenatal corticosteroids significantly reduced the risk of respiratory distress syndrome (any) (RR 0.66, 95%CI 0.56 to 0.78; 25 trials, n=4590 infants). For these Clinical Practice Guidelines a random effects model was used due to significant heterogeneity.

- The absolute risk difference was -9% (95%CI -14% to -5%). The number of women needing to be treated with a single course of antenatal corticosteroids to prevent one case of respiratory distress syndrome (any) was 13 (95%CI 10 to 18).

Table 9: Primary infant outcomes following exposure to a single course of antenatal corticosteroids compared with no exposure*

Outcome	Risk ratio (RR) (95% Confidence Interval)	Number of trials	Trials contributing data	Number of infants
Perinatal death	RR 0.72 (0.58 to 0.89)^	13	Amorim 1999; Block 1977; Collaborative 1981; Dexiprom 1999; Doran 1980; Gamsu 1989; Garite 1992; Kari 1994; Liggins 1972; Parsons 1988; Qublan 2001; Schutte 1980; Taeusch 1979	3627
Fetal death	RR 0.98 (0.73 to 1.30)	13	Amorim 1999; Block 1977; Collaborative 1981; Dexiprom 1999; Doran 1980; Gamsu 1989; Garite 1992; Kari 1994; Liggins 1972; Parsons 1988; Qublan 2001; Schutte 1980; Taeusch 1979	3627
Neonatal death	RR 0.68 (0.58 to 0.80)	21	Amorim 1999; Block 1977; Collaborative 1981; Dexiprom 1999; Doran 1980; Fekih 2002; Gamsu 1989; Garite 1992; Goodner 1979; Kari 1994; Liggins 1972; Lewis 1996; Lopez 1989; Morales 1989; Nelson 1985; Parsons 1988; Porto 2011; Qublan 2001; Schutte 1980; Silver 1996; Taeusch 1979	4408
Respiratory distress syndrome (any)	RR 0.66 (0.56 to 0.78)^	25	Amorim 1999; Balci 2010; Block 1977; Cararach 1991; Carlan 1991; Collaborative 1981; Dexiprom 1999; Doran 1980; Fekih 2002; Gamsu 1989; Garite 1992; Goodner 1979; Kari 1994; Liggins 1972; Lewis 1996; Lopez 1989; Morales 1989; Nelson 1985; Parsons 1988; Porto 2011; Qublan 2001; Schutte 1980; Silver 1996; Taeusch 1979; Teramo 1980	4590

* Source Roberts CPG version 2015; ^random effects model used due to significant heterogeneity;
^Meta-analysis conducted for these Clinical Practice Guidelines using random effects model due to significant heterogeneity

These Clinical Practice Guidelines investigated whether there was a differential effect on the severity of respiratory distress syndrome (mild versus moderate/severe respiratory distress syndrome) by extracting data from six trials that had reported both respiratory distress (any) and moderate/severe respiratory distress (Amorim 1999, Fekih 2002, Liggins 1972, Nelson 1985, Silver 1996, Taeusch 1979) and conducting a subgroup interaction test.

- Examining the data for severity of respiratory disease (mild, moderate/severe) separately the subgroup interaction test, using a random effects model due to significant heterogeneity, was not statistically significant ($Chi^2 = 1.68$, $p = 0.19$, $I^2 = 40.6\%$). This can be interpreted as indicating no differential treatment effect based on the severity of respiratory distress syndrome with a single course of antenatal corticosteroids (Appendix N, **Figure 1**).

Composite of serious infant outcomes - No trials included in the Roberts CPG version 2015 systematic review reported on a composite primary outcome measure for the infant.

Infant secondary outcomes for these Clinical Practice Guidelines:

Interval between trial entry and birth **-** Three trials included in the Roberts CPG version 2015 systematic review reported on the mean interval (days) between trial entry and birth (Amorim 1999, Lewis 1996, Liggins 1972) and no difference was seen between infants exposed to antenatal corticosteroids and those not exposed (Appendix E).

Other respiratory outcomes **-** In keeping with the beneficial reduction in respiratory distress syndrome, there were benefits seen for infants exposed to antenatal corticosteroids compared with no exposure in other respiratory outcomes including

- a significantly reduced need for respiratory support (27% relative risk reduction);
- significantly reduced duration of respiratory support (reduced by almost one and a half days) ;
- significantly reduced mean duration of oxygen supplementation (reduced by almost 3 days) (**Table 10**).

No differences were seen between exposure to a single course of antenatal corticosteroids and no exposure for chronic lung disease, surfactant use or air leak syndrome (Appendix E).

Intraventricular haemorrhage **-** Intraventricular haemorrhage (any) was reported in 13 trials and five trials reported on severe intraventricular haemorrhage (Grade 3 or 4). Exposure to a single course of antenatal corticosteroids compared with no exposure significantly reduced the risk of intraventricular haemorrhage (any) (RR 0.54, 95%CI 0.43 to 0.69; 13 trials, n=2872 infants) and severe intraventricular haemorrhage (RR 0.28, 95%CI 0.16 to 0.50; 5 trials, n=572 infants) (**Table 10**).

- The absolute risk reduction for intraventricular haemorrhage (any) was -5% (95%CI -7% to -3%). The number of women needing to be treated with a single course of antenatal corticosteroids to prevent one case of intraventricular haemorrhage (any) in their infant was 21 (95%CI 15 to 36).
- For severe intraventricular haemorrhage (Grade 3 or 4) the absolute risk reduction was -12% (95%CI -17% to -7%) and the number of women needing to be treated with a single course of antenatal corticosteroids to prevent one case of severe intraventricular haemorrhage in their infant was 8 (95%CI 6 to 14).

Necrotising enterocolitis **-** Necrotising enterocolitis was reported in eight trials. The risk of necrotising enterocolitis was significantly reduced in infants exposed to a single course of antenatal corticosteroids compared with no exposure (RR 0.46, 95%CI 0.29 to 0.74, 8 trials, n=1675 infants) (**Table 10**).

- The absolute risk reduction was -3% (95%CI -5% to -1%). The number of infants who required exposure to a single course of antenatal corticosteroids to prevent one case of necrotising enterocolitis was 29 (95%CI 18 to 72).

Table 10: Significant secondary infant outcomes following exposure to a single course of antenatal corticosteroids compared with no exposure*

Outcome	Risk ratio (RR), Mean difference (MD) (95% Confidence Interval)	Number of trials	Trials contributing data	Number of infants
Need for respiratory support	RR 0.73 (0.59 to 0.92)	7	Amorim 1999; Balci 2010; Block 1977; Dexiprom 1999; Garite 1992; Porto 2011; Shanks 2010	1021
Duration of respiratory support (days)	MD -1.42 (-2.28 to -0.56)#	3	Garite 1992; Morales 1989; Porto 2011	518
Mean duration of oxygen supplementation (days)	MD -2.86 (-5.51 to -0.21)	1	Amorim 1999	73
Intraventricular haemorrhage (any)	RR 0.54 (0.43 to 0.69)	13	Amorim 1999; Dexiprom 1999; Doran 1980; Fekih 2002; Gamsu 1989; Garite 1992; Kari 1994; Liggins 1972; Lewis 1996; Morales 1989; Qublan 2001; Silver 1996; Taeusch 1979	2872
Severe intraventricular haemorrhage (Grade 3 to 4)	RR 0.28 (0.16 to 0.50)	5	Amorim 1999; Garite 1992; Kari 1994; Lewis 1996; Morales 1989	572
Necrotising enterocolitis	RR 0.46 (0.29 to 0.74)	8	Amorim 1999; Collaborative 1981; Dexiprom 1999; Kari 1994; Lewis 1996; Morales 1989; Qublan 2001; Silver 1996	1675
Systemic infection in first 48 hours after birth	RR 0.57 (0.38 to 0.86)	6	Amorim 1999; Collaborative 1981; Dexiprom 1999; Gamsu 1989; Lopez 1989; Parsons 1988	1319

* Source Roberts CPG version 2015; # random effects used due to significant heterogeneity

Systemic infection within 48 hours of birth **-** Six trials reported on the risk of systemic infection within 48 hours of birth (Table 10). The risk of systemic infection within the first 48 hours of birth was significantly reduced for infants who had been exposed to antenatal corticosteroids compared to those with no exposure (RR 0.57, 95%CI 0.38 to 0.86; 6 trials, n=1319 infants) (**Table 10**).

- The absolute risk reduction for systemic infection in the infant with a single course of antenatal corticosteroids was -4% (95%CI -6 to -1%). The number infants requiring exposure to a single course of antenatal corticosteroids to prevent one case of systemic infection within 48 hours of birth was 28 (95%CI 16 to 104).

Hypothalamic Pituitary Adrenal axis function - A single trial (Teramo 1980) found no differences in cortisol concentrations between infants exposed to a single course of antenatal corticosteroids and no exposure to corticosteroids for infants born <24 hours (n=6), 24 to ≤48 hours (n=10) and >48 hours (n=11) after the first dose.

Other Clinical Practice Guidelines secondary outcomes -

- *There were no statistical differences* for any of the other infant secondary outcomes for these Clinical Practice Guidelines based on the Roberts CPG version 2015 systematic review including small for gestational age, birthweight, Apgar score <7 at 5 minutes, admission to neonatal intensive care unit or length of neonatal hospitalisation (Appendix E).

- *No data were reported in the included trials* for the remaining infant secondary outcomes for these Clinical Practice Guidelines. These included transient tachypnoea of the newborn, pulmonary hypertension, use of oxygen supplementation, inotropic support, use of nitric oxide for respiratory support, periventricular leukomalacia, retinopathy of prematurity, patent ductus arteriosus, neonatal blood pressure, neonatal hypoglycaemia, neonatal hyperglycaemia requiring treatment, gestational age at birth, birth length, birth head circumference, z scores at birth, anthropometry at hospital discharge, placental weight or use of postnatal corticosteroids.

Infant as a child primary outcomes for these Clinical Practice Guidelines:
None of the trials included in the Roberts CPG version 2015 systematic review reported on:

- ***neurosensory disability in childhood;***
- ***survival free of neurosensory disability in childhood; or***
- ***survival free of metabolic disease in childhood.***

Infant as a child secondary outcomes for these Clinical Practice Guidelines:
Five randomised trials reported on secondary outcomes in childhood (Collaborative 1981; Kari 1994, Schutte 1980, Amorim 1999, Liggins 1972). Developmental delay and other impairments were variously defined by individual trials.

- Kari (1994) followed 82 of 91 surviving children (79% of those born before 34 weeks' gestation) up to 24 months of age (Salokorpi 1997).
- The Collaborative (1981) trial followed 406 of 646 surviving children up to 36 months of age (55% of 739 infants who entered the trial) (Collaborative Group on Antenatal Steroid Therapy 1984).
- Liggins (1972) followed up 258 surviving children up to 4 years of age (81% of the 318 infants included in the trial) (MacArthur 1981, MacArthur 1982).
- Schutte (1980) followed 90 of 102 surviving children up to 12 years of age (73% of the original 123 infants) for psychological development and 84 of 102 children (68%) for physical development (Schmand 1990).
- No data detailing the age at the time of follow-up are available for the Amorim (1999) trial although additional unpublished data were provided to the Cochrane systematic review authors (Roberts 2006).

Developmental outcomes **-** The Schutte (1980) trial follow-up, reported by Schmand (1990), found no differences between children exposed to antenatal corticosteroids and those not exposed for learning/behavioural disabilities as measured by requirement of special education or having to repeat a class at 10 to 12 years of age (Schmand 1990) (**Table 11**).

Developmental delay in childhood was reported in two trials (Amorim 1999, Collaborative 1981). The Amorim (1999) trial did not detail the outcome assessment used, the Collaborative (1981) trial used the Bayleys Motor Development Index. There was a borderline reduction in developmental delay for children who had been exposed *in utero* to antenatal corticosteroids compared to those with no exposure (RR 0.49, 95%CI 0.24 to 1.00; 2 trials, n=518 children). There was an imbalance in the number of children followed up in the Amorim (1999) trial with more children being followed up in the antenatal corticosteroid group (n=60) compared with the no exposure group (n=34).

Neurodevelopmental outcomes were reported by one trial (Kari 1994). Kari (1994) reported on severe disability that was defined as tetraplegic cerebral palsy and/or mental retardation (Bayleys Mental Index < 70). This trial found no difference in neurodevelopmental delay between children who had been exposed

in utero to antenatal corticosteroids compared to those with no exposure (RR 0.64, 95%CI 0.14 to 2.98; 1 trial, n=82 children). There was an imbalance in the number of children followed up in the Kari (1994) trial with more children being followed up in the antenatal corticosteroid group (n=50) compared with the no exposure group (n=32).

Neurosensory disability or impairment - There was no statistically significant difference in the risk of cerebral palsy in childhood between children who had been exposed to antenatal corticosteroids *in utero* and those with no exposure (RR 0.60, 95% CI 0.34 to 1.03, 5 trials (Amorim, 1999; Collaborative 1981; Kari 1994; Liggins 1972; Schutte 1980; n=904 children) (**Table 11**).

There were no differences between exposure to a single course of antenatal corticosteroids and no exposure for visual or auditory sensory impairment (**Table 11**).

Other infant as a child secondary outcomes for these Clinical Practice Guidelines -

- *Where data were reported*, no statistically significant differences were seen between exposure to a single course of antenatal corticosteroids and no exposure for death in childhood, anthropometric measures in childhood (weight, head circumference, height), respiratory measures (vital capacity, forced expiratory volume), systolic blood pressure or age at puberty (Roberts 2006) (Appendix F). At four years of age there were no differences seen between exposure to a single course of antenatal corticosteroids and no exposure for standardised measurements of intelligence in the follow-up of the Liggins trial (MacArthur 1981). At the six year follow-up of the Liggins trial (MacArthur 1982) there were no differences seen between exposure to a single course of antenatal corticosteroids and no exposure for teachers' estimates of general progress at school or reading progress at school. There were no formalised tests for educational attainment reported.

- *No data were reported in the included trials* for the following infant as a child secondary outcomes for these Clinical Practice Guidelines*:* child behaviour, educational attainment, insulin sensitivity, hypothalamic pituitary adrenal axis suppression or diabetes.

Table 11: Developmental outcomes for the infant in childhood following exposure to a single course of antenatal corticosteroids compared with no exposure*

Outcome in childhood	Risk ratio (RR) (95% Confidence Interval)	Number of trials	Trials contributing data	Number of infants	Proportion of infants followed up
Cerebral palsy	RR 0.60 (0.34 to 1.03)	5	Amorim, 1999; Collaborative 1981; Kari 1994; Liggins 1972; Schutte 1980	904	36%
Learning/behavioural difficulties	RR 0.86 (0.35 to 2.09)	1	Schutte 1980 (Schmand 1990)	90	73%
Developmental delay	RR 0.49 (0.24 to 1.00)	2	Amorim, 1999; Collaborative 1981	518	53%
Neurodevelopmental delay	RR 0.64 (0.14 to 2.98)	1	Kari, 1994	82	43%
Visual impairment	RR 0.55 (0.24 to 1.23)	2	Kari 1994; Schutte 1980	166	53%
Hearing impairment	RR 0.64 (0.04 to 9.87)	2	Kari 1994; Schutte 1980	166	53%

* Source Roberts CPG version 2015

Infant as an adult primary outcomes for the Clinical Practice Guidelines:

None of the 26 trials included in the Roberts CPG version 2015 systematic review reported on

- ***neurosensory disability for the infant followed into adulthood;***
- ***survival free of neurosensory disability for the infant followed into adulthood; or***
- ***survival free of metabolic disease for the infant followed into adulthood.***

Infant as an adult secondary outcomes for these Clinical Practice Guidelines:

Two of the 26 randomised controlled trials included in the Roberts CPG version 2015 systematic review reported follow-up of the infant into adulthood following exposure to a single antenatal course of corticosteroids prior to preterm birth (Liggins 1972; Schutte 1980) (**Table 12**).

- The Auckland Steroid Trial (Liggins 1972) recruited 1142 women who gave birth to 1218 infants. At 30 years follow up 713 (73%) of the neonatal survivors were traced of whom 534 (75%) participated in the follow-up (Dalziel 2005, Dalziel 2006a, Dalziel 2006b).
- The Schutte (1980) trial at 20 years followed-up 102 survivors of the 119 infants and 81 (68%) participated in the follow-up study (48 antenatal corticosteroid and 33 placebo group) (Dessens 2000).

Sensory impairment **-** Follow-up into adulthood of infants from the Auckland Steroid Trial (Liggins 1972) found no differences between *in utero* exposure and no exposure to antenatal corticosteroids for either visual or auditory impairment (**Table 12**).

Anthropometry **-** Small size at birth is associated with reduced adult bone mass, however no differences were found between *in utero* exposure to a single course of antenatal corticosteroids and no exposure to antenatal corticosteroids for bone mineral density, femoral geometry or bone mineral content in 174 adults who were followed up after a mean of 31 years (Dalziel 2006a).

Respiratory outcomes **-** No differences were found between *in utero* betamathasone exposure and no exposure for any of the respiratory outcomes reported including current asthma or respiratory function measures (forced vital capacity, forced expiratory volume in 1 second) (Dalziel 2006b).

Blood pressure **-** At the 30 year follow-up from the Liggins (1972) trial there was no difference in systolic blood pressure between groups reported by Dalziel (2006b). At 20 years follow-up of the Schutte trial systolic blood pressure was significantly lower in the antenatal corticosteroid exposed group but there were no differences found in diastolic blood pressure compared with no exposure to antenatal corticosteroids (Dessens 2000). When the data for systolic blood pressure were combined in a meta-analysis there was no overall difference (**Table 12**).

Hypothalamic pituitary adrenal axis function **-** At the 30 year follow-up of the Liggins (1972) trial there was no evidence of any suppressed function of the hypothalamic adrenal axis function between adults who had been exposed in utero to antenatal corticosteroids and those with no exposure (Dalziel 2006b) (**Table 12**).

Table 12: Outcomes for infant as an adult following exposure to a single course of antenatal corticosteroids compared with no exposure*

Outcome in adulthood	Risk ratio (RR)/ mean difference (MD) (95% Confidence Interval)	Number of trials	Trials contributing data	Number of adults
Hearing impairment	RR 0.24 (0.03 to 2.03)	1	Liggins 1972	192
Visual impairment	RR 0.91 (0.53 to 1.55)	1	Liggins 1972	192
Educational attainment	RR 0.94 (0.80 to 1.10)	1	Liggins 1972	534
Adult weight (kg)	MD 0.80 (-2.02 to 3.62)	2	Liggins 1972; Schutte 1980	538
Adult height (cm)	MD 0.91 (-0.28 to 2.10)	2	Liggins 1972; Schutte 1980	537
Skinfold thickness (cm)				
Triceps	MD -0.02 (-0.11 to 0.07)	1	Liggins 1972	456
Biceps	MD -0.01 (-0.11 to 0.09)	1	Liggins 1972	456
Subscapular	MD 0.01 (-0.08 to 0.10)	1	Liggins 1972	441
Suprailiac	MD -0.01 (-0.12 to 0.10)	1	Liggins 1972	452
Respiratory outcomes				
FVC (% predicted)	MD -0.70 (-3.16 to 1.76)	1	Liggins 1972	383
FEV1 (% predicted)	MD 0.40 (-2.31 to 3.11)	1	Liggins 1972	383
FEV1/FVC	MD 0.01 (-0.01 to 0.03)	1	Liggins 1972	383
PEF	MD 2.20 (-0.77 to 5.17)	1	Liggins 1972	383
F50	MD 3.00 (-1.57 to 7.57)	1	Liggins 1972	383
F25	MD 0.40 (-3.82 to 4.62)	1	Liggins 1972	383
FEF 25-75%	MD 2.20 (-2.10 to 6.50)	1	Liggins 1972	383
FEV1/FVC <70%	MD 0.86 (0.4 to, 1.65)	1	Liggins 1972	383
Wheezing in last 12 months	OR 1.10 (0.77 to 1.57)	1	Liggins 1972	534
Current Asthma	OR 1.06 (0.69 to 1.63)	1	Liggins 1972	534
Further respiratory diagnosis (pneumonia, upper airway conditions, bronchitis)	OR 1.36 (0.67 to 2.76)	1	Liggins 1972	534
Mean systolic blood pressure (mm/Hg)	MD -0.87 (-2.81 to 1.07)	2	Liggins 1972; Schutte 1980	545
Adult lumbar spine (g/cm2) areal bone mineral density	MD 0.00 (-0.04 to 0.04)	1	Liggins 1972	174
Adult lumbar spine (g/cm3) volumetric bone mineral density	MD 0.00 (-0.01 to 0.01)	1	Liggins 1972	174
Adult total body (grams) bone mineral content	MD 18.00 (-151.30 to 187.30)	1	Liggins 1972	174
Adult total body (g/cm3) areal bone mineral density	MD 0.00 (-0.03 to 0.03)	1	Liggins 1972	174
Adult femoral neck (g/cm2) areal bone mineral density	MD 0.02 (-0.03 to 0.07)	1	Liggins 1972	174
Adult femoral trochanter (g/cm2) areal bone mineral density	MD 0.02 (-0.02 to 0.06)	1	Liggins 1972	174
Adult femoral shaft (g/cm2) areal bone mineral density	MD 0.01 (-0.04 to 0.06)	1	Liggins 1972	174
Total proximal femur areal bone mineral density (g/cm2)	MD 0.02 (-0.03 to 0.07)	1	Liggins 1972	174
Hypothalamic pituitary adrenal axis function (fasting plasma cortisol [log values])	MD 0.06 (-0.02, 0.14)	1	Liggins 1972	444
Fasting plasma glucose concentration (mmol/L)	MD 0.01 (-0.09, 0.11)	1	Liggins 1972	432
Plasma glucose concentration (mmol/L) after 2 hour 75g oral glucose tolerance test	MD -0.27 (-0.52, -0.02)	1	Liggins 1972	410
Plasma insulin concentration [log values] after 2 hour 75g oral glucose tolerance test	MD -0.10 (-0.27, 0.07)	1	Liggins 1972	428

* Source Roberts CPG version 2015

Diabetes - Thirty year follow-up of the Liggins (1972) trial by Dalziel (2005) included a 2 hour, 75 g oral glucose tolerance test.

- Fasting plasma glucose concentrations or fasting plasma insulin were not different in adulthood between those exposed to antenatal corticosteroids *in utero* and those with no exposure.

- At 30 minutes plasma glucose concentrations were similar between those exposed to antenatal corticosteroids *in utero* and those with no exposure (7.5 mmol/L vs 7.3 mmol/L) although plasma insulin concentration was significantly higher at 30 minutes (60.5 mIU/L vs 52 mIU/L; p=0.02).

- At 120 minutes the plasma insulin concentrations were similar between those exposed to antenatal corticosteroids *in utero* and those with no exposure (21.0 mIU/L vs 23.5 mIU/L) and plasma glucose concentrations were lower (p=0.05) in the antenatal betamethasone group compared with the placebo group (4.6±1.1 vs 4.9±1.5 mmol/L; p=0.05) (**Table 12**) (Dalziel 2005).

The authors concluded that the changes in the glucose-insulin axis were small and the clinical significance, if any, was unclear (Dalziel 2005). They suggested that their results at 30 years follow-up could indicate increased risk of diabetes and cardiovascular disease later in life. Further exploration of data on the glucose-insulin axis is required from cases of earlier *in utero* exposure and repeat exposure to antenatal corticosteroids.

Other infant as an adult secondary outcomes for these Clinical Practice Guidelines -

- *Where data were reported*, no differences were seen in a number of infant as an adult secondary outcomes for these Clinical Practice Guidelines between adults who had been exposed *in utero* to antenatal corticosteroids and those who had not been exposed including mortality (Dalziel 2005), educational attainment (Dalziel 2006b, Dessens 2000), cognitive functioning (Dessens 2000) or body size (Dalziel 2006a, Dessens 2000). Follow-up into adulthood of infants from the Auckland Steroid Trial (Liggins 1972) found no differences between *in utero* exposure and no exposure to antenatal corticosteroids for diabetes or cardiovascular disease in the adults followed up (Appendix F).

- Data on cerebral palsy for the infant as an adult was not reported in the Roberts CPG version 2015 systematic review.

Chapter 5: Evidence Summary for the use of a single course of antenatal corticosteroids for women and their infants at risk of preterm birth

For the mother

Randomised controlled trial evidence shows no maternal health benefits or serious health harms to women at risk of preterm birth treated with antenatal corticosteroids for fetal lung maturation.

There was no evidence of increased risk of maternal infection variously reported as chorioamnionitis, puerperal sepsis, pyrexia requiring treatment with antibiotics after trial entry, intrapartum or postnatally.

There was minimal high quality evidence on the association of antenatal corticosteroid treatment and increased maternal blood glucose concentration. The evidence from one randomised trial (Amorim 1999) was based on a population of 123 women with severe pre-eclampsia where an increased risk of glucose intolerance (O'Sullivan 1964) was reported in those women who had been treated with antenatal corticosteroids compared with no antenatal corticosteroids. Caution is advised when extrapolating this evidence to all women receiving antenatal corticosteroids.

Better information is required on elevation, if any, of blood glucose concentration with antenatal corticosteroid use and, if present, the degree, duration of effect and impact on the mother and infant. Any transitory increases in maternal blood glucose concentration due to antenatal corticosteroids in non-diabetic women are likely to be outweighed by the significant health benefits to the infant and are unlikely to require additional monitoring.

For the infant

Exposure to a single course of antenatal corticosteroids, when there is a risk of preterm birth, compared with no exposure was associated with clear and significant major health benefits for the infant including reduced risk for:

- perinatal death;
- neonatal death;
- respiratory distress syndrome;
- need for and duration of respiratory support;
- intraventricular haemorrhage (including both any type and severe);
- necrotising enterocolitis;
- risk of systemic infection within 48 hours.

Overall there were no significant differences between exposure to antenatal corticosteroids and no exposure for birthweight, Apgar score <7 at 5 minutes and no evidence of suppressed hypothalamic pituitary adrenal axis, although the evidence for the latter is based on a single trial.

For the infant as a child

There has been minimal follow-up of the infants of mothers recruited into the original trials of a single course of antenatal corticosteroids (5 of 26 trials).

None of the 26 trials included in the Roberts CPG version 2015 systematic review reported data for any of the infant as a child primary outcomes for these Clinical Practice Guidelines (neurosensory disability;

and survival free of neurosensory disability, survival free of metabolic disease). There was a borderline reduction in developmental delay reported in two trials.

There were no differences seen in sensory impairment, body size or respiratory measures for infants in childhood who had been exposed to antenatal corticosteroids compared with those who had not been exposed.

For the infant as an adult

Only two of the 26 trials have provided follow-up of infants of mothers recruited into the original trials of a single course of antenatal corticosteroids (Liggins 1972, Schutte 1980) with one trial reporting follow-up at 30 years (Liggins, 1972).

- Reassuringly, no overall difference was seen in sensory impairment, body size, systolic blood pressure, respiratory outcomes, cardiovascular or hypothalamic pituitary adrenal axis function between *in utero* exposure to antenatal corticosteroids and no exposure. One study (Dalziel 2005) at 30 year follow-up of survivors of the Liggins (1972) trial reported that adults who had been exposed to betamethasone *in utero* did show small changes in the glucose-insulin axis (higher plasma insulin concentration 30 minutes after a glucose load and lower plasma glucose concentrations after 120 minutes) without immediate clinical impact. The authors suggested that the results could indicate an increased risk of diabetes and cardiovascular disease later in life.

See Appendix M1 – Evidence summary (Page 311)

What are the short and long term benefits and harms of a single course of antenatal corticosteroids for the mother, fetus, infant, child and adult prior to preterm birth?

Clinical recommendation	Strength of recommendation	
	NHMRC	GRADE
In women at risk of preterm birth use a single course of antenatal corticosteroids.	A	STRONG

Research recommendations:

- There is a need to better assess the degree and health impact, if any, of changes in maternal blood glucose control from administration of a single course of antenatal corticosteroids on maternal and infant health outcomes.
- There is a need to better assess the impact, if any, of *in utero* exposure to a single course of antenatal corticosteroids on:
  - the hypothalamic-pituitary adrenal axis of the infant, child and adult.
  - the glucose-insulin axis in childhood
  - the later risk of the infant developing diabetes in adulthood.
- Future research that investigates the use of a single course of antenatal corticosteroids should include outcomes on maternal quality of life.

Chapter 6: Benefits and harms of repeat dose(s) of antenatal corticosteroids for the mother at ongoing risk of preterm birth

For a woman at risk of preterm birth, who has received a single course of antenatal corticosteroids and remains at ongoing risk of preterm birth, what are the short and long term benefits and harms of a repeat dose(s) of antenatal corticosteroids for the mother?

There still remains the uncertainty about the use of a repeat dose(s) of antenatal corticosteroids for women who remain at risk of preterm birth and who have already received a single course of antenatal corticosteroids.

Chapter 2 outlined the Cochrane systematic review *Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes* (Crowther 2011) which included 10 randomised controlled trials (4733 women and 5700 infants) comparing repeat course(s) of antenatal corticosteroids with no repeat antenatal corticosteroids where there was a risk for preterm birth. Details of all maternal outcomes reported in the Crowther (2011) systematic review can be found in Appendix G.

Maternal primary outcomes for these Clinical Practice Guidelines:

Maternal infection - Treatment with repeat antenatal corticosteroids compared with no repeat treatment did not increase the risk of maternal infectious morbidity for any of the pre-specified outcomes for these Clinical Practice Guidelines (**Table 13**).

Chorioamnionitis - No difference was seen in the risk for chorioamnionitis between women treated with repeat doses of antenatal corticosteroids compared with women who received no repeat treatment (RR 1.16, 95%CI 0.92 to 1.46; 6 trials, n=4261 women)

Puerperal sepsis - No difference was seen in the risk for puerperal sepsis between women treated with repeat doses of antenatal corticosteroids compared with women who received no repeat doses (RR 1.15, 95%CI 0.83 to 1.60; 5 trials, n=3091 women).

Postnatal pyrexia requiring treatment - No difference was seen in the risk for postnatal pyrexia requiring treatment between women treated with repeat doses of antenatal corticosteroids compared with women who received no repeat doses (RR 0.87, 95%CI 0.55 to 1.38; 1 trial, n=982 women).

Other maternal infection outcomes - No trials included in the Crowther (2011) systematic review reported on pyrexia after entry into the trial or intrapartum pyrexia requiring antibiotics.

Other maternal primary outcomes for these Clinical Practice Guidelines **-** No trials in the Crowther CPG version 2015 systematic review reported on maternal quality of life.

Table 13: Maternal primary outcomes in women treated with repeat doses of antenatal corticosteroids compared with women who received no repeat doses*

Outcome	Risk ratio RR (95% Confidence Interval)	Number of trials	Trials contributing data	Number of women
Chorioamnionitis	RR 1.16 (0.92 to 1.46)	6	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Murphy 2008; Wapner 2006	4261
Puerperal sepsis	RR 1.15 (0.83 to 1.60)	5	Aghajafari 2002; Guinn 2001; Murphy 2008; Peltoniemi 2007; Wapner 2006	3091
Postnatal pyrexia^	RR 0.87 (0.55 to 1.38)	1	Crowther 2006	982

*Source: Crowther (2011),
^Requiring treatment with antibiotics

Maternal secondary outcomes for these Clinical Practice Guidelines:

Adverse effects of antenatal corticosteroid therapy - Repeat doses of antenatal corticosteroids were associated with reduced bruising at injection site compared with placebo (no details provided) where increased bruising was found (RR 0.38, 95%CI 0.21 to 0.71, 1 trial, n=492 women) (Wapner 2006).

Women given repeat dose(s) of antenatal corticosteroids were more likely to experience increased insomnia (RR 2.60, 95%CI 1.10 to 6.30; 3 trials, n=1486 women) compared with no repeat dose(s) (absolute risk 2 % versus 0.8%). There were no details provided on the duration of the insomnia (Crowther 2011). The absolute risk difference was 1% (95%CI 0% to 3%) between women receiving a repeat dose(s) and those with no repeat dose(s).

There was no difference seen in the risk of maternal hyperglycaemia, defined as an abnormal 1 hour oral glucose tolerance test (no other details given), between women who had received a repeat course of antenatal corticosteroids and those who had no repeat antenatal corticosteroid treatment reported in one trial (Wapner 2006) (RR 1.31, 95%CI 0.89 to 1.93, 1 trial, n=492 women). The trial protocol stated a course to be two doses of 12 mg betamethasone (as 6 mg betamethasone sodium phosphate and 6 mg betamethasone acetate) as the repeat antenatal corticosteroid; the regimen providing a total of 24 mg betamethasone completed in 24 hours.

Other maternal secondary outcomes for these Clinical Practice Guidelines -

- *Where data were reported*, no significant differences were seen for any of the other pre-specified maternal secondary outcomes for these Clinical Practice Guidelines including hypertension, mode of birth, postpartum haemorrhage, or pain at injection site reported in the Crowther systematic review (2011) (Appendix G).

- *No data were reported in the included trials* for the other maternal secondary outcomes from these Clinical Practice Guidelines for the outcomes of maternal mortality, breastfeeding at hospital discharge, breastfeeding at 6 months postnatally, anxiety or insulin use after trial entry in the Crowther (2011) systematic review.

Chapter 7: Benefits and harms of repeat dose(s) of antenatal corticosteroids prior to preterm birth for the infant

For a woman at risk of preterm birth, who has received a single course of antenatal corticosteroids and is at ongoing risk of preterm birth, what are the short and long term benefits and harms of a repeat dose(s) of antenatal corticosteroids for the fetus, infant, child and adult?

There still remains the uncertainty about the use of repeat antenatal corticosteroids for the infant of a woman who remains at risk of preterm birth and who has already received a single course of antenatal corticosteroids.

Chapter 2 outlined the Cochrane systematic review *Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes* (Crowther 2011) which included 10 randomised controlled trials (4733 women and 5700 infants) comparing repeat dose(s) of antenatal corticosteroids with no repeat antenatal corticosteroids where there was a risk for preterm birth. Details of all infant outcomes reported in the Crowther (2011) systematic review can be found in Appendix H. Details of all early childhood and adulthood outcomes can be found in Appendix I. For these Clinical Practice Guidelines we calculated the absolute risk and the number needed to treat, where reported.

Infant primary outcomes for these Clinical Practice Guidelines:

Fetal, neonatal or later death - There were no differences seen between repeat and no repeat exposure to antenatal corticosteroids for perinatal death, fetal or neonatal death in the Crowther (2011) systematic review (**Table 14**).

Respiratory distress syndrome - Eight trials including 3206 infants reported on respiratory distress syndrome in the Crowther (2011) systematic review. Repeat exposure compared with no repeat exposure to antenatal corticosteroids was associated with a significant reduction in respiratory distress syndrome (RR 0.83, 95%CI 0.75 to 0.91, 8 trials, n=3206 infants) (**Table 14**) (Crowther 2011).

- The absolute risk reduction was -6% (-9% to -3%) the number of women needing to be treated with repeat antenatal corticosteroids to prevent one case of respiratory distress syndrome in their infant was 16 (95%CI 10 to 31).

These Clinical Practice Guidelines investigated whether the severity of respiratory distress differed by treatment. Data for mild/moderate and severe respiratory distress syndrome were available from five trials including 2522 infants (Crowther 2006, Guinn 2001, Mazumder 2008, Peltoniemi 2007, Wapner 2006). We used a random effects model due to significant heterogeneity.

- Examining the data for the severity of respiratory disease separately (mild/moderate, severe) the subgroup interaction test was not significant (Chi^2=1.14, p=0.28, I^2=12.6%). This can be interpreted as indicating that the overall treatment effect was similar regardless of the severity of respiratory disease (Appendix N - **Figure 2**).

Composite of serious infant outcomes - Seven trials reported on a composite of serious infant outcomes (variously defined by the trials that included fetal, neonatal or later death, severe respiratory distress, severe intraventricular haemorrhage (Grades 3 or 4), chronic lung disease, necrotising enterocolitis, retinopathy of prematurity, cystic periventricular leukomalacia, patent ductus arteriosus, neonatal encephalopathy). Repeat exposure compared with no repeat exposure to antenatal corticosteroids significantly reduced the risk of serious infant outcome (RR 0.84, 95%CI 0.75 to 0.94; 7 trials n=5094 infants) (**Table 14**).

- The absolute risk reduction was -3% (95%CI -5% to -1%). The number of women needing to be treated with repeat antenatal corticosteroids to prevent one case of a composite of serious infant outcomes was 29 (95%CI 18 to 80).

Table 14: Primary outcomes in infants exposed to repeat doses of antenatal betamethasone compared with no repeat antenatal betamethasone*

Outcome	Risk ratio (RR) (95% Confidence Interval)	Number of trials	Trials contributing data	Number of infants
Perinatal death	RR 0.94 (0.71 to 1.23)	9	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Mazumder 2008; McEvoy 2010; Murphy 2008; Peltoniemi 2007; Wapner 2006	5554
Fetal death	RR 0.82 (0.24 to 2.84)	7	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Mazumder 2008; McEvoy 2010; Peltoniemi 2007	2755
Neonatal death	RR 0.91 (0.62 to 1.34)	7	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Mazumder 2008; McEvoy 2010; Peltoniemi 2007	2713
Respiratory distress syndrome	RR 0.83 (0.75 to 0.91)	8	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Mazumder 2008; McEvoy 2002; Peltoniemi 2007; Wapner 2006	3206
Composite serious outcome	RR 0.84 (0.75 to 0.94)	7	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Mazumder 2008; Peltoniemi 2007; Wapner 2006	5094

* Source: Crowther (2011)

Table 15: Significant secondary outcomes in infants exposed to repeat doses of antenatal betamethasone compared with no repeat antenatal betamethasone*

Outcome	Risk ratio (RR) (95% Confidence Interval)	Number of trials	Trials contributing data	Number of infants
Use of mechanical ventilation	RR 0.84 (0.71 to 0.99)	6	Crowther 2006; Garite 2009; McEvoy 2002; Murphy 2008; Peltoniemi 2007; Wapner 2006	4918
Use of oxygen supplementation	RR 0.92 (0.85 to 0.99)	2	Crowther 2006; Murphy 2008	3448
Use of surfactant	RR 0.78 (0.65 to 0.95)	9	Crowther 2006; Garite 2009; Guinn 2001; Mazumder 2008; McEvoy 2002; McEvoy 2010; Murphy 2008; Peltoniemi 2007; Wapner 2006	5525
Inotropic support	RR 0.80 (0.66 to 0.97)	2	Crowther 2006; Peltoniemi 2007	1470
Patent ductus arteriosus	RR 0.80 (0.64 to 0.98)	6	Aghajafari 2002; Crowther 2006; Mazumder 2008; Murphy 2008; Peltoniemi 2007; Wapner 2006	4356

* Source: Crowther (2011)

Infant secondary outcomes for these Clinical Practice Guidelines:

Other respiratory outcomes - Repeat antenatal corticosteroids were associated with:

- a significant reduction in use of mechanical ventilation (RR 0.84, 95%CI 0.71 to 0.99; 6 trials, n=4918 infants). The absolute risk reduction was -5% (95%CI -9% to -1%). The number of women needing to be treated with repeat antenatal corticosteroids to prevent one infant requiring mechanical ventilation was 22 (95%CI 14 to 46).
- a significant reduction in use of oxygen supplementation (RR 0.92, 95%CI 0.85 to 0.99; 2 trials, n=3448 infants). The absolute risk reduction was -4% (95%CI -7% to -0%). The number of women needing to be treated with repeat antenatal corticosteroids to prevent one infant requiring supplemental oxygen was 26 (95%CI 14 to 170).
- a significant reduction in use of surfactant (RR 0.78, 95%CI 0.65 to 0.95; 9 trials, n=5525 infants). The absolute risk reduction was -5% (95%CI -9% to -2%). The number of women needing to be treated with repeat antenatal corticosteroids to prevent one infant requiring surfactant was 21 (95%CI 14 to 38).
- a reduction in use of inotropic support (RR 0.80, 95%CI 0.66 to 0.97; 2 trials n=1470 infants). The absolute risk reduction was -5% (95%CI -8% to -1%). The number of women needing to be treated with repeat antenatal corticosteroids to prevent one infant requiring inotropic support was 22 (95%CI 11 to 164) (**Table 15**).

No differences were seen between groups for chronic lung disease, air leak syndrome, duration of oxygen supplementation, duration of respiratory support or use of nitric oxide (Appendix H). The latter outcomes are limited to evidence from a single trial.

Intraventricular haemorrhage - No differences were seen between repeat and no repeat exposure for the risk of intraventricular haemorrhage (any grade) (RR 0.94, 95%CI 0.75 to 1.18; 6 trials, n=3065 infants) or for severe intraventricular haemorrhage (Grades 3/4) (RR 1.13, 95%CI 0.69 to 1.86; 6 trials, n=4819 infants).

Patent ductus arteriosus - The risk of patent ductus arteriosus was reduced for infants who had been exposed to repeat antenatal corticosteroids compared with no repeat exposure (RR 0.80, 95%CI 0.64 to 0.98, 6 trials, n=4356 infants) (**Table 15**).

- The absolute risk reduction was -2% (95%CI -3% to 0%). The number of women needing to be treated with repeat antenatal corticosteroids to prevent one case of patent ductus arteriosus in their infant was 59 (95%CI 31 to 549).

Cardiovascular disease - Only one trial (Crowther 2006) reported on data for neonatal blood pressure. No significant differences were seen between repeat exposure and no repeat exposure to antenatal corticosteroids for mean infant blood pressure on the first day after birth or at six weeks postnatal age. A subset of infants from the Crowther (2006) trial were followed up at 48 to 72 hours after birth and there was no evidence of cardiac hypertrophy between those exposed to antenatal corticosteroids and those with no exposure (Mildenhall 2006) (Appendix H).

Gestational age at birth - No differences were seen between infants exposed to repeat antenatal corticosteroids and those not exposed for gestational age at birth (MD -0.09 weeks, 95%CI -0.33 to 0.15; 8 trials, n=3179 infants), or in the risk of being born preterm <37 weeks' gestation (RR 0.97, 95%CI 0.92 to 1.02; 2 trials, n=1181 infants), very preterm <34 weeks' gestation (RR 1.01, 95%CI 0.95 to 1.07; 4 trials, n=2140 infants), or extremely preterm <28 weeks' gestation (RR 1.07, 95%CI 0.83 to 1.38; 2 trials, n=1632 infants).

Body size -

Body size at birth - Repeat antenatal corticosteroids were associated with a reduction in a number of body size measurements at birth including unadjusted mean weight (MD -75.79 grams, 95%CI -117.63 to -33.96; 9 trials, n=5626 infants), head circumference at birth (MD -0.32 centimetres, 95%CI -0.49 to -0.15; 9 trials, n=5625 infants) and length at birth (MD -0.56 centimetres, 95%CI -0.89 to -0.23) (**Table 16**).

Measures of body size are dependent on gestational age at birth. The z score adjusts for gestational age to more fully assess the actual effects that repeat antenatal corticosteroid treatment may have on body size. Repeat doses of antenatal corticosteroids were associated with a borderline reduction in z scores at birth for birthweight (MD -0.11, 95%CI 0.23 to 0.00; 2 trials, n=1256 infants) and head circumference (MD -0.14, 95%CI -0.27 to 0.00; 2 trials, n= 1256 infants) but not for length (MD -0.05, 95%CI -0.19 to 0.09; 2 trials, n=1256 infants). The clinical significance, if any, of small differences in z scores for birthweight or head circumference at birth are unclear.

Repeat antenatal corticosteroids compared to no repeat exposure was not associated with any differences in the risk of being small for gestational age (RR 1.18; 95%CI 0.97 to 1.43; 7 trials, n=3975 infants) reported in seven trials (Aghajafari 2002, Garite 2009, Mazumder 2008, McEvoy 2010, Murphy 2008, Peltoniemi 2007, Wapner 2006).

Table 16: Body size measurements following exposure to repeat doses of antenatal corticosteroids compared with no repeat doses*

Outcome	Mean difference (MD) (95% Confidence Interval)	Number of trials	Trials contributing data	Number of infants
Mean measurements at birth				
Weight (grams)	MD -75.79 (-117.63 to -33.96)	9	Crowther 2006; Garite 2009; Guinn 2001; Mazumder 2008; McEvoy 2002; McEvoy 2010; Murphy 2008; Peltoniemi 2007; Wapner 2006	5626
Head circumference (centimetres)	MD -0.32 (-0.49 to -0.15)	9	Crowther 2006; Garite 2009; Guinn 2001; Mazumder 2008; McEvoy 2002; McEvoy 2010; Murphy 2008; Peltoniemi 2007; Wapner 2006	5625
Length (centimetres)	MD -0.56 (-0.89 to -0.23)	6	Crowther 2006; Mazumder 2008; McEvoy 2010; Murphy 2008; Peltoniemi 2007; Wapner 2006	4550
z scores at birth				
Weight	MD -0.11 (0.23 to 0.00)	2	Crowther 2006; McEvoy 2010	1256
Head circumference	MD -0.14 (-0.27 to 0.00)	2	Crowther 2006; McEvoy 2010	1256
Length	MD -0.05 (-0.19 to 0.09)	2	Crowther 2006; McEvoy 2010	1256

* Source: Crowther (2011)

Body size at primary hospital discharge - In two trials of 1256 infants (Crowther 2006, McEvoy 2010), at primary hospital discharge, no significant differences were seen between repeat exposure and no repeat exposure to antenatal corticosteroids for infant body size measurements or the corresponding z scores (**Table 17**).

Infants at one centre within the ACTORDS trial (Crowther 2006) (n=145) were followed up and the effects of repeat antenatal corticosteroids on postnatal changes in linear growth were reported (Battin 2012). Infants exposed to repeat doses of antenatal corticosteroids grew more rapidly in the postnatal period than those not exposed to repeat corticosteroids. Accelerated growth included weight, head

circumference and length, and continued for 3 to 5 weeks postpartum. Again the clinical significance, if any, of these reported differences is unclear. There were no significant differences between repeat and no repeat corticosteroid groups in: measurements from birth to discharge; change in z score in the first six weeks in the whole cohort of 145 infants, or change in z score in the first six weeks in the subgroup of infants still in hospital at 6 weeks.

Hypothalamic pituitary adrenal axis function - One report (Ashwood 2006) detailed data from one centre within the ACTORDS trial (Crowther 2006). The mean basal cortisol concentration from cord blood at birth was significantly lower in the infants exposed to repeat antenatal corticosteroids compared with no repeat exposure (MD -44.90 mmol/L, 95%CI -78.41 to -11.39, 1 trial, n=67 infants). Two nested studies within the ACTORDS trial (Crowther 2006) reported no on-going alteration to neonatal hypothalamic adrenal axis function following exposure to repeat courses of antenatal steroids using plasma cortisol collected on day 2 (median) of life (range 1-5 days) (Battin 2007) and using salivary cortisol up to 21 days after birth (Ashwood 2006).

Table 17: Body size at primary hospital discharge for infants exposed to repeat doses of antenatal corticosteroids compared no repeat antenatal corticosteroids*

Outcome at primary hospital discharge	Mean difference (MD) (95% Confidence Interval)	Number of trials	Trials contributing data	Number of infants
Mean measurements at hospital discharge				
Weight (grams)	MD -1.00 (-77.15 to 75.15)	1	Crowther 2006	1090
Head circumference (centimetres)	MD 0.12 (-0.10 to 0.35)	2	Crowther 2006; McEvoy 2010	1195
Length (centimetres)	MD 0.02 (-0.44 to 0.47)	2	Crowther 2006; McEvoy 2010	1189
z scores at hospital discharge				
Weight	MD -0.05 (-0.16 to 0.06)	2	Crowther 2006; McEvoy 2010	1195
Head circumference	MD -0.03 (-0.15 to 0.10)	2	Crowther 2006; McEvoy 2010	1195
Length	MD -0.06 (-0.23 to 0.10)	2	Crowther 2006; McEvoy 2010	1189

* Source: Crowther (2011)

Other infant secondary outcomes for these Clinical Practice Guidelines -

- *Where data were reported*, no differences were seen between repeat exposure and no repeat exposure to antenatal corticosteroids for periventricular leukomalacia, necrotising enterocolitis, retinopathy of prematurity, Apgar score < 7 at 5 minutes, early systemic infection or late neonatal infection, use of postnatal corticosteroids or admission to the neonatal intensive care unit (Appendix H).

- *No data were reported in the included trials for:* Interval between trial entry and birth, transient tachypnoea of the newborn, pulmonary hypertension, neonatal hypoglycaemia, neonatal hyperglycaemia and placental weight.

Infant as a child (early childhood) primary outcomes for these Clinical Practice Guidelines

These Clinical Practice Guidelines defined early childhood follow-up as being up to 3 years of age. Four trials, included in the Crowther (2011) systematic review have contributed data to the follow-up of the infant as a child ≤3 years of age (Crowther 2006, Murphy 2008, Peltoniemi 2007, Wapner 2006).

- In the Crowther (2006) trial there were 1146 fetuses alive at randomisation of which 1090 (95%) babies survived to initial hospital discharge. Of the 1085 children who were alive at 2 years of age, 1047 (96.5%) were seen at two years for assessment (521 exposed to repeat-corticosteroid treatment and 526 exposed to placebo) (Crowther 2007).
- In the Murphy (2008) trial, 2318 fetuses were alive at randomisation, of which 2221 (96%) babies survived to initial hospital discharge. A total of 2104 (94%) were assessed at 18 to 24 months of age (Asztalos 2010).
- In the Peltoniemi (2007) trial 326 fetuses were alive at randomisation, of which 313 (96%) babies survived to initial hospital discharge. At 2 year follow up, 259 (82%) surviving infants completed the assessment (120 in the antenatal corticosteroid group and 139 in the placebo group) (Peltoniemi 2009).
- In the Wapner (2006) trial, 591 fetuses were alive at randomisation, of which 582 (98%) survived to initial hospital discharge. Of the 556 infants available for 2 year follow-up; 486 children (87%) underwent physical examination and 465 (84%) underwent developmental testing (Wapner 2007).

Neurosensory disability - Two trials (Asztalos 2010, Crowther 2007) reported on a neurosensory disability composite score (including severe cerebral palsy, severe developmental delay, blindness) for the infant as a child. No difference was seen in early childhood follow-up for infants exposed to repeat antenatal corticosteroids compared to those with no repeat exposure (RR 0.99, 95%CI 0.87 to 1.12, 2 trials, n=3164 children) (**Table 18**).

Survival free of major neurosensory disability - Two trials (Crowther 2007, Peltoniemi 2009) reported on survival free of major neurosensory disability in Crowther (2011). No significant difference was seen at early childhood follow-up for infants exposed to repeat antenatal corticosteroids compared to those with no repeat exposure (RR 1.01, 95%CI 0.92 to 1.11; 2 trials, n=1317 children) (**Table 18**).

Survival free of metabolic disease - No randomised controlled trials in Crowther (2011) reported data for survival free of metabolic disease at early childhood follow-up (Appendix I).

Table 18: Primary early childhood outcomes following repeat doses of antenatal corticosteroids compared to no repeat exposure*

Outcome at early childhood follow-up	Risk ratio (RR) (95% Confidence Interval)	Number of trials	Trials contributing data	Number of children
Neurosensory disability	RR 0.99 (0.87 to 1.12)	2	Crowther 2006; Murphy 2008	3164
Survival free of major neurosensory disability	RR 1.01 (0.92 to 1.11)	2	Crowther 2006; Peltoniemi 2007	1317

* Source: Crowther (2011)

Infant as a child (early childhood) secondary outcomes of these Clinical Practice Guidelines:

Total mortality - No difference was seen for mortality at early childhood follow-up for infants who had been exposed to repeat courses of antenatal corticosteroids and those with no repeat exposure (**Table 19**).

Disability and impairment - No differences were seen in outcomes associated with developmental delay, neurosensory disability, cognitive disability, cerebral palsy, or sensory impairment between children at early childhood follow-up who had been exposed to repeat courses of antenatal corticosteroids and those with no repeat exposure (**Table 19**).

Anthropometry - No differences were seen between children at early childhood follow-up who had been exposed to repeat courses of antenatal corticosteroids and those with no repeat exposure for any of the body size measurements reported in Crowther (2011).

Cardiovascular disease - There was a significantly lower systolic blood pressure in the children exposed to repeat antenatal corticosteroids (MD -2.90 mmHg, 95%CI -5.40 to -0.40; 1 trial, n=486 children). The clinical significance of the difference is unclear (Wapner 2006) (**Table 19**). There were no differences between groups in diastolic blood pressure and no differences in risk of hypertension in early childhood reported in the Crowther (2006) trial (RR 0.97, 95%CI 0.77 to 1.23; 1 trial, n= 628 children).

Other infant as a child secondary outcomes for these Clinical Practice Guidelines -

- *Where data were reported* no differences were seen at early childhood follow-up for the following secondary outcomes between children who had been exposed *in utero* to repeat antenatal corticosteroids and those with no repeat antenatal corticosteroids for respiratory disease in childhood or lung function or child behaviour.

- *No data were reported in the included trials* for these Clinical Practice Guidelines: insulin sensititvy, glucose intolerance, hypothalamic pituitary adrenal axis function or diabetes.

Infant as a child (later childhood) primary outcomes for these Clinical Practice Guidelines:

The following evidence is based on the Crowther CPG version 2015 systematic review prepared for these Clinical Practice Guidelines. These Clinical Practice Guidelines defined later childhood follow-up as being for ≥3 years up to 8 years of age. Two trials reported on follow-up into later childhood (Crowther 2006, Murphy 2008).

- In the Crowther (2006) trial there were 1146 fetuses alive at randomisation of whom 1090 (95%) babies survived to initial hospital discharge. At 6 to 8 year follow-up 957 children (88%) of the survivors were seen Crowther (2011b), McKinlay (2011a), McKinlay (2013a, b). McKinlay (2015) reported on cardiovascular follow-up of 258 of 320 eligible survivors.
- The Multiple Courses of Antenatal Corticosteroids for Preterm Birth Study (MACS) (Murphy 2008) has reported its 5 year follow-up data (Asztalos 2013). Of the original 1,858 women enrolled in the trial, 1,724 women and their 2,141 children were eligible for the 5 year follow-up and data were available for 1728 (80%).

Neurosensory disability - No differences were seen for a composite outcome including risk of death or severe disability (neuromotor, neurosensory or neurocognitive) between children exposed to multiple or single courses of antenatal corticosteroids (OR 1.02; 95%CI 0.81 to 1.29, n=1,719) (Asztalos 2013).

Survival free of neurosensory disability - The overall rate of survival free of neurosensory disability was 78% and was similar in both children who had been exposed to repeat antenatal corticosteroids (78.2%) and those not exposed (77.5%) (Crowther 2011b).

Survival free of metabolic disease - No data have yet been reported on survival free of metabolic disease in later childhood follow-up.

Table 19: Secondary early childhood (up to 3 years of age) outcomes following repeat dose(s) of antenatal corticosteroids compared to no repeat dose(s)*

Outcome at early childhood follow-up	Risk ratio (RR) or Mean Difference (MD) (95% Confidence Interval)	Number of trials	Trials contributing data	Number of infants
Total mortality	RR 1.06 (0.80 to 1.41)	4	Crowther 2006; Murphy 2008; Peltoniemi 2007; Wapner 2006	4370
Cerebral Palsy	RR 1.03 (0.71 to 1.50)	4	Crowther 2006; Murphy 2008; Peltoniemi 2007; Wapner 2006	3800
Survival free of any disability	RR 1.01 (0.97 to 1.05)	2	Crowther 2006; Murphy 2008	3155
Any disability	RR 0.98 (0.83 to 1.16)	1	Crowther 2006	999
Major neurosensory disability	RR 1.08 (0.31 to 3.76)	2	Crowther 2006; Peltoniemi 2007	1256
Developmental delay	RR 0.97 (0.84 to 1.13)	3	Crowther 2006; Murphy 2008; Peltoniemi 2007	3202
Mental developmental index	MD 1.23 (-0.65 to 3.11)	2	Crowther 2006; Peltoniemi 2007	1162
Psychomotor developmental index	MD 0.40 (-1.75 to 2.55)	1	(Crowther 2006)	958
Blindness	RR 1.17 (0.65 to 2.10)	2	Crowther 2006; Murphy 2008	3151
Deafness	RR 0.85 (0.29 to 2.52)	3	Crowther 2006; Murphy 2008; Peltoniemi 2007	3405
Asthma / wheeze	RR 0.89 (0.63 to 1.27)	3	Crowther 2006; Peltoniemi 2007; Wapner 2006	1720
Hypertension	RR 0.97 (0.77 to 1.23)	1	Crowther 2006	628
Systolic blood pressure (mmHg)	MD -2.90 (-5.40 to -0.40)	1	Wapner 2006	486
Diastolic blood pressure (mmHg)	MD -1.0 (-2.86 to 0.86)	1	Wapner 2006	486
Hospital readmission	RR 1.02 (0.93 to 1.11)	4	Crowther 2006; Murphy 2008; Peltoniemi 2007; Wapner 2006	3824
Body size in early childhood				
Weight (kilogrammes)	MD -0.03 (-0.21 to 0.15)	3	Crowther 2006; Peltoniemi 2007;Wapner 2006	1776
Head circumference (centimetres)	MD -0.05 (-0.22 to 0.11)	3	Crowther 2006; Peltoniemi 2007; Wapner 2006	1776
Height (centimetres)	MD -0.13 (-0.55 to 0.30)	3	Crowther 2006; Peltoniemi 2007; Wapner 2006	1776
Weight z score	MD -0.03 (-0.19 to 0.13)	1	Crowther 2006	1047
Head circumference z score	MD 0.04 (-0.09 to 0.18)	2	Crowther 2006; Peltoniemi 2007	1290
Height z score	MD -0.04 (-0.17 to 0.09)	2	Crowther 2006; Peltoniemi 2007	1290
Body size z scores in early childhood				
Weight	MD -0.03 (-0.19 to 0.13)	1	Crowther 2006	1047
Head circumference	MD 0.04 (-0.09 to 0.18)	2	Crowther 2006; Peltoniemi 2007	1290
Height	MD -0.04 (-0.17 to 0.09)	2	Crowther 2006; Peltoniemi 2007	1290
Body size in early childhood associated with small for age (as defined by trials)				
Weight	RR 0.92 (0.71 to 1.19)	2	Crowther 2006; Wapner 2006	1448
Head circumference	RR 1.10 (0.77 to 1.56)	2	Crowther 2006; Wapner 2006	1442
Height	RR 1.12 (0.63 to 2.02)	2	Crowther 2006; Wapner 2006	1441

* Source: Crowther (2011), mmHg millimetres of mercury

Infant as a child (later childhood) secondary outcomes for these Clinical Practice Guidelines:

Total mortality - The Multiple Courses of Antenatal Corticosteroids for Preterm Birth Study (MACS) found no significant differences for risk of death up to five years (OR 0.94; 95%CI 0.61 to 1.46, n=1,728) between those exposed to repeat antenatal corticosteroids and those with no repeat exposure (Asztalos 2013).

Cognitive development and neurosensory disability - In the later childhood follow-up from the Crowther (2006) randomised trial, neurobehavioural development (including cognitive function and behaviour) was similar between those exposed to repeat antenatal corticosteroids and those with no repeat exposure (Crowther 2011b).

Similarly, data from the MACS trial found there was no evidence of harms associated with neuromotor disability (non-ambulatory cerebral palsy) (OR 0.35; 95%CI 0.11 to 1.10; n=1635), neurosensory disability (including blindness and/or deafness) (OR 1.12; 95%CI 0.77 to 1.63, n=1635) and neurocognitive/neurobehavioural disability (OR 0.98; 95%CI 0.73 to 1.33, n=1615) for multiple compared with single courses of antenatal corticosteroids (Asztalos 2013).

Body size - Body size measurements including weight, height, and head circumference were similar between groups at 6 to 8 year follow-up (Crowther 2011b). In an in depth study of the ACTORDS school age follow-up in New Zealand of 258 children those who were exposed to repeat dose(s) of antenatal betamethasone were not different from unexposed children for total body fat percentage (Crowther 2006, McKinlay 2011a, McKinlay 2015). Exposure to repeat antenatal betamethasone compared with no repeat course did not alter bone mass, whole body bone mineral content, bone area, spinal mineral apparent density or fracture incidence at 6 to 8 year follow-up (McKinlay 2013a).

Follow-up of the MACS trial (Murphy 2008) did not find any significant differences in body size measurements at 5 years of age for weight in 1,635 children (MD -0.21kg; 95%CI -0.60 to 0.17), height (MD -0.40cm; 95%CI -1.04 to 0.25), head circumference (MD -0.06cm; 95%CI -0.30 to 0.18) between the children exposed to repeat antenatal corticosteroids and not those not exposed (Asztalos 2013).

Respiratory outcomes - In the 6 to 8 year childhood follow-up from the Crowther (2006) randomised trial spirometry was attempted on 740 children aged 6 to 8 years. Preliminary data found no significant differences in lung function measures (forced vital capacity, forced vital capacity in 1 second, ratio of forced vital capacity and forced vital capacity in 1 second or maximal mid-expiratory flow) between children who had been exposed to repeat antenatal corticosteroids and those who had no repeat exposure (McKinlay 2013).

Blood pressure - In the ACTORDS school age follow-up in New Zealand of 258 children those who were exposed to repeat courses of antenatal betamethasone were not different from unexposed children for 24 hour ambulatory blood pressure (Systolic blood pressure MD 0 mmHg, 95%CI -2 to 2; Diastolic blood pressure MD 0 mmHg, 95%CI -1 to 1) (Crowther 2006, McKinlay 2011a, McKinlay 2015).

Follow-up of the MACS trial (Murphy 2008) found no differences for systolic blood pressure or diastolic blood pressure between the children exposed to repeat antenatal corticosteroids and those not exposed (MD 0.30 mmHg, 95%CI -0.95 to -1.55, and MD 0.70 mmHg, 95%CI -0.36 to -1.77 respectively) (Asztalos 2013).

Insulin sensitivity - In the ACTORDS school age follow-up in New Zealand of 258 children, those who were exposed to repeat courses of antenatal betamethasone were not different from unexposed children for insulin sensitivity (Crowther 2006, McKinlay 2011a, McKinlay 2015).

Hypothalamic pituitary adrenal axis function - No differences were seen in basal endogenous glucocorticoid secretion (salivary measurement) between children who had been exposed to repeat antenatal corticosteroids and those who had no repeat exposure suggesting normal regulation of the hypothalamic pituitary adrenal axis in the children at follow-up of the Crowther (2006) randomised trial (McKinlay 2011b).

Primary outcomes for the infant as an adult associated with exposure to repeat dose(s) of antenatal corticosteroids

No randomised controlled trials have yet reported on adult outcomes as most of the trials participants have not yet reached adulthood.

Chapter 8: Evidence summary for the use of repeat antenatal corticosteroids in women at ongoing risk of preterm birth

For the mother

Randomised controlled trial evidence shows no maternal health benefits or serious health harms to women at risk of preterm birth treated with repeat antenatal corticosteroids for fetal lung maturation.

There was no increased risk of maternal infection variously reported as chorioamnionitis, puerperal sepsis or postnatal pyrexia requiring treatment with antibiotics.

For a small percentage of women insomnia, a known side effect of corticosteroids, was more common with a repeat dose(s) (2%) compared with a no repeat antenatal corticosteroids (0.8%) although the duration of the insomnia is not reported for any of the individual trials. The absolute risk difference was 1%. Evidence from one trial found no differences in the risk of an abnormal glucose tolerance test.

For the infant

Exposure to a repeat dose(s) of antenatal corticosteroids, when there is a continued risk of preterm birth, compared with no repeat exposure is associated with clear and significant benefits for the infant that include reduced risk of:

- respiratory distress syndrome
- serious neonatal outcome (composite outcome including death, chronic lung disease, respiratory distress syndrome, patent ductus arteriosus and necrotising enterocolitis)
- patent ductus arteriosus.
- use of mechanical ventilation, oxygen supplementation, surfactant and inotropic support

There was no evidence of a difference between single and repeat courses for outcomes of death (perinatal, fetal, neonatal death), chronic lung disease, intraventricular haemorrhage, necrotising enterocolitis or admission to neonatal intensive care.

Mean body size measurements at birth were significantly reduced in infants exposed to repeat antenatal corticosteroids compared with no repeat exposure, although by hospital discharge, in two trials that reported data, there were no differences in mean body size. When body size was assessed using z scores, that adjusts for gestational age, there was a borderline reduction in z score for birthweight and head circumference for infants exposed to repeat antenatal corticosteroids compared with those with no repeat exposure, but no difference for length. The clinical significance, if any, of the differences in body size is unclear.

For the infant in childhood

At follow-up in early and later childhood no significant differences were seen in health outcomes between children who had been exposed to antenatal corticosteroids and those with no repeat exposure. Follow-up of the infant as a child to school age and beyond to a minimum of 8 years to date, although currently limited to two trials, has not indicated harms relating to health outcomes, body size, cardiovascular disease, hypothalamic pituitary adrenal axis function or metabolic disease to those children exposed to repeat antenatal corticosteroids compared with no repeat exposure.

For the infant as an adult

There is currently no adult follow-up of the children from randomised controlled trials of single compared with repeat antenatal corticosteroids as they have not yet reached adulthood.

See Appendix M2 – Evidence Summary (Page 315)

For a woman at risk of preterm birth, who has received a single course of antenatal corticosteroids and remains at ongoing risk of preterm birth, what are the short and long term benefits and harms of a repeat dose(s) of antenatal corticosteroids for the mother, fetus, infant, child and adult?

Clinical recommendation	Strength of recommendation	
	NHMRC	GRADE
Use repeat antenatal corticosteroids in women at risk of early preterm, imminent birth following a single course of antenatal corticosteroids.	A	STRONG

Research recommendations:

- There is a need to better assess the impact, if any, of *in utero* exposure to repeat antenatal corticosteroids on:
  - the glucose-insulin axis in childhood,
  - hypothalamic-pituitary adrenal axis,
  - bone mass,
  - body size and body composition,
  - neurosensory impairments,
  - respiratory function,
  - cardiovascular disease,
  - metabolic disease,
  - diabetes,
  - psychological health,
  - the later risk of developing diabetes in adulthood,
  - educational attainment,
  - behaviour,
  - cognitive ability,
- Any future research to investigate the effects of treatment with repeat antenatal corticosteroids should:
  - include outcomes for maternal quality of life.
  - Report on the risk factors for preterm birth of the included participants.
  - Assess the degree and health impact of changes in maternal blood glucose control.

Chapter 9: Which antenatal corticosteroid to use for women at risk of preterm birth

Do benefits or harms in the mother vary by whether betamethasone or dexamethasone is administered as a single course of antenatal corticosteroids?

Do benefits or harms in the fetus, infant, child or adult vary by whether betamethasone or dexamethasone is administered as a single course of antenatal corticosteroids?

The evidence is based on:

- The Brownfoot (2013) systematic review '*Different corticosteroids and regimens for accelerating fetal lung maturation for women at risk of preterm birth'* included 10 relevant randomised trials for head to head comparisons of antenatal corticosteroids (1159 women and 1218 infants). No additional head to head trials were identified in the Brownfoot CPG version 2015 systematic review.

- The Roberts CPG version 2015 systematic review prepared for these Clinical Practice Guidelines included 19 randomised trials of betamethasone (3028 women and 3289 infants) and six randomised trials of dexamethasone (1391 women and 1514 infants) as the antenatal corticosteroid in the treatment arm. One trial did not specify the corticosteroid used (Cararach 1991)(18 women and their infants).

Maternal primary outcomes for these Clinical Practice Guidelines:

Maternal infection -

Direct comparison of betamethasone and dexamethasone:

None of the randomised trials included in the Brownfoot (2013) systematic review reported on maternal outcomes. So there is, as yet, no evidence from randomised controlled trials directly comparing betamethasone with dexamethasone on maternal infection.

Single course of antenatal corticosteroids:

Chorioamnionitis - There was no overall difference in the risk of chorioamnionitis between women treated with a single course of antenatal corticosteroids and those with no antenatal corticosteroids (RR 0.90, 95%CI 0.69 to 1.17; 13 trials, n=2525 women). Betamethasone was used as the antenatal corticosteroid in nine trials and dexamethasone in four trials.

- Examining the data for a single course of antenatal betamethasone and dexamethasone (compared with no antenatal corticosteroid treatment) separately the subgroup interaction test was significant for chorioamnionitis (Chi^2=5.63; p=0.02, I^2=82.2%). This can be interpreted as betamethasone having a significant protective effect compared with no antenatal corticosteroids (RR 0.70, 95%CI 0.49 to 0.99; 9 trials, n=1950 women), whereas dexamethasone had no significant effect on the risk of chorioamnionitis compared with no antenatal corticosteroids (RR.1.35; 95%CI 0.89 to 2.05; 4 trials, n=575 women) (**Table 20**) (Appendix N- **Figure 3**).

Puerperal sepsis - Overall there was no difference in the risk of puerperal sepsis between women treated with a single course of antenatal corticosteroids and those with no antenatal corticosteroids (RR 1.35, 95%CI 0.93 to 1.95; 8 trials, n=1003 women). Betamethasone was used as the antenatal corticosteroid in four trials and dexamethasone in four trials.

- Examining the data for a single course of antenatal betamethasone and dexamethasone (compared with no antenatal corticosteroid treatment) separately the subgroup interaction test was not significant (Chi^2=0.99, p=0.32, I^2=0%) (Appendix N, **Figure 4**). This can be interpreted

as indicating there was no differential effect between betamethasone and dexamethasone for the risk of puerperal sepsis compared with no antenatal corticosteroids (**Table 20**).

Pyrexia after trial entry - There was no overall difference in the risk for pyrexia after trial entry requiring treatment with antibiotics between women treated with a single course of antenatal corticosteroids and those with no antenatal corticosteroids using a random effects model due to significant heterogeneity (RR 0.95, 95%CI 0.43 to 2.06; 4 trials, n=481 women). Betamethasone was used as the antenatal corticosteroid in three trials and dexamethasone in one trial.

- Examining the data for a single course of antenatal betamethasone and dexamethasone (compared with no antenatal corticosteroid treatment) separately the subgroup interaction test was significant for pyrexia after trial entry (Chi^2 = 6.54; p=0.01; I^2=84.7%) (Appendix N - **Figure 5**). This can be interpreted as indicating betamethasone had no significant effect on pyrexia after trial entry compared with no antenatal corticosteroids (RR 0.68, 95%CI 0.37 to 1.25; 3 trials, n=363 women) and dexamethasone significantly increased the risk of pyrexia after trial entry compared with no antenatal corticosteroids (RR 2.05, 95%CI 1.14 to 3.69; 1 trial, n=118 women) (**Table 20**).

However, the evidence for dexamethasone is based on a single US trial (Taeusch 1979). Caution is required when interpreting the data as the results of the Taeusch (1979) trial show evidence of imprecision (wide confidence intervals). The small trial of 118 women compared dexamethasone phosphate (Decadron®) 6 doses of 4 mg given 8 hours apart with placebo. Women were eligible for the trial if they were at a gestation of 33 weeks' or less; were in preterm labour, or had preterm prelabour rupture of membranes or cervical dilatation <5 cm.

Intrapartum pyrexia - Two trials reported data for intrapartum pyrexia requiring treatment with antibiotics, both used betamethasone and there was no difference between women who received antenatal betamethasone and those who had no antenatal corticosteroids (RR 0.60, 95%CI 0.15 to 2.49; 2 trials, n=319 women). No data for intrapartum pyrexia were reported from trials using dexamethasone as the antenatal corticosteroid.

Postnatal pyrexia - There was no overall difference in the risk for postnatal pyrexia requiring treatment with antibiotics between women treated with a single course of antenatal corticosteroids and those with no antenatal corticosteroids (RR 0.92, 95%CI 0.64 to 1.33; 5 trials, n=1323 women). Betamethasone was used as the antenatal corticosteroid in three trials and dexamethasone in two trials.

- Examining the data for a single course of antenatal betamethasone and dexamethasone (compared with no antenatal corticosteroid treatment) separately the subgroup interaction test between betamethasone and dexamethasone was not significant for postnatal pyrexia (Chi^2 = 0.02; p=0.88; I^2= 0%) (Appendix N, **Figure 6**). This can be interpreted as indicating no differential impact of either drug on the risk of postnatal pyrexia compared with no antenatal corticosteroid (**Table 20**).

Other maternal primary outcomes for these Clinical Practice Guidelines - No trials included in the Brownfoot CPG version 2015 systematic reviews reported on maternal quality of life.

Table 20: Maternal primary outcomes for a single course of betamethasone or dexamethasone compared with no antenatal corticosteroids [$]

Outcome	Betamethasone		Dexamethasone	
	Risk ratio (RR) (95% Confidence Interval)	**Trials contributing data**	**Risk ratio (RR) (95% Confidence Interval)**	**Trials contributing data**
Chorioamnionitis	RR 0.70 (0.49 to 0.99); 9 trials, n=1950 women	Amorim 1999; Carlan 1991; Fekih 2002; Garite 1992; Lewis 1996; Liggins 1972; Lopez 1989; Morales 1989; Schutte 1980	RR 1.35 (0.89 to 2.05); 4 trials, n=575 women	Dexiprom 1999; Kari 1994; Qublan 2001; Silver 1996
Subgroup interaction test	**Chi^2=5.63; p=0.02, I^2=82.2%; 13 trials, n=2525 women**			
Puerperal sepsis	RR 1.00 (0.58 to 1.72); 4 trials, n=467 women	Amorim 1999; Garite 1992; Lewis 1996; Schutte 1980	RR 1.74 (1.04 to 2.89); 4 trials, n=536 women	Dexiprom 1999; Qublan 2001; Silver 1996; Taeusch 1979
Subgroup interaction test	**Chi^2=0.99, p=0.32, I^2=0%; 8 trials, n=1003 women**			
Pyrexia after trial entry*^	RR 0.68 (0.37 to 1.25); 3 trials, n=363 women	Amorim 1999; Schutte 1980; Nelson 1985	RR 2.05 (1.14 to 3.69), 1 trial, n=118 women	Taeusch 1979
Subgroup interaction test	**Chi^2 = 6.54; p=0.01; I^2=84.7%; 4 trials, n=481 women**			
Intrapartum pyrexia*^	RR 0.60 (0.15 to 2.49); 2 trials, n=319 women	Amorim 1999; Schutte 1980	Not reported	-
Subgroup interaction test	Not performed			
Postnatal pyrexia*^	RR 0.88 (0.46 to 1.68); 3 trials, n=437 women	Amorim 1999; Fekih 2002; Schutte 1980	RR 0.94 (0.60 to 1.47); 2 trials, n=886 women	Collaborative 1981; Dexiprom 1999
Subgroup interaction test	**Chi^2=0.02; p=0.88; I^2=0%; 5 trials, n=1323 women**			

[$] Source Roberts CPG version 2015; *requiring treatment with antibiotics; ^ meta-analyses conducted for the purpose of these Clinical Practice Guidelines

Infant primary outcomes for these Clinical Practice Guidelines:

Fetal, neonatal or later death -

Direct comparisons of betamethasone and dexamethasone:

No difference in neonatal death was found in a meta-analysis of data from four trials that made a direct comparison between betamethasone and dexamethasone summarised in the Brownfoot (2013) systematic review (RR 1.41, 95%CI 0.54 to 3.67; 4 trials, n=596 infants) (**Table 21**).

No data were reported for perinatal or fetal death in the Brownfoot (2013) systematic review.

Table 21: Infant primary outcomes for betamethasone compared with dexamethasone*

Outcome	Risk ratio (RR) (95% Confidence Interval)	Number of trials	Trials contributing data	Number of infants
Neonatal death	RR 1.41 (0.54 to 3.67)	4	Elimian 2007; Subtil 2003; Senat 1998; Mulder 1997	596
Respiratory distress syndrome	RR 1.06 (0.88 to 1.27)	5	Chen 2005; Elimian 2007; Subtil 2003; Senat 1998; Mulder 1997	753

*Source: Brownfoot (2013)

Single course of antenatal corticosteroids:

Perinatal death - Overall the risk of perinatal death was significantly reduced following exposure to a single course of antenatal corticosteroids compared with no exposure (RR 0.72, 95%CI 0.58 to 0.89; 13 trials, n=3627 infants) using a random effects model. Betamethasone was used as the antenatal corticosteroid in eight trials and dexamethasone in five trials.

- Examining the data for a single course of antenatal betamethasone and dexamethasone (compared with no antenatal corticosteroid exposure) separately the subgroup interaction test for perinatal death was not significant for perinatal death (Chi^2=0.00, p=0.98, I^2=0%) (**Table 22**) (Appendix N - **Figure 7**). This can be interpreted as both betamethasone and dexamethasone being effective in reducing the risk of perinatal death when compared with no antenatal corticosteroid exposure.

Fetal death - Overall there was no difference in the risk of fetal death following exposure to a single course of antenatal corticosteroids compared with no exposure (RR 0.98, 95%CI 0.75 to 1.30; 13 trials, n=3627 infants). Betamethasone was used as the antenatal corticosteroid in eight trials and dexamethasone in five trials.

- Examining the data for a single course of antenatal betamethasone and dexamethasone (compared with no antenatal corticosteroid exposure) separately the subgroup interaction test was not significant for fetal death (Chi^2=0.1, p=0.15, I^2=0%) (**Table 22**) (Appendix N - **Figure 9**). This can be interpreted as there being no differential effect between betamethasone or dexamethasone on the risk of fetal death compared with no exposure to antenatal corticosteroids.

Neonatal death - Overall the risk of neonatal death was significantly reduced by exposure to a single course of antenatal corticosteroids compared with no exposure (RR 0.68, 95%CI 0.58 to 0.80, 21 trials, n=4408 infants). Betamethasone was used as the antenatal corticosteroid in 15 trials and dexamethasone in six trials.

- Examining the data for a single course of antenatal betamethasone and dexamethasone (compared with no antenatal corticosteroid exposure) separately the subgroup interaction test was not significant for neonatal death (Chi^2=0.21, p=0.65, I^2=0%) (**Table 22**). (Appendix N - **Figure 8**). This can be interpreted as both betamethasone and dexamethasone are effective in reducing the risk of perinatal death compared with no exposure to antenatal corticosteroids.

Table 22: Infant primary outcomes for betamethasone and dexamethasone compared with no antenatal corticosteroids*

Outcome	Betamethasone		Dexamethasone	
	Risk ratio (RR) (95% Confidence Interval)	**Trials contributing data**	**Risk ratio (RR) (95% Confidence Interval)**	**Trials contributing data**
Perinatal death	RR 0.72 (0.55 to 0.94); 8 trials, n=2207 infants	Amorim 1999; Block, 1977; Doran, 1980; Gamsu, 1989; Garite, 1992; Liggins, 1972; Parsons, 1988; Schutte, 1980	RR 0.72 (0.46 to 1.11); 5 trials, n=1420 infants	Collaborative, 1981; Dexiprom, 1999; Kari, 1994; Qublan, 2001; Taeusch, 1979
Subgroup interaction test	**Chi^2=0.00, p=0.98, I^2=0%; 13 trials, n=3627 infants**			
Fetal death	RR 1.01 (0.73 to 1.39); 8 trials, n=2207 infants	Amorim 1999; Block, 1977; Doran, 1980; Gamsu, 1989; Garite, 1992; Liggins, 1972; Parsons, 1988; Schutte, 1980	RR 0.92 (0.56 to 1.50); 5 trials, n=1420 infants	Collaborative, 1981; Dexiprom, 1999; Kari, 1994; Qublan, 2001; Taeusch, 1979
Subgroup interaction test	**Chi^2=0.1, p=0.15, I^2=0%; 13 trials, n=3627 infants**			
Neonatal death	RR 0.67 (0.54 to 0.82); 15 trials, n=2940 infants	Amorim 1999; Block, 1977; Doran, 1980; Fekih, 2002; Gamsu, 1989; Garite, 1992; Goodner, 1979; Lewis, 1996; Liggins, 1972; Lopez, 1989; Morales, 1989, Nelson, 1985; Parsons, 1988; Porto, 2011; Schutte, 1980	RR 0.72 (0.55 to 0.94); 6 trials, n=1468 infants	Collaborative, 1981; Dexiprom, 1999; Kari, 1994; Qublan, 2001; Silver, 1996; Taeusch, 1979
Subgroup interaction test	**Chi^2=0.21, p=0.65, I^2=0%; 21 trials, n=4408 infants**			
Respiratory distress syndrome	RR 0.59 (0.48 to 0.72)^; 18 trials, n=3115 infants	Amorim 1999; Balci, 2010; Block, 1977; Carlan, 1991; Doran, 1980; Fekih, 2002; Gamsu, 1989; Garite, 1992; Goodner, 1979; Lewis, 1996; Liggins, 1972; Lopez, 1989; Morales, 1989, Nelson, 1985; Parsons, 1988; Porto, 2011; Schutte, 1980; Teramo, 1980	RR 0.81 (0.65 to 1.02)^; 6 trials, n=1457 infants	Collaborative, 1981; Dexiprom, 1999; Kari, 1994; Qublan, 2001; Silver, 1996; Taeusch, 1979
Subgroup interaction test	**Chi^2=4.59, p=0.03; I^2=78.2%; 24 trials, n=4490 infants**			

*Source: Roberts CPG version 2015; meta-analyses conducted for the purpose of these Clinical Practice Guidelines ;
^Random effects model used for subgroup analysis due to heterogeneity

Respiratory distress syndrome -

Head to head comparisons of betamethasone and dexamethasone -

For respiratory distress no difference was seen between those infants exposed to betamethasone compared with exposure to dexamethasone in five trials that made a direct comparison in the Brownfoot (2013) systematic review (RR 1.06, 95%CI 0.88 to 1.27, 5 trials, n=753) (**Table 21**).

One trial (Elimian 2007) allowed weekly repeats after the first course was completed if at continued risk of preterm birth.

Single course of antenatal corticosteroids -

Overall the risk for respiratory distress syndrome was significantly reduced following exposure to a single course of antenatal corticosteroids compared with no exposure (RR 0.66, 95%CI 0.56 to 0.78; 24 trials, n=4590 infants) using a random effects model. Betamethasone was used as the antenatal corticosteroid in 18 trials and dexamethasone in only 6 trials.

- Examining the data for a single course of antenatal betamethasone and dexamethasone (compared with no antenatal corticosteroid exposure) separately the subgroup interaction test was significant for respiratory distress syndrome (Chi^2=4.59, p=0.03; I^2=78.2%) (**Table 22**) (Appendix N - **Figure 10**). This can be interpreted as indicating that the benefit for betamethasone was more pronounced than for dexamethasone although both are effective in reducing the risk of respiratory distress syndrome when compared with placebo as shown by indirect comparison analyses presented in the Roberts CPG version 2015 systematic review.

Composite of serious infant outcomes -

No data were reported for a composite of serious outcomes from trials using:
Head to head comparisons of betamethasone and dexamethasone; or
Single course of antenatal corticosteroids.

Other relevant outcomes for these Clinical Practice Guidelines:

Intraventricular haemorrhage -

Head to head comparisons of betamethasone and dexamethasone - For intraventricular haemorrhage, there was a significant reduction in risk for infants exposed to dexamethasone compared with betamethasone reported in four trials (Chen 2005; Elimian 2007; Senat 1998; Subtil 2003) (RR 0.44, 95%CI 0.21 to 0.92; 4 trials, n=549 infants).

Single course of antenatal corticosteroids - Overall the risk for intraventricular haemorrhage was significantly reduced following exposure to a single course of antenatal corticosteroids compared with no exposure (RR 0.54, 95%CI 0.43 to 0.69; 13 trials, n= 2872 infants). Betamethasone was used as the antenatal corticosteroid in 8 trials and dexamethasone in 5 trials.

- Examining the data for a single course of antenatal betamethasone and dexamethasone (compared with no antenatal corticosteroid exposure) separately the subgroup interaction test was not significant for intraventricular haemorrhage (Chi^2=0.24, p=0.62; I^2=0%) (Appendix N, **Figure 11**). This can be interpreted as indicating that there was no differential effect between betamethasone and dexamethasone on the risk of intraventricular haemorrhage and both were effective in reducing the risk compared with no antenatal corticosteroids.

Infant as a child primary outcomes for these Clinical Practice Guidelines:

Head to head comparisons of betamethasone and dexamethasone - No difference in neurosensory disability was found at 18 month follow-up in a small subgroup of only 12 children (11% of the original sample) from a

single trial (Subtil 2003) between those exposed to *in utero* betamethasone compared with dexamethasone (RR 1.67, 95%CI 0.08 to 33.75, n=12 children) reported in the Brownfoot (2013) systematic review.

Single course of antenatal corticosteroids - None of the infant as a child primary outcomes for these Clinical Practice Guidelines were reported for a single course of antenatal betamethasone or dexamethasone in the Roberts CPG version 2015 systematic review.

Ongoing trials

One ongoing trial was identified 'Australasian randomised trial to evaluate the role of maternal intramuscular dexamethasone versus betamethasone prior to preterm birth to increase survival free of childhood neurosensory disability (A*STEROID): study protocol (ACTRN12608000631303)' (Crowther 2013). The trial recruited women at risk of preterm birth before 34 weeks gestational age and is expected to report in 2016. The treatment regimens used were 2 doses of 11.4 mg betamethasone (Celestone Chronodose®) 24 hours apart compared with 2 doses of 12 mg dexamethasone sodium phosphate 24 hours apart with clinician's discretion to use repeat courses when judged necessary. The primary outcomes were death or any neurosensory disability measured at two years' corrected age.

Evidence summary for the optimal antenatal corticosteroid to administer in a single course of antenatal corticosteroids to women at risk of preterm birth

For the mother

Direct comparisons of betamethasone and dexamethasone - There were no randomised trial data for direct head to head comparisons between betamethasone and dexamethasone for any of the maternal infection primary outcomes of these Clinical Practice Guidelines.

Single course of antenatal corticosteroids - Overall there were no differences in the risks for maternal infection outcomes for these Clinical Practice Guidelines (chorioamnionitis, pyrexia after trial entry, intrapartum pyrexia, postnatal pyrexia, puerperal sepsis) between women who had been treated with a single course of antenatal corticosteroids and those with no treatment. No data were reported for maternal quality of life.

Subgroup interaction tests were used to examine the effects of a single course of antenatal betamethasone and dexamethasone separately. There were significant subgroup interaction tests for:

- Chorioamnionitis - betamethasone had a protective effect compared with no antenatal corticosteroids and there were no differences in the risk of chorioamnionitis for dexamethasone compared with no antenatal corticosteroids.
- Pyrexia after trial entry - For betamethasone there was no difference in the risk for pyrexia after trial entry compared with no antenatal corticosteroids. For dexamethasone in one trial there was an increased risk of pyrexia after trial entry compared with no antenatal corticosteroids in one trial.
- No significant differences were seen for the other subgroup interaction tests (postnatal pyrexia requiring treatment, puerperal sepsis) which can be interpreted as indicating that there was no differential effect between a single course of antenatal betamethasone or dexamethasone compared with no antenatal corticosteroids.

For the infant

Direct comparisons of betamethasone and dexamethasone - There were no differences in the risks for neonatal death or respiratory distress syndrome in the trials that reported data for head to head comparisons between betamethasone and dexamethasone. No data are currently reported for perinatal death, fetal death or a composite of serious infant outcomes.

Single course of antenatal corticosteroids - Overall there were significant reductions in the risks for perinatal death, neonatal death and respiratory distress syndrome for infants exposed to a single course of antenatal corticosteroids compared with no exposure. There were no overall differences in the risk for fetal death between infants who had been exposed to a single course of antenatal corticosteroids and those with no exposure. No data were reported for a composite of serious infant outcomes.

Subgroup interaction tests were used to examine the effects of a single course of antenatal betamethasone and dexamethasone separately. There was a non-significant subgroup interaction test for:

- Perinatal death and neonatal death, suggesting that there was no differential effect between a single course of antenatal betamethasone or dexamethasone compared with no antenatal corticosteroids and both were effective at reducing the risks.
- Fetal death, suggesting that there were no differences between betamethasone or dexamethasone and no antenatal corticosteroids for the risk of fetal death.

There was a significant subgroup interaction test for:

- Respiratory distress syndrome - Both betamethasone and dexamethasone reduced the risk for respiratory distress syndrome compared with no antenatal corticosteroids. The benefit for betamethasone seemed more pronounced than for dexamethasone although both are effective in reducing the risk of respiratory distress syndrome when compared with placebo as shown by indirect comparison analyses presented in the Roberts CPG version 2015 systematic review.
- Intraventricular haemorrhage - Both betamethasone and dexamethasone reduced the risk for intraventricular haemorrhage compared with no antenatal corticosteroids. The benefit for dexamethasone seemed more pronounced then for betamethasone although both are effective as shown by indirect comparison analyses presented in the Roberts CPG version 2015 systematic review.

For the infant as a child

Direct comparison of betamethasone and dexamethasone -

- There was limited follow-up from a single trial of a subgroup of 12 children (11%) at 18 months of age. No differences were seen in neurosensory disability between exposure to betamethasone or dexamethasone.

Single course of antenatal corticosteroids -

- None of the infant as a child primary outcomes for these Clinical Practice Guidelines were reported for a single course of antenatal betamethasone or dexamethasone.

See Appendix M3 – Evidence Summary (Page 319)

Do benefits or harms in the mother, fetus, infant, child or adult vary by whether betamethasone or dexamethasone is administered as a single course of antenatal corticosteroids?

Clinical recommendation	Strength of recommendation	
	NHMRC	GRADE
Use betamethasone or dexamethasone as a single course of antenatal corticosteroid in women at risk of preterm birth.	A	STRONG

Research recommendation:
• A randomised trial is needed to compare betamethasone and dexamethasone to assess the effect on the short term and long term outcomes for the infant.

Do benefits or harms in the mother vary by whether betamethasone or dexamethasone is administered as the repeat dose(s) of antenatal corticosteroids?

Do benefits or harms in the fetus, infant, child or adult vary by whether betamethasone or dexamethasone is administered as the repeat dose(s) of antenatal corticosteroids?

The evidence is based on one sentinel Cochrane systematic review previously summarised in detail in Chapter 2 of these Clinical Practice Guidelines (Crowther 2011). The literature search, updated for these Clinical Practice Guidelines is referred to as Crowther CPG version 2015.

- The Crowther (2011) systematic review *'Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes'* included 10 randomised trials (4733 women and 5700 infants) and used betamethasone as the repeat antenatal corticosteroid treatment. The Crowther CPG version 2015 found no new randomised trials.

No randomised trials currently report the use of dexamethasone as the repeat antenatal corticosteroid.

The evidence for the benefits and harms of repeat antenatal betamethasone is found in Chapter 6 and Chapter 7 of these Clinical Practice Guidelines. A summary of the evidence is found in Chapter 8 of these Clinical Practice Guidelines.

Evidence summary for the optimal antenatal corticosteroid to administer for repeat antenatal corticosteroids to women at risk of preterm birth

For the mother

Repeat antenatal corticosteroids - The trials of repeat antenatal corticosteroids summarised in the Crowther (2011) systematic review only used betamethasone.

- There were no differences between repeat antenatal betamethasone and no repeat treatment for any of the maternal infection primary outcomes (chorioamnionitis, postnatal pyrexia, puerperal sepsis) for these Clinical Practice Guidelines, where data were available.

For the infant

Repeat antenatal corticosteroids - The trials of repeat antenatal corticosteroids summarised in the Crowther (2011) systematic review only used betamethasone.

- For perinatal, neonatal and fetal death there were no differences between a repeat exposure to antenatal betamethasone and no repeat exposure.
- The risk of respiratory distress syndrome and a composite of serious infant outcomes were significantly reduced following exposure to repeat betamethasone compared with no repeat exposure.

For the infant as a child

Repeat antenatal corticosteroids - The available trials using repeat antenatal corticosteroids only used antenatal betamethasone.

- No differences were reported between repeat *in utero* exposure to betamethasone and no repeat exposure for neurosensory disability or survival free of major neurosensory disability in early childhood (2 years) reported in the Crowther (2011) systematic review.

- Similarly, in later childhood (5 to 8 years) there were no differences in death or severe disability or survival free of neurosensory disability (Crowther CPG version 2015).
- No data were reported for survival free of metabolic disease in either early or later childhood (Crowther CPG version 2015).

See Appendix M4 –Evidence Summary (Page 323)

Do benefits or harms in the mother, fetus, infant, child or adult vary by whether betamethasone or dexamethasone is administered as the repeat dose(s) of antenatal corticosteroids?

Clinical Recommendation	Strength of recommendation	
	NHMRC	GRADE
Use betamethasone as the repeat course antenatal corticosteroid in women at continued risk of preterm birth regardless of the corticosteroid preparation used in the first course.	A	STRONG

Practice point:

- If betamethasone is not available use dexamethasone.

Research recommendation:

- A randomised trial of dexamethasone as the repeat corticosteroid is required.

Chapter 10: Antenatal corticosteroid regimens for women at risk of preterm birth

What is the most effective dose, number of doses in a course and optimal interval between doses when using a single course of antenatal corticosteroids?

The antenatal corticosteroid regimen used varied in the 26 trials included in the Roberts CPG version 2015 systematic review of use of a single course of antenatal corticosteroids compared with no antenatal corticosteroid. Both betamethasone and dexamethasone have been administered in different dose(s), number of doses given in a course and timing between doses (Chapter 2, **Table 2**). One of the 26 trials (Cararach 1991), did not report on the type or dose of antenatal corticosteroid used.

For the 19 trials that used a single course of antenatal betamethasone (3028 women and 3289 infants), the majority (12 trials) used a total dose of 24 mg, given in two doses and completed in 24 hours (**Table 23**). Nelson (1985) used 12 mg completed in 12 hours and 24 mg completed in 12 hours. No details for the dose given or interval between doses of betamethasone were provided for Goodner (1979).

Table 23: Regimens of trials using a single course of antenatal betamethasone compared with no antenatal corticosteroids*

Total dose	Time to complete course	Betamethasone regimen	Number of trials	Trials contributing data
12 mg	Immediate	1 dose of 12 mg	1	Balci 2010
12 mg	12 hours	2 doses of 6 mg 12 hours apart	1	Nelson 1985
24 mg	12 hours	2 doses of 12 mg 12 hours apart	3	Nelson 1985, Parsons 1988, Lopez 1989
24 mg	24 hours	2 doses of 12 mg 24 hours apart	12	Amorim 1999, Block 1977, Carlan 1991, Fekih 2002, Garite 1992, Lewis 1996, Liggins 1972, Lopez 1989, Morales 1989, Porto 2011, Shanks 2010 Teramo 1980.
24 mg	≥36 hours	4 doses of 6 mg 12 hours apart	1	Doran 1980
	≥36 hours	6 doses of 4 mg 8 hours apart	1	Gamsu 1989
28 mg	24 hours	2 doses of 14 mg over 2 days^	1	Schutte 1980

* Source: Roberts CPG version 2015; ^exact timing not reported,
mg milligrams

For the seven trials that used a single course of antenatal dexamethasone as the antenatal corticosteroid (1391 women and 1514 infants), the majority of these trials (five trials) used a total dose of 24 mgs dexamethasone completed within 24 to 40 hours. The number of trials are limited and four different regimens were used (**Table 24**).

Table 24: Regimens of trials using a single course of antenatal dexamethasone compared with no antenatal corticosteroids*

Total dose	Time to complete course	Dexamethasone regimen	Number of trials	Trials contributing data
20 mg	36 hours	4 doses of 5 mg 12 hours apart	2	Collaborative 1981, Silver 1996
24 mg	24 hours	2 doses of 12 mg 24 apart	1	Dexiprom 1999
24 mg	36 hours	4 doses of 6 mg 12 hours apart	3	Kari 1994, Qublan 2001, Shanks 2010
24 mg	40 hours	6 doses of 4 mg 8 hours apart	1	Taeusch 1979

* Source: Roberts CPG version 2015; mg milligrams

Primary maternal outcomes for these Clinical Practice Guidelines:

We have summarised the risk estimates for two of the commonly reported maternal infection primary outcomes for these Clinical Practice Guidelines (chorioamnionitis and puerperal sepsis) and have analysed the data using total dose of antenatal corticosteroid and time to complete the course (**Table 25**; **Table 26**):

Betamethasone:

- 12 mg immediately
- 12 mg completed in 12 hours
- 24 mg completed in 24 hours
- 24 mg completed in ≥36 hours
- 28 mg completed in 24 hours

Dexamethasone:

- 20 mg completed in 36 hours
- 24 mg completed in 24 hours
- 24 mg completed in 36 hours
- 24 mg completed in 40 hours

Chorioamnionitis -

For betamethasone the overall risk of chorioamnionitis was significantly reduced following treatment with a single course of antenatal betamethasone compared with no antenatal corticosteroids (RR 0.70, 95%CI 0.49 to 0.99; 9 trials, n=1950 women).

- Examining the available data for the regimens separately the subgroup interaction test for different betamethasone regimens (24 mg completed in 12 hours, 24 mg completed in 24 hours, 28 mg completed in 24 hours) was not significant for chorioamnionitis (Chi^2=1.13, p=0.57, I^2=0%) (Appendix N - **Figure 12**). This can be interpreted as indicating that these betamethasone regimens did not differentially influence the risk of chorioamnionitis. No data for chorioamnionitis were reported for a single dose of 12 mg betamethasone or a course of 24 mg of betamethasone completed in ≥36 hours.

For dexamethasone there was no overall difference for the risk of chorioamnionitis with a single course of antenatal dexamethasone compared with no antenatal corticosteroids (RR 1.35, 95%CI 0.89 to 2.05; 4 trials, n=575 women).

- Examining the available data for the regimens separately, the subgroup interaction test for different dexamethasone regimens (20 mg completed in 36 hours, 24 mg completed in 24 hours, 24 mg completed in 40 hours) was not significant for chorioamnionitis (Chi^2=1.31, p=0.52, I^2=0%) (Appendix N - **Figure 13**). This can be interpreted as indicating that these regimens of dexamethasone did not differentially influence the risk of chorioamnionitis.

No data for chorioamnionitis were reported for a course of 24 mg of dexamethasone completed in 40 hours.

Puerperal sepsis -

For betamethasone there was no overall difference in the risk of puerperal sepsis following treatment with a single course of antenatal betamethasone compared with no antenatal corticosteroids (RR 1.00, 95%CI 0.58 to 1.72; 4 trials, n=467 women).

- Examining the available data for the regimens separately, the subgroup interaction test for different betamethasone regimens (24 mg completed in 24 hours, 28 mg completed in 24 hours) was not

significant for puerperal sepsis (Chi²=0.00, p=0.99, I²=0%) (Appendix N - **Figure 14**). This can be interpreted as indicating that these betamethasone regimens did not differentially influence the risk of puerperal sepsis.

No data were reported for puerperal sepsis using a course of betamethasone 12 mg completed in ≥36 hours, 24 mg completed in ≥36 hours or 24 mg completed in 12 hours.

For dexamethasone no difference was seen for the risk for puerperal sepsis following treatment with a single course of antenatal dexamethasone compared with no antenatal corticosteroids (RR 1.71, 95%CI 0.86 to 3.43, 4 trials, n=536 women) using a random effects model (I^2=38%). Two of these trials were conducted in the USA (Silver 1996, Taeusch 1979). The Dexiprom (1999) trial was conducted in South Africa and the Qublan (2001) trial in Jordan.

- Examining the available data for regimens separately, the subgroup interaction test for different dexamethasone regimens (20 mg completed in 36 hours, 24 mg completed in 24 hours, 24 mg completed in 36 hours, 24 mg completed in 40 hours) was not significant for puerperal sepsis (Chi²=4.84, p=0.18, I^2=38%) (Appendix N - **Figure 15**). This can be interpreted as indicating that these dexamethasone regimens did not differentially influence the risk of puerperal sepsis.

Table 25: Primary maternal outcomes for different regimens of a single course of betamethasone compared with no antenatal corticosteroids*

Total dose betamethasone	Time to complete course	Chorioamnionitis		Puerperal sepsis	
		Risk ratio RR (95%Confidence Interval)	Trials contributing data	Risk ratio RR (95%Confidence Interval)	Trials contributing data
12 mg	Immediate	NR	-	NR	-
12 mg	12 hours	NR	-	NR	-
24 mg	12 hours	0.33 (0.01 to 7.72); 1 trial, n=40 women	Lopez 1989	NR	-
24 mg	24 hours	0.74 (0.52 to 1.05); 7 trials, n=1809 women	Amorim 1999; Carlan 1991; Fekih 2002; Garite 1992; Lewis 1996; Liggins 1972; Morales 1989	1.00 (0.57 to 1.73); 3 trials, n=366 women	Amorim 1999; Garite 1992; Lewis 1996
24 mg	≥36 hours	NR	-	NR	-
28 mg	24 hours	0.26 (0.03 to 2.20); 1 trial, n=101 women	Schutte 1980	1.02 (0.07 to 15.86); 1 trial, n=101 women	Schutte 1980
Overall treatment effect		**0.70 (0.49 to 0.99); 9 trials, n=1950 women**		**1.00 (0.58 to 1.72); 4 trials, n=467 women**	
Subgroup interaction tests		**Chi²=1.13, p=0.57, I^2=0%**		**Chi²=0.00, p=0.99, I^2=0%**	

* Source: Roberts CPG version 2015; NR not reported, mg milligrams

Table 26: Primary maternal outcomes for different regimens of a single course of dexamethasone versus no antenatal corticosteroids*

Total dose dexamethasone	Time to complete course	Chorioamnionitis		Puerperal sepsis	
		Risk ratio RR (95%Confidence Interval)	Trials contributing data	Risk ratio RR (95%Confidence Interval)	Trials contributing data
20 mg	36 hours	1.00 (0.53 to 1.90); 1 trial, n=75 women	Silver 1996	2.03 (0.78 to 5.28); 1 trial, n=75 women	Silver 1996
24 mg	24 hours	1.38 (0.58 to 3.28); 1 trial, n=204 women	Dexiprom 1999	0.57 (0.17 to 1.89); 1 trial, n=204 women	Dexiprom 1999
24 mg	36 hours	1.74 (0.86 to 3.51); 2 trials, n=296 women	Kari 1994; Qublan 2001	4.19 (0.94 to 18.68); 1 trial, n=139 women	Qublan 2001
24 mg	40 hours	NR	-	1.99 (0.83 to 4.79); 1 trial n=158	Taeusch 1979
Overall treatment effect		**1.35 (0.89 to 2.05); 4 trials, n=575 women**		**1.71 (0.86 to 3.43)^; 4 trials, n=536 women**	
Subgroup interaction tests		**Chi²=1.31, p=0.52, I²=0%**		**Chi² =4.84, p=0.18, I²=38%**	

*Source: Roberts CPG version 2015; ^ random effects model; NR not reported, mg milligrams

Primary infant outcomes for these Clinical Practice Guidelines:

The risk estimates for two of the commonly reported infant primary outcomes for these Clinical Practice Guidelines (neonatal death and respiratory distress syndrome) have been analysed using data for total dose of antenatal corticosteroid and time to complete the course (**Table 27**, **Table 28**):

Betamethasone:

- 12 mg immediately
- 12 mg completed in 12 hours
- 24 mg completed in 24 hours
- 24 mg completed in ≥36 hours
- 28 mg completed in 24 hours

Dexamethasone:

- 20 mg completed in 36 hours
- 24 mg completed in 24 hours
- 24 mg completed in 36 hours
- 24 mg completed in 40 hours

Neonatal death -

For betamethasone the overall the risk of neonatal death was significantly reduced following a single course of antenatal betamethasone compared with no antenatal corticosteroids (RR 0.67, 95%CI 0.54 to 0.82, 15 trials, n=2940 infants).

- Examining the available data for regimens separately, the subgroup interaction test for different regimens of betamethasone (24 mg completed in 12 hours, 24 mg completed in 24 hours, 24 mg completed ≥36 hours, 28 mg completed in 24 hours) was not significant for neonatal death (Chi²=3.67, p=0.39, I²=18.2%) (Appendix N - **Figure 16**). This can be interpreted as indicating that each of these regimens had a protective effect against neonatal death. No data for neonatal death were reported for a single dose of 12 mg betamethasone completed immediately or 12 mg betamethasone completed in 12 hours.

For dexamethasone no difference was seen for the overall risk of neonatal death following exposure to a single course of dexamethasone (RR 0.70, 95%CI 0.47 to 1.03; 6 trials, n=1468 infants) using a random effects model.

- Examining the available data for regimens separately, the subgroup interaction test for different regimens of dexamethasone (20 mg completed in 36 hours, 24 mg completed in 24 hours, 24 mg completed in 36 hours, 24 mg completed in 40 hours) was not significant for neonatal death (Chi^2=7.20, p=0.07, I^2 =58.4%) (Appendix N - **Figure 17**). This can be interpreted as indicating that each of these regimens had the same effect against neonatal death.

Table 27: Primary infant outcomes for different regimens of a single course of antenatal betamethasone compared with no antenatal corticosteroids*

Total dose betamethasone	Time to complete course	Neonatal death		Respiratory distress syndrome	
		Risk ratio RR (95%Confidence Interval)	Trials contributing data	Risk ratio RR (95%Confidence Interval)	Trials contributing data
12 mg	Immediate	NR	-	0.25 (0.06 to 1.12); 1 trial, n=100 infants	Balci 2010
12 mg	12 hours	NR	-	NR	-
24 mg	12 hours	0.88 (0.37 to 2.07); 3 trials, n=129 infants	Lopez 1989; Nelson 1985; Parsons 1988	0.91 (0.59 to 1.40); 3 trials, n=129 infants	Lopez 1989; Nelson 1985; Parsons 1988
24 mg	24 hours	0.67 (0.54 to 0.84); 8 trials, n= 2197 infants	Amorim 1999; Block 1977; Fekih 2002; Garite 1992; Lewis 1996; Liggins 1972; Morales 1989; Porto 2011	0.57 (0.43 to 0.74); 10 trials, n= 2272 infants	Amorim 1999; Block 1977; Carlan 1991; Fekih 2002; Garite 1992; Lewis 1996; Liggins 1972; Morales 1989; Porto 2011; Teramo 1980
24 mg	≥36 hours	0.60 (0.34 to 1.03); 2 trials, n= 402 infants	Doran 1980; Gamsu 1989	0.38 (0.20 to 0.76); 2 trials, n= 402 infants	Doran 1980; Gamsu 1989
28 mg	24 hours	0.23 (0.07 to 0.79), 1 trial, n= 120 infants	Schutte 1980	0.61 (0.31 to 1.18), 1 trial, n= 120 infants	Schutte 1980
Overall treatment effect		**0.67 (0.55 to 0.82); 14 trials, n=2848 infants**		**0.59 (0.48 to 0.73)^; 17 trials, n= 3013 infants**	
Subgroup interaction tests		**Chi^2=3.67, p=0.39, I^2=18.2%**		**Chi^2=6.75, p=0.15, I^2=40.7%**	

*Source: Roberts CPG version 2015; ^random effects model NR not reported, mg milligrams
Goodner (1979) did not provide details on the regimen of betamethasone.

Table 28: Primary infant outcomes for different regimens of a single course of antenatal dexamethasone versus no antenatal corticosteroids*

Total dose dexamethasone	Time to complete course	Neonatal death		Respiratory distress syndrome	
		Risk ratio RR (95% Confidence Interval)	Trials contributing data	Risk ratio RR (95% Confidence Interval)	Trials contributing data
20 mg	36 hours	0.97 (0.64 to 1.47); 2 trials, n= 825 infants	Collaborative 1981; Silver 1996	0.85 (0.56 to 1.29); 2 trials, n=816 infants	Collaborative 1981; Silver 1996
24 mg	24 hours	0.48 (0.15 to 1.55); 1 trial, n=206 infants	Dexiprom 1999	1.16 (0.75 to 1.79); 1 trial, n=202 infants	Dexiprom 1999
24 mg	36 hours	0.47 (0.31 to 0.71); 2 trials, n=314 infants	Kari 1994; Qublan 2001	0.68 (0.51 to 0.90); 2 trials, n=316 infants	Kari 1994; Qublan 2001
24 mg	40 hours	1.02 (0.43 to 2.41); 1 trial, n=123 infants	Taeusch 1979	0.64 (0.28, 1.47); 1 trial, n=123 infants	Taeusch 1979
Overall treatment effect		**0.70 (0.47 to 1.03)^; 6 trials, n=1468 infants**		**0.81 (0.65 to 1.02); 6 trials, n=1457 infants**	
Subgroup interaction tests		**Chi^2=7.20, p=0.07, I^2 =58.4%**		**Chi^2=4.53, p=0.21, I^2=33.8%**	

*Source: Roberts CPG version 2015; ^ random effects model; mg milligrams

Respiratory distress syndrome -

For betamethasone the overall risk of respiratory distress syndrome was significantly reduced following exposure to a single course of antenatal betamethasone compared with no exposure (RR 0.59, 95%CI 0.48 to 0.73; 17 trials, n=3013 infants) using a random effects model.

- Examining the available data for different regimens separately, the subgroup interaction test for different betamethasone regimens (12 mg completed immediately, 24 mg completed in 12 hours, 24 mg completed in 24 hours, 24 mg completed in ≥36 hours, 28 mg completed in 24 hours) was not significant for respiratory distress syndrome (Chi^2=6.75, p=0.15, I^2=40.7%) (Appendix N - **Figure 18**). This can be interpreted as indicating that each of these betamethasone regimens had a protective effect for respiratory distress syndrome. There were no data reported for 12 mg betamethasone completed in 12 hours.

For dexamethasone there was no overall difference for the risk of respiratory distress syndrome following exposure to a single course of antenatal dexamethasone compared with no exposure (RR 0.81, 95%CI 0.65 to 1.02; 6 trials, n=1457 infants). The lack of statistical significance is probably due to low numbers of infants.

- Examining the available data for different regimens (20 mg completed in 36 hours, 24 mg completed in 24 hours, 24 mg completed in 36 hours, 24 mg completed in 40 hours), the subgroup interaction test for different dexamethasone regimens was not significant for respiratory distress syndrome (Chi^2=4.53, p=0.21, I^2=33.8%) (Appendix N - **Figure 19**). This can be interpreted as indicating that there was no differential effect between these regimens on the risk of respiratory distress syndrome.

Trials directly comparing different doses or timing of antenatal corticosteroids -

Two trials directly compared different doses or timing of antenatal corticosteroids (Khandelwal 2012, Romejko-Wolniewicz 2013).

Neonatal death -

- No differences were seen for risk of perinatal death between 2 doses of 12 mg of betamethasone 12 hours apart (24 mg completed in 12 hours) with 2 doses of 12 mg of betamethasone 24 hours apart

(24 mg completed in 24 hours) (no details on type of betamethasone used) (RR 0.93, 95%CI 0.46 to 1.87; 1 trial, n=260 infants) (Khandelwal 2012).

Respiratory distress syndrome -

- No differences were seen between two betamethasone regimens for the risk of respiratory distress syndrome between 2 doses of 12 mg betamethasone 12 hours apart (24 mg completed in 12 hours) or 24 hours apart (24 mg completed in 24 hours) in one trial (RR 0.98, 95%CI 0.69 to 1.40) (Khandelwal 2012).
- There was no difference in moderate respiratory disorder between exposure to betamethasone 24 mg completed in 30 hours and 24 mg completed in 24 hours (15.6% vs 25% respectively). Similarly, there were no differences for severe respiratory distress (24.4% vs 23.7% respectively). No risk estimates were presented for the respiratory outcomes (Romejko-Wolniewicz 2013).

Evidence summary for the most effective number of doses and interval between doses for a single course of antenatal corticosteroids

Betamethasone

The most commonly used regimen reported in the randomised controlled trials of a single course of betamethasone was 24 mg of betamethasone given in two doses and completed in 24 hours.

For the mother

The overall risk of chorioamnionitis was significantly reduced for women who were treated with a single course of antenatal betamethasone (24 mg completed in 12 hours, 24 mg completed in 24 hours, 28 mg completed in 24 hours) compared with no antenatal corticosteroids.

There was no difference in the overall risk of puerperal sepsis between women who had been treated with a single course of antenatal betamethasone (24 mg completed in 24 hours, 28 mg completed in 24 hours) compared with no antenatal corticosteroids. Subgroup interaction tests found no differential effect between the regimens reporting relevant data for either outcome.

All of the above regimens are considered to have a similar efficacy for the risks of chorioamnionitis and puerperal sepsis when compared with no antenatal corticosteroids.

For the infant

The overall risk of neonatal death was significantly reduced for infants who had been exposed to a single course of antenatal betamethasone (24 mg completed in 12 hours, 24 mg completed in 24 hours, 24 mg completed ≥36 hours, 28 mg completed in 24 hours) compared with no antenatal corticosteroids.

The overall risk of respiratory distress syndrome was significantly reduced following exposure to a single course of antenatal betamethasone (12 mg completed immediately, 24 mg completed in 12 hours, 24 mg completed in 24 hours, 24 mg completed in ≥36 hours, 28 mg completed in 24 hours) compared with no antenatal corticosteroids.

All of the above regimens are considered to have a similar efficacy for the reduction of risks for neonatal death and respiratory distress syndrome when compared with no antenatal corticosteroids.

Dexamethasone

For the mother

There was no difference in the overall risk of chorioamnionitis following exposure to a single course of antenatal dexamethasone (20 mg completed in 36 hours, 24 mg completed in 24 hours, 24 mg completed in 40 hours) compared with no exposure to antenatal corticosteroids.

- Subgroup interaction tests were not significant. All of the regimens above are considered to have similar effects on the risks of chorioamnionitis when compared with no antenatal corticosteroids.

There was no difference seen in the overall risk of puerperal sepsis following exposure to a single course of antenatal dexamethasone (20 mg completed in 36 hours, 24 mg completed in 24 hours, 24 mg completed in 36 hours, 24 mg completed in 40 hours) compared with no exposure to antenatal corticosteroids. Evidence is based on single trials for each regimen.

- Subgroup interaction tests for puerperal sepsis were not significant. This can be interpreted as indicating all of the regimens above increase the risks of puerperal sepsis when compared with no antenatal corticosteroids.

For the infant

No difference was seen in overall risk of neonatal death following exposure to a single course of antenatal dexamethasone (20 mg completed in 36 hours, 24 mg completed in 24 hours, 24 mg completed in 36 hours, 24 mg completed in 40 hours) compared with no exposure to antenatal corticosteroids. The subgroup interaction test was not significant.

All of the regimens above are considered to have the same effect for neonatal death when compared with no antenatal corticosteroids.

For respiratory distress syndrome there was no overall difference between exposure to antenatal dexamethasone (20 mg completed in 36 hours, 24 mg completed in 24 hours, 24 mg completed in 36 hours, 24 mg completed in 40 hours) and no exposure to antenatal corticosteroids. The subgroup interaction test was not significant. All of the regimens are considered to have a similar effect for the risk of respiratory distress syndrome when compared with no antenatal corticosteroids. The evidence for each regimen is based on small numbers of trials and participants, and is likely to be underpowered to detect significant differences.

The recommendations made by the Clinical Practice Guidelines Panel are based on the regimens most frequently used in the trials included in the Roberts CPG version 2015 systematic review.

See Appendix M5 – Evidence Summary (Page 327)

What is the most effective dose, number of doses in a course and optimal interval between doses when using a single course of antenatal corticosteroids?

Clinical recommendations	Strength of recommendation	
	NHMRC	GRADE
For women at risk of preterm birth use: EITHER a single course of 24 mg of betamethasone in divided doses completed between 12 and 36 hours	A	STRONG
OR a single course of 24 mg of dexamethasone in divided doses completed between 24 and 40 hours.	A	STRONG

Practice Point:
Administer Celestone® Chronodose®,** as two intramuscular doses of 11.4 mg, 24 hours apart. OR Administer dexamethasone phosphate## intramuscularly, in four doses of 6 mg, 12 hours apart.

** Celestone® Chronodose® Injection, available in New Zealand and Australia, is a sterile aqueous suspension containing betamethasone sodium phosphate and betamethasone acetate. A single dose provided in 2 mL of Celestone Chronodose Injection contains betamethasone 11.4 mg, as betamethasone sodium phosphate 7.8 mg (in solution) and betamethasone acetate 6 mg (in suspension) in an aqueous vehicle containing sodium phosphate, sodium phosphate monobasic, disodium edetate, benzalkonium chloride and water for Injections.

##Dexamethasone phosphate is available as a 4 mg/mL injection which contains 4.37 mg dexamethasone sodium phosphate, in addition propylene glycol, disodium edetate, sodium hydroxide and water for injections. The preparation in New Zealand is Dexamethasone-Hameln and in Australia is Dexamethasone Sodium Phosphate - Hospira Australia Pty Ltd Australia

Research recommendations:
To maximise benefit and minimise harm to the mother and infant there is a need to establish: • the minimally effective dose per course of both betamethasone and dexamethasone; • the optimal timing interval per course between doses for both betamethasone and dexamethasone; • the optimal number of doses per course for betamethasone; • the optimal number of doses per course for dexamethasone.

What is the most effective dose, number of doses in a course and optimal interval between courses for repeat antenatal corticosteroids?

Is a single repeat dose/course (or rescue dose(s)/course) more effective than multiple repeat dose(s)/courses?

All of the randomised controlled trials included in the Crowther (2011) Cochrane systematic review only used betamethasone as the repeat antenatal corticosteroid:

- Celestone® Chronodose® - Crowther (2006)
- Celestone® Soluspan® - Aghajafari (2002); McEvoy (2002); McEvoy (2010); Murphy (2008)
- Brand of betamethasone not reported – Garite (2009); Guinn (2001); Mazumder (2008); Peltoniemi (2007); Wapner (2006).

No additional randomised trials were identified in the updated search of the literature for these Clinical Practice Guidelines (Crowther CPG version 2015).

Trial protocols allowed for repeat courses when the woman was at continued risk of preterm birth. None of the trials allowed repeat dose(s) after 34 weeks' and 6 days gestational age (Chapter 2 - **Table 3**) and the majority of trials (8) used a total dose of 24 mg betamethasone per course completed within 24 hours (Aghajafari 2002, Garite 2009, Guinn 2001, McEvoy 2002, McEvoy 2010, Mazumder 2008, Murphy 2008, Wapner 2006). Further repeat dose(s) allowed in six trials (Aghajafari 2002, Guinn 2001, McEvoy 2002, Mazumder 2008, Murphy 2008, Wapner 2006).

Two trials used a total dose of 12 mg per course as a single dose (Peltoniemi 2007) (brand of betamethasone not specified) or 11.4 mg betamethasone (Celestone® Chronodose®) (Crowther 2006) (**Table 29**).

There are currently no randomised controlled trials reported that use dexamethasone as the repeat antenatal corticosteroid.

Table 29: Regimens of trials using repeat antenatal betamethasone compared with no repeat antenatal corticosteroids*

Total dose of betamethasone	Time to complete course	Betamethasone regimen	Protocol allowed further repeat dose(s)	Number of trials	Trials contributing data
12 mg	Immediate	1 dose of 12 mg	No	1	Peltoniemi 2007
11.4 mg	Immediate	1 dose of 11.4 mg	Yes	1	Crowther 2006
24 mg	24 hours	2 doses of 12 mg 24 hours apart	No	2	Garite 2009; McEvoy 2010
24 mg	24 hours	2 doses of 12 mg 24 hours apart	Yes	6	Aghajafari 2002; Guinn 2001; McEvoy 2002; Mazumder 2008; Murphy 2008; Wapner 2006

*Source: Crowther (2011)
^exact timing not reported,
mg milligrams

Primary maternal outcomes for these Clinical Practice Guidelines:

We have summarised the risk estimates for two of the commonly reported maternal infection primary outcomes for these Clinical Practice Guidelines (chorioamnionitis and puerperal sepsis) and have analysed the data using total dose of betamethasone given as the repeat antenatal corticosteroid and time to complete the course (**Table 30**):

Betamethasone:

- ≤12 mg completed immediately
- 24 mg completed in 24 hours

Chorioamnionitis -

Overall no difference was seen in the risk for chorioamnionitis between women treated with repeat antenatal corticosteroids and those with no repeat treatment (RR 1.16, 95%CI 0.92 to 1.46; 6 trials, n=4261 women).

Total dose of betamethasone ≤12 mg

- One repeat dose of 11.4 mg of Celestone® Chronodose® (betamethasone sodium phosphate and betamethasone acetate) was used as the repeat antenatal corticosteroid and further repeat doses were allowed in the trial protocol if the woman was eligible was reported in one trial (Crowther 2006). There was no difference in the risk for chorioamnionitis between treatment with repeat antenatal corticosteroids and no repeat treatment (RR 1.08; 95%CI 0.72 to 1.62; 1 trial, n=982 women) (**Table 30**).

Total dose of betamethasone 24 mg

- 24 mg antenatal betamethasone (brand of betamethasone not reported) completed in 24 hours with no further repeat courses was reported in one trial (Garite 2009). There was no difference in the risk of chorioamnionitis between treatment with repeat antenatal corticosteroids and no repeat treatment (RR 0.64, 95%CI 0.23 to 1.77; 1 trial, n=437 women) (**Table 30**).

- 24 mg completed in 24 hours and further repeat courses allowed in the trial protocol if the woman remained at risk of preterm birth was reported in four trials (Aghajafari 2002, Guinn 2001, Murphy 2008, Wapner 2006). Aghajafari (2002) and Murphy (2008) used Celestone® Soluspan®, Guinn (2001) and Wapner (2006) did not report details on the brand of betamethasone used. There was no difference in the risk for chorioamnionitis between women who had been treated with repeat antenatal betamethasone and those with no repeat treatment (RR 1.27, 95%CI 0.95 to 1.70, 4 trials, n=2842 women) (**Table 30**).

Examining the available data for regimens of repeat antenatal betamethasone (11.4 mg completed immediately, 24 mg completed in 24 hours (no additional repeat courses allowed), 24 mg completed in 24 hours (further repeat courses allowed)) separately the subgroup interaction test was not significant for chorioamnionitis ($Chi^2 = 1.79$, $p = 0.41$, $I^2 = 0\%$) (Appendix N - **Figure 20**). This can be interpreted as indicating that there was no difference between these regimens for the risk of chorioamnionitis.

Puerperal sepsis -

Overall no difference was seen in the risk for puerperal sepsis between treatment with repeat antenatal corticosteroids and no repeat treatment with antenatal corticosteroids (RR 1.15, 95%CI 0.83 to 1.60; 5 trials, n=3091 women).

Total dose of betamethasone ≤12 mg

- One dose of 12 mg antenatal betamethasone (brand of betamethasone not reported) with no further repeat doses allowed in the trial protocol was reported in one trial (Peltoniemi 2007). There was no difference in the risk of puerperal sepsis between women treated with repeat antenatal betamethasone and those with no repeat treatment (RR 1.57, 95%CI 0.80 to 3.10; 1 trial, n=249 women) (**Table 30**).

Total dose of betamethasone 24 mg

- 24 mg completed in 24 hours and further repeat courses allowed in the trial protocol if the woman remained at risk of preterm birth was reported in four trials (Aghajafari 2002, Guinn 2001, Murphy 2008, Wapner 2006). Aghajafari (2002) and Murphy (2008) used Celestone® Soluspan®, Guinn (2001) and Wapner (2006) did not report details on the brand of betamethasone used. There was no difference in the risk for puerperal sepsis between women who had been treated with repeat antenatal betamethasone and those with no repeat treatment (RR 1.05, 95%CI 0.72 to 1.54, 4 trials, n=2842 women) (**Table 30**).

Examining the available data for regimens of repeat antenatal betamethasone (12 mg completed immediately, 24 mg completed in 24 hours with further repeat courses allowed) separately the subgroup interaction test for puerperal sepsis was not significant (Chi^2=1.03, p=0.31, I^2=2.9%) (Appendix N - **Figure 21**). This can be interpreted as indicating that there was no difference between the regimens for the risk of puerperal sepsis.

Table 30: Primary maternal outcomes for repeat betamethasone regimens compared with no repeat antenatal corticosteroids*

Total dose of betamethasone	Time to complete course	Chorioamnionitis		Puerperal sepsis	
		Risk ratio RR (95% Confidence Interval)	Trials contributing data	Risk ratio RR (95% Confidence Interval)	Trials contributing data
≤12 mg betamethasone					
12 mg	Immediate (no repeat doses)	NR		1.57 (0.80 to 3.10), 1 trial, n= 249 women	Peltoniemi 2007
11.4 mg	Immediate (repeat dose(s) allowed)	1.08 (0.72 to 1.62), 1 trial, n=982 women	Crowther 2006	NR	
24 mg betamethasone					
24 mg	24 hours (no repeat doses)	0.64 (0.23 to 1.77); 1 trial, n= 437 women	Garite 2009	NR	
24 mg	24 hours (repeat doses allowed)	1.27 (0.95 to 1.70), 4 trials, n= 2842 women	Aghajafari 2002; Guinn 2001; Murphy 2008; Wapner 2006	1.05 (0.72 to 1.54), 4 trials, n= 2842 women	Aghajafari 2002; Guinn 2001; Murphy 2008; Wapner 2006
Overall treatment effect		**1.16 (0.92 to 1.46); 6 trials, n=4261 women**		**1.15 (0.83 to 1.60); 5 trials, n=3091 women**	
Subgroup interaction tests		**Chi^2=1.79, p=0.41, I^2=0%**		**Chi^2=1.03, p=0.31, I^2=2.9%**	

*Source: Crowther (2011); Meta-analyses conducted for these Clinical Practice Guidelines, NR not reported, mg milligrams

Therefore, where data were available, there were no differences found for the risk of chorioamnionitis (betamethasone 11.4 mg completed immediately, 24 mg completed in 24 hours (no additional repeat courses allowed), 24 mg completed in 24 hours (further repeat courses allowed)) or puerperal sepsis (betamethasone 12 mg completed immediately, 24 mg completed in 24 hours with further repeat courses

allowed) between treatment with the different dosing regimens used for repeat antenatal corticosteroids compared with no repeat treatment.

Other maternal primary outcomes for these Clinical Practice Guidelines - Maternal quality of life was not reported in any of the trials included in the Crowther (2011) systematic review.

Primary infant outcomes for these Clinical Practice Guidelines:

We have summarised the risk estimates for two of the commonly reported infant primary outcomes for these Clinical Practice Guidelines (neonatal death and respiratory distress syndrome) and have analysed the data using total dose given of the repeat antenatal corticosteroid and time to complete the course (**Table 31**):

Betamethasone:

- ≤12 mg completed immediately
- 24 mg completed in 24 hours

Neonatal death -

Overall no difference was seen in the risk for neonatal death between infants who had been exposed to repeat antenatal corticosteroids and those with no repeat exposure (RR 0.91, 95%CI 0.62 to 1.34; 7 trials, n=2713 infants).

Total dose of betamethasone ≤12 mg

- One dose of 12 mg antenatal betamethasone (brand of betamethasone not reported) with no further repeat doses allowed in the trial protocol was reported in one trial (Peltoniemi 2007). There was no difference found for the risk of neonatal death between infants exposed to repeat antenatal corticosteroids and those with no repeat exposure (RR 2.80, 95%CI 0.76 to 10.37; 1 trial, n=326 infants) (**Table 31**). The confidence intervals are very wide for this suggesting imprecision and caution is required when interpreting the results.

- One repeat dose of 11.4 mg of Celestone® Chronodose® (betamethasone sodium phosphate and betamethasone acetate) was used as the repeat antenatal corticosteroid and further repeat doses were allowed in the trial protocol if the woman was eligible in one trial (Crowther 2006). There was no difference in the risk for neonatal death compared with no repeat exposure to antenatal corticosteroids (RR 0.94, 95%CI 0.56 to 1.59; 1 trial, n=1144 infants) (**Table 31**).

Total dose of betamethasone 24 mg

- 24 mg betamethasone completed in 24 hours as the repeat antenatal corticosteroid but no further repeat courses were allowed by the trial protocol reported in two trials (Garite 2009; McEvoy 2010). There was no difference in the risk of neonatal death following exposure to repeat antenatal corticosteroids compared with no repeat exposure (RR 0.86, 95%CI 0.28 to 2.66; 2 trials, n=668 infants) (**Table 31**).

- 24 mg betamethasone completed in 24 hours as the repeat antenatal corticosteroid and the trial protocol allowed for further repeat courses was reported in three trials (Aghajafari 2002; Guinn 2001; Mazumder 2008). This regimen also found no difference in the risk of neonatal death between exposure to repeat antenatal corticosteroids and no repeat exposure (RR 0.52, 95%CI 0.23 to 1.18; 3 trials, n=575 infants) (**Table 31**).

Examining the available data for different regimens of repeat antenatal betamethasone (12 mg completed immediately, 11.4 mg completed immediately, 24 mg completed in 24 hours (no further repeat courses allowed), 24 mg completed in 24 hours (further repeat courses allowed)) separately, the subgroup interaction test for neonatal death was not significant (Chi^2=4.64, p=0.20, I^2=35.4%) (Appendix N, **Figure 22**). This can be interpreted as indicating that there were no differential effects between the regimens for the risk of neonatal death.

Table 31: Primary infant outcomes for repeat betamethasone regimens compared with no repeat antenatal corticosteroids*

Total dose of betamethasone	Time to complete course	Neonatal death		Respiratory distress syndrome	
		Risk ratio RR (95% Confidence Interval)	**Trials contributing data**	**Risk ratio RR (95% Confidence Interval)**	**Trials contributing data**
≤12 mg betamethasone					
12 mg	Immediate (no repeat courses)	2.80 (0.76 to 10.37); 1 trial, n=326 infants	Peltoniemi 2007	1.08 (0.87 to 1.34); 1 trial, n=326 infants	Peltoniemi 2007
11.4 mg	Immediate (repeat courses allowed)	0.94 (0.56 to 1.59); 1 trial, n=1144 infants	Crowther 2006	0.79 (0.68 to 0.92); 1 trial, n=1144 infants	Crowther 2006
24 mg betamethasone					
24 mg	24 hours (no repeat doses)	0.86 (0.28 to 2.66); 2 trials, n=668 infants	Garite 2009; McEvoy 2010	0.72 (0.58 to 0.89); 2 trials, n=668 infants	Garite 2009; McEvoy 2010
24 mg	24 hours (repeat doses allowed)	0.52 (0.23 to 1.18); 3 trials, n=575 infants	Aghajafari 2002; Guinn 2001; Mazumder 2008	0.86 (0.68 to 1.10); 4 trials, n=1068 infants	Aghajafari 2002; Guinn 2001; Mazumder 2008
Overall treatment effect		**0.91 (0.62 to 1.34); 7 trials, n=2713 infants**		**0.83 (0.75 to 0.91); 8 trials, n=3206 infants**	
Subgroup interaction tests		**Chi^2=4.64, p=0.20, I^2=35.4%**		**Chi^2=7.72, p=0.05, I^2=61.2%**	

*Source: Crowther 2011; Meta-analyses conducted for these Clinical Practice Guidelines, mg milligrams

Respiratory distress syndrome -

Overall there was a significant reduction in the risk for respiratory distress syndrome following exposure to repeat antenatal corticosteroids compared with no repeat exposure (RR 0.83, 95%CI 0.75 to 0.91; 8 trials, n=3206 infants).

Total dose of betamethasone ≤12 mg

- One dose of 12 mg antenatal betamethasone (brand of betamethasone not reported) with no further repeat doses allowed in the trial protocol was reported in one trial (Peltoniemi 2007). There was no difference in the risk of respiratory distress syndrome following repeat antenatal corticosteroids compared with no repeat exposure (RR 1.08, 95%CI 0.87 to 1.34; 1 trial, n=326 infants) (**Table 31**).

- One repeat dose of 11.4 mg of Celestone® Chronodose® (betamethasone sodium phosphate and betamethasone acetate) was used as the repeat antenatal corticosteroid and further repeat dose(s) were allowed in the trial protocol if the woman remained at risk or preterm birth 7 days later in one trial (Crowther 2006). There was a significant reduction in the risk of respiratory distress syndrome (RR 0.79, 95%CI 0.68 to 0.92; 1 trial, n=1144 infants) (**Table 31**).

When the trials of ≤12 mg betamethasone per course were combined in a meta-analysis there was no difference in the risk of respiratory distress syndrome found between repeat exposure to antenatal betamethasone and no repeat exposure to antenatal betamethasone (RR 0.91, 95%CI 0.68 to 1.24; 2 trials, n=1470 infants) using a random effects model due to significant heterogeneity.

Total dose of betamethasone 24 mg

- 24 mg betamethasone completed in 24 hours as the repeat antenatal corticosteroid but no further repeat dose(s) were allowed by the trial protocol was reported in two trials (Garite 2009; McEvoy 2010). There was a significant reduction in respiratory distress syndrome following exposure to one repeat course of betamethasone compared with no repeat exposure (RR 0.72, 95%CI 0.58 to 0.89; 2 trials, n=668 infants) (**Table 31**).

- 24 mg betamethasone completed in 24 hours as the repeat antenatal corticosteroid and the trial protocol allowed for further repeat doses(s) was reported in four trials (Aghajafari 2002, Guinn 2001, Mazumder 2008, Wapner 2006). There was no difference in the risk of respiratory distress syndrome in these trials for repeat antenatal corticosteroids compared with no repeat exposure (RR 0.86, 95%CI 0.68 to 1.10; 4 trials, n=1068 infants) (**Table 31**).

When the six trials that used a repeat antenatal corticosteroid regimen of 24 mg antenatal betamethasone completed in 24 hours were combined in a meta-analysis the risk of respiratory distress syndrome was significantly reduced (RR 0.78, 95%CI 0.67 to 0.92; 6 trials, n=1736 infants).

Examining the available data for different regimens of repeat antenatal betamethasone (12 mg completed immediately, 11.4 mg completed immediately, 24 mg completed in 24 hours (no further repeat courses allowed), 24 mg completed in 24 hours (further repeat courses allowed)) separately, the subgroup interaction test reached borderline significance (Chi^2=7.72, p=0.05, I^2=61.2%) (Appendix N - **Figure 23**). This can be interpreted as suggesting a difference between the regimens.

The dose(s) and course regimens of repeat antenatal corticosteroids that significantly reduced the risk of respiratory distress syndrome were:

- a single dose of 11.4 mg Celestone® Chronodose® with weekly repeat dose(s) allowed in the trial protocol if the woman remained at risk of preterm birth after seven days.
- 24 mg of betamethasone completed in 24 hours with no further repeat dose(s) allowed in the trial protocol.

Composite of serious infant outcomes -

Overall there was a significant reduction in the risk of a composite of serious infant outcomes following repeat antenatal corticosteroids compared with no repeat exposure (RR 0.84, 95%CI 0.75 to 0.94; 7 trials, n=5094 infants).

Total dose of betamethasone ≤12 mg

- One repeat dose of 11.4 mg of Celestone® Chronodose® (betamethasone sodium phosphate and betamethasone acetate) was used as the repeat antenatal corticosteroid and further repeat dose(s) were allowed in the trial protocol if the woman remained at risk of preterm birth after seven days in one trial (Crowther 2006). There was a significant reduction in the risk of a composite of serious infant outcomes when infants were exposed to a repeat antenatal

corticosteroids compared with no repeat exposure (RR 0.77, 95%CI 0.62 to 0.96; 1 trial, n=1144 infants).

Total dose of betamethasone 24 mg

- 24 mg betamethasone completed in 24 hours as the repeat antenatal corticosteroid but no further repeat dose(s) were allowed by the trial protocol in one trial (Garite 2009). There was a reduction in the risk of a composite of serious infant outcomes for infants who had been exposed to repeat antenatal corticosteroids compared with no repeat exposure (RR 0.75, 95%CI 0.60 to 0.93; 1 trial, n=558 infants).

- 24 mg betamethasone completed in 24 hours as the repeat antenatal corticosteroid and the trial protocol allowed for further repeat dose(s) was reported in four trials (Aghajafari 2002, Guinn 2001, Mazumder 2008, Murphy 2008, Wapner 2006). There was no difference in the risk of a composite of serious infant outcomes for infants who had been exposed to repeat antenatal corticosteroids (RR 0.92, 95%CI 0.78 to 1.08; 5 trials, n=3392 infants) when compared with no repeat exposure.

When the six trials that used a repeat antenatal corticosteroid regimen of 24 mg antenatal betamethasone completed in 24 hours (regardless of whether further repeat dose(s) were allowed in the trial protocol) were combined in a meta-analysis there was a significant reduction in the risk of a composite of serious infant outcomes (RR 0.87, 95%CI 0.76 to 0.99; 6 trials, n=3950 infants).

Examining the available data for different regimens of repeat antenatal betamethasone (11.4 mg completed immediately, 24 mg completed in 24 hours (no further repeat dose(s) allowed), 24 mg completed in 24 hours (further repeat dose(s) allowed)) the subgroup interaction test for a composite of serious infant outcomes was not significant (Chi^2=2.80, p=0.25, I^2=28.5%) (Appendix N - **Figure 24**). This can be interpreted as indicating that all regimens of repeat antenatal corticosteroids reporting data were effective at reducing the risk of a composite of serious infant outcomes compared with no repeat exposure.

The regimens of repeat antenatal corticosteroids that significantly reduced the risk of a composite of serious infant outcomes were:

- a single dose of 11.4 mg Celestone® Chronodose® with weekly repeat dose(s) allowed in the trial protocol if the woman remained at risk of preterm birth after seven days;
- 24 mg of betamethasone completed in 24 hours with no further repeat dose(s) allowed in the trial protocol.

Other relevant outcomes for these Clinical Practice Guidelines **-** These Clinical Practice Guidelines have provided data for total dose and birthweight. For birthweight, there was a small but statistically significant overall reduction (mean difference -76 grams) following exposure to repeat antenatal corticosteroids compared with no repeat exposure (MD -75.79 grams; 95%CI -117.63 to -33.96; 9 trials, n=5626 infants).

Total dose of betamethasone ≤12 mg

- One dose of 12 mg antenatal betamethasone (brand of betamethasone not reported) with no further repeat doses allowed in the trial protocol was reported in one trial (Peltoniemi 2007). There was no difference in birthweight between infants who had been exposed to repeat

antenatal corticosteroids and those with no repeat exposure (MD -98 grams, 95%CI -205. 22 to 9.22; 1 trial, n=326 infants) (**Table 32**).

- One repeat dose of 11.4 mg of Celestone® Chronodose® (betamethasone sodium phosphate and betamethasone acetate) was used as the repeat antenatal corticosteroid and further repeat dose(s) were allowed in the trial protocol if the woman remained at risk of preterm birth after 7days in one trial (Crowther 2006). There was no difference in birthweight between infants who had been exposed to repeat antenatal corticosteroids and those with no repeat exposure (MD -10 grams, 95%CI -105.04 to 85.04; 1 trial, n=1144 infants) (**Table 32**). A significant reduction in adjusted birthweight z scores was seen following exposure to repeat antenatal corticosteroids compared with no repeat exposure (MD -0.13, 95%CI -0.26 to -0.00; 1 trial, n=1144 infants).

When the two trials (Peltoniemi 2007; Crowther 2006) that used a repeat course of ≤12 mg betamethasone were combined in a meta-analysis there was no difference in birthweight found between infants who had been exposed to repeat antenatal corticosteroids and those with no repeat exposure (MD –48.72 grams, 95%CI -119.84 to 22.40; 2 trials, n=1470 infants).

Table 32: Primary infant outcomes for repeat betamethasone regimens compared with no repeat antenatal corticosteroids*

Total dose of betamethasone	Time to complete course	Mean difference MD (95% Confidence Interval)
		Birthweight
≤12 mg betamethasone		
12 mg	Immediate (no repeat courses)	-98 g (-205. 22 to 9.22); 1 trial, n=326 infants
11.4 mg^	Immediate (repeat courses allowed)	-10 g (-105.04 to 85.04); 1 trial, n=1144 infants
24 mg betamethasone		
24 mg	24 hours (no repeat doses)	-16.45 g (-123.60 to 90.69); 2 trials, n=668 infants
24 mg	24 hours (repeat doses allowed)	-112.51 g (-171.58 to -53.44); 5 trials, n=3488 infants
Overall mean difference		**-75.79 g (-117.63 to -33.96); 9 trials, n=5626 infants**
Interaction test result		**Chi^2 = 4.67, p = 0.20, I^2 = 36%**

*Source Crowther 2011; Meta-analysis conducted for these Clinical Practice Guidelines,
^ Celestone® Chronodose®
g – grams

Total dose of betamethasone 24 mg

- 24 mg betamethasone completed in 24 hours as the repeat antenatal corticosteroid but no further repeat courses were allowed by the trial protocol was reported in two trials (Garite 2009; McEvoy 2010). There was no difference in the birthweight for infants exposed to repeat antenatal corticosteroids compared with no repeat exposure (MD -16.45 grams, 95%CI -123.60 to 90.69; 2 trials, n=668 infants). McEvoy (2010) reported on adjusted birthweight z scores and found no differences between exposure to one planned repeat course of antenatal corticosteroids and no repeat exposure (MD 0.00 grams, 95%CI -0.34 to 0.34, 1 trial, n=112 infants).

- 24 mg betamethasone completed in 24 hours as the repeat antenatal corticosteroid and the trial protocol allowed for further repeat dose(s) was reported in five trials (Aghajafari 2002, Guinn 2001, Mazumder 2008, McEvoy 2002, Wapner 2006). There was a significant reduction in birthweight following exposure to repeat dose(s) of betamethasone compared with no repeat exposure (MD -112.51 grams, 95%CI -171.58 to -53.44; 5 trials, n=3488 infants).

When the seven trials that used a repeat antenatal corticosteroid regimen of 24 mg antenatal betamethasone completed in 24 hours were combined in a meta-analysis there was a significant decrease in birthweight (MD -90.12 grams, 95%CI -141.85 to -38.39; 7 trials, n=4156 infants). Six of the seven trials included in the analysis had effect estimates that crossed the line of no effect and there were wide confidence intervals indicating imprecision. The clinical effect of the reduced birthweight is unclear.

Examining the available data for different regimens of repeat antenatal betamethasone (12 mg completed immediately, 11.4 mg completed immediately, 24 mg completed in 24 hours (no further repeat courses allowed), 24 mg completed in 24 hours (further repeat courses allowed)) the subgroup interaction test for birthweight was not significant (Chi^2=4.67, p=0.20, I^2=36%) (Appendix N, **Figure 25**). This can be interpreted as indicating there was no differential effect between the regimens for the risk of reduced birthweight.

Effects of four or more repeat courses on birthweight - One trial (Wapner 2006) reported on a subgroup of 376 infants where four or more repeat courses of antenatal betamethasone were given (24 mg completed in 24 hours and further repeat courses allowed in the trial protocol if the woman remained at risk of preterm birth). Data were reported for anthropometric outcomes including birthweight for women who had received one to three courses of antenatal corticosteroids and those who had received four or more courses. There were no differences in birthweight between repeat antenatal corticosteroid exposure (one to three courses) and no repeat exposure. The mean difference was -58.80 grams (95%CI -277.46 to 159.86). For infants who had been exposed to four or more courses there was a significant decrease in birthweight. The mean difference was -161.00 grams (95%CI-290.52 to -31.48).

There was no difference in the number of infants born small for gestational age (below the 5th percentile) who had been exposed to one to three courses of antenatal corticosteroids (4.6%) compared with no repeat exposure (8.6%). There were significantly more infants with birthweight small for gestational age (below the 5th percentile) who had been exposed to four or more courses of antenatal corticosteroids compared with no exposure (17.3% and 8.7% respectively). The relative risk was increased two-fold RR 2.00 (95%CI 1.07 to 3.73) and the absolute risk difference increased by 7% (95%CI 1 to 14%). The trial was stopped early following the second interim analysis due to concerns about the reduced birthweight outcomes with no evidence of a reduction in the primary outcome of a composite of serious infant outcomes (including severe respiratory distress syndrome, intraventricular haemorrhage (Grades 3/4), periventricular leukomalacia, chronic lung disease, perinatal death) and because of difficulties in recruitment. There is evidence of imprecision reflected in wide confidence intervals for these outcomes.

Primary infant as a child outcomes for these Clinical Practice Guidelines:

Survival free of any major disability **-** Overall there was no difference in the risk for survival free of any major neurosensory disability for children who had been exposed *in utero* to repeat antenatal corticosteroids and those with no repeat exposure (RR 1.01, 95%CI 0.92 to 1.11; 2 trials, n=1317 children) using a random effects model due to significant heterogeneity.

Total dose of betamethasone ≤12 mg

- One dose of 12 mg antenatal betamethasone (brand of betamethasone not reported) with no further repeat doses allowed in the trial protocol in one trial (Peltoniemi 2007). There was no difference in the risk for survival free of any major neurosensory disability for children who had been exposed *in utero* to repeat antenatal corticosteroids and those with no repeat exposure (RR 0.98, 95%CI 0.95 to 1.01; 1 trial, n=257 children).

- One repeat dose of 11.4 mg of Celestone® Chronodose® (betamethasone sodium phosphate and betamethasone acetate) was used as the repeat antenatal corticosteroid and further repeat doses were allowed in the trial protocol if the woman was eligible in one trial (Crowther 2006). There was no difference in the risk for survival free of any major neurosensory disability for children who had been exposed *in utero* to repeat antenatal corticosteroids and those with no repeat exposure (RR 1.04, 95%CI 0.99 to 1.10; 1 trial, n=1060 children).

Total dose of betamethasone 24 mg

- 24 mg betamethasone completed in 24 hours was given was used as the repeat antenatal corticosteroid in one trial (Murphy, 2008). There was no difference in the risk for survival free of disability between children who had been exposed *in utero* to repeat antenatal corticosteroids and those with no repeat exposure (RR 1.01, 95%CI 0.97 to 1.04; 1 trial, n=2095 children).

Major neurosensory disability at early childhood follow up -

Overall no difference was seen in the risk for major neurosensory disability at early childhood follow-up for children who had been exposed *in utero* to repeat antenatal corticosteroids and those with no repeat exposure (RR 1.08, 95%CI 0.31 to 3.76, n=1256 children).

Total dose of betamethasone ≤12 mg

- One dose of 12 mg antenatal betamethasone (brand of betamethasone not reported) with no further repeat doses allowed in the trial protocol was reported in one trial (Peltoniemi 2007). There was no difference in the risk for major neurosensory disability at early childhood follow-up for children who had been exposed *in utero* to repeat antenatal corticosteroids and those with no repeat exposure (RR 3.53, 95%CI 0.37 to 33.52; 1 trial, n=257 children). Confidence intervals are extremely wide suggesting imprecision.

- One repeat dose of 11.4 mg of Celestone® Chronodose® (betamethasone sodium phosphate and betamethasone acetate) was used as the repeat antenatal corticosteroid and further repeat doses were allowed in the trial protocol if the woman was eligible in one trial (Crowther 2006). There was no difference in the risk for major neurosensory disability at early childhood follow-up for children who had been exposed *in utero* to repeat antenatal corticosteroids and those with no repeat exposure (RR 0.77, 95%CI 0.55 to 1.08; 1 trial, n=999 children).

Total dose of betamethasone 24 mg

- 24 mg betamethasone completed in 24 hours was given was used as the repeat antenatal corticosteroid in one trial (Murphy, 2008). There was no difference in the risk for blindness (RR 1.07, 95%CI 0.58 to 1.98; 1 trial, n=2104 children); deafness (RR 0.97, 95%CI 0.14 to 6.68; 1 trial, n=2104 children) or cerebral palsy (RR 0.93, 95%CI 0.53 to 1.62; 1 trial, n=2008 children) for children who had been exposed *in utero* to repeat antenatal corticosteroids and those with no repeat exposure.

Summary of evidence for dose, number of doses for a course and interval between repeat courses of antenatal corticosteroids following a single course of antenatal corticosteroids

All the current evidence is from trials using betamethasone as the repeat antenatal corticosteroid.

For the mother
There was no increased risk for chorioamnionitis or puerperal sepsis using any of the regimens of repeat antenatal corticosteroids reporting relevant data compared with no repeat treatment.

For the infant
There were no differences in neonatal death between any of the repeat betamethasone regimens compared with no repeat exposure.

The regimens of repeat antenatal corticosteroids that significantly reduced the risk of respiratory distress syndrome were:

- a single dose of 11.4 mg Celestone® Chronodose® with weekly repeat dose(s) allowed if the woman remained at risk of preterm birth 7 or more days later.
- 24 mg of betamethasone completed in 24 hours with no further repeat dose(s) allowed in the trial protocol.

The regimens of repeat antenatal corticosteroids that significantly reduced the risk of a composite of serious infant outcomes were:

- a single dose of 11.4 mg Celestone® Chronodose® with weekly repeat doses allowed in the trial protocol if the woman remained at risk of preterm birth 7 or more days later.
- 24 mg of betamethasone completed in 24 hours with no further repeat dose(s) allowed in the trial protocol.

Overall birthweight was significantly reduced following repeat antenatal corticosteroids compared with no repeat exposure. There were no subgroup differences between the regimens of repeat antenatal corticosteroids. The evidence suggested that one planned repeat dose of antenatal betamethasone did not reduce birthweight compared with no repeat exposure. Four or more courses of betamethasone 24 mg completed over 24 hours and repeated weekly were associated with reduced birthweight and increased risk of small for gestational age.

There was no evidence of any differences in follow-up for the infant as a child for neurosensory disability.

Comparative evidence for more than one repeat dose/course of antenatal corticosteroids is limited. Individual patient data meta-analysis from the trials of repeat antenatal corticosteroids would be very helpful to answer the question '*which is the most effective dose, number of doses in a course and optimal interval between courses for repeat antenatal corticosteroids?*'

See Appendix M6 – Evidence Summaries (Page 331)

What is the most effective dose, number of doses in a course and optimal interval between courses for repeat antenatal corticosteroids?
Is a single repeat dose/course (or rescue dose(s)/course) more effective than multiple repeat dose(s)/courses?

Clinical Recommendations	Strength of recommendation		
	NHMRC	GRADE	Refer to Chapter
EITHER **Use a single repeat dose(s)** of 12 mg betamethasone following a single course of antenatal corticosteroid seven or more days prior, where the woman is still at risk of preterm birth within the next seven days. After this dose, if the woman has not given birth seven or more days and less than 14 days from administration of the previous repeat dose and is still considered to be at risk of preterm birth within the next seven days a further repeat dose(s) of 12 mg betamethasone can be administered. **OR** **Use a single repeat course** of 24 mg betamethasone in divided doses completed within 24 hours following a single course of antenatal corticosteroids seven or more days prior, where the woman is still at risk of preterm birth within the next seven days Do not give further repeat courses.	A	STRONG	Chapter 10

Practice Points:

As repeat antenatal corticosteroid use

EITHER
A single repeat dose of Celestone® Chronodose®** 11.4 mg, intramuscularly as one dose.
Use up to a maximum of three, single, repeat doses only.

OR
A single repeat course of Celestone® Chronodose®** 11.4 mg, as two intramuscular doses, 24 hours apart.
Do not give any further repeat courses.

** Celestone® Chronodose® Injection (the only currently registered product in New Zealand) is a sterile aqueous suspension containing betamethasone sodium phosphate and betamethasone acetate. A single dose provided in 2 mL of Celestone Chronodose Injection contains betamethasone 11.4 mg, as betamethasone sodium phosphate 7.8 mg (in solution) and betamethasone acetate 6 mg (in suspension) in an aqueous vehicle containing sodium phosphate, sodium phosphate monobasic, disodium edetate, benzalkonium chloride and water for injection.

Research recommendations:

Further research is required to explore betamethasone and dexamethasone as the repeat antenatal corticosteroid for:

- the optimal dose;
- the optimal number of dose(s) in a course;
- the optimal interval between courses;
- the effect of multiple, repeat doses/courses.

Chapter 11: Optimal time prior to preterm birth to administer antenatal corticosteroids

What is the optimal time prior to preterm birth to administer a single course of antenatal corticosteroids?

There are no randomised controlled trials that have reported on comparing the use of different timing of a single course of antenatal corticosteroids prior to preterm birth where preterm birth is expected or planned, for example where there is a maternal medical indication or fetal compromise.

The Cochrane systematic review of *Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth* (Roberts 2006) grouped participants into four different time intervals from administration of first dose of antenatal corticosteroids to birth, *noted to be a post randomisation event*, using the following categories:

- <24 hours
- <48 hours
- between one to seven days
- seven days or more

The Roberts CPG version 2015 used the same categories for these Clinical Practice Guidelines. It was not possible to carry out any subgroup interaction tests as these time intervals are not mutually exclusive.

Primary maternal outcomes for these Clinical Practice Guidelines:

Maternal infection -

Chorioamnionitis - No differences were seen in the risk of chorioamnionitis between a single course of antenatal corticosteroids and no antenatal corticosteroids when birth occurred at <24 hours (Dexiprom 1999; Liggins 1972), <48 hours (Liggins 1972), between one to seven days (Liggins 1972) or seven days or more (Liggins 1972) from administration of first dose of antenatal corticosteroids to birth (Appendix D).

Puerperal sepsis - No differences were seen in the risk of puerperal sepsis for women giving birth <24 hours from receiving the first dose reported from a single trial (Dexiprom 1999). No data were reported for other time points for this outcome (Appendix D).

Other maternal infection outcomes - No data were reported for timing of antenatal corticosteroids for the other maternal infection outcomes of pyrexia after trial entry, intrapartum pyrexia or postnatal pyrexia requiring treatment.

Other maternal primary outcomes for these Clinical Practice Guidelines - Maternal quality of life was not reported in any of the trials in the Roberts CPG version 2015 systematic review.

Primary infant outcomes for these Clinical Practice Guidelines:

Fetal, neonatal or later death -

<24 hours from first dose of antenatal corticosteroids to birth

- Perinatal death - When exposure to antenatal corticosteroids was less than 24 hours from first dose to birth, perinatal death was significantly reduced compared with no exposure (RR 0.60, 95%CI 0.39 to 0.94; 3 trials, n=293 infants) (Dexiprom 1999, Doran 1980, Liggins 1972) (**Table 33**).

- Fetal death - There was no difference in fetal death between infants exposed to a single course of antenatal corticosteroids and no exposure (RR 0.68, 95%CI 0.34 to 1.38; 3 trials, n=293 infants) (Dexiprom 1999, Doran 1980, Liggins 1972) (**Table 33**).
- Neonatal death - When exposure to antenatal corticosteroids was less than 24 hours from first dose to birth neonatal death was significantly reduced compared with no exposure (RR 0.53, 95%CI 0.29 to 0.96; 4 trials, n=295 infants) (Dexiprom 1999, Doran 1980, Kari 1994, Liggins) (**Table 33**).

<48 hours from first dose of antenatal corticosteroids to birth

- Perinatal death - In infants born <48 hours from the first dose of antenatal corticosteroids there was a significant reduction in perinatal death compared with no exposure (RR 0.59, 95%CI 0.41 to 0.86, 1 trial, n=373 infants) (Liggins 1972)
- Fetal death - There was no difference between treatment groups for fetal death in infants born <48 hours after first dose (RR 0.78, 95%CI 0.40 to 1.51; 1 trial, n=373 infants) (Liggins 1972) (**Table 33**).
- Neonatal death - In infants born <48 hours from the first dose of antenatal corticosteroids there was a significant reduction in neonatal death compared to no exposure (RR 0.49, 95%CI 0.30 to 0.81; 1 trial, n=339 infants) (Liggins 1972) (**Table 33**).

Between one to seven days from first dose of antenatal corticosteroids to birth

- Perinatal death - In infants born between one and seven days after the first dose of a single course of antenatal corticosteroids there was no difference between exposure to antenatal corticosteroids and no exposure for perinatal death (RR 0.84, 95%CI 0.31 to 2.29; 3 trials, n= 606 infants) (Doran 1980, Garite 1992, Liggins) (**Table 33**).
- Fetal death - In infants born between one and seven days after the first dose of a single course of antenatal corticosteroids there was no difference between exposure to antenatal corticosteroids and no exposure for fetal death (RR 1.01, 95%CI 0.58 to 1.76; 3 trials, n= 606 infants) (Doran 1980, Garite 1992, Liggins 1972) (**Table 33**)
- Neonatal death - In infants born between one and seven days after the first dose of a single course of antenatal corticosteroids there was no difference between exposure to antenatal corticosteroids and no exposure for neonatal death (RR 0.80, 95%CI 0.34 to 1.88; 3 trials, n= 563 infants) (Doran 1980, Garite 1992, Liggins 1972) (**Table 33**).

Seven days or more from first dose of antenatal corticosteroids to birth

- Perinatal death - In infants born seven days or more following the first dose of antenatal corticosteroids, there no difference was seen between exposure to a single course of antenatal corticosteroids compared with no exposure for perinatal death (RR 1.42, 95%CI 0.91 to 2.23; 3 trials, n= 598 infants) (Doran 1980, Liggins 1972, Schutte 1980) (**Table 33**).
- Fetal death - In infants born seven days or more following the first dose of antenatal corticosteroids, no difference was seen between exposure to a single course of antenatal corticosteroids compared with no exposure for fetal death (RR 1.36, 95%CI 0.73 to 2.53; 3 trials, n=598 infants) (Doran 1980, Liggins 1972, Schutte 1980) (**Table 33**).
- Neonatal death - In infants born seven days or more following the first dose of antenatal corticosteroids, no difference was seen between exposure to a single course of antenatal corticosteroids compared with no exposure for or neonatal death (RR 0.67, 95%CI 0.10 to 4.42; 3 trials, n=561 infants) (Doran 1980, Liggins 1972, Schutte 1980) (**Table 33**).

Respiratory distress syndrome

<24 hours from first dose of antenatal corticosteroids to birth

- No difference was seen between infants exposed to a single course of antenatal corticosteroids and those with no exposure for respiratory distress syndrome in those infants born less than 24 hours from the first dose of antenatal corticosteroids (RR 0.87, 95%CI 0.66 to 1.15; 9 trials, n=517 infants) (Block 1977, Collaborative Group on Antenatal Steroid Therapy 1981, Dexiprom 1999, Doran 1980, Gamsu 1989, Kari 1994, Liggins 1972, Schutte 1980, Taeusch 1979) (**Table 33**).

<48 hours from first dose of antenatal corticosteroids to birth

- In infants born <48 hours from the first dose of antenatal corticosteroids there was a significant reduction in respiratory distress syndrome compared to no exposure (RR 0.83, 95%CI 0.45 to 1.54; 3 trials, n=374 infants) using a random effects model due to significant heterogeneity (Garite 1992, Liggins 1972, Taeusch 1979) (**Table 33**).

Between one to seven days from first dose of antenatal corticosteroids to birth

- In infants born between one and seven days after the first dose of antenatal corticosteroids there was a significant reduction in respiratory distress syndrome (RR 0.52, 95%CI 0.33 to 0.83; 9 trials, n=1110 infants) (Block 1977, Collaborative Group on Antenatal Steroid Therapy 1981, Doran 1980, Gamsu 1989, Garite 1992, Liggins 1972, Schutte 1980, Taeusch 1979, Teramo 1980) (**Table 33**). A random effects model was used due to the presence of significant heterogeneity. The absolute risk reduction was -11% (95%CI -15% to -7%).

Seven days or more from first dose of antenatal corticosteroids to birth

- For infants born seven days or more following the first dose of antenatal corticosteroids, no difference was seen in respiratory distress syndrome for infants exposed to antenatal corticosteroids compared with no exposure (RR 0.82, 95%CI 0.53 to 1.28; 8 trials, n=988 infants) (Collaborative Group on Antenatal Steroid Therapy 1981, Doran 1980, Gamsu 1989, Garite 1992, Liggins 1972, Schutte 1980, Taeusch 1979, Teramo 1980) (**Table 33**).

Composite of serious infant outcomes - No trials summarised in the Roberts CPG version 2015 systematic review reported on a composite primary outcome measure for the infant.

Table 33: Effect of timing of antenatal corticosteroids on primary infant outcomes for these Clinical Practice Guidelines*

Outcome	Risk ratio (RR) (95%Confidence Interval)	Number of trials	Trials contributing data	Number of infants
< 24 hours from first dose to birth				
Perinatal death	RR 0.60 (0.39 to 0.94)	3	Dexiprom 1999; Doran 1980; Liggins 1972	293
Fetal death	RR 0.68 (0.34 to 1.38)	3	Dexiprom 1999; Doran 1980; Liggins 1972	293
Neonatal death	RR 0.53 (0.29 to 0.96)	4	Dexiprom 1999; Doran 1980; Kari, 1994; Liggins 1972	295
Respiratory distress syndrome	RR 0.87 (0.66 to 1.15)	9	Block 1977; Collaborative 1981; Dexiprom 1999; Doran 1980; Gamsu 1989; Kari, 1994; Liggins 1972; Schutte 1980; Taeusch 1979	517
Composite of serious infant outcomes	NR	NR	NR	NR
<48 hours from first dose to birth				
Perinatal death	RR 0.59 (0.41 to 0.86)	1	Liggins 1972	373
Fetal death	RR 0.78 (0.40 to 1.51)	1	Liggins 1972	373
Neonatal death	RR 0.49 (0.30 to 0.81)	1	Liggins 1972	339
Respiratory distress syndrome	RR 0.83 (0.45 to 1.54)^	3	Garite 1992; Liggins 1972; Taeusch 1979	374
Composite of serious infant outcomes	NR	NR	NR	NR
Between one to seven days from first dose to birth				
Perinatal death	RR 0.84 (0.31 to 2.29)^	3	Doran 1980; Garite 1992; Liggins 1972	606
Fetal death	RR 1.01 (0.58 to 1.76)	3	Doran 1980; Garite 1992; Liggins 1972	606
Neonatal death	RR 0.80 (0.34 to 1.88)^	3	Doran 1980; Garite 1992; Liggins 1972	563
Respiratory distress syndrome	RR 0.52 (0.33 to 0.83)^	9	Block 1977; Collaborative 1980; Doran 1980; Gamsu 1989; Garite 1992; Liggins 1972; Schutte 1980; Taeusch 1977; Teramo 1980	1110
Composite of serious infant outcomes	NR	NR	NR	NR
Seven days or more from first dose to birth				
Perinatal death	RR 1.42 (0.91 to 2.23)	3	Doran 1980; Liggins 1972; Schutte 1980	598
Fetal death	RR 1.36 (0.73 to 2.53)	3	Doran 1980; Liggins 1972; Schutte 1980	598
Neonatal death	RR 0.67 (0.10 to 4.42)^	3	Doran 1980; Liggins 1972; Schutte 1980	561
Respiratory distress syndrome	RR 0.82 (0.53 to 1.28)	8	Collaborative 1980; Doran 1980; Gamsu 1989; Garite 1992; Liggins 1972; Schutte 1980; Taeusch 1977; Teramo 1980	988
Composite of serious infant outcomes	NR	NR	NR	NR

*Source: Roberts CPG version 2015; NR – not reported; ^ random effects model used for these Clinical Practice Guidelines due to significant heterogeneity

Other relevant outcomes for these Clinical Practice Guidelines - These Clinical Practice Guidelines have provided some additional data for birthweight.

There was no difference for birthweight between infants exposed to antenatal corticosteroids and those with no exposure who were born

- less than 24 hours following the first dose (MD 46.52 grams, 95%CI -94.26 to 187.29; 2 trials, n=142 infants) reported in two trials (Kari 1994, Liggins 1972) (Appendix E).
- <48 hours (-5.90 grams, 95%CI -131.95 to 120.15; 1 trial, n= 373 infants) or between one and seven days (MD -105.92 grams, 95%CI -212.52 to 0.68; 1 trial, n=520 infants) following the first dose of antenatal corticosteroids reported in one trial (Liggins 1972) (Appendix E).

For infants born seven days or more following the first dose of antenatal corticosteroids, one trial (Liggins 1972) reported that birthweight was significantly reduced (MD -147.01 grams, 95%CI -291.97 to -2.05; 1 trial, n=486) in infants exposed to antenatal corticosteroids when compared with no exposure (p=0.05).

Summary of evidence for the optimal time prior to birth to administer a single course of antenatal corticosteroids.

There are currently no randomised trials that have compared different exposure times antenatal corticosteroids were given prior to preterm birth. The data that have been used to inform these Clinical Practice Guidelines are based on post-randomisation subgroup analysis, where data were available, on the time interval from first dose of antenatal corticosteroid to birth.

For the mother

There was no increased risk of maternal infection between those who had received antenatal corticosteroids and those who had no antenatal corticosteroids at any of the time points reported in the Roberts CPG version 2015 systematic review (< 24 hours before birth, < 48 hours before birth, between one to seven days before birth, seven days or more before birth).

For the infant

For the infant, the risk of perinatal or neonatal death was significantly reduced even when there had been exposure to antenatal corticosteroids <24 hours and <48 hours before birth compared with no exposure to antenatal corticosteroids. For exposure between one and up to seven days and seven days or more after exposure to antenatal corticosteroids compared with no exposure, no benefit was seen for mortality outcomes.

The benefits for reduced risk of respiratory distress syndrome are observed where the infant had been exposed to antenatal corticosteroids for <48 hours and between one and up to seven days before birth compared with no exposure. There was no reduced risk of respiratory distress syndrome from exposure to a single course of antenatal corticosteroids after seven days or more.

There was no difference in infant birthweight between those exposed to antenatal corticosteroids and those with no exposure where the interval between exposure to the first dose and birth was <24 hours, <48 hours, or between one and up to seven days. Birthweight was significantly reduced in the infants exposed to antenatal corticosteroids compared with no exposure when the interval from the first dose to birth was seven days or more (MD -147.01 grams, 95%CI -291.97 to -2.05, 1 trial, n=486 infants). The latter evidence is based on data from the Liggins (1972) trial only.

Evidence indicates that:

- for reduction in the risk of death, the optimal time prior to birth to administer a single course of antenatal corticosteroids is when preterm birth is anticipated within 48 hours.
- for reduction in the risks of respiratory distress syndrome the benefits are observed up to seven days following exposure to a single course of antenatal corticosteroids.
- there is an increased risk of reduced birthweight when birth is seven days or more after exposure to a single course of antenatal corticosteroids.

Evidence from an individual patient data meta-analysis may be useful to address the question of the optimal time prior to preterm birth to administer a single course of antenatal corticosteroids.

See Appendix M7 – Evidence Summaries (Page 335)

What is the optimal time prior to preterm birth to administer a single course of antenatal corticosteroids?

Clinical recommendation	Strength of recommendation	
	NHMRC	GRADE
Use a single course of antenatal corticosteroids in women at risk of preterm birth when birth is planned or expected within the next seven days even if birth is likely within 24 hours.	A	STRONG

Practice points:

- Where appropriate, estimate the risk of preterm birth by considering the use of adjunct prediction tests including fetal fibronectin and assessment of cervical length.
- The optimal time to administer antenatal corticosteroids is when preterm birth is planned or expected within the next 48 hours.

Research recommendations:

- Evidence from randomised trials is required to investigate the optimal timing for antenatal corticosteroids where preterm birth is planned (e.g. maternal medical indications or fetal compromise) and women can be randomised to administration of antenatal corticosteroids at different time intervals prior to birth.
- An individual patient data meta-analysis may provide further information on optimal timing from administration of first dose to birth.

What is the optimal time prior to preterm birth to administer a repeat dose(s) of antenatal corticosteroids?

No randomised controlled trials have compared the use of different timing of repeat antenatal corticosteroids prior to preterm birth where preterm birth is definitely expected or planned.

Primary maternal outcomes for these Clinical Practice Guidelines:

Maternal infection - None of the randomised controlled trials identified in the Cochrane review *'Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes'* (Crowther 2011) or the Crowther CPG version 2015 systematic review reported post-randomisation subgroup analysis of optimal timing to administer a repeat course of antenatal corticosteroids prior to preterm birth and the effect on maternal infection.

Other maternal primary outcomes for these Clinical Practice Guidelines - No trials in the Crowther CPG version 2015 systematic review reported on maternal quality of life.

Primary infant outcomes for these Clinical Practice Guidelines:

None of the randomised controlled trials identified in the Crowther CPG version 2015 systematic review reported post-randomisation subgroup analysis of optimal timing to administer a repeat course of antenatal corticosteroids prior to preterm birth and the effect on:

- ***Fetal, neonatal or later death;***
- ***Respiratory distress syndrome;***
- ***Composite of serious infant outcomes.***

See Appendix M8 – Evidence Summary (Page 339)

What is the optimal time prior to preterm birth to administer a repeat dose(s) of antenatal corticosteroids?

Clinical recommendation	Strength of recommendation	
	NHMRC	GRADE
Use repeat antenatal corticosteroids in women at continued risk of preterm birth where the antenatal corticosteroids were given seven or more days prior, when birth is planned or expected within the next seven days, even if birth is likely within 24 hours	A	STRONG

Practice points:

- Where appropriate, estimate the risk of preterm birth by considering the use of adjunct prediction tests including fetal fibronectin and assessment of cervical length.
- If betamethasone is not available use dexamethasone.

Research recommendations:

- An individual patient data meta-analysis may provide further information on optimal timing prior to preterm birth to administer a repeat course of antenatal corticosteroids.
- Randomised trials should be conducted that compare the use of different timing of administration of repeat antenatal corticosteroids prior to preterm birth where preterm birth is definitely expected or planned.

What is the optimal timing between a first course of antenatal corticosteroids and initiating a repeat dose(s)?

None of the trials included in the Crowther (2011) systematic review gave repeat antenatal corticosteroids before seven days following an initial course. No new randomised trials were identified in the updated literature search for the Crowther CPG version 2015. For these Clinical Practice Guidelines we have examined the evidence on timing of repeat antenatal corticosteroids after a first course in two subgroups:

- Between seven days and up to 14 days (Aghajafari 2002, Crowther 2006, Guinn 2001, Mazumder 2008, McEvoy 2002, Peltoniemi 2007, Wapner 2006);
- ≥14 days (Garite 2009, McEvoy 2010, Murphy 2008).

Primary maternal outcomes for these Clinical Practice Guidelines:

Maternal infection -

Chorioamnionitis - Overall no difference was seen in the risk of chorioamnionitis between treatment with a repeat course of antenatal corticosteroids and no repeat treatment (RR 1.16, 95%CI 0.92 to 1.46; 6 trials, n=4261 women).

- No difference was seen for the risk of chorioamnionitis when treatment with a repeat course of antenatal corticosteroids was received ≥7 and up to 14 days or ≥14 days after the first course compared with no repeat treatment (**Table 34**).

- Examining the available data for timing interval from the single course to the first repeat course separately the subgroup interaction test was not significant (Chi^2=0.81, p=0.37, I^2=0%) (Appendix N - **Figure 26**). This can be interpreted as indicating that neither interval had an effect of benefit or harm for the risk of chorioamnionitis.

Puerperal sepsis - Overall no difference was seen in the risk of puerperal sepsis between repeat antenatal corticosteroids and no repeat treatment (RR 1.15, 95%CI 0.83 to 1.60; 5 trials, n=3091 infants).

- No difference was seen for the risk of puerperal sepsis when treatment with a repeat course of antenatal corticosteroids was received ≥7 and up to 14 days or ≥14 days after the first course compared with no repeat treatment (**Table 34**).

- Examining the available data for timing interval from the single course to the first repeat course separately the subgroup interaction test was not significant (Chi^2 = 0.60, p=0.44, I^2=0%) (Appendix N - **Figure 27**). This can be interpreted as indicating that neither interval had an effect of benefit or harm for the risk of puerperal sepsis.

Postnatal pyrexia - Postnatal pyrexia was only reported as an outcome in a single trial (Crowther 2006). The interval from a single course to the repeat course was between ≥7 and up to 14 days. No difference was seen in the risk of postnatal pyrexia requiring treatment between women who had received repeat antenatal corticosteroids and those with no repeat treatment (**Table 34**).

Other primary maternal infection outcomes - No other data for primary maternal infections outcomes (pyrexia after trial entry, intrapartum pyrexia requiring treatment) for these Clinical Practice Guidelines were reported in the trials included in the Crowther CPG version 2015 systematic review.

Other maternal primary outcomes for these Clinical Practice Guidelines **-** No trials in the Crowther (2011) systematic review reported on maternal quality of life.

Table 34: Maternal primary outcomes for these Clinical Practice Guidelines following administration of a repeat course of antenatal corticosteroids from the first course of antenatal corticosteroids (≥7 days up to 14 days and ≥14 days)*

Outcome	Risk Ratio RR (95% Confidence Interval)^	Number of trials	Authors	Number of women
≥7 and up to 14 days following first course				
Chorioamnionitis	RR1.23 (0.95 to 1.59)	4	Aghajafari 2002; Crowther 2006; Guinn 2001; Wapner 2006	1971
Puerperal sepsis	RR 1.02 (0.66 to 1.59)	4	Aghajafari 2002; Guinn 2001; Peltoniemi 2007; Wapner 2006	1238
Postnatal pyrexia*	RR 0.87 (0.55 to 1.38)	1	Crowther, 2006	982
≥14 days following first course				
Chorioamnionitis	RR 0.94 (0.56 to 1.57)	2	Garite 2009; Murphy 2007	2290
Puerperal sepsis	RR 1.34 (0.80 to 2.22)	1	Murphy 2007	1853

*Source: Crowther (2011); ^ meta-analyses performed for the purpose of these Clinical practice Guidelines, *requiring treatment with antibiotics

Primary infant outcomes for these Clinical Practice Guidelines:

Fetal, neonatal or later death - Overall no differences were seen for measures of infant mortality (perinatal, neonatal, fetal death) between exposure to repeat antenatal corticosteroids and no repeat exposure.

Perinatal death - No difference was seen for the risk of perinatal death when treatment with a repeat course of antenatal corticosteroids was received ≥7 and up to 14 days or ≥14 days after the first course compared with no repeat treatment (**Table 35**).

- Examining the available data for timing interval from the single course to the first repeat course separately the subgroup interaction tests were not significant for perinatal death (Chi^2=0.06, p=0.81, I^2=0%) (Appendix N - **Figure 28**). This can be interpreted as indicating no differential effect between the two timing intervals of ≥7 and up to 14 days or ≥14 days.

Fetal death - No difference was seen for the risk of fetal death when treatment with a repeat course of antenatal corticosteroids was received ≥7 and up to 14 days or ≥14 days after the first course compared with no repeat treatment (**Table 35**).

- Examining the available data for timing interval from the single course to the first repeat course separately the subgroup interaction tests were not significant for fetal death (Chi^2=0.04, p=0.83, I^2=0%) (Appendix N - **Figure 29**). This can be interpreted as indicating no differential effect between the two timing intervals of ≥7 and up to 14 days or ≥14 days.

Neonatal death - No difference was seen for the risk of neonatal death when treatment with a repeat course of antenatal corticosteroids was received ≥7 and up to 14 days or ≥14 days after the first course compared with no repeat treatment (**Table 35**).

- Examining the available data for timing interval from the single course to the first repeat course separately the subgroup interaction test was not significant for neonatal death (Chi^2=0.01, p=0.91, I^2=0%) (Appendix N, **Figure 30**). This can be interpreted as indicating no differential effect between the two timing intervals of ≥7 and up to 14 days or ≥14 days.

Respiratory distress syndrome - Overall there was a significant reduction in the risk of respiratory distress syndrome following exposure to repeat antenatal corticosteroids compared with no repeat exposure (RR 0.83, 95%CI 0.75 to 0.91; 8 trials, n=3206 infants).

- Respiratory distress syndrome was significantly reduced when treatment with a repeat course of antenatal corticosteroids was received ≥7 and up to 14 days and ≥14 days after the first course compared with no repeat treatment (**Table 35**).

- Examining the available data for timing interval from the single course to the first repeat dose(s) separately the subgroup interaction test was not significant (Chi^2=2.28, p=0.13, I^2=56.2%) (Appendix N - **Figure 31**). This can be interpreted as indicating that both intervals of ≥7 days and up to 14 days and ≥14 days had a protective effective in reducing the risk of respiratory distress syndrome.

Composite of serious infant outcomes **-** Overall a composite of serious infant outcomes was significantly reduced for infants exposed to repeat antenatal corticosteroids compared with no repeat exposure (RR 0.84, 95%CI 0.75 to 0.94; 7 trials, n=5094 infants).

- A composite of serious infant outcomes was significantly reduced when the fetus was exposed to a repeat course of antenatal corticosteroids ≥7 days and up to 14 days following a single course of antenatal corticosteroids compared with no exposure to repeat antenatal corticosteroids (RR 0.78, 95%CI 0.66 to 0.91; 5 trials, n=2232 infants). There was no difference in the risk of a composite of serious infant outcomes when the interval from the first course to the repeat course of antenatal corticosteroids was ≥14 days (RR 0.90, 95%CI 0.77 to 1.05; 2 trials, n=2862 infants) (**Table 35**).

- Examining the available data for timing interval from the single course to the first repeat course separately the subgroup interaction test was not significant (Chi^2=1.75, p=0.19, I^2=42.8%) (Appendix N - **Figure 32**). This can be interpreted as indicating no differential effect between groups for the risk of a composite of serious infant outcomes.

Table 35: Infant primary outcomes following administration of a repeat course of antenatal corticosteroids from the first course of antenatal corticosteroids (≥7 days up to 14 days and ≥14 days)*

Outcome	Risk Ratio (RR) (95% Confidence Interval)	Number of trials	Trials contributing data	Number of infants
≥7 and up to 14 days following first course				
Perinatal death	RR 0.96 (0.67 to 1.37)	6	Aghajafari, 2002; Crowther, 2006; Guinn, 2002; Mazumder, 2008; Peltoniemi, 2007; Wapner, 2006	2871
Fetal death	RR 0.71 (0.14 to 3.57)	4	Aghajafari, 2002; Crowther, 2006; Guinn, 2002; Mazumder, 2008	1740
Neonatal death	RR 0.92 (0.61 to 1.38)	5	Aghajafari, 2002; Crowther, 2006; Guinn, 2002; Mazumder, 2008; Peltoniemi, 2007	2045
Respiratory distress syndrome	RR 0.86 (0.77 to 0.96)	6	Aghajafari, 2002; Crowther, 2006; Guinn, 2002; Mazumder, 2008; Peltoniemi, 2007; Wapner, 2006	2538
Composite serious infant outcome	RR 0.78 (0.66 to 0.91)	5	Aghajafari, 2002; Crowther, 2006; Guinn, 2002; Mazumder, 2008; Wapner, 2006	2232
≥14 days following first course				
Perinatal death	RR 1.02 (0.69 to 1.51)	3	Garite 2009; McEvoy 2010; Murphy 2008	2993
Fetal death	RR 1.0 (0.06 to 15.86)	2	Garite 2009; McEvoy 2010	689
Neonatal death	RR 0.86 (0.28 to 2.66)	2	Garite 2009; McEvoy 2010	668
Respiratory distress syndrome	RR 0.72 (0.58 to 0.89)	2	Garite 2009; McEvoy 2010	668
Composite serious infant outcome	RR 0.90 (0.77 to 1.05)	2	Garite 2009; Murphy 2008	2862

*Source: Crowther (2011)

Other relevant outcomes for these Clinical Practice Guidelines **-** These Clinical Practice Guidelines have provided some additional data for birthweight.

Overall birthweight was significantly reduced following exposure to repeat antenatal corticosteroids compared with no repeat exposure (MD -75.79 grams, 95%CI -117.63 to -33.96; 9 trials, n=5626 infants). There was no difference in birthweight z score between exposure to repeat antenatal corticosteroids and no repeat exposure (MD -0.11 grams, 95%CI 0.23 to 0.00; 2 trials, n=1256 infants).

- When examining the available data separately for the intervals between the first course of antenatal corticosteroids and the repeat course of ≥7 and up to 14 days and ≥14 days the subgroup interaction test was not significant (Chi^2=0.02, p=0.88, I^2=0%) (Appendix N - **Figure 33**). This can be interpreted as indicating no difference for birthweight between the timing intervals (≥7 and up to 14 days and ≥14 days). Infants in both timing intervals (≥7 and up to 14 days and ≥14 days) were found to have a reduced birthweight.

- Similarly there was no difference in the subgroup interaction test for birthweight z score the first course of antenatal corticosteroids and the repeat course of ≥7 and up to 14 days and ≥14 days (Chi^2=0.49, p=0.48, I^2=0%) (Appendix N - **Figure 34**). This can be interpreted as indicating that

there were no differences in birthweight z score between the timing intervals (≥7 and up to 14 days and ≥14 days).

Primary outcomes of the infant in early childhood (up to 2 years corrected age) for these Clinical Practice Guidelines:

Neurosensory disability -

- For neurosensory disability, reported in one trial (Crowther 2007), there was no difference between *in utero* exposure to repeat antenatal corticosteroids and no repeat exposure when the interval between the single course of antenatal corticosteroids and the first repeat course was ≥7 days and up to 14 days (RR 0.98, 95%CI 0.84 to 1.13; 1 trial, n=1060 children).

- No difference was seen between infants exposed *in utero* to repeat doses of antenatal corticosteroid and those with no repeat exposure for a composite of serious childhood outcomes including risk of death or severe disability (neuromotor, neurosensory or neurocognitive) where the interval between the single course of antenatal corticosteroids and the repeat course was ≥14 days (RR 1.01, 95%CI 0.81 to 1.25, 1 trial, n=1104 children) (Asztalos 2010).

Survival free of neurosensory disability -

- No difference was seen in survival free of neurosensory disability in early childhood between *in utero* exposure to repeat antenatal corticosteroids and no repeat exposure when the interval between the single and repeat courses was ≥7 days and up to 14 days (RR 1.03, 95%CI 0.98 to 1.04; 2 trials, n=1317 children) (Crowther 2006, Peltoniemi 2007).

- No data were reported for survival free of neurosensory disability where the interval between single and repeat antenatal corticosteroids was ≥14 days.

Survival free of metabolic disease - No data were reported for survival free of metabolic disease where the interval between single and repeat antenatal corticosteroids was ≥7 days and up to 14 days or ≥14 days.

Primary outcomes of the infant in later childhood (5 to 8 years) for the Clinical Practice Guidelines:

The evidence for the outcomes in later childhood (5 to 8 years) is from the Crowther CPG version 2015 systematic review.

Neurosensory disability -

- Where the interval between single and repeat antenatal corticosteroids was ≥7 days and up to 14 days no differences in neurosensory disability were reported (Crowther 2011b).

- Where the interval between single and repeat antenatal corticosteroids was ≥14 days there were no differences for a composite outcome including risk of death or severe disability (neuromotor, neurosensory or neurocognitive) between children exposed to multiple or single courses of antenatal corticosteroids (OR 1.02; 95%CI 0.81 to 1.29, n=1,719) (Asztalos 2013).

Survival free of neurosensory disability -

- The overall rate of survival free of neurosensory disability was 78% and was similar in both children who had been exposed to repeat antenatal corticosteroids (78.2%) and those not exposed (77.5%) where the interval between single and repeat antenatal corticosteroids was ≥7 days and up to 14 days (Crowther 2011b).
- No data were reported for survival free of neurosensory disability where the interval between single and repeat antenatal corticosteroids was ≥14 days.

Survival free of metabolic disease - No data were reported for survival free of metabolic disease where the interval between single and repeat antenatal corticosteroids was either ≥7 days and up to 14 days or ≥14 days.

Summary of evidence for the optimal time prior to birth to administer a repeat course of antenatal corticosteroids following a single course of antenatal corticosteroids

For the mother

There was no increased risk of maternal infection outcomes (chorioamnionitis, puerperal sepsis) between women treated with repeat antenatal corticosteroids and those with no repeat treatment when the interval between the dose(s) was ≥7 days and up to 14 days or when the interval was ≥14 days.

For the infant

There was no difference in the risk of infant mortality (perinatal, fetal, neonatal death) between infants exposed to repeat antenatal corticosteroids and those with no repeat exposure when the interval between the single and the repeat course was ≥7 days and up to 14 days or when the interval was ≥14 days.

Respiratory distress syndrome was significantly reduced following exposure to repeat antenatal corticosteroids compared with no repeat exposure when the interval between the single and the repeat dose(s) was ≥7 days and up to 14 days and when the interval was ≥14 days.

Overall a composite of serious infant outcomes was significantly reduced following exposure to repeat antenatal corticosteroids compared with no repeat exposure. The subgroup interaction test comparing ≥7 days and up to 14 days and ≥14 days was not significant. This can be interpreted as indicating that there was no differential effect between the timing intervals (≥7 days and up to 14 days and ≥14 days) for this outcome.

Overall there was a statistical difference in the risk of reduced birthweight when the interval between a single course of antenatal corticosteroids and the first repeat dose(s) was ≥7 days and up to 14 days, and when the interval between dose(s) was ≥14 days.

Overall there was no difference in the birthweight z score when the interval between a single course of antenatal corticosteroids and the first repeat dose(s) was ≥7 days and up to 14 days, and when the interval between dose(s) was ≥14 days.

At early childhood follow-up there were no differences in neurosensory disability and survival free of neurosensory disability, where reported, between those who had been exposed to antenatal corticosteroids ≥7 days and up to 14 days or ≥14 days of the single course and those with no repeat exposure.

An interval between the single course and repeat antenatal corticosteroids of ≥7 days and up to 14 days has been the most commonly reported in randomised trials and is associated with reduced risk of

respiratory distress syndrome and reduced risk of a composite of serious infant outcomes in infants exposed to repeat antenatal corticosteroids compared with no repeat exposure.

See Appendix M9 – Evidence Summary (Page 342).

What is the optimal timing between a first course of antenatal corticosteroids and initiating a repeat dose(s)?

Clinical recommendation	Strength of recommendation	
	NHMRC	GRADE
EITHER **Use a single repeat dose** of repeat antenatal corticosteroids if preterm has not occurred seven or more days and less than fourteen days following a single course and preterm birth is still expected within the next seven days. If the woman has not given birth after a repeat dose(s) and is still considered to be at risk of preterm birth within the next seven days, a further repeat dose of 12 mg betamethasone can be administered.	A	STRONG
OR **Use a single repeat course** of repeat antenatal corticosteroids if preterm birth has not occurred seven or more days and less than fourteen days following a single course and preterm birth is still expected within the next seven days. Do not give further repeat courses.	A	STRONG

Practice Points:

- Use up to a maximum of three single repeat doses.
- If using a single repeat dose, use of a further repeat dose, up to a maximum of three single repeat doses, should be re-evaluated after seven or more days and less than 14 days from administration of a previous repeat course. The clinical decision to use a repeat dose should be based on an assessment of ongoing risk for preterm birth.
- Where appropriate, estimate the risk of preterm birth by considering the use of adjunct prediction tests including fetal fibronectin and assessment of cervical length.

Chapter 12: Gestational age for administration of antenatal corticosteroids

At what gestational ages is a single course of antenatal corticosteroids effective?

Table 36 shows the varied gestational ages for study entry criteria of the trials included in the Roberts CPG version 2015 systematic review.

Table 36: Gestational age range entry criteria for randomised trials of a single course of antenatal corticosteroids included in the Roberts CPG version 2015 systematic review

Author	Year	Gestational age reported by trials (weeks^{+days})	
		Minimum (weeks $^{+days}$)	Maximum (weeks $^{+days}$)
Amorim	1999	28^{+0}	34^{+6}
Balci	2010	34^{+0}	36^{+6}
Block	1976	No lower gestational age limit reported	36^{+6}
Carlan	1991	24^{+0}	34^{+6}
Cararach	1994	28^{+0}	30^{+6}
Collaborative	1981	26^{+0}	37^{+0}
Dexiprom	1999	28^{+0}	34^{+6}
Doran	1980	24^{+0}	34^{+6}
Fekih	2002	26^{+0}	34^{+6}
Gamsu	1989	No lower gestational age limit reported	34^{+6}
Garite	1992	24^{+0}	27^{+6}
Goodner	1979	No lower gestational age limit reported	33^{+6}
Kari	1994	24^{+0}	31^{+6}
Lewis	1996	24^{+0}	34^{+6}
Liggins	1972	24^{+0}	36^{+6}
Lopez	1989	27^{+0}	35^{+0}
Morales	1989	26^{+0}	34^{+6}
Nelson	1985	28^{+0}	34^{+6}
Parsons	1988	25^{+0}	32^{+6}
Porto	2011	34^{+0}	36^{+6}
Qublan	2001	27^{+0}	34^{+6}
Schutte	1980	26^{+0}	32^{+6}
Shanks	2010	34^{+0}	36^{+6}
Silver	1996	24^{+0}	29^{+6}
Taeusch	1979	No lower gestational age limit reported	33^{+6}
Teramo	1980	28^{+0}	35^{+6}

For the purpose of these Clinical Practice Guidelines we categorised gestational age entry criteria into the following groups:

- <34 weeks' and 6 days
- ≥34 weeks' and 0 days

Given the inclusion gestational ages of the individual trials, we were unable to perform subgroup interaction tests as the categories were not mutually exclusive.

Six trials reported the primary outcomes of these Clinical Practice Guidelines by gestational age at birth rather than gestational age at trial entry and have been excluded from this analysis (Block 1977, Collaborative Group on Antenatal Steroid Therapy 1981, Gamsu 1989, Liggins 1972, Schutte 1980, Taeusch 1979).

Four trials were excluded from this analysis as their gestational age ranges did not fit the dichotomous categories defined for these Clinical Practice Guidelines (Block 1977, Collaborative Group on Antenatal Steroid Therapy 1981, Liggins 1972, Lopez 1989).

No relevant data for these Clinical Practice Guidelines were reported by the Shanks (2010) trial.

Primary maternal outcomes for these Clinical Practice Guidelines:
Maternal infection -

Gestational age ≤34 weeks' and 6 days
Chorioamnionitis – Overall no difference was seen in the risk for chorioamnionitis between women who had been treated with a single course of antenatal corticosteroids and those with no corticosteroid treatment (RR 0.90, 95%CI 0.69 to 1.17; 13 trials, n=2525 women).

- No difference was seen in the risk of chorioamnionitis between women treated with a single course of antenatal corticosteroids compared with no antenatal corticosteroids when the gestation at trial entry was ≤34 weeks' and 6 days (RR 1.13, 95%CI 0.81 to 1.56; 10 trials, n=1248 women).

Puerperal sepsis - Overall no difference was seen in the risk for puerperal sepsis between women who had been treated with a single course of antenatal corticosteroids and those with no corticosteroid treatment (RR 1.35, 95%CI 0.93 to 1.95; 8 trials, n=1003 women).

- No difference was seen in the risk of puerperal sepsis between women treated with a single course of antenatal corticosteroids compared with no antenatal corticosteroids when the gestation at trial entry was ≤34 weeks' and 6 days (RR 1.26, 95%CI 0.66 to 2.39; 6 trials, n=784 women) using a random effects model.

Pyrexia after trial entry - Overall no difference was seen in the risk for pyrexia after trial entry between women who had been treated with a single course of antenatal corticosteroids and those with no corticosteroid treatment (RR 1.11, 95%CI 0.74 to 1.67; 4 trials, n=481 women).

- No difference was seen in the risk for pyrexia after trial entry between women treated with a single course of antenatal corticosteroids compared with no antenatal corticosteroids when the gestation at trial entry was ≤34 weeks' and 6 days (RR 0.60, 95%CI 0.33 to 1.31; 2 trials, n=262 women).

Intrapartum pyrexia - Overall no difference was seen in the risk for intrapartum pyrexia between women who had been treated with a single course of antenatal corticosteroids and those with no corticosteroid treatment (RR 0.60, 95%CI 0.15 to 2.49; 2 trials, n=319 women).

- No difference was seen in the risk of intrapartum pyrexia between women treated with a single course of antenatal corticosteroids compared with no antenatal corticosteroids when the gestation at trial entry was ≤34 weeks' and 6 days (RR 1.96, 95%CI 0.18 to 21.34, 1 trial, n=218).

Postnatal pyrexia - Overall no difference was seen in the risk for postnatal pyrexia between women who had been treated with a single course of antenatal corticosteroids and those with no corticosteroid treatment) (RR 0.92, 95%CI 0.64 to 1.33; 5 trials, n=1323 women).

- No difference was seen in the risk for postnatal pyrexia requiring treatment between women treated with a single course of antenatal corticosteroids compared with no antenatal corticosteroids when the gestation at trial entry was ≤34 weeks' and 6 days (RR 0.81, 95%CI 0.45 to 1.47, 3 trials, n=540 women).

Gestational age ≥34 weeks' and 0 days
No trials that recruited and randomised women with a gestation at trial entry ≥34 weeks' and 0 days reported on maternal infection outcomes (chorioamnionitis, puerperal sepsis, pyrexia after trial entry, intrapartum pyrexia or postnatal pyrexia requiring treatment with antibiotics).

Other maternal primary outcomes for these Clinical Practice Guidelines - No trials in the Roberts CPG version 2015 systematic review reported on maternal quality of life.

Primary infant outcomes for these Clinical Practice Guidelines:

Fetal, neonatal or later death -

Perinatal death - Overall there was a significant reduction in the risk for perinatal death for infants who had been exposed to a single course of antenatal corticosteroids compared with no exposure (RR 0.77, 95%CI 0.67 to 0.89; 13 trials, n=3627 infants).

- *Gestational age ≤34 weeks' and 6 days* - There was a significant reduction in the risk of perinatal death for infants exposed to a single course of antenatal corticosteroids compared with no exposure when gestational age at trial entry was ≤34 weeks' and 6 days (RR 0.57, 95%CI 0.45 to 0.73; 7 trials, n=1020 infants).
- *Gestational age ≥34weeks' and 0 days* - No trials that recruited and randomised women with a gestation at trial entry ≥34 weeks' and 0 days reported on perinatal death

Fetal death - Overall no difference was seen in the risk for fetal death between infants who had been exposed to antenatal corticosteroids and those with no exposure (RR 0.98, 95%CI 0.73 to 1.30; 13 trials, n=3627 infants).

- *Gestational age ≤34 weeks' and 6 days* - No difference was seen in the risk for fetal death between infants exposed to a single course of antenatal corticosteroids compared with no exposure when gestational age at trial entry was ≤34 weeks' and 6 days (RR 1.02, 95%CI 0.54 to 1.94; 7 trials, n=1020 infants).
- *Gestational age ≥34weeks' and 0 days* - No trials that recruited and randomised women with a gestation at trial entry ≥34 weeks' and 0 days reported on fetal death

Neonatal death - Overall there was a significant reduction in the risk for neonatal death for infants who had been exposed to a single course of antenatal corticosteroids compared with no exposure (RR 0.68, 95%CI 0.58 to 0.80; 21 trials, n=4408 infants).

- *Gestational age* ≤34 weeks' and 6 days - There was a significant reduction in the risk for neonatal death for infants exposed to a single course of antenatal corticosteroids compared with no exposure when gestational age at trial entry was ≤34 weeks' and 6 days (RR 0.53, 95%CI 0.42 to 0.68; 13 trials, n=1583 infants).
- *Gestational age ≥34 weeks' and 0 days* - No difference was seen in the risk for neonatal death between infants exposed to a single course of antenatal corticosteroids and those with no exposure when gestational age at trial entry was ≥34 weeks' and 0 days (RR 0.19, 95%CI 0.01 to 3.98; 1 trial, n=320 infants). The event rates in this single trial (Porto 2011) are very low with only 2 deaths reported in the non-exposed group and no deaths in the antenatal corticosteroid group. There is also evidence of imprecision with wide confidence intervals.

Respiratory distress syndrome -
Overall there was a significant reduction in the risk of respiratory distress syndrome for infants exposed to a single course of antenatal corticosteroids compared with those with no exposure (RR 0.65, 95%CI 0.58 to 0.73; 25 trials, n=4590 infants).

- *Gestational age ≤34 weeks' and 6 days* - There was a significant reduction in the risk of respiratory distress syndrome for infants exposed to a single course of antenatal corticosteroids compared with no exposure when gestational age at trial entry was ≤34 weeks' and 6 days (RR 0.69, 95%CI 0.55 to 0.87; 16 trials, n=1632 infants) using a random effects model.
- *Gestational age ≥34 weeks' and 0 days* - No difference was seen in the risk for respiratory distress syndrome between infants who were exposed to a single course of antenatal corticosteroids and those with no exposure when the gestational age at trial entry was ≥34 weeks' and 0 days (RR 0.56, 95%CI 0.08 to 3.93; 2 trials, n=420 infants). Event rates are also low, as would be expected at greater gestation, with 4/213 (1.9%) of infants exposed to antenatal corticosteroids and 9/207 (4.3%) of those not exposed having respiratory distress syndrome.

Composite of serious infant outcomes - No data were reported for a composite of serious infant outcomes in trials included in the Roberts CPG version 2015 systematic review for the use of a single course of antenatal corticosteroids.

Other relevant outcomes for these Clinical Practice Guidelines - These Clinical Practice Guidelines have provided some additional data for birthweight.

Overall no difference was seen in mean birthweight between infants exposed to a single course of antenatal corticosteroids and those with no exposure (MD -6.93 grams, 95%CI -39.41 to 25.55; 13 trials, n=3961 infants).

- *Gestational age ≤34 weeks' and 6 days* - No difference was seen in birthweight between infants who had been exposed to a single course of antenatal corticosteroids and those with no exposure when the gestational age at trial entry was ≤34 weeks' and 6 days (MD -13.08 grams, 95%CI -67.87 to 41.71; 8 trials, n=989 infants)
- *Gestational age ≥34 weeks' and 0 days* - No difference was seen in birthweight between infants who had been exposed to a single course of antenatal corticosteroids and those with no exposure when the gestational age at trial entry was ≥34 weeks' and 0 days (MD 4.98 grams, 95%CI -42.42 to 52.38; 2 trials, n=373 infants).

Infant as a child primary outcomes for these Clinical Practice Guidelines:
There were no data for infant as a child primary outcomes for these Clinical Practice Guidelines in trials that reported gestational age at trial entry.

Infant as an adult primary outcomes for these Clinical Practice Guidelines:
There were no data for infant as an adult primary outcomes for these Clinical Practice Guidelines in trials that reported gestational age at trial entry.

Ongoing trials
One multicentre USA randomised controlled trial investigating the effect of antenatal corticosteroids at 34 to 36 weeks was due to complete July 2013 (Antenatal Late preterm Steroids: A Randomized Placebo-Controlled Trial [ALPS]) (ClinicalTrials.gov.identifier: NCT01222247. The trial included women with a

singleton pregnancy randomised between 34 weeks' and 0 days and 36 weeks' and 5 days gestation to receive either betamethasone 2 x 6 mg (3 mg betamethasone sodium phosphate, 3mg betamethasone acetate) 24 hours apart compared with placebo. Women are eligible for inclusion in the trial if there is a high probability of delivery in the late preterm period (membrane rupture, preterm labour with intact membranes, planned delivery by induction or caesarean section in no less than 24 hours and no more than 7 days). The primary outcome is a composite including need for respiratory support: Continuous positive airway pressure or humidified high-flow nasal cannula for greater than or equal to 2 hours or more in the first 72 hours, or fraction of inspired oxygen greater than or equal to 0.30 for 4 hours or more in the first 72 hours, or mechanical ventilation in the first 72 hours, or extracorporeal membrane oxygenation; stillbirth, or neonatal death less than 72 hours of age.

Summary of evidence for the timing of administration of a single course of antenatal corticosteroids

For the mother

The risk of maternal infection (chorioamnionitis, puerperal sepsis, pyrexia after trial entry, intrapartum pyrexia and postnatal pyrexia requiring treatment with antibiotics) following treatment with a single course of antenatal corticosteroids was not increased compared with no antenatal corticosteroids when gestation at trial entry was ≤34 weeks' and 6 days weeks. No trials included in the Roberts CPG version 2015 systematic review reported data for maternal infection when gestation at trial entry was ≥34 weeks' and 0 days.

For the infant

When gestational age at trial entry was ≤34 weeks' and 6 days, perinatal, neonatal death and respiratory distress syndrome were significantly reduced following exposure to a single course of antenatal corticosteroids compared with no antenatal corticosteroids. No differences were seen for fetal death or birthweight.

When gestational age at trial entry was ≥34 weeks' and 0 days, no differences were seen in the risks for neonatal death, respiratory distress syndrome or birthweight. Evidence was based on one or two trials with low event rates and evidence of statistical imprecision with wide confidence intervals. No data were reported for perinatal or fetal death when gestational age at trial entry was ≥34 weeks' and 0 days.

There are no data on the use of antenatal corticosteroids <24 weeks' gestation.

The evidence indicates that between 24 and 34 weeks' gestational age there are benefits associated with the use of antenatal corticosteroids compared with no antenatal corticosteroids that include reduced infant mortality and respiratory distress syndrome with no increased risk of maternal infection. Previous recommendations in these Clinical Practice Guidelines have been to use a single course of antenatal corticosteroids when preterm birth is expected in the next seven days. Based on this a single course of antenatal corticosteroids should be used at <34 weeks' gestation.

There is currently insufficient evidence to make a recommendation on the use of a single course of antenatal corticosteroids at gestational ages >34 weeks' and 6 days. Evidence is based on trials with low event rates and imprecision for neonatal death and respiratory distress outcomes.

Individual patient data meta-analysis would provide further details for which gestational ages antenatal corticosteroids are most effective.

See Appendix M10 - Evidence Summary (Page 348)

At what gestational ages is a single course of antenatal corticosteroids effective?

Practice Points:

- Use a single course of antenatal corticosteroids in women of 34 weeks' and 6 days or less gestation if birth is expected within the next seven days.
- If considering use of antenatal corticosteroids prior to 24 weeks' gestation, there should be careful consideration of benefit and risks with parental consultation.

Research recommendations:

Randomised trials are needed to:

- investigate the neonatal benefits of antenatal corticosteroids administered to women at less than 24 weeks' gestation.
- investigate if smaller doses are needed at lower gestational ages.
- investigate the neonatal benefits of antenatal corticosteroids administered late preterm (34 weeks' and 6 days to <37 weeks' gestation).

At what gestational ages is a repeat dose(s) of antenatal corticosteroids effective?

For the purpose of these Clinical Practice Guidelines gestational age at trial entry was categorised into the following subgroups for analysis:
≤31 weeks' and 6 days;
≤32 weeks' and 6 days;
≤33 weeks' and 6 days.

The gestational age range used as eligibility criteria for trials of repeat antenatal corticosteroids included in the Crowther (2011) systematic review varied (**Table 37**).

Table 37: Gestational age range for inclusion in randomised controlled trials of repeat antenatal corticosteroids included the Crowther (2011) systematic review*

		Gestational age range for inclusion in trial (weeks^{+days})	
Author	**Year**	**Minimum (weeks $^{+days}$)**	**Maximum (weeks $^{+days}$)**
Aghajafari	2002	24^{+0}	30^{+6}
Crowther	2006	No lower gestational age limit reported	31^{+6}
Garite	2009	25^{+0}	32^{+6}
Guinn	2002	24^{+0}	32^{+6}
Mazumder	2008	25^{+0}	32^{+6}
McEvoy	2002	25^{+0}	33^{+6}
McEvoy	2010	26^{+0}	33^{+6}
Murphy	2008	25^{+0}	32^{+6}
Peltoniemi	2007	No lower gestational age limit reported	33^{+6}
Wapner	2007	23^{+0}	31^{+6}

*Source: Crowther (2011)

Primary maternal outcomes for these Clinical Practice Guidelines:

Maternal infection -

Chorioamnionitis - Overall no difference was seen in the risk for chorioamnionitis between women who had been treated with repeat antenatal corticosteroids and those with no repeat corticosteroid treatment (RR 0.90, 95%CI 0.69 to 1.17; 13 trials, n=2525 women).

- *≤31weeks' and 6 days* - No difference was seen in the risk for chorioamnionitis between women who were treated with repeat antenatal corticosteroids and those with no repeat treatment when the gestational age at trial entry was ≤31 weeks' and 6 days (RR 1.11, 95%CI 0.76 to 1.62; 3 trials, n=1486 women).
- *≤32 weeks' and 6 days* - No difference was seen in the risk for chorioamnionitis between women who were treated with repeat antenatal corticosteroids and those with no repeat treatment when the gestational age at trial entry was ≤32 weeks' and 6 days (RR 1.19, 95%CI 0.89 to 1.59; 3 trials, n=2775 women).
- *≤33 weeks' and 6 days* - No data were reported when the gestational age at trial entry was ≤33 weeks' and 6 days (**Table 38**).

Puerperal sepsis - Overall no difference was seen in the risk for puerperal sepsis between women who had been treated with repeat antenatal corticosteroids and those with no repeat corticosteroid treatment (RR 1.35, 95%CI 0.93 to 1.95; 8 trials, n=1003 women).

- *≤31weeks' and 6 days* - No difference was seen in the risk for puerperal sepsis between women who were treated with repeat antenatal corticosteroids and those with no repeat treatment when the gestational age at trial entry was ≤31 weeks' and 6 days (RR 0.58, 95%CI 0.21 to 1.57; 2 trials, n=504 women).

- *≤32 weeks' and 6 days* - No difference was seen in the risk for puerperal sepsis between women who were treated with repeat antenatal corticosteroids and those with no repeat treatment when the gestational age at trial entry was ≤32 weeks' and 6 days (RR 1.17, 95%CI 0.77 to 1.77; 2 trials, n=2338 women).
- *≤33 weeks' and 6 days* - No difference was seen in the risk for puerperal sepsis between women who were treated with repeat antenatal corticosteroids and those with no repeat treatment when the gestational age at trial entry was ≤33 weeks' and 6 days (RR 1.57, 95%CI 0.80 to 3.10; 1 trial, n=249 women) (**Table 38**).

Postnatal pyrexia requiring treatment - Overall no difference was seen in the risk for postnatal pyrexia between women who had been treated with repeat antenatal corticosteroids and those with no repeat corticosteroid treatment (RR 0.92, 95%CI 0.64 to 1.33; 5 trials, n=1323 women).

- One trial (Crowther 2006) that randomised women at ≤31 weeks' and 6 days gestation found no difference in postnatal pyrexia requiring treatment between women who had received repeat antenatal corticosteroids and those with no repeat treatment (RR 0.87, 95%CI 0.55 to 1.38; 1 trial, n=972 women).

Other maternal infection outcomes - There were no data for other maternal infection outcomes including pyrexia after trial entry or intrapartum pyrexia requiring treatment.

Table 38: Maternal primary outcomes for these Clinical Practice Guidelines by gestational age at trial entry: repeat antenatal corticosteroids$*

Outcome Gestational age at trial entry (weeks $^{+days}$)	Risk Ratio (RR) (95% Confidence Interval)	Trials contributing data	Number of women
Chorioamnionitis			
$\leq 31^{+6}$	1.11 (0.76 to 1.62), 3 trials	Aghajafari 2002; Crowther 2006; Wapner 2007	1486
$\leq 32^{+6}$	1.19 (0.89 to 1.59), 3 trials	Garite 2009; Guinn 2001; Murphy 2008	2775
$\leq 33^{+6}$	Not reported	Not reported	Not reported
Puerperal sepsis			
$\leq 31^{+6}$	0.58 (0.21 to 1.57), 2 trials	Aghajafari 2002; Wapner 2007	504
$\leq 32^{+6}$	1.17 (0.77 to 1.77), 2 trials	Garite 2009; Murphy 2008	2338
$\leq 33^{+6}$	1.57 (0.80 to 3.10), 1 trial	Peltoniemi 2007	249

$Source: Crowther (2011); *Meta-analysis conducted for these Clinical Practice Guidelines.

Other maternal primary outcomes for these Clinical Practice Guidelines **-** No trials in the Crowther CPG version 2015 systematic review reported on maternal quality of life.

Primary infant outcomes for these Clinical Practice Guidelines:

Fetal, neonatal or later death **-**

Perinatal death - Overall there was no difference in the risk of perinatal death for infants exposed to repeat antenatal corticosteroids compared with infants with no exposure (RR 0.94, 95%CI 0.71 to 1.23; 9 trials, n=5554 infants).

- *≤31weeks' and 6 days* - No difference was seen in the risk for perinatal death between infants who were exposed to repeat antenatal corticosteroids and those with no repeat exposure when the gestational age at trial entry was ≤31 weeks' and 6 days (RR 0.87, 95%CI 0.54 to 1.39; 3 trials, n=1657 infants).

- *≤32 weeks' and 6 days* - No difference was seen in the risk for perinatal death between infants who were exposed to repeat antenatal corticosteroids and those with no repeat exposure when the gestational age at trial entry was ≤32 weeks' and 6 days (RR 0.87, 95%CI 0.62 to 1.24; 4 trials, n=3459 infants).
- *≤33 weeks' and 6 days* - No difference was seen in the risk for perinatal death between infants who were exposed to repeat antenatal corticosteroids and those with no repeat exposure when the gestational age at trial entry was ≤33 weeks' and 6 days (RR 2.83, 95%CI 0.84 to 9.49; 2 trials, n=438 infants) (**Table 39**).

Fetal death - Overall no difference was seen in the risk for fetal death between exposure to repeat antenatal corticosteroids and no repeat exposure (RR 0.82, 95%CI 0.24 to 2.84; 7 trials, n=2755 infants).

- *≤31weeks' and 6 days* - No difference was seen in the risk for fetal death between infants who were exposed to repeat antenatal corticosteroids and those with no repeat exposure when the gestational age at trial entry was ≤31weeks' and 6 days (RR 1.02, 95%CI 0.06 to 16.23; 2 trials, n=1162 infants).
- *≤32 weeks' and 6 days* - No difference was seen in the risk for fetal death between infants who were exposed to repeat antenatal corticosteroids and those with no repeat exposure when the gestational age at trial entry was ≤32 weeks' and 6 days (RR 0.70, 95%CI 0.14 to 3.55; 3 trials, n=1115 infants).
- *≤33 weeks' and 6 days* - No difference was seen in the risk for fetal death between infants who were exposed to repeat antenatal corticosteroids and those with no repeat exposure when the gestational age at trial entry was ≤33 weeks' and 6 days (RR 1.05, 95%CI 0.07 to 16.65; 2 trials, n=438 infants) (**Table 39**).

Data are limited by statistical imprecision with wide confidence intervals for each of the gestational categories examined and caution should be taken when interpreting the analysis.

Neonatal death - Overall no difference was seen in the risk of neonatal death between exposure to repeat antenatal corticosteroids and no repeat exposure (RR 0.91, 95%CI 0.62 to 1.34; n= 2713 infants).

- *≤31weeks' and 6 days* - No difference was seen in the risk for neonatal death between women who were treated with repeat antenatal corticosteroids and those with no repeat treatment when the gestational age at trial entry was ≤31weeks' and 6 days (RR 0.94, 95%CI 0.56 to 1.59, 2 trials, n=1160 infants).
- *≤32 weeks' and 6 days* - No difference was seen in the risk for neonatal death between women who were treated with repeat antenatal corticosteroids and those with no repeat treatment when the gestational age at trial entry was ≤32 weeks' and 6 days (RR 0.56, 95%CI 0.28 to 1.12, 3 trials, n=1155 infants).
- *≤33 weeks' and 6 days* - No difference was seen in the risk for neonatal death between women who were treated with repeat antenatal corticosteroids and those with no repeat treatment when the gestational age at trial entry was ≤33 weeks' and 6 days (RR 2.83, 95%CI 0.84 to 9.49, 2 trials, n=438 infants) (**Table 39**).

Respiratory distress syndrome **-** Overall respiratory distress syndrome was significantly reduced following exposure to repeat antenatal corticosteroids compared with no repeat exposure (RR 0.83, 95%CI 0.75 to 0.91; 8 trials, n=3206 infants).

- *≤31weeks' and 6 days* - Respiratory distress syndrome was significantly reduced for infants who had been exposed to repeat antenatal corticosteroids compared with those with no repeat

exposure when the gestational age at trial entry was 31weeks' and 6 days (RR 0.78, 95%CI 0.68 to 0.91; 3 trials , n=1655 infants).

- *≤32 weeks' and 6 days* - Respiratory distress syndrome was significantly reduced for infants who were exposed to repeat antenatal corticosteroids compared those with no repeat exposure when the gestational age at trial entry was ≤32 weeks' and 6 days (RR 0.81, 95%CI 0.68 to 0.96; 3 trials, n=1113 infants).
- *≤33 weeks' and 6 days* - No difference was seen in the risk for respiratory distress syndrome between infants who were exposed to repeat antenatal corticosteroids and those with no repeat exposure when the gestational age at trial entry was ≤33 weeks' and 6 days (RR 0.98, 95%CI 0.80 to 1.20; 2 trials, n=438 infants) (**Table 39**). The lack of effect is probably due to the small number of babies and lower risk of respiratory distress syndrome with increasing gestational age.

Table 39: Infant primary outcomes for these Clinical Practice Guidelines by gestational age at trial entry$*

Gestational age at trial entry (weeks$^{+\text{ days}}$)	Risk Ratio (RR) (95% Confidence Interval)	Trials contributing data	Number of infants
Perinatal death			
≤ 31^{+6}	0.87 (0.54 to 1.39), 3 trials	Aghajafari 2002; Crowther 2006; Wapner 2007	1657
≤ 32^{+6}	0.87 (0.62 to 1.24), 4 trials	Garite 2009; Guinn 2001; Mazumder 2008; Murphy 2008	3459
≤ 33^{+6}	2.83 (0.84 to 9.49), 2 trials	McEvoy 2010; Peltoniemi 2007	438
Fetal death			
≤ 31^{+6}	1.02 (0.06 to 16.23); 2 trials	Aghajafari 2002; Crowther 2006	1162
≤ 32^{+6}	0.70 (0.14 to 3.55); 3 trials	Garite 2009; Guinn 2001; Mazumder 2008	1155
≤ 33^{+6}	1.05 (0.07 to 16.65); 2 trials	McEvoy 2010; Peltoniemi 2007	438
Neonatal death			
≤ 31^{+6}	0.94 (0.56 to 1.59), 2 trials	Aghajafari 2002; Crowther 2006	1160
≤ 32^{+6}	0.56 (0.28 to 1.12), 3 trials	Garite 2009; Guinn 2001; Mazumder 2008	1115
≤ 33^{+6}	2.83 (0.84 to 9.49), 2 trials	McEvoy 2010; Peltoniemi 2007	438
Respiratory distress syndrome			
≤ 31^{+6}	0.78 (0.68 to 0.91); 3 trials	Aghajafari 2002; Crowther 2006; Wapner 2007	1655
≤ 32^{+6}	0.81 (0.68 to 0.96); 3 trials	Garite 2009; Guinn 2001; Mazumder 2008	1113
≤ 33^{+6}	0.98 (0.80 to 1.20); 2 trials	McEvoy 2010; Peltoniemi 2007	438
Composite serious infant outcome			
≤ 31^{+6}	0.78 (0.64 to 0.95); 3 trials	Aghajafari 2002; Crowther 2006; Wapner 2007	1655
≤ 32^{+6}	0.83 (0.67 to 1.03)** 4 trials	Garite 2009; Guinn 2001; Mazumder 2008; Murphy 2008	3439
≤ 33^{+6}	Not reported	Not reported	Not reported

$Source: Crowther (2011); *Meta-analysis conducted for these Clinical Practice Guidelines, ** random effects model used for these Clinical Practice Guidelines due to heterogeneity

Composite of serious infant outcomes - Overall there was a significant reduction in the relative risk for a composite of serious infant outcomes following exposure to repeat antenatal corticosteroids compared with no repeat exposure (RR 0.84, 95%CI 0.75 to 0.94; 7 trials, n= 5094 infants) using a random effects model.

- *≤31 weeks' and 6 days* - A composite of serious infant outcomes was significantly reduced for infants who had been exposed to repeat antenatal corticosteroids compared with those with no repeat exposure when the gestational age at trial entry was ≤31 weeks' and 6 days (RR 0.78, 95%CI 0.64 to 0.95; 3 trials, n=1655 infants).
- *≤32 weeks' and 6 days* - No difference was seen in the risk for a composite of serious infant outcomes between infants who were exposed to repeat antenatal corticosteroids compared with those with no repeat exposure when the gestational age at trial entry was ≤32 weeks' and 6 days (RR 0.83, 95%CI 0.67 to 1.03; 4 trials, n=3439 infants).
- *≤33 weeks' and 6 days* - No data were reported for a composite of serious infant outcomes in the trials included in the Crowther (2011) systematic review when the gestational age at trial entry was ≤33 weeks' and 6 days (**Table 39**).

Other relevant outcomes for these Clinical Practice Guidelines - These Clinical Practice Guidelines have provided some additional data for birthweight.

Birthweight - Overall birthweight was significantly reduced following repeat antenatal corticosteroids compared with no repeat exposure (MD-75.79 grams, 95%CI -117.63 to -33.96; 9 trials, n=5626 infants) (Crowther 2006, Garite 2009, Guinn 2001, Mazumder 2008, McEvoy 2002, McEvoy 2010, Murphy 2008, Peltoniemi 2007, Wapner 2006).

- *≤31 weeks' and 6 days* - No difference was see in birthweight when the gestational age at trial entry was ≤31 weeks' and 6 days (MD -41.11 grams, 95%CI -116.86 to 34.64; 2 trials, n= 1734 infants).
- *≤32 weeks' and 6 days* - There was a significant reduction in birthweight seen when the gestational age at trial entry was ≤32 weeks' and 6 days (MD -90.19 grams, 95%CI -148.79 to -31.58; 4 trials, n=3417 infants).
- *≤33 weeks' and 6 days* - No difference was seen in birthweight when the gestational age at trial entry was ≤33 weeks' and 6 days (-93.29 grams, 95%CI -190.43 to 3.86; 3 trials, n=475 infants).

Birthweight z score - Overall no difference was seen in birthweight z scores reported in two trials (MD -0.11, 95%CI -0.23 to 0.00; 2 trials, n=1256 infants) (Crowther 2006, McEvoy 2010).

- *≤31 weeks' and 6 days* - There was a borderline significant reduction in birthweight z score reported in a single trial (Crowther, 2006) (MD -0.13, 95%CI -0.26 to -0.00; 1 trial, n=1144 infants).
- *≤33 weeks' and 6 days* - No significant difference was seen in birthweight z scores in a single trial (McEvoy 2010) (MD 0.00, 95%CI -0.34 to 0.34; 1 trial, n=112 infants).

Infant as a child secondary outcomes for these Clinical Practice Guidelines:

Neurosensory disability -

≤31 weeks' and 6 days - No difference was seen in survival free of neurosensory disability at early childhood follow-up from the Crowther (2006) trial when the gestational age at trial entry was ≤31 weeks' and 6 days (RR 1.04, 95% CI 0.99 to 1.10; 1 trial, n=1060 children) (Crowther 2007). No difference was seen in survival free of disability when the gestational age at trial entry was ≤31 weeks' and 6 days (RR 1.02, 95%CI 0.92 to 1.12; 1 trial, n=1060 children).

≤32 weeks' and 6 days - No difference was seen in survival free of disability at early childhood follow-up from the Murphy (2008) trial when the gestational age at trial entry was ≤32 weeks' and 6 days (RR 1.01, 95%CI 0.97 to 1.04; 1 trial, n=2095 children) (Asztalos 2010).

≤33 weeks' and 6 days - No difference was seen in survival free of neurosensory disability at early childhood follow-up from the Peltoniemi (2007) trial when the gestational age at trial entry was ≤33 weeks' and 6 days (RR 0.98, 95% CI 0.95 to 1.01; 1 trial, n=257 children) (Peltoniemi 2009).

Survival free of metabolic disease **-** No randomised controlled trials included in the Crowther CPG version 2015 systematic review reported data for survival free of metabolic disease at early childhood follow-up (Appendix I).

Summary of evidence for the timing of repeat antenatal corticosteroids.

For the mother

No differences were seen in the risks of maternal infection outcomes including chorioamnionitis, puerperal sepsis and postnatal pyrexia requiring treatment with antibiotics following treatment with repeat antenatal corticosteroids compared with no repeat treatment when the gestational age at trial entry was ≤31 weeks' and 6 days, ≤32 weeks' and 6 days or ≤33 weeks' and 6 days.

For the infant

No differences were seen in the risks of infant mortality (perinatal, fetal, neonatal) between exposure to repeat antenatal corticosteroids compared with no repeat exposure when the gestational age at trial entry was ≤31 weeks' and 6 days, ≤32 weeks' and 6 days or ≤33 weeks' and 6 days.

Respiratory distress syndrome was significantly reduced following repeat antenatal corticosteroids compared with no repeat exposure when gestational age at trial entry was ≤31 weeks' and 6 days and ≤32 weeks' and 6 days. There was no difference in the risk for respiratory distress syndrome when the gestational age at trial entry was ≤33 weeks' and 6 days between infants exposed to repeat antenatal corticosteroids and those with no repeat antenatal corticosteroids.

A composite of serious infant outcomes was significantly reduced following exposure to repeat antenatal corticosteroids compared with no repeat exposure when the gestational age at trial entry was ≤31 weeks' and 6 days but there was no difference when the gestational age at trial entry was ≤32 weeks' and 6 days compared with no repeat exposure. No data were reported when the gestational age at trial entry was ≤33 weeks' and 6 days.

There was no significant difference in birthweight when gestational age at trial entry was ≤31 weeks' and 6 days or ≤33 weeks' and 6 days between infants exposed to repeat antenatal corticosteroids and those with no repeat exposure. Birthweight was significantly reduced when gestational age at trial entry was ≤ 32 weeks' and 6 days. The clinical importance of the reduction in birthweight is unclear.

Overall there was no difference in birthweight z scores between infants exposed to repeat antenatal corticosteroids and those with no repeat exposure. Individual patient data meta-analysis may be of value in interpreting this information.

See Appendix M11 – Evidence Summary (Page 352)

At what gestational ages is a repeat dose(s) of antenatal corticosteroids effective?

Practice points:

- Use repeat antenatal corticosteroids in women at risk of preterm birth (<32 weeks' and 6 days gestation). Refer to Chapter 10 of these Clinical Practice Guidelines.

Research recommendation

- Randomised trials are needed to investigate the effects of repeat antenatal corticosteroids in women ≥32 weeks' and 6 days gestation.

Chapter 13: Use of antenatal corticosteroids for women planning an elective caesarean section at term

What are the benefits and harms for the mother of administering antenatal corticosteroids for fetal lung maturation to women planning an elective caesarean section at term?

What are the benefits and harms for the fetus, infant, child and adult of administering antenatal corticosteroids for fetal lung maturation to women planning an elective caesarean section at term?

The following evidence is based on the sentinel Cochrane systematic review '*Corticosteroids for preventing neonatal respiratory morbidity after elective caesarean section at term'* (Sotiriadis 2009) including a single trial of 942 women (Stutchfield 2005). A long term follow-up report from the Stutchfield (2005) trial was identified in the Sotiriadis CPG version 2015 systematic review (Stutchfield 2013). A second randomised trial (Ahmed 2014) was also identified in the updated literature searches for the Sotiriadis CPG version 2015 systematic review and has been summarised in Chapter 2 of these Clinical Practice Guidelines.

Maternal primary outcomes for these Clinical Practice Guidelines

No data were reported in the Sotiriadis (2009) systematic review on the maternal primary outcomes for these Clinical Practice Guidelines. The Ahmed (2014) trial did not pre-specify or report on any maternal outcomes.

Infant primary outcomes for these Clinical Practice Guidelines

Fetal, neonatal or later death -

Perinatal death - There were no cases of perinatal death in either group reported in the Stutchfield (2005) trial.

Fetal death - Fetal death was not reported in either the Stutchfield (2005) or the Ahmed (2014) trials.

Neonatal death - There were no cases of neonatal death in either group reported in the Ahmed (2014) trial. The Stutchfield (2005) trial did not report on neonatal death.

Respiratory distress syndrome - Overall there was a significant reduction in respiratory distress syndrome for infants exposed to antenatal corticosteroids compared with no exposure (RR 0.29, 95%CI 0.10 to 0.83; 2 trials, n=1390 infants). Respiratory distress syndrome was diagnosed in both trials by chest radiograph where a reticular granular pattern was identified. The event rates for respiratory distress syndrome were low in both trials, probably reflecting the lower incidence of respiratory distress syndrome in infants at term gestation (antenatal corticosteroids 3/695 (0.4%) versus no antenatal corticosteroids 13/695 (1.9%)). The absolute risk difference was not significant -1% (95%CI -2% to 1%), a random effects model was used due to significant heterogeneity (I^2=50%). The number of women needed to be treated with antenatal corticosteroids to prevent one case of respiratory distress syndrome in their infant was 71 (95%CI 40 to 356).

Composite of serious infant outcomes - No data were reported on a composite of serious infant outcomes in the Stutchfield (2005) or Ahmed (2014) trials.

Other relevant outcomes for these Clinical Practice Guidelines:

Transient tachypnoea of the newborn - There was a significant reduction in transient tachypnoea of the newborn (RR 0.45, 95%CI 0.23 to 0.88; 2 trials, n=1394 infants); a random effects model was used due to heterogeneity (I^2=44%). The absolute risk difference was not significant -6% (95%CI -13% to 1%) a random effects model was used due to significant heterogeneity (I^2=92%).

Need for respiratory support - Only the Stutchfield (2005) trial reported on 'time on oxygen (hours)' as an outcome. There was a significant reduction for those infants exposed to antenatal corticosteroids compared with no exposure (MD -2.80 hours, 95%CI -5.24 to -0.36; 1 trial, n=942 infants). Caution is required in interpreting the results from this single trial due to the wide confidence intervals suggesting statistical imprecision.

Admission to neonatal intensive care - There was a significant reduction in admissions to neonatal intensive care for respiratory distress for infants exposed to antenatal corticosteroids (4/695, 0.61%) compared with no exposure (28/699, 4%) following elective caesarean section at term (RR 0.14, 95%CI 0.05 to 0.40; 2 trials, n= 1394 infants). Event rates are low for admission to neonatal intensive care. The absolute risk difference was significant -4% (95%CI -6% to -1%); a random effects model was used due to heterogeneity (I^2=60%). The number of women needed to treat to prevent one admission to neonatal intensive care for their infant was 29 (95%CI 20 to 54).

Duration of stay in neonatal intensive care - There was a significant reduction in the length of stay in neonatal intensive care for infants exposed to antenatal corticosteroids prior to elective caesarean section compared with no exposure (MD -2.70 days, 95%CI -2.76 to -2.64, 2 trials, n= 32 infants).

Other outcomes - There are no data on other outcomes including pulmonary hypertension or mechanical ventilation.

Infant as a child (later childhood 8 to 15 years) primary outcomes for these Clinical Practice Guidelines

Long term follow-up of has been conducted for the Stutchfield (2005) trial for children aged 8 to 15 years (median 12.2 years, 52% female) (Stutchfield 2013). Follow-up was based on parentally completed questionnaires and school reports of national standard assessment tests, general progress, behavioural characteristics and special educational needs. Follow-up took place in 862 children from the four largest recruiting centres in the trial, this was 92% of the original study. Of these, 824 (96%) were traced and 799 (93%) were successfully contacted. Only 51% (407/799) completed and returned the questionnaire. Parental responders to the questionnaires were more likely to be older, non-smokers, and have had a baby admitted to special care for respiratory difficulties than non-responders.

- There were no adverse effects on behavioural, cognitive or developmental outcome for those born following exposure to a single course of betamethasone (2 x 12 mg, 24 hours apart) at term compared to controls who did not receive betamethasone.

No follow-up has as yet been reported for the Ahmed (2014) trial.

Other relevant outcomes for these Clinical Practice Guidelines -

- School performance data was available from 352 children (37% of original study) followed-up from the Stutchfield (2005) trial. There was no difference between groups for attainment of national standard assessment tests. No other assessments of academic ability were reported. Children who had been exposed to antenatal corticosteroids *in utero* were more likely to be in the lowest achievement group at school (33/186; 18%) compared with children who had not been exposed to antenatal corticosteroids (14/164; 9%) (RR 2.1, 95%CI 1.1 to 3.7; 1 trial, n=350 children). Not all of the parents approached allowed the researchers to contact the school for academic information. Feedback from the schools found that 25 children (12%) who had received antenatal corticosteroids and had learning difficulties compared with 27 (14%) of those who were not exposed to antenatal corticosteroids. The most common learning difficulties were dyslexia and attention deficit disorder (Stutchfield 2013).

Ongoing trials

These Clinical Practice Guidelines identified a French randomised controlled trial 'Caesarean and Corticotherapy' planning to recruit 600 women (NCT00446953). This trial compares women where a caesarean section is planned at 38 weeks' given 2 x 12 mg betamethasone 24 hours apart with caesarean section planned at 39 weeks' with no antenatal corticosteroid. Exclusion criteria are women with a multiple pregnancy, pre-eclampsia, Rhesus immunisation, fetal infection, maternal gastro-duodenal ulcer, HIV^+ and previous injection of corticosteroid during the pregnancy. The primary outcome is respiratory distress syndrome. There are no details available regarding when data is likely to be reported.

Summary of evidence for the use of antenatal corticosteroids before elective caesarean section

The evidence for the use of antenatal corticosteroids at term and with elective caesarean section is currently based on two trials, neither of which was placebo controlled. Overall the risk of bias of these trials is unclear. Respiratory distress syndrome was not the primary outcome of the Stutchfield (2005) trial.

For the mother

No maternal primary outcomes for these Clinical Practice Guidelines were reported when antenatal corticosteroids were used before elective caesarean section at term.

For the infant

There were no cases of perinatal death reported. There was a significant reduction in neonatal respiratory disease which was mainly attributable to a significant reduction in transient tachypnoea of the newborn for infants exposed to antenatal corticosteroids prior to elective caesarean section at term compared with no exposure. Admission to neonatal intensive care and length of stay in neonatal intensive care were significantly reduced in infants exposed to antenatal corticosteroids prior to elective caesarean section at term compared with no exposure.

Follow-up into childhood is limited to one trial (Stutchfield 2005). Although there were no harms found for behavioural, cognitive or developmental outcomes, children who had been exposed to antenatal corticosteroids at term, prior to elective caesarean section were more likely to be in the lowest achievement group at school compared to controls who did not receive betamethasone. No formalised academic testing or psychological testing was performed.

There is evidence of reduced respiratory distress, less need for respiratory support and fewer admissions with shorter duration of stay in neonatal intensive care. However, respiratory distress was not the reported primary outcome of these. There remain concerns regarding long term neurodevelopmental outcomes and educational attainment in children who have been exposed to antenatal corticosteroids at term gestation (≥37 weeks' gestational age). The balance between benefits and harms is unclear based on the current evidence.

The Royal Australian and New Zealand College of Obstetricians and Gynaecologists (2012) College Statement C-Obc 23 Timing of Elective Caesarean Section at Term recommends that 'elective caesarean section in women without additional risks should be carried out at "approximately" 39 weeks' gestation'.

See Appendix M12 – Evidence Summary (Page 356)

What are the benefits and harms for the mother, fetus, infant, child and adult of administering antenatal corticosteroids for fetal lung maturation to women planning an elective caesarean section at term?

Practice points:

- For elective caesarean section at term, where possible, plan at ≥39 weeks' gestation.
- Use antenatal corticosteroids 48 hours prior to caesarean birth planned beyond 34 weeks' and 6 days gestation if there is known fetal lung immaturity.

Research recommendation:

- Randomised trials are needed to investigate the neonatal effects and childhood disability rates when antenatal corticosteroids are administered to women prior to planned caesarean section at term gestation (≥37 weeks') where their infants are at increased risk of neonatal respiratory disease.

Chapter 14: Use of antenatal corticosteroids for women with specific risk factors for preterm birth

What is the safety for the mother, fetus, infant, child, adult of administering a single course or a repeat course(s) of antenatal corticosteroids to women with the following risk factors for preterm birth:

- **a) women with a history of previous preterm birth**
- **b) women in preterm labour**
- **c) women with preterm prelabour rupture of membranes**
- **d) women with chorioamnionitis**
- **e) women with an antepartum haemorrhage**
- **f) women with a multiple pregnancy (twins and higher order)**
- **g) women with diabetes mellitus or gestational diabetes**
- **h) women with systemic infection (eg tuberculosis/sepsis)**
- **i) women with pregnancy associated hypertension or pre-eclampsia**
- **j) women with intrauterine growth restriction/fetal compromise**
- **k) women with ultrasound evidence of cervical shortening/funnelling**
- **l) women with results of a fetal fibronectin (FFN) test**
- **m) women where preterm birth is medically indicated?**

To find evidence to address these clinical questions on the use of antenatal corticosteroids for women with specific risk factors for preterm birth we reviewed the eligibility criteria for trials included in the Roberts CPG version 2015 systematic review for use of a single course of antenatal corticosteroids (**Table 40** and Appendix J) and the Crowther CPG version 2015 systematic review for repeat antenatal corticosteroids (**Table 41** and Appendix K). Whether women with specific risk factors for preterm birth were eligible for recruitment in the individual trials is tabulated and the proportion of the total study participants this represented (**Table 40**, **Table 41**).

These specific groups of women were selected as there was uncertainty about the use of antenatal corticosteroids.

Table 40: Women at risk of preterm birth with specific risk factors for preterm birth* reported in trials included in the Roberts CPG version 2015 systematic review

Author (Year)	Women with history of previous preterm birth		Women in preterm labour		Preterm prelabour rupture of membranes at trial entry		Women with chorioamnionitis		Women with antepartum haemorrhage		Women with multiple pregnancies (twins and higher order)	
	Eligible	% reported	Eligible	% reported	Eligible	% reported	Eligible	% reported	Eligible	% reported	Eligible	% reported
Amorim (1999)	NS	-	NS	-	No	0	NS	-	NS	-	No	0
Balci (2010)	NS	-	Yes	100	No	0	No	0	No	0	No	0
Block (1977)	NS	-	Yes	-	Yes	-	NS	-	NS	-	Yes	-
Cararach (1991)	NS	-	NS	-	Yes	100	No	0	No	0	No	0
Carlan (1991)	NS	-	NS	-	Yes	100	Yes	14	NS	-	NS	-
Collaborative (1981)	NS	-	No	0	Yes	47	No	0	NS	-	Yes	16
Dexiprom (1999)	NS	-	No	0	Yes	100	No	0	No	0	Yes	2
Doran (1980)	NS	-	Yes	95	Yes	-	NS	-	NS	-	Yes	5 twin
Fekih (2002)	NS	-	Yes	-	NS	-	Yes	2	NS	-	Yes	9
Gamsu (1989)	NS	-	Yes	95	NS	-	No	0	Yes	12	Yes	12
Garite (1992)	NS	-	Yes	53	No	0	No	0	Yes	20	Yes	8
Goodner (1979)	NS	-	Yes	-	NS	-	NS	-	NS	-	NS	-
Kari (1994)	NS	-	Yes	78	No	0	No	0	Yes	36	Yes	20
Lewis (1996)	Yes	18	NS	-	Yes	-	No	0	NS	-	No	0
Liggins (1972)	NS	-	Yes	20	Yes	28	NS	-	NS	-	Yes	12
Lopez (1989)	NS	-	No	0	Yes	100	No	0	NS	-	NS	-
Morales (1989)	NS	-	No	0	Yes	100	No	0	NS	-	No	0
Nelson (1985)	NS	-	No	0	Yes	100	No	0	NS	-	NS	-
Parsons (1988)	NS	-	No	0	Yes	100	No	0	NS	-	NS	-
Porto (2011)	Yes	12	Yes	67	Yes	40	No	0	NS	-	No	0
Qublan (2001)	NS	-	Yes	-	Yes	-	Yes	-	Yes	4	No	0
Schutte (1980)	NS	-	Yes	-	Yes	-	No	0	NS	-	Yes	11
Shanks (2010)	NS	-	NS	-	No	0	NS	-	NS	-	No	0
Silver (1996)	Yes	23	Yes	62	Yes	23	Yes	33	Yes	12	Yes	23
Taeusch (1979)	NS	-	Yes	-	NS	-	NS	-	Yes	20	Yes	11
Teramo (1980)	NS	-	Yes	100	NS	-	NS	-	NS	-	NS	-

- = not reported; NS = not stated; *eligibility as per individual trial criteria (Appendix J)

Table 40: (continued): Women with specific risk factors for preterm birth* reported in trials included in the Roberts CPG version 2015 systematic review

Author (Year)	Women with diabetes in pregnancy		Women for whom preterm birth is medically indicated		Women with systemic infection at trial entry		Women with pregnancy associated hypertension		Women with intrauterine growth restriction		Women with cervical shortening / funnelling		Fetal fibronectin test	
	Eligible	% reported	Eligible	% reported	Eligible	% reported	Eligible	% reported	Eligible	% reported	Eligible	% reported	Eligible	% reported
Amorim (1999)	Yes	18^^	NS	-	NS	-	Yes	78#, 10$	NS	-	NS	-	NS	-
Balci (2010)	No^	0	NS	-	NS	-	No	0	No	0	NS	-	NS	-
Block (1977)	NS	-	NS	-	NS	-	NS	-	NS	-	NS	-	NS	-
Cararach (1991)	NS	-	NS	-	NS	-	NS	-	NS	-	NS	-	NS	-
Carlan (1991)	NS	-	NS	-	NS	-	NS	-	NS	-	NS	-	NS	-
Collaborative (1981)	NS	-	NS	-	No	0	Yes	11#	NS	-	NS	-	NS	-
Dexiprom (1999)	NS	-	NS	-	No	0	NS	-	NS	-	NS	-	NS	-
Doran (1980)	Yes	4	NS	-	NS	-	No	0	NS	-	NS	-	NS	-
Fekih (2002)	No	0	NS	-	NS	-	Yes	16	NS	-	NS	-	NS	-
Gamsu (1989)	No	0	NS	-	NS	-	Yes	7.2	NS	-	Yes	11	NS	-
Garite (1992)	No	0	NS	-	NS	-	Yes	10$$	Yes	6	NS	-	NS	-
Goodner (1979)	NS	-	NS	-	NS	-	NS	-	NS	-	NS	-	NS	-
Kari (1994)	No	0	NS	-	NS	-	Yes	31	NS	-	NS	-	NS	-
Lewis (1996)	NS	-	NS	-	No	0	NS	-	NS	-	NS	-	NS	-
Liggins (1972)	NS	-	NS	-	NS	-	Yes	7	NS	-	NS	-	NS	-
Lopez (1989)	NS	-	NS	-	NS	-	NS	-	NS	-	NS	-	NS	-
Morales (1989)	NS	-	NS	-	NS	-	NS	-	NS	-	NS	-	NS	-
Nelson (1985)	NS	-	NS	-	No	0	NS	-	NS	-	NS	-	NS	-
Parsons (1988)	NS	-	NS	-	No	0	NS	-	NS	-	NS	-	NS	-
Porto (2011)	Yes	2	NS	-	NS	-	Yes	26	Yes	1	NS	-	NS	-
Qublan (2001)	NS	-	NS	-	No	0	NS	-	NS	-	NS	-	NS	-
Schutte (1980)	No	0	NS	-	No	0	No	0	No	0	NS	-	NS	-
Shanks (2010)	Yes	16	NS	-	NS	-	Yes	12	NS	-	NS	-	NS	-
Silver (1996)	NS	-	NS	-	No	-	Yes	5	Yes	9	NS	-	NS	-
Taeusch (1979)	Yes	5	NS	-	NS	-	No	0	NS	-	NS	-	NS	-
Teramo (1980)	No	0	NS	-	NS	-	No	0	NS	-	NS	-	NS	-

NR = not reported; NS = not stated; *eligibility as per individual trial criteria (Appendix J), ^ diabetes mellitus, ^^ gestational diabetes mellitus, #pre-eclampsia, $ severe hypertension, $$ pregnancy induced hypertension

Table 41: Women at risk of preterm birth with specific risk factors for preterm birth* reported included in the Crowther 2011, Cochrane systematic review

Author (Year)	Women with history of previous preterm birth		Women in preterm labour		Preterm prelabour rupture of membranes at trial entry		Women with chorioamnionitis		Women with antepartum haemorrhage		Women with multiple pregnancies (twins and higher order)	
	Eligible	% reported	Eligible	% reported	Eligible	% reported	Eligible	% reported	Eligible	% reported	Eligible	% reported
Aghajafari (2002)	Yes	-	Yes	25	Yes	34	No	0	Yes	17	Yes	34
Crowther (2006)	Yes	15	Yes	27	Yes	34	No	0	Yes	29	Yes	16
Garite (2009)	NS	-	Yes	31	No	0	No	0	Yes	4	Yes	32 twins^
Guinn (2002)	NS	-	Yes	54	Yes	24	NS	-	NS	-	Yes	7
Mazumder (2008)	NS	-	Yes	-	NS	-	No	0	NS	-	Yes	-
McEvoy (2002)	NS	-	Yes	30	NS	-	NS	-	Yes	19	No	0
McEvoy (2010)	NS	-	Yes	76	Yes	-	No	0	Yes	22	Yes	33 twins^
Murphy (2008)	Yes	35	Yes	84	Yes	16	No	0	Yes	14	Yes	11
Peltoniemi (2007)	NS	-	NS	-	Yes	39	No	0	NS	-	Yes	29
Wapner (2006)	Yes	47	Yes	67	No	0	No	0	Yes	11	Yes	20

NR = not reported; NS = not stated; *eligibility as per individual trial criteria (Appendix K), ^ triplets were not eligible

Table 41 (continued): Women at risk of preterm birth with specific risk factors for preterm birth* reported included in the Crowther 2011, Cochrane systematic review

Study ID	Women with diabetes mellitus or gestational diabetes		Women for whom preterm birth is medically indicated		Women with systemic infection at trial entry		Women with pregnancy associated hypertension		Women with intrauterine growth restriction		Women with cervical shortening / funnelling		Fetal fibronectin test	
	Eligible	% reported	Eligible	% reported	Eligible	% reported	Eligible	% reported	Eligible	% reported	Eligible	% reported	Eligible	% reported
Aghajafari (2002)	NS	-	NS	-	NS	-	NS	-	Yes	0	Yes	33	NS	-
Crowther (2006)	NS	-	NS	-	NS	-	Yes	10	Yes	7	NS	-	NS	-
Garite (2009)	NS	-	NS	-	No	0	Yes	6	Yes	2	NS	-	NS	-
Guinn (2002)	Yes	-	NS	-	No	0	Yes	NR	Yes	7	NS	-	NS	-
Mazumder (2008)	NS	-	NS	-	NS	-	NS	-	NS	-	NS	-	NS	-
McEvoy (2002)	No	0	NS	-	NS	-	Yes	14	Yes	19	NS	-	NS	-
McEvoy (2010)	No^	9#	NS	-	NS	-	Yes	6	NS	-	NS	-	NS	-
Murphy (2008)	Yes	5	NS	-	NS	-	Yes	6$, 8$$	Yes	9	Yes	49	NS	-
Peltoniemi (2007)	Yes	5#,6^	NS	-	NS	-	Yes	5$	NS	-	NS	-	NS	-
Wapner (2006)	No	0	NS	-	NS	-	NS	-	No	0	NS	-	NS	-

NR = not reported; NS = not stated; *eligibility as per individual trial criteria (Appendix K), ^ insulin dependent diabetes mellitus, # gestational diabetes mellitus, $ pre-eclampsia/hypertension, $$ hypertension

14.1 Women with a history of previous preterm birth

What is the safety for the mother with a history of a previous preterm birth of administering a single course of antenatal corticosteroids?

What is the safety for the fetus, infant, child, adult of administering a single course of antenatal corticosteroids to women with a history of previous preterm birth?

The risk of recurrence of a preterm birth for women in their next pregnancy is reported to be about 30% (Laughon 2014, van der Heyden 2013). We identified no randomised trials assessing the use of antenatal corticosteroids that recruited only women with a history of a previous preterm birth as the sole risk factor for preterm birth.

Single course of antenatal corticosteroids

The Roberts CPG version 2015 systematic review included three randomised controlled trials where a known, although small, proportion of women had a history of a previous preterm birth (**Table 40**):

- Lewis (1996) 18%
- Porto (2011) 12%
- Silver (1996) 23%.

A history of a previous preterm birth was not a specific inclusion criterion for any of the trials (Appendix I). Inclusion criteria for the trials included preterm prelabour rupture of membranes (Lewis 1996) and risk of preterm birth (reason not specified) (Lewis 1996, Porto 2011, Silver 1996).

Therefore all of the women recruited to these trials who had a history of a preterm birth also had an additional risk factor of risk of preterm birth in their current pregnancy.

In the summary of the evidence we report the overall treatment effects from all trials with available data, for the primary outcomes of these Clinical Practice Guidelines, for a single course of antenatal corticosteroids. We then report on the subset of these trials that specifically reported that a proportion of the women recruited into their trial had a *history of a previous preterm birth.*

Maternal primary outcomes for these Clinical Practice Guidelines:

Maternal infection -

Chorioamnionitis - Overall no difference was seen in the risk of chorioamnionitis between women treated with a single course of antenatal corticosteroids and those with no antenatal corticosteroids (RR 0.90, 95%CI 0.69 to 1.17; 13 trials, n=2525 women).

- Two trials reported they included a proportion of women with a history of a previous preterm birth (range 18% to 23%) and provided data for chorioamnionitis (Lewis 1996, Porto 2011, Silver 1996). The size of the treatment effect was similar to the overall effect and showed no difference between groups (RR 1.01, 95%CI 0.58 to 1.75; 2 trials, n=152 women) (**Table 42**).

Puerperal sepsis - Overall no difference was seen in the risk of puerperal sepsis between women treated with a single course of antenatal corticosteroids and those with no antenatal corticosteroids (RR 1.35, 95%CI 0.93 to 1.95; 8 trials, n=1003 women) (**Table 42**).

- Two trials reported they included a proportion of women with a history of a previous preterm birth (range 18% to 23%) and provided data for puerperal sepsis (Lewis 1996, Porto 2011, Silver 1996). The size of the treatment effect was similar to the overall effect and showed no difference between groups (RR 1.38, 95%CI 0.63 to 3.03; 2 trials, n=152 women) (**Table 42**).

Other maternal infection outcomes - No data on the other maternal infection outcomes for these Clinical Practice Guidelines were reported in the three trials that detailed that a proportion of the women in their trial had a history of a previous preterm birth (pyrexia after trial entry, intrapartum pyrexia, postnatal pyrexia requiring treatment with antibiotics).

Other primary maternal outcomes for these clinical practice guidelines - No data on quality of life were reported in the trials that recruited and reported a proportion of the women in their trial had a history of a previous preterm birth.

Infant primary outcomes for these Clinical Practice Guidelines:

Fetal, neonatal or later death -

No data were reported for:

- *Perinatal death;* or
- *Fetal death*

in the three trials that reported they included a proportion of women in their trial who had a history of a previous preterm birth (Lewis 1996, Porto 2011, Silver 1996).

Neonatal death - Overall there was a significant reduction in the risk of neonatal death in infants exposed to a single course of antenatal corticosteroids compared with those who had no exposure (RR 0.68, 95%CI 0.58 to 0.80; 21 trials, n=4408 infants).

- Three trials reported they recruited a proportion of women with a history of a previous preterm birth (range 11.5% to 22.5%) and provided data for neonatal death (Lewis 1996, Porto 2011, Silver 1996). The size of the treatment effect was similar to the overall effect but did not reach statistical significance (RR 0.61, 95%CI 0.26 to 1.40; 3 trials, n=493 infants) (**Table 43**); probably attributable to the smaller number of babies.

Respiratory distress syndrome - Overall there was a significant reduction in the risk for respiratory distress syndrome seen in infants exposed to a single course of antenatal corticosteroids compared with no exposure (RR 0.65, 95%CI 0.58 to 0.73; 25 trials, n=4590 infants).

- Three trials reported they included a proportion of women with a history of a previous preterm birth (range 11.5% to 22.5%) and provided data for respiratory distress syndrome (Lewis 1996, Porto 2011, Silver 1996). The size of the treatment effect was similar to the overall effect but did not reach statistical significance (RR 0.77, 95%CI 0.34 to 1.72; 3 trials, n=493 infants) using a random effects model due to heterogeneity (**Table 43**); probably attributable to the smaller number of babies and the heterogeneity of the trials for this clinical outcome.

Composite of serious infant outcomes - A composite of serious infant outcomes was not reported in any of the trials of a single course of antenatal corticosteroids that recruited a proportion of women with a history of a previous preterm birth in their trials (Lewis 1996, Porto 2011, Silver 1996).

Table 42: Comparison of the overall effect estimate for use of a single course of antenatal corticosteroids with trials that reported including a proportion of women with a history of a previous preterm birth – Maternal primary outcomes*

Primary outcome	Single course of antenatal corticosteroid*			Trials known to include women with a history of a previous preterm birth^				
	Trials contributing data	Number of women	Overall risk ratio (RR) (95% Confidence Interval)	Trials contributing data	Number of women	Risk ratio (RR) (95% Confidence Interval)	Actual proportion detailed in trials	Actual number of mothers
Chorioamnionitis	Amorim 1999; Carlan 1991; Dexiprom 1999; Fekih 2002; Garite 1992; Kari 1994; Lewis 1996; Liggins 1972; Lopez 1989; Morales 1989; Qublan 2001; Schutte 1980; Silver 1996	2525	RR 0.90 (0.69 to 1.17), 13 trials	Lewis 1996; Silver 1996	152	RR 1.01 (0.58 to 1.75), 2 trials, n=152 women	Lewis 1996; Silver 1996	31
Puerperal sepsis	Amorim 1999; Dexiprom 1999; Garite 1992; Lewis 1996; Qublan 2001; Schutte 1980; Silver 1996; Taeusch 1979	1003	RR 1.35 (0.93 to 1.95), 8 trials	Lewis 1996; Silver 1996	152	RR 1.38 (0.63 to 3.03), 2 trials, n=152 women	Lewis 1996; Silver 1996	31
Pyrexia after trial entry requiring treatment	Amorim 1999; Nelson 1985; Schutte 1980; Taeusch 1979	481	RR 1.11 (0.67 to 1.67), 4 trials	-	-	Not reported	-	-
Intrapartum pyrexia requiring treatment	Amorim 1999; Schutte 1980	319	RR 0.60 (0.15 to 2.49), 2 trials	-	-	Not reported	-	-
Postnatal pyrexia requiring treatment	Amorim 1999; Collaborative 1981; Dexiprom 1999; Fekih 2002; Schutte 1980	1323	RR 0.92 (0.64 to 1.33), 5 trials	-	-	Not reported	-	-

*Source: Roberts CPG version 2015 ; ^meta-analyses conducted for these Clinical Practice Guidelines

Table 43: Comparison of the overall effect estimate for use of a single course of antenatal corticosteroids with trials reported including a proportion of women with a history of a previous preterm birth – Infant primary outcomes*

Primary outcome	Single course of antenatal corticosteroid*			Trials known to have included women with a history of a previous preterm birth^				
	Trials contributing data	Number of infants	Overall risk ratio (RR) (95%Confidence Interval)	Trials contributing data	Number of infants	Risk ratio (RR) (95%Confidence Interval)	Actual proportion detailed in trials	Actual number of infants
Perinatal death	Amorim 1999; Block 1977; Collaborative 1981; Dexiprom 1999; Doran 1980; Gamsu 1989; Garite 1992; Kari 1994; Liggins 1972; Parsons 1988; Qublan 2001; Schutte 1980; Taeusch 1979	3627	RR 0.77 (0.67 to 0.89), 13 trials	-	-	Not reported	-	-
Fetal death	Amorim 1999; Block 1977; Collaborative 1981; Dexiprom 1999; Doran 1980; Gamsu 1989; Garite 1992; Kari 1994; Liggins 1972; Parsons 1988; Qublan 2001; Schutte 1980; Taeusch 1979	3627	RR 0.98 (0.73 to 1.30), 13 trials	-	-	Not reported	-	-
Neonatal death	Amorim 1999; Block 1977; Collaborative 1981; Dexiprom 1999; Doran 1980; Fekih 2002; Gamsu 1989; Garite 1992; Goodner 1979; Kari 1994; Lewis 1996; Liggins 1972; Lopez 1989; Morales 1989; Nelson 1985; Parsons 1988; Porto 2011; Qublan 2001; Schutte 1980; Silver 1996; Taeusch 1979	4408	RR 0.68 (0.58 to 0.80), 21 trials	Lewis 1996; Porto 2011; Silver 1996	493	RR 0.61 (0.26 to 1.40), 3 trials, n=493 infants	Lewis 1996; Porto 2011; Silver 1996	74
Respiratory distress syndrome	Amorim 1999; Balci 2010; Block 1977; Cararach 1991; Carlan 1991; Collaborative 1981; Dexiprom 1999; Doran 1980; Fekih 2002; Gamsu 1989; Garite 1992; Goodner 1979; Kari 1994; Lewis 1996; Liggins 1972; Lopez 1989; Morales 1989; Nelson 1985; Parsons 1988; Porto 2011; Qublan 2001; ; Schutte 1980; Silver 1996; Taeusch 1979; Teramo 1980	4590	RR 0.65 (0.58 to 0.73), 25 trials	Lewis 1996; Porto 2011; Silver 1996	493	RR 0.77 (0.34 to 1.72)$, 3 trials, n=493 infants	Lewis 1996; Porto 2011; Silver 1996	74

*Source: Roberts CPG version 2015 ; ^meta-analyses conducted for these Clinical Practice Guidelines; $ Random effects model used due to heterogeneity

Evidence summary for safety of a single course of antenatal corticosteroids in women with a history of a previous preterm birth

The main trial inclusion criteria for trials included in the Roberts CPG version 2015 systematic review were that the women were at risk of preterm birth. Although some of these women had a history of a previous preterm birth and this was stated in three of the trials, this risk factor was not a specified inclusion criterion for trial entry. Some women recruited into the other 23 included trials may also have had a history of a previous preterm birth but no information about this was provided in these trial reports.

Where found, women with a previous history of preterm birth made up a small proportion, range 11.5% to 22.5%, of the women recruited into the trials of a single course of antenatal corticosteroids.

For the mother

Overall, where reported in 26 trials, no differences were seen between women treated with a single course of antenatal corticosteroids and women with no corticosteroids in the risk for chorioamnionitis, pyrexia after trial entry, intrapartum pyrexia, postnatal pyrexia or puerperal sepsis.

Three trials reported including a proportion of women with a previous history of preterm birth. The evidence is consistent with the overall treatment effect:

- For chorioamnionitis and puerperal sepsis, the size of the treatment effect was similar to the overall effect and there was no difference between groups.

No data were reported for pyrexia after trial entry, intrapartum pyrexia, postnatal pyrexia or maternal quality of life from these three trials.

For the infant

Overall, where reported in 26 trials, there was a significant reduction in the risks for perinatal death, neonatal death and respiratory distress syndrome. No difference was seen in the risk for fetal death between infants exposed to a single course of antenatal corticosteroids and infants with no exposure.

Three trials reported including a proportion of women with a previous history of preterm birth. The evidence is consistent with the overall treatment effect:

- For neonatal death and respiratory distress syndrome the size of the treatment effect was similar to the overall effect but did not reach statistical significance.

No data were reported for perinatal death, fetal death or a composite of serious infant outcomes from these three trials.

There is no evidence from all 26 included trials to support the use of a single course of antenatal corticosteroids when the only risk factor is that of a history of a previous preterm birth.

Evidence from all 26 included trials does not indicate that there is a differential effect from a single course of antenatal corticosteroids when the woman has a history of a previous preterm birth and preterm birth is expected.

Evidence is based on a subset of data from trials that reported they included a proportion of women with a history of a previous preterm birth. This level of evidence cannot be used to form a clinical recommendation.

See Appendix M13 – Evidence Summary (Page 360)

What is the safety for the mother, fetus, infant, child, adult of administering a single course of antenatal corticosteroids to women with a history of previous preterm birth?

Practice points

- Use a single course of antenatal corticosteroids in women with a history of a previous preterm birth and with an additional risk factor(s) for preterm birth.
- Where appropriate, estimate the risk of preterm birth by considering the use of adjunct prediction tests including fetal fibronectin and assessment of cervical length.

Research recommendation:

- Any future randomised trials of a single course of antenatal corticosteroids should report on the risk factors for preterm birth of the included participants.

What is the safety for the mother with a history of a previous preterm birth of administering repeat antenatal corticosteroids?

What is the safety for the fetus, infant, child, adult of administering repeat antenatal corticosteroids to women with a history of previous preterm birth?

Repeat dose(s) of antenatal corticosteroids-

Four randomised controlled trials of repeat antenatal corticosteroids, included in the Crowther CPG version 2015 systematic review, recruited and reported a proportion of women who had a history of a previous preterm birth (**Table 41**):

- Aghajafari (2002) (proportion not reported)
- Crowther (2006) 15%
- Murphy (2008) 35%
- Wapner (2006) 47%.

A history of a previous preterm birth was not a specific inclusion criterion for any of the trials (Appendix K). An inclusion criteria for these trials included women who had previously received a single course of antenatal corticosteroids seven or more days earlier and were considered to be still at risk of preterm birth.

Therefore all of the women recruited to these trials who had a history of a preterm birth also had an additional risk factor of risk of preterm birth in their current pregnancy.

In the summary of the evidence we report the overall treatment effects from all trials with available data, for the primary outcomes of these Clinical Practice Guidelines, for repeat antenatal corticosteroids. We then report on the subset of four trials that specifically reported that a proportion of the women recruited into their trial had a *history of a previous preterm birth*.

Maternal primary outcomes for these Clinical Practice Guidelines:

Maternal infection -

Chorioamnionitis - Overall no difference was seen in the risk for chorioamnionitis between women who had been treated with repeat antenatal corticosteroids and those with no repeat treatment (RR 1.16, 95%CI 0.92 to 1.46; 6 trials, n=4261 women).

- Four trials reported they recruited a proportion of women with a history of a previous preterm birth (15% to 47%, where detailed) and provided data for chorioamnionitis (Aghajafari 2002, Crowther 2006, Murphy 2008, Wapner 2006). The size of the treatment effect was similar to the overall effect and there was no difference between groups (RR 1.10, 95%CI 0.80 to 1.52; 4 trials, n=3339 women) (**Table 44**).

Puerperal sepsis - Overall no difference was seen in the risk for puerperal sepsis between women who had been treated with repeat antenatal corticosteroids and those with no repeat treatment (RR 1.15, 95%CI 0.83 to 1.60; 5 trials, n=3091 women).

- Three trials reported they included a proportion of women with a history of a previous preterm birth (35% to 47%, where detailed) and provided data for puerperal sepsis (Aghajafari 2002, Murphy 2008, Wapner 2006). The size of the treatment effect was similar to the overall treatment effect and there was no difference between groups (RR 1.12, 95%CI 0.72 to 1.75; 3 trials, n=2357 women) (**Table 44**).

Postnatal pyrexia - Only one trial reported including 15% of women with a history of a previous preterm birth and provided data for postnatal pyrexia (Crowther 2006). No difference was seen for the risk of postnatal pyrexia between women who had been treated with repeat antenatal corticosteroids and those with no repeat treatment (RR 0.87, 95%CI 0.55 to 1.38; 1 trial, n=982 women) (**Table 44**).

Other maternal infection outcomes - There were no data reported for pyrexia after trial entry or intrapartum pyrexia requiring treatment (**Table 44**).

Other primary maternal outcomes for these Clinical Practice Guidelines - No data on quality of life were reported in the subgroup of trials that recruited a proportion of the women in their trial had a history of a previous preterm birth.

Infant primary outcomes for these Clinical Practice Guidelines:

Fetal, neonatal or later death -

Perinatal death - Overall no difference was seen in the risk of perinatal death between infants who had been exposed to repeat antenatal corticosteroids and those with no repeat exposure (RR 0.94, 95%CI 0.71 to 1.23; 9 trials, n=5554 infants).

- Four trials reported they included a proportion of women with a history of a previous preterm birth (15% to 47%, where detailed) and provided data for perinatal death (Aghajafari 2002, Crowther 2006, Murphy 2008, Wapner 2006). The size of the treatment effect was similar to the overall effect and there was no difference between groups (RR 0.97, 95%CI 0.70 to 1.33; 4 trials, n=3961 infants) (**Table 45**).

Fetal death - Overall no difference was seen in the risk of fetal death between infants who had been exposed to repeat antenatal corticosteroids and those with no repeat exposure (RR 0.82, 95%CI 0.24 to 2.84; 7 trials, n=2755 infants).

- Two trials reported they included a proportion of women with a history of a previous preterm birth (15%, where reported) and provided data for fetal death (Aghajafari 2002, Crowther 2006). The size of the treatment effect was similar to the overall effect and there was no difference between groups (RR 1.02, 95%CI 0.06 to 16.23; 2 trials, n=1162 infants) (**Table 45**).

Neonatal death - Overall no difference was seen in the risk of neonatal death between infants who had been exposed to repeat antenatal corticosteroids and those with no repeat exposure (RR 0.91, 95%CI 0.62 to 1.34; 7 trials, n=2713 infants).

- Two trials reported they included a proportion of women with a history of a previous preterm birth (15%, where reported) and provided data for neonatal death (Aghajafari 2002, Crowther 2006). The size of the treatment effect was similar to the overall effect and there was no difference between groups (RR 0.94, 95%CI 0.56 to 1.59; 2 trials, n=1160 infants) (**Table 45**).

Respiratory distress syndrome - Overall there was a significant reduction for the risk of respiratory distress syndrome between infants who had been exposed to repeat antenatal corticosteroids and those with no repeat exposure (RR 0.83, 95%CI 0.75 to 0.91; 8 trials, n=3206 infants).

- Three trials reported they included a proportion of women with a history of a previous preterm birth (range 15% to 47%, where detailed) and provided data for respiratory distress syndrome (Aghajafari 2002, Crowther 2006, Wapner 2006). The size of the treatment effect was similar to the overall effect and was statistically significant (RR 0.78, 95%CI 0.68 to 0.91; 3 trials, n=1655 infants) (**Table 45**).

Composite of serious infant outcomes - Overall there was a significant reduction in the risk for a composite of serious infant outcomes between infants who had been exposed to repeat antenatal corticosteroids and those with no repeat exposure (RR 0.84, 95%CI 0.75 to 0.94; 7 trials, n=5094).

- Four trials reported they included a proportion of women with a history of a previous preterm birth (range 15% to 47%, where detailed) and provided data for a composite of serious infant outcomes (Aghajafari 2002, Crowther 2006; Murphy 2008; Wapner 2006). The size of the treatment effect was similar to the overall effect but there was no difference between groups (RR 0.89, 95%CI 0.77 to 1.03; 4 trials, n=3959 infants) (**Table 45**).

Table 44: Comparison of the overall effect estimate for use of repeat antenatal corticosteroids with trials that reported including a proportion of women with a history of a previous preterm birth – Maternal primary outcomes

Primary outcome	Repeat course of antenatal corticosteroid*			Trials known to have included women with a history of a previous preterm birth^				
	Trials contributing data	Number of women	Overall risk ratio (RR) (95%Confidence Interval)	Trials contributing data	Number of women	Risk ratio (RR) (95%Confidence Interval)	Actual proportion detailed in trials	Actual number of women
Chorioamnionitis	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Murphy 2008; Wapner 2006	4261	RR 1.16 (0.92 to 1.46), 6 trials	Aghajafari 2002; Crowther 2006; Murphy 2008; Wapner 2006	3339	RR 1.10 (0.80 to 1.52), 4 trials, n=3339 women	Crowther 2006; Murphy 2008; Wapner 2006	1027
Puerperal sepsis	Aghajafari 2002; Guinn 2001; Murphy 2008; Peltoniemi 2007; Wapner 2006	3091	RR 1.15 (0.83 to 1.60), 5 trials	Aghajafari 2002; Murphy 2008; Wapner 2006	2357	RR 1.12 (0.72 to 1.75), 3 trials, n=2357 women	Murphy 2008; Wapner 2006	880
Pyrexia after trial entry requiring treatment	NR	NR	NR	NR	NR	NR	-	-
Intrapartum pyrexia requiring treatment	NR	NR	NR	NR	NR	NR	-	-
Postnatal pyrexia requiring treatment	Crowther 2006	982	RR 0.87 (0.55 to 1.38), 1 trial	Crowther 2006	982	RR 0.87 (0.55 to 1.38), 1 trial, n=982 women	Crowther 2006	147

*Source: Crowther (2011); ^meta-analyses conducted for these Clinical Practice Guidelines

Table 45: Comparison of the overall effect estimate for use of repeat antenatal corticosteroids with trials that reported including a proportion of women with a history of a previous preterm birth – Infant primary outcomes

Primary outcome	Repeat course of antenatal corticosteroid*			Trials known to have included women with a history of a previous preterm birth^				
	Trials contributing data	Number of infants	Overall risk ratio (RR) (95% Confidence Interval)	Trials contributing data	Number of infants	Risk ratio (RR) (95% Confidence Interval)	Actual proportion detailed in trials	Actual number of infants
Perinatal death	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Mazumder 2008; McEvoy 2010; Murphy 2008; Peltoniemi 2007; Wapner 2006	5554	RR 0.94 (0.71 to 1.23), 9 trials	Aghajafari 2002; Crowther 2006; Murphy 2008; Wapner 2006	3961	RR 0.97 (0.70 to 1.33), 4 trials, n=3961 infants	Crowther 2006; Murphy 2008; Wapner 2006	1211
Fetal death	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Mazumder 2008; McEvoy 2010; Peltoniemi 2007	2755	RR 0.82 (0.24 to 2.84), 7 trials	Aghajafari 2002; Crowther 2006	1162	RR 1.02 (0.06 to 16.23), 2 trials, n=1162 infants	Crowther 2006	172
Neonatal death	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Mazumder 2008; McEvoy 2010; Peltoniemi 2007	2713	RR 0.91 (0.62 to 1.34), 7 trials	Aghajafari 2002; Crowther 2006	1160	RR 0.94 (0.56 to 1.59), 2 trials, n=1160 infants	Crowther 2006	172
Respiratory distress syndrome	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Mazumder 2008; McEvoy 2010; Peltoniemi 2007; Wapner 2006	3206	RR 0.83 (0.75 to 0.91), 8 trials	Aghajafari 2002; Crowther 2006; Wapner 2006	1655	RR 0.78 (0.68 to 0.91), 3 trials, n=1655 infants	Crowther 2006; Wapner 2006	405
Composite outcome of serious infant outcomes	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Mazumder 2008; Murphy 2008; Wapner 2006	5094	RR 0.84 (0.75 to 0.94), 7 trials	Aghajafari 2002; Crowther 2006; Murphy 2008; Wapner 2006	3959	RR 0.89 (0.77 to 1.03), 4 trials, n=3959 infants	Crowther 2006; Murphy 2008; Wapner 2006	1211

*Source: Crowther 2011; ^meta-analyses conducted for these Clinical Practice Guidelines

Evidence summary for safety of repeat antenatal corticosteroids in women with a history of a previous preterm birth

The main trial inclusion criteria for trials included in the Crowther (2011) systematic review were that the women were at risk of preterm birth. Although some of these women had a history of a previous preterm birth and this was stated in four of the trials, this risk factor was not a specified inclusion criterion for trial entry. Some women recruited into the other six included trials may also have had a history of a previous preterm birth but no information about this was provided in their trial reports.

Four of 10 trials included in the systematic review reported including a proportion of women in their trials who had a history of previous preterm birth. The proportion of women recruited with a history of previous preterm birth ranged from 15% to 47%, where reported, in the trials of repeat antenatal corticosteroids.

For the mother

Overall, where reported in 10 trials, no differences were seen between women treated with repeat antenatal corticosteroids and women with no repeat corticosteroids in the risk for chorioamnionitis, postnatal pyrexia or puerperal sepsis.

Four trials reported including a proportion of women with a history of previous preterm birth. The evidence is consistent with the overall treatment effect:

- For chorioamnionitis, postnatal pyrexia and puerperal sepsis, the size of the treatment effect was similar to the overall effect and there was no difference between groups.

No data were reported for pyrexia after trial entry, intrapartum pyrexia or maternal quality of life from these four trials.

For the infant

Overall, where reported in 10 trials, there was a significant reduction in the risks for respiratory distress syndrome and a composite of serious infant outcomes. No differences were seen in the risks for perinatal death, fetal death or neonatal death between infants exposed to a repeat antenatal corticosteroids and infants with no repeat exposure.

Four trials reported including a proportion of women with a history of previous preterm birth. The evidence is consistent with the overall treatment effect:

- For respiratory distress syndrome the size of the treatment effect was similar to the overall effect and there was a significant reduction in risk for infants exposed to a repeat antenatal corticosteroids compared with no repeat exposure;
- For perinatal death, fetal death, neonatal death and a composite of serious infant outcomes the size of the treatment effect was similar to the overall effect and there was no difference between groups.

There is no evidence from the 10 included trials to support the use of repeat antenatal corticosteroids when the only risk factor is that of a history of a previous preterm birth.

Evidence from all 10 included trials does not indicate that there is a differential effect from repeat antenatal corticosteroids when the woman has a history of a previous preterm birth and preterm birth is expected. Evidence is based on a subset of data from trials that reported they included a proportion of women with a history of a previous preterm birth. This level of evidence cannot be used to form a clinical recommendation

See Appendix M14 – Evidence Summary (Page 364)

What is the safety for the mother, fetus, infant, child, adult of administering repeat antenatal corticosteroids to women with a history of previous preterm birth?

Practice points:

- Repeat antenatal corticosteroids for a woman with a history of preterm birth and with an additional risk factor(s) for preterm birth.
- Where appropriate, estimate the risk of preterm birth by considering the use of adjunct prediction tests including fetal fibronectin and assessment of cervical length.

Research recommendation:

- Any future randomised trials of repeat antenatal corticosteroids should report on the risk factors for preterm birth of the included participants.

14.2 Women in preterm labour

What is the safety for the mother of administering a single course of antenatal corticosteroids to women in preterm labour?

What is the safety for the fetus, infant, child, adult of administering a single course of antenatal corticosteroids to women in preterm labour?

Single course of antenatal corticosteroids

The Roberts CPG version 2015 systematic review included 15 trials that stated they included a proportion of the women who were in preterm labour (**Table 40**):

- Balci (2010) 100%
- Block (1977) (proportion not reported)
- Doran (1980) 95%
- Fekih (2002) (proportion not reported)
- Gamsu (1989) 95%
- Garite (1992) 53%
- Goodner (1979) (proportion not reported)
- Kari (1994) 78%
- Liggins (1972) 20%
- Porto (2011) 67%
- Qublan (2001) (proportion not reported)
- Schutte (1980) (proportion not reported)
- Silver (1996) 62%
- Taeusch (1979) (proportion not reported)
- Teramo (1980) 100%.

Of the remaining 11 trials, women in active labour were not eligible for one trial (Nelson 1985).
The other 10 trials did not state whether women in preterm labour were included or not (Appendix J).

In the summary of the evidence we report the overall treatment effects from all trials with available data, for the primary outcomes of these Clinical Practice Guidelines, for a single course of antenatal corticosteroids. We then report on the subset of 14 trials that specifically reported that a proportion of the women recruited into their trial were in spontaneous *preterm labour*.

Maternal primary outcomes for these Clinical Practice Guidelines:

Maternal infection -

Chorioamnionitis - Overall no difference was seen in the risk for chorioamnionitis between women treated with a single course of antenatal corticosteroids and those with no antenatal corticosteroids (RR 0.90, 95%CI 0.69 to 1.17; 13 trials, n=2525 women).

- Seven trials reported they included a proportion of women in preterm labour (range 20% to 78%, where detailed) and provided data for chorioamnionitis (Feikh, 2002; Garite 1993; Kari 1994; Liggins 1972; Qublan 2001; Schutte 1980; Silver 1996). The size of the treatment effect was similar to the overall effect and there was no significant difference between groups (RR 0.97, 95%CI 0.70 to 1.33; 7trials, n=1797 women) (**Table 46**).

Puerperal sepsis - Overall no difference was seen in the risk for puerperal sepsis between women treated with a single course of antenatal corticosteroids and those with no antenatal corticosteroids (RR 1.35, 95%CI 0.93 to 1.95; 8 trials, n=1003 women).

- Five trials reported they included a proportion of women in preterm labour (range 53% to 62%, where detailed) and provided data for puerperal sepsis (Garite 1992, Qublan 2001, Schutte 1980, Silver 1996, Taeusch 1979). The direction of the treatment effect was similar to the overall treatment effect but was statistically significant (RR 2.27, 95%CI 1.38 to 3.27; 5 trials, n=504 women) (**Table 46**). Caution is required in interpreting the data as the confidence intervals overlap with those of the overall treatment effect that was not statistically significant.

Pyrexia after trial entry - Overall no difference was seen in the risk for pyrexia after trial entry requiring treatment with antibiotics between women treated with a single course of antenatal corticosteroids and those with no antenatal corticosteroids (RR 1.11, 95%CI 0.67 to 1.67; 4 trials, n=481 women).

- Only one trial reported including women in preterm labour although no details were provided of the proportion (Schutte 1980). The direction of the treatment effect was opposite to the overall effect but there was no significant difference between groups (RR 0.68, 95%CI 0.20 to 2.27; 1 trial, n=101 women) (**Table 46**).

Intrapartum pyrexia - Overall no difference was seen in the risk for intrapartum pyrexia requiring treatment with antibiotics between women treated with a single course of antenatal corticosteroids and those with no antenatal corticosteroids (RR 0.60, 95%CI 0.15 to 2.49; 2 trials, n=319 women).

- Only one trial reported including women in preterm labour although no details were provided of the proportion (Schutte 1980). The treatment effect was similar to the overall treatment effect and there was no significant difference between groups (RR 0.26, 95%CI 0.03 to 2.20; 1 trial, n=101 women) (**Table 46**).

Postnatal pyrexia - Overall no difference was seen in the risk for postnatal pyrexia requiring treatment with antibiotics between women treated with a single course of antenatal corticosteroids and those with no antenatal corticosteroids (RR 0.92, 95%CI 0.64 to 1.33; 5 trials, n=1323 women).

- Two trials reported including women in preterm labour although no details were provided of the proportion (Fekih 2002, Schutte 1980). The direction of the treatment effect was opposite to the overall effect but there was no significant difference between groups (RR 1.42, 95%CI 0.47 to 4.31; 2 trials, n=219 women) (**Table 46**).

Other maternal primary outcomes for these Clinical Practice Guidelines - No data on quality of life were reported in the trials that reported including a proportion of the women in their trial in spontaneous preterm labour.

Table 46: Comparison of the overall effect estimate for use of a single course of antenatal corticosteroids with trials that reported including a proportion of women in preterm labour – Maternal primary outcomes

Primary outcome	Single course of antenatal corticosteroid*			Trials known to have included women in preterm labour^				
	Trials contributing data	Number of women	Risk ratio (RR) (95%Confidence Interval)	Trials contributing data	Number of women	Risk ratio (RR) (95%Confidence Interval)	Actual proportion detailed in trials	Actual number of women
Chorioamnionitis	Amorim 1999; Carlan 1991; Dexiprom 1999; Fekih 2002; Garite 1992; Kari 1994; Lewis 1996; Liggins 1972; Lopez 1989; Morales 1989; Qublan 2001; Schutte 1980; Silver 1996	2525	RR 0.90 (0.69 to 1.17), 13 trials	Fekih 2002; Garite 1992; Kari 1994; Liggins 1972; Qublan 2001; Schutte 1980; Silver 1996	1797	RR 0.97 (0.70 to 1.33), 7 trials; n=1797 women	Garite 1992; Kari 1994; Liggins 1972; Silver 1996	435
Puerperal sepsis	Amorim 1999; Dexiprom 1999; Garite 1992; Lewis 1996; Qublan 2001; Schutte 1980; Silver 1996; Taeusch 1979	1003	RR 1.35 (0.93 to 1.95), 8 trials	Garite 1992; Qublan 2001; Schutte 1980; Silver 1996; Taeusch 1979	504	RR 2.27 (1.38 to 3.72), 5 trials, n=504 women	Garite 1992; Silver 1996	85
Pyrexia after trial entry requiring treatment	Amorim 1999; Nelson 1985; Schutte 1980; Taeusch 1979	481	RR 1.11 (0.67 to 1.67), 4 trials	Schutte 1980	101	RR 0.68 (0.20 to 2.27), 1 trial, n=101 women	-	-
Intrapartum pyrexia requiring treatment	Amorim 1999; Schutte 1980	319	RR 0.60 (0.15 to 2.49), 2 trials	Schutte 1980	101	RR 0.26 (0.03 to 2.20), 1 trial, n=101 women	-	-
Postnatal pyrexia requiring treatment	Amorim 1999; Collaborative 1981; Dexiprom 1999; Fekih 2002; Schutte 1980	1323	RR 0.92 (0.64 to 1.33), 5 trials	Fekih 2002; Schutte 1980	219	RR 1.47 (0.47 to 4.31), 2 trials, n=219 women	-	-

*Source: Roberts CPG version 2015 ; ^meta-analyses conducted for these Clinical Practice Guidelines, NR not reported

Infant primary outcomes for these Clinical Practice Guidelines:

Fetal, neonatal or later death -

Perinatal death - Overall there was a significant reduction in the risk for perinatal death for infants who had been exposed to antenatal corticosteroids compared with no exposure (RR 0.77, 95%CI 0.67 to 0.89; 13 trials, n=3627 infants).

- Nine trials reported they included a proportion of women in preterm labour (range 53% to 95%, where detailed) and provided data for perinatal death (Block 1977; Doran 1980; Gamsu 1989; Garite 1992; Kari 1994; Liggins 1972; Qublan 2001; Schutte 1980; Taeusch 1979). The size of the treatment effect was similar to the overall treatment effect and was statistically significant (RR 0.76, 95%CI 0.64 to 0.90; 9 trials, n=2399 infants) (**Table 47**).

Fetal death - Overall no difference was seen in the risk of fetal death between infants who had been exposed to antenatal corticosteroids and infants with no exposure (RR 0.98, 95%CI 0.73 to 1.30; 13 trials, n=3627 infants).

- Nine trials reported they included a proportion of women in preterm labour (range 20% to 95%, where detailed) and provided data for fetal death (Block 1977; Doran 1980; Gamsu 1989; Garite 1992; Kari 1994; Liggins 1972; Qublan 2001; Schutte 1980; Taeusch 1979). The size of the treatment effect was similar to the overall effect and there was no significant difference between groups (RR 1.00, 95%CI 0.72 to 1.40; 9 trials, n=2399 infants) (**Table 47**).

Neonatal death - Overall there was a significant reduction in the risk for neonatal death between infants exposed to a single course of antenatal corticosteroids and those with no antenatal corticosteroids (RR 0.68, 95%CI 0.58 to 0.80; 21 trials, n=4408 infants).

- Thirteen trials reported they included a proportion of women in preterm labour (range 20% to 95%, where detailed) and provided data for neonatal death (Block 1977; Doran 1980; Fekih 2002; Gamsu 1989; Garite 1992; Goodner 1979; Kari 1994; Liggins 1972; Porto 2011; Qublan 2001; Schutte 1980; Silver 1996; Taeusch 1979). The size of the treatment effect was similar to the overall treatment effect and was statistically significant (RR 0.65, 95%CI 0.54 to 0.79; 13 trials, n=2810 infants) (**Table 47**).

Respiratory distress syndrome - Overall there was a significant reduction in the risk for respiratory distress syndrome between infants exposed to a single course of antenatal corticosteroids and those with no antenatal corticosteroids (RR 0.65, 95%CI 0.58 to 0.73; 25 trials, n=4590 infants).

- Fifteen trials reported they included a proportion of women in preterm labour (range 20% to 100%, where detailed) and provided data for respiratory distress syndrome (Balci 2010; Block 1977; Doran 1980; Fekih 2002; Gamsu 1989; Garite 1992; Goodner 1979; Kari 1994; Liggins 1972; Porto 2011; Qublan 2001; Schutte 1980; Silver 1996; Taeusch 1979; Teramo 1980). The size of the treatment effect was similar to the overall treatment effect and was statistically significant (RR 0.65, 95%CI 0.57 to 0.74; 15 trials, n=3683 infants) (**Table 47**).

Composite of serious infant outcomes - This outcome was not reported in any of the trials of a single course of antenatal corticosteroids.

Table 47: Comparison of the overall effect estimate for use of a single course of antenatal corticosteroids with trials that reported including a proportion of women in preterm labour – Infant primary outcomes

Primary outcome	Single course of antenatal corticosteroid*			Trials known to have included women in preterm labour^				
	Trials contributing data	Number of infants	Risk ratio (RR) (95% Confidence Interval)	Trials contributing data	Number of infants	Risk ratio (RR) (95% Confidence Interval)	Actual proportion detailed in trials	Actual number of infants
Perinatal death	Amorim 1999; Block 1977; Collaborative 1981; Dexiprom 1999; Doran 1980; Gamsu 1989; Garite 1992; Kari 1994; Liggins 1972; Parsons 1988; Qublan 2001; Schutte 1980; Taeusch 1979	3627	RR 0.77 (0.67 to 0.89), 13 trials	Block 1977; Doran 1980; Gamsu 1989; Garite 1992; Kari 1994; Liggins 1972; Qublan 2001; Schutte 1980; c	2399	RR 0.76 (0.64 to 0.90), 9 trials, n=2399 infants	Doran 1980; Gamsu 1989; Garite 1992; Kari 1994; Liggins 1972;	824
Fetal death	Amorim 1999; Block 1977; Collaborative 1981; Dexiprom 1999; Doran 1980; Gamsu 1989; Garite 1992; Kari 1994; Liggins 1972; Parsons 1988; Qublan 2001; Schutte 1980; Taeusch 1979	3627	RR 0.98 (0.73 to 1.30), 13 trials	Block 1977; Doran 1980; Gamsu 1989; Garite 1992; Kari 1994; Liggins 1972; Qublan 2001; Schutte 1980; Taeusch 1979	2399	RR 1.00 (0.72 to 1.40), 9 trials, n=2399 infants	Doran 1980; Gamsu 1989; Garite 1992; Kari 1994; Liggins 1972;	824
Neonatal death	Amorim 1999; Block 1977; Collaborative 1981; Dexiprom 1999; Doran 1980; Fekih 2002; Gamsu 1989; Garite 1992; Goodner 1979; Kari 1994; Lewis 1996; Liggins 1972; Lopez 1989; Morales 1989; Nelson 1985; Parsons 1988; Porto 2011; Qublan 2001; Schutte 1980; Silver 1996; Taeusch 1979	4408	RR 0.68 (0.58 to 0.80), 21 trials	Block 1977; Doran 1980; Fekih 2002;Gamsu 1989; Garite 1992; Goodner 1979; Kari 1994; Liggins 1972; Porto 2011; Qublan 2001; Schutte 1980; Silver 1996; Taeusch 1979	2810	RR 0.65 (0.54 to 0.79), 13 trials, n=2810 infants	Doran 1980; Gamsu 1989; Garite 1992; Kari 1994; Liggins 1972; Porto 2011; Silver 1996	1058
Respiratory distress syndrome	Amorim 1999; Balci 2010; Block 1977; Cararach 1991; Carlan 1991; Collaborative 1981; Dexiprom 1999; Doran 1980; Fekih 2002; Gamsu 1989; Garite 1992; Goodner 1979; Kari 1994; Lewis 1996; Liggins 1972; Lopez 1989; Morales 1989; Nelson 1985; Parsons 1988; Porto 2011; Qublan 2001; Schutte 1980; Silver 1996; Taeusch 1979; Teramo 1980	4590	RR 0.65 (0.58 to 0.73), 25 trials	Balci 2010; Block 1977; Doran 1980; Fekih 2002; Gamsu 1989; Garite 1992; Goodner 1979; Kari 1994; Liggins 1972; Porto 2011; Qublan 2001; Schutte 1980; Silver 1996; Taeusch 1979; Teramo 1980	3683	RR 0.65 (0.57 to 0.74), 15 trials, n=3683 infants	Balci 2010; Doran 1980; Gamsu 1989; Garite 1992; Kari 1994; Liggins 1972; Porto 2011; Silver 1996; Teramo 1980	1233

*Source: Roberts CPG version 2015; ^meta-analyses conducted for these Clinical Practice Guidelines

Evidence summary for safety of a single course of antenatal corticosteroids in women in preterm labour

Fifteen of 26 trials included in the Roberts CPG version 2015 systematic review reported including a proportion of women in preterm labour at trial entry. Where reported, the proportion of women in preterm labour ranged from 20% to 100% of the women recruited into the trials of a single course of antenatal corticosteroids.

For the mother

Overall, where reported in 26 trials, no differences were seen between women treated with a single course of antenatal corticosteroids and women with no corticosteroids in the risk for chorioamnionitis, pyrexia after trial entry, intrapartum pyrexia, postnatal pyrexia or puerperal sepsis.

Fifteen trials reported including a proportion of women in preterm labour.

- For chorioamnionitis and intrapartum pyrexia the size of the treatment effect was similar to the overall effect and there was no difference between groups;
- For pyrexia after trial entry and postnatal pyrexia the direction of the treatment effect was opposite to the overall effect but there was no difference between groups;
- For puerperal sepsis the direction of the treatment effect was similar to the overall effect and was statistically significant. However the confidence intervals overlap with the overall effect which was not statistically significant.

No data were reported for maternal quality of life from any of the trials included in the Roberts CPG version 2015 systematic review.

For the infant

Overall, where reported in 26 trials, there was a significant reduction in the risks for perinatal death, neonatal death and respiratory distress syndrome. No difference was seen in the risk for fetal death between infants exposed to a single course of antenatal corticosteroids and infants with no exposure.

Fifteen trials reported including a proportion of women in preterm labour. The evidence is consistent with the overall treatment effect:

- For perinatal death, neonatal death and respiratory distress syndrome the size of the treatment effect was similar to the overall effect and the difference was statistically significant for infants exposed to a single course of antenatal corticosteroids compared with no exposure.
- For fetal death, the size of the treatment effect was similar to the overall and there was no difference between groups;

No data were reported for a composite of serious infant outcomes in any of the trials included in the Roberts CPG version 2015 systematic review.

Evidence is based on a subset of data from trials that reported they included a proportion of women in preterm labour. This level of evidence cannot be used to form a clinical recommendation

See Appendix M15 – Evidence Summary (Page 368)

What is the safety for the mother, fetus, infant, child, adult of administering a single course of antenatal corticosteroids to women in preterm labour?

Practice Points:
• Use a single course of antenatal corticosteroids in women in preterm labour. • Where appropriate, estimate the risk of preterm birth by considering the use of adjunct prediction tests including fetal fibronectin and assessment of cervical length. • Where appropriate, monitor women in preterm labour for signs of puerperal sepsis when antenatal corticosteroids have been given.

What is the safety for the mother of administering repeat dose(s) of antenatal corticosteroids to women in preterm labour?

What is the safety for the fetus, infant, child, adult of administering repeat antenatal corticosteroids to women in preterm labour?

Repeat dose(s) of antenatal corticosteroids

Nine of the 10 trials in the '*Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes'* (Crowther 2011) reported that a proportion of the women included were in preterm labour (**Table 41**):

- Aghajafari (2002) 25%
- Crowther (2006) 27%
- Garite (2009) 31%
- Guinn (2002) 54%
- Mazumder (2008) (proportion not reported)
- McEvoy (2002) 30%
- McEvoy (2010) 76%
- Murphy (2008) 84%
- Wapner (2006) 67%.

Peltoniemi (2007) did not provide details as to whether women in preterm labour were eligible for inclusion. An inclusion criterion for recruitment into each of the trials was that the woman had already received a single course of antenatal corticosteroids seven or more days prior and there was a risk of preterm birth. Preterm labour was considered to be a risk factor for preterm birth (Appendix K). No additional trials were identified for the Crowther CPG version 2015 systematic review.

In the summary of the evidence we report the overall treatment effects from all trials with available data, for the primary outcomes of these Clinical Practice Guidelines, for repeat antenatal corticosteroids. We then report on the subset of nine trials that specifically reported that a proportion of the women recruited into their trial were in spontaneous *preterm labour*.

Maternal primary outcomes for these Clinical Practice Guidelines:

Maternal infection -

Chorioamnionitis - Overall no difference was seen in the risk for chorioamnionitis between women who had received repeat antenatal corticosteroids and those with no repeat treatment (RR 1.16, 95%CI 0.92 to 1.46; 6 trials, n=4261 women). All six trials reported that they had included women in preterm labour (range 25% to 84%) (Aghajafari 2002, Crowther 2006, Garite 2009, Guinn 2001, Murphy 2008, Wapner 2006) (**Table 48**).

Puerperal sepsis - Overall no difference was seen in the risk for puerperal sepsis between women who had received repeat antenatal corticosteroids and those with no repeat treatment (RR 1.15, 95%CI 0.83 to 1.60; 5 trials, n=3091 women).

- Four trials reported they included a proportion of women in preterm labour (range 25% to 84%) and provided data for puerperal sepsis (Aghajafari 2002, Guinn 2001, Murphy 2008, Wapner 2006). The size of the treatment effect was similar to the overall effect and there was no significant difference between groups (RR 1.05, 95%CI 0.72 to 1.54; 4 trials, n=2842 women) (**Table 48**).

Postnatal pyrexia - Overall no difference was seen in the risk for postnatal pyrexia requiring treatment with antibiotics between women who had received repeat antenatal corticosteroids and those with no repeat treatment in one trial (Crowther 2006) reporting this outcome (RR 0.87, 95%CI 0.55 to 1.38; 1 trial, n=982 women). This trial reported 27% of women included were in preterm labour.

Other maternal infection outcomes - No data for pyrexia after entry into trial or intrapartum pyrexia requiring antibiotics were reported in the trials included in the Crowther (2011) systematic review (**Table 48**).

Other maternal primary outcomes for these Clinical Practice Guidelines - No data from trials included in the Crowther (2011) systematic review were reported for maternal quality of life.

Table 48: Comparison of the overall effect estimate for use of repeat antenatal corticosteroids with trials that reported including a proportion of women in preterm labour – Maternal primary outcomes

Primary outcome	Repeat course of antenatal corticosteroid*			Trials known to have included women in preterm labour^				
	Trials contributing data	Number of women	Risk ratio (RR) (95% Confidence Interval)	Trials contributing data	Number of women	Risk ratio (RR) (95% Confidence Interval)	Actual proportion detailed in trials	Actual number of women
Chorioamnionitis	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Murphy 2008; Wapner 2006	4261	RR 1.16 (0.92 to 1.46), 6 trials	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Murphy 2008; Wapner 2006	4261	RR 1.16 (0.92 to 1.46), 6 trials, n=4261 women	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Murphy 2008; Wapner 2006	2553
Puerperal sepsis	Aghajafari 2002; Guinn 2001; Murphy 2008; Peltoniemi 2007; Wapner 2006	3091	RR 1.15 (0.83 to 1.60), 5 trials	Aghajafari 2002; Guinn 2001; Murphy 2008; Wapner 2006	2842	RR 1.05 (0.72 to 1.54), 4 trials, n=2842 women	Aghajafari 2002; Guinn 2001; Murphy 2008; Wapner 2006	2152
Pyrexia after trial entry requiring treatment	-	-	Not reported	-	-	Not reported	-	-
Intrapartum pyrexia requiring treatment	-	-	Not reported	-	-	Not reported	-	-
Postnatal pyrexia requiring treatment	Crowther 2006	982	RR 0.87 (0.55 to 1.38), 1 trial	Crowther 2006	982	RR 0.87 (0.55 to 1.38), 1 trial, n=982 women	Crowther 2006	265

*Source: Crowther (2011); ^meta-analyses conducted for these Clinical Practice Guidelines

Infant primary outcomes for these Clinical Practice Guidelines:

Fetal, neonatal or later death -

Perinatal death - Overall no difference was seen in the risk for perinatal death between infants who had been exposed to repeat antenatal corticosteroids and those with no repeat exposure (RR 0.94, 95%CI 0.71 to 1.23; 9 trials, n=5554 infants).

- Eight trials reported they had included a proportion of women in preterm labour (range 25% to 84%, where detailed) and provided data for perinatal death (Aghajafari 2002, Crowther 2006, Garite 2009, Guinn 2001, Mazumder 2008, McEvoy 2010, Murphy 2008, Wapner 2006). The size of the treatment effect was similar to the overall effect and there was no significant difference between groups (RR 0.88, 95%CI 0.67 to 1.17; 8 trials, n=5228 infants) (**Table 49**).

Fetal death - Overall no difference was seen in the risk for fetal death between infants who had been exposed to repeat antenatal corticosteroids and those with no repeat exposure (RR 0.82, 95%CI 0.24 to 2.84; 7 trials, n=2755 infants).

- Six trials reported they had included a proportion of women in preterm labour (range 25% to 76%, where detailed) and provided data for fetal death (Aghajafari 2002, Crowther 2006, Garite 2009, Guinn 2001, Mazumder 2008, McEvoy 2010). The size of the treatment effect was similar to the overall effect and there was no significant difference between groups (RR 0.77, 95%CI 0.19 to 3.11; 6 trials, n=2429 infants) (**Table 49**).

Neonatal death - Overall no difference was seen in the risk for neonatal death between infants who had been exposed to repeat antenatal corticosteroids and those with no repeat exposure (RR 0.91, 95%CI 0.62 to 1.34; 7 trials, n=2713 infants).

- Six trials reported they had included a proportion of women in preterm labour (range 25% to 76%, where detailed) and provided data for neonatal death (Aghajafari 2002, Crowther 2006, Garite 2009, Guinn 2001, Mazumder 2008, McEvoy 2010). The size of the treatment effect was similar to the overall effect and there was no significant difference between groups (RR 0.80, 95%CI 0.53 to 1.21; 6 trials, n=2387 infants) (**Table 49**).

Respiratory distress syndrome - Overall there was a significant reduction for the risk of respiratory distress syndrome for infants who had been exposed to repeat antenatal corticosteroids compared with no repeat exposure (RR 0.83, 95%CI 0.75 to 0.91; 8 trials, n=3206 infants).

- Seven trials reported they had included a proportion of women in preterm labour (range 25% to 84%, where detailed) and provided data for respiratory distress syndrome (Aghajafari 2002, Crowther 2006, Garite 2009, Guinn 2001, Mazumder 2008, McEvoy 2010, Wapner 2006). The size of the treatment effect was similar to the overall effect and also was statistically significant (RR 0.79, 95%CI 0.70 to 0.88; 7 trials, n=2880 infants) (**Table 49**).

Composite of serious infant outcomes **-** Overall there was a significant reduction in the risk for a composite of serious infant outcomes for infants who had been exposed to repeat antenatal corticosteroids compared with no repeat exposure (RR 0.84, 95%CI 0.75 to 0.94; 7 trials, n= 5094). All seven of these trials reported that they included a proportion of women in preterm labour (range 25% to 84%, where detailed) (Aghajafari 2002, Crowther 2006, Garite 2009, Guinn 2001, Mazumder 2008, Murphy 2008, Wapner 2006) (**Table 49**).

Table 49: Comparison of the overall effect estimate for use of repeat antenatal corticosteroids with trials that reported including a proportion of women in preterm labour – Infant primary outcomes

Primary outcome	Repeat course of antenatal corticosteroid*			Trials known to have included women in preterm labour^				
	Trials contributing data	Number of infants	Risk ratio (RR) (95% Confidence Interval)	Trials contributing data	Number of infants	Risk ratio (RR) (95% Confidence Interval)	Actual proportion detailed in trials	Actual number of infants
Perinatal death	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Mazumder 2008; McEvoy 2010; Murphy 2008; Peltoniemi 2007; Wapner 2006	5554	RR 0.94 (0.71 to 1.23), 9 trials	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Mazumder 2008; McEvoy 2010; Murphy 2008; Wapner 2006	5228	RR 0.88 (0.67 to 1.17), 8 trials, n=5228 infants	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; McEvoy 2010; Murphy 2008; Wapner 2006	3115
Fetal death	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Mazumder 2008; McEvoy 2010; Peltoniemi 2007	2755	RR 0.82 (0.24 to 2.84), 7 trials	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Mazumder 2008; McEvoy 2010	2429	RR 0.77 (0.19 to 3.11), 6 trials, n=2429 infants	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; McEvoy 2010	848
Neonatal death	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Mazumder 2008; McEvoy 2010; Peltoniemi 2007	2713	RR 0.91 (0.62 to 1.34), 7 trials	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Mazumder 2008; McEvoy 2010	2387	RR 0.80 (0.53 to 1.21), 6 trials, n=2387 infants	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; McEvoy 2010	823
Respiratory distress syndrome	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Mazumder 2008; McEvoy 2010; Peltoniemi 2007; Wapner 2006	3206	RR 0.83 (0.75 to 0.91), 8 trials	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Mazumder 2008; McEvoy 2010; Wapner 2006	2880	RR 0.79 (0.70 to 0.88), 7 trials, n=2880 infants	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; McEvoy 2010; Wapner 2006	1155
Composite outcome of serious infant outcomes	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Mazumder 2008; Murphy 2008; Wapner 2006	5094	RR 0.84 (0.75 to 0.94), 7 trials	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Mazumder 2008; Murphy 2008; Wapner 2006	5094	RR 0.84 (0.75 to 0.94), 7 trials, n=5094 infants	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Murphy 2008; Wapner 2006	3016

*Source: Crowther (2011) ; ^meta-analyses conducted for these Clinical Practice Guidelines

Evidence summary for safety of repeat antenatal corticosteroids in women in preterm labour

Nine of 10 trials included in the Crowther (2011) systematic review reported including a proportion of women in preterm labour at trial entry. The proportion of women included in the trials in preterm labour ranged from 25% to 84%, where reported.

For the mother

Overall, where reported in 10 trials, no differences were seen between women treated with repeat antenatal corticosteroids and women with no repeat corticosteroids in the risk for chorioamnionitis, postnatal pyrexia or puerperal sepsis.

Nine trials reported including a proportion of women in preterm labour. The evidence is consistent with the overall treatment effect:

- For chorioamnionitis, postnatal pyrexia and puerperal sepsis, the size of the treatment effect was the same or similar to the overall effect and there was no difference between groups.

No data were reported for pyrexia after trial entry, intrapartum pyrexia or maternal quality of life from these nine trials.

For the infant

Overall, where reported in 10 trials, there was a significant reduction in the risks for respiratory distress syndrome and a composite of serious infant outcomes. No differences were seen in the risks for perinatal death, fetal death or neonatal death between infants exposed to a repeat antenatal corticosteroids and infants with no repeat exposure.

Nine trials reported including a proportion of women in preterm labour. The evidence is consistent with the overall treatment effect:

- For respiratory distress syndrome and a composite of serious infant outcomes the size of the treatment effect was similar to the overall effect and there was a significant reduction in risk for infants exposed to a repeat antenatal corticosteroids compared with no repeat exposure;
- For perinatal death, fetal death and neonatal death the size of the treatment effect was similar to the overall effect and there was no difference between groups.

Evidence is based on a subset of data from trials that reported they included a proportion of women in preterm labour. This level of evidence cannot be used to form a clinical recommendation

See Appendix M16 – Evidence Summary (Page 372)

What is the safety for the mother, fetus, infant, child, adult of administering repeat dose(s) of antenatal corticosteroids to women in preterm labour?

Practice points:

- Repeat antenatal corticosteroids for a woman in preterm labour.
- Where appropriate, estimate the risk of preterm birth by considering the use of adjunct prediction tests including fetal fibronectin and assessment of cervical length.

14.3 Women with preterm prelabour rupture of membranes at risk of preterm birth

What is the safety for the mother of administering a single course of antenatal corticosteroids to women with preterm prelabour rupture of membranes (at trial entry) at risk of preterm birth?

What is the safety for the fetus, infant, child, adult of administering a single course of antenatal corticosteroids to women with preterm prelabour rupture of membranes (at trial entry) at risk of preterm birth?

Single course of antenatal corticosteroids

Sixteen out of 26 randomised trials in the Roberts CPG version 2015 systematic review stated that they included a proportion of women with preterm prelabour rupture of membranes who were at risk of preterm birth in their trials although not all reported the proportion (**Table 40**):

- Block (1977) proportion not reported
- Cararach (1991) 100%
- Carlan (1991) 100%
- Collaborative (1981) 47%
- Dexiprom (1999) 100%
- Doran (1980) proportion not reported
- Lewis 1996 proportion not reported
- Liggins (1972) 28%
- Lopez (1989) 100%
- Morales (1989) 100%
- Nelson (1985) 100%
- Parsons (1988) 100%
- Porto (2011) 40%
- Qublan (2001) proportion not reported
- Schutte (1980) proportion not reported
- Silver (1996) 23%

For five of the remaining trials women with preterm prelabour rupture of membranes were not eligible (Amorim 1999, Balci 2010, Garite 1992, Kari 1994, Shanks 2010). Women with prolonged preterm prelabour rupture of membranes (>24 hours) were not eligible in one trial (Nelson 1985). Five trials did not state if women with preterm prelabour rupture of membranes were eligible (Fekih 2002, Gamsu 1989, Goodner 1979, Lewis 1996, Teramo 1980) (Appendix J).

In the summary of the evidence we report the overall treatment effects from all trials with available data, for the primary outcomes of these Clinical Practice Guidelines, for a single course of antenatal corticosteroids. We then report on the subset of 16 trials that specifically reported that they included a proportion of women recruited into their trial with *preterm prelabour rupture of membranes at trial entry*. Where data are available we report on trials that only recruited women with preterm prelabour rupture of membranes.

Maternal primary outcomes for these Clinical Practice Guidelines:

Maternal infection -

Chorioamnionitis - Overall no difference was seen in the risk for chorioamnionitis between women who had been treated with a single course of antenatal corticosteroids and those with no antenatal corticosteroids (RR 0.90, 95%CI 0.69 to 1.17; 13 trials, n=2525 women).

- Nine trials reported they included a proportion of women with preterm prelabour rupture of membranes at trial entry (range 23% to 100% where detailed) and provided data for chorioamnionitis (Carlan 1991, Dexiprom 1999, Lewis 1996, Liggins 1972, Lopez 1989, Morales 1989, Qublan 2001, Schutte 1980, Silver 1996). The size of the treatment effect was similar to the overall effect and there was no significant difference between groups (RR 0.82, 95%CI 0.61 to 1.09; 9 trials, n=1961 women) (**Table 50**).
- Four trials reported they included only women at with preterm prelabour rupture of membranes at trial entry at risk of preterm birth and provided data for chorioamnionitis (Carlan 1991, Dexiprom 1999, Lopez 1989, Morales 1989). The size of the treatment effect was similar to the overall effect and there was no significant difference between groups (RR 0.69, 95%CI 0.41 to 1.18; 4 trials, n=433 women) (**Table 50**).

Puerperal sepsis - Overall no difference was seen in the risk for puerperal sepsis between women who had been treated with a single course of antenatal corticosteroids and those with no antenatal corticosteroids (RR 1.35, 95%CI 0.93 to 1.95; 8 trials, n=1003 women).

- Five trials reported they included a proportion of women with preterm prelabour rupture of membranes at trial entry (range 23% to 100% where reported) and provided data for puerperal sepsis (Dexiprom 1999, Lewis 1996, Qublan 2001, Schutte 1980, Silver 1996). The direction of the treatment effect was similar to the overall effect and there was no significant difference between groups (RR 1.42, 95%CI 0.76 to 2.63; 5 trials, n=596 women).
- One trial reported including only women with preterm prelabour rupture of membranes at trial entry at risk of preterm birth and provided data for puerperal sepsis (Dexiprom, 1999). Although the direction of the treatment effect was opposite to the overall effect, showing reduced risk, there was no significant difference between groups (RR 0.57, 95%CI 0.27 to 2.89; 1 trial, n=204 women) (**Table 50**).

Pyrexia after trial entry - Overall no difference was seen in the risk for pyrexia after trial entry between women who had been treated with a single course of antenatal corticosteroids and those with no antenatal corticosteroids (RR 1.11, 95%CI 0.67 to 1.67; 4 trials, n=481 women).

- Two trials reported they included a proportion of women with preterm prelabour rupture of membranes at trial entry (Nelson 1985 100%; Schutte 1980) and provided data for pyrexia after trial entry. The treatment effect was in the opposite direction to the overall effect, showing reducing risk, but there was no significant difference between groups (RR 0.51, 95%CI 0.18 to 1.41; 2 trials, n=145 women).
- One trial reported that including only women with preterm prelabour rupture of membranes at trial entry at risk of preterm birth and provided data for pyrexia after trial entry (Nelson 1985).The direction of the treatment effect was opposite to the overall effect, showing reduced risk, but there was no significant difference between groups (RR 0.25, 95%CI 0.03 to 2.06; 1 trial, n=44 women) (**Table 50**).

Intrapartum pyrexia - Overall no difference was seen in the risk for intrapartum pyrexia requiring treatment between women who had been treated with a single course of antenatal corticosteroids and those with no antenatal corticosteroids (RR 0.60, 95%CI 0.15 to 2.49; 2 trials, n=319 women).

- Only one trial (Schutte 1980) reported including a proportion of women with preterm prelabour rupture of membranes at trial entry and provided data for intrapartum pyrexia requiring treatment. The size of the treatment effect was similar to the overall effect and there was no significant difference between groups (RR 0.26, 95%CI 0.03 to 2.20; 1 trial, n=101 women) (**Table 50**).

Postnatal pyrexia - Overall no difference was seen in the risk for postnatal pyrexia requiring treatment between women who had been treated with a single course of antenatal corticosteroids and those with no antenatal corticosteroids (RR 0.92, 95%CI 0.64 to 1.33; 5 trials, n=1323 women).

- Three trials reported they included a proportion of women with preterm prelabour rupture of membranes at trial entry (range 47% to 100% where detailed) and provided data for postnatal pyrexia requiring treatment (Collaborative Group on Antenatal Steroid Therapy 1981, Dexiprom 1999, Schutte 1980). The size of the treatment effect was similar to the overall effect and there was no significant difference between groups (RR 1.00, 95%CI 0.65 to 1.53; 3 trials, n=987 women).
- One trial reported including only women with preterm prelabour rupture of membranes at trial entry at risk of preterm birth and provided data for postnatal pyrexia requiring treatment (Dexiprom, 1999). The direction of the treatment effect was similar to the overall effect and there was no significant difference between groups (RR 1.00, 95%CI 0.36 to 2.75; 1 trial, n=204 women) (**Table 50**).

Other maternal primary outcomes for these Clinical Practice Guidelines - No data on quality of life were reported in the trials that recruited a proportion of the women with preterm prelabour rupture of membranes at trial entry.

Table 50: Comparison of the overall effect estimate for use of a single course of antenatal corticosteroids with trials that reported including a proportion of women with preterm prelabour rupture of membranes at trial entry – Maternal primary outcomes

Primary outcome	Single course of antenatal corticosteroid*			Trials known to have included women with preterm prelabour rupture of membranes at trial entry^				
	Trials contributing data	Number of women	Risk ratio (RR) (95% Confidence Interval)	Trials contributing data	Number of women	Risk ratio (RR) (95% Confidence Interval)	Actual proportion detailed in trials	Actual number of women
Chorioamnionitis	Amorim 1999; Carlan 1991; Dexiprom 1999; Fekih 2002; Garite 1992; Kari 1994; Lewis 1996; Liggins 1972; Lopez 1989; Morales 1989; Qublan 2001; Schutte 1980; Silver 1996	2525	RR 0.90 (0.69 to 1.17), 13 trials	Carlan 1991; Dexiprom 1999; Lewis 1996; Liggins 1972; Lopez 1989; Morales 1989; Qublan 2001; Schutte 1980; Silver 1996	1961	RR 0.82 (0.61 to 1.09), 9 trials, n=1961 women	Carlan 1991; Dexiprom 1999; Liggins 1972; Lopez 1989; Morales 1989; Silver 1996	768
				**Carlan 1991; Dexiprom 1999; Lopez 1989; Morales 1989	433	RR 0.69 (0.41 to 1.18), 4 trials, n=433 women	**Carlan 1991; Dexiprom 1999; Lopez 1989; Morales 1989	433
Puerperal sepsis	Amorim 1999; Dexiprom 1999; Garite 1992; Lewis 1996; Qublan 2001; Schutte 1980; Silver 1996; Taeusch 1979	1003	RR 1.35 (0.93 to 1.95), 8 trials	Dexiprom 1999; Lewis 1996; Qublan 2001; Schutte 1980; Silver 1996	596	RR 1.42 (0.76 to 2.63), 5 trials, n=596 women,	Dexiprom 1999; Silver 1996	221
				**Dexiprom 1999	204	RR 0.57 (0.27 to 2.89), 1 trial, n=204 women	**Dexiprom 1999	204
Pyrexia after trial entry requiring treatment	Amorim 1999; Nelson 1985; Schutte 1980; Taeusch 1979	481	RR 1.11 (0.67 to 1.67), 4 trials	Nelson 1985; Schutte 1980	145	RR 0.51 (0.18 to 1.41), 2 trials, n=145 women	Nelson 1985	44
				**Nelson 1985	44	RR 0.25 (0.03 to 2.06), 1 trial, n=44 women	**Nelson 1985	44
Intrapartum pyrexia requiring treatment	Amorim 1999; Schutte 1980	319	RR 0.60 (0.15 to 2.49), 2 trials	Schutte 1980	101	RR 0.26 (0.03 to 2.20), 1 trial, n=101 women	-	-
Postnatal pyrexia requiring treatment	Amorim 1999; Collaborative 1981; Dexiprom 1999; Fekih 2002; Schutte 1980	1323	RR 0.92 (0.64 to 1.33), 5 trials	Collaborative 1981; Dexiprom 1999; Schutte 1980	987	RR 1.00 (0.65 to 1.53), 3 trials, n=987 women	Collaborative 1981; Dexiprom 1999	525
				**Dexiprom 1999	204	RR 1.00 (0.36 to 2.75), 1 trial, n=204 women	**Dexiprom 1999	204

*Source: Roberts CPG version 2015 ; ^meta-analyses conducted for these Clinical Practice Guidelines; ** Trials specifying preterm prelabour rupture of membranes as entry criteria

Infant primary outcomes for these Clinical *Practice Guidelines:*

Fetal, neonatal or later death -

Perinatal death - Overall there was a significant reduction in the risk of perinatal death for infants that been exposed to a single course of antenatal corticosteroids compared with no exposure (RR 0.77, 95%CI 0.67 to 0.89; 13 trials, n=3627 infants).

- Eight trials reported they included a proportion of women with preterm prelabour rupture of membranes at trial entry (28% to 100% where reported) and provided data for perinatal death (Block 1977, Collaborative 1981, Dexiprom 1999, Doran 1980, Liggins 1972, Parsons 1988, Qublan 2001, Schutte 1980). The size of the treatment effect was similar to the overall effect and was statistically significant (RR 0.76, 95%CI 0.64 to 0.90; 8 trials, n=2748 infants).
- Two trials reported they included only women with preterm prelabour rupture of membranes at trial entry and provided data for perinatal death (Dexiprom 1999, Parsons 1998). The size of the treatment effect was similar to the overall effect but did not reach statistical significance (RR 0.38, 95%CI 0.13 to 1.11; 2 trials, n=253 infants), probably due to fewer infants (**Table 51**).

Fetal death - Overall no difference was seen in the risk of fetal death between infants that been exposed to a single course of antenatal corticosteroids and those with no exposure (RR 0.98, 95%CI 0.73 to 1.30; 13 trials, n=3627 infants).

- Eight trials reported they included a proportion of women with preterm prelabour rupture of membranes at trial entry (28% to 100% where reported) and provided data for fetal death (Block 1977, Collaborative 1981, Dexiprom 1999, Doran 1980, Liggins 1972, Parsons 1988, Qublan 2001,, Schutte 1980). The size of the treatment effect was similar to the overall effect and there was no significant difference between groups (RR 0.95, 95%CI 0.69 to 1.30; 8 trials, n=2748 infants).
- Two trials reported they included only women with preterm prelabour rupture of membranes at trial entry and provided data for fetal death (Dexiprom 1999, Parsons 1988). The direction of the treatment effect was similar to the overall effect and there was no significant difference between groups (RR 0.20, 95%CI 0.01 to 4.04; 2 trials, n=253 infants), probably due to fewer infants (**Table 51**).

Neonatal death - Overall there was a significant reduction in the risk of neonatal death for infants that been exposed to a single course of antenatal corticosteroids compared with no exposure (RR 0.68, 95%CI 0.58 to 0.80; 21 trials, n=4408 infants).

- Fourteen trials reported they included a proportion of women with preterm prelabour rupture of membranes at trial entry (23% to 100% where reported) and provided data for neonatal death (Block 1977, Collaborative 1981, Dexiprom 1999, Doran 1980, Lewis 1996, Liggins 1972, Lopez 1989, Morales 1989, Nelson 1985, Parsons 1988, Porto 2011, Qublan 2001, Schutte 1980, Silver 1996). The size of the treatment effect was similar to the overall effect and was also statistically significant (RR 0.69, 95%CI 0.57 to 0.84; 14 trials, n=3348 infants).
- Five trials reported they included only women with preterm prelabour rupture of membranes at trial entry and provided data for neonatal death (Dexiprom 1999; Lopez 1989; Morales 1989; Nelson 1985; Parsons 1988). The size of the treatment effect was similar to the overall effect but there was no significant difference between groups (RR 0.72, 95%CI 0.41 to 1.26; 5 trials, n=501 infants), probably due to fewer infants (**Table 51**).

Respiratory distress syndrome - Overall there was a significant reduction in the risk of respiratory distress syndrome for infants that been exposed to a single course of antenatal corticosteroids compared with no exposure (RR 0.65, 95%CI 0.58 to 0.73; 25 trials, n=4590 infants).

- Sixteen trials reported they included a proportion of women with preterm prelabour rupture of membranes at trial entry (23% to 100% where reported) and provided data for respiratory distress syndrome (Block 1977, Cararach 1991, Carlan 1991, Collaborative 1981, Dexiprom 1999, Doran 1980, Lewis 1996, Liggins 1972, Lopez 1989, Morales 1989, Nelson 1985, Parsons 1988, Porto 2011, Qublan 2001, Schutte 1980, Silver 1996). The size of the treatment effect was similar to the overall effect and was also statistically significant (RR 0.68, 95%CI 0.60 to 0.78; 16 trials, n=3348 infants).
- Seven trials reported they included only women with preterm prelabour rupture of membranes at trial entry and provided data for respiratory distress syndrome (Cararach 1991, Carlan 1991, Dexiprom 1999, Lopez 1989, Morales 1989, Nelson 1985, Parsons 1988). The size of the treatment effect was similar to the overall effect and there was no significant difference between groups, probably due to fewer infants (RR 0.80, 95%CI 0.57 to 1.14; 7 trials, n=538) (**Table 51**).

Composite of serious infant outcomes - This outcome was not reported in any of the trials of a single course of antenatal corticosteroids.

Table 51: Comparison of the overall effect estimate for use of a single course of antenatal corticosteroids with trials that reported including a proportion of women with preterm prelabour rupture of membranes at trial entry – Infant primary outcomes

Primary outcome	Single course of antenatal corticosteroid*			Trials known to have included women with preterm prelabour rupture of membranes at trial entry^				
	Trials contributing data	Number of infants	Risk ratio (RR) (95% Confidence Interval)	Trials contributing data	Number of infants	Risk ratio (RR) (95% Confidence Interval)	Actual proportion detailed in trials	Actual number of infants
Perinatal death	Amorim 1999; Block 1977; Collaborative 1981; Dexiprom 1999; Doran 1980; Gamsu 1989; Garite 1992; Kari 1994; Liggins 1972; Parsons 1988; Qublan 2001; Schutte 1980; Taeusch 1979	3627	RR 0.77 (0.67 to 0.89), 13 trials	Block 1977; Collaborative 1981; Dexiprom 1999; Doran 1980; Liggins 1972; Parsons 1988; Qublan 2001; Schutte 1980	2748	RR 0.76 (0.64 to 0.90), 8 trials, n=2748 infants	Collaborative 1981; Dexiprom 1999; Liggins 1972; Parsons 1988	950
				**Dexiprom 1999; Parsons 1988	253	RR 0.38 (0.13 to 1.11), 2 trials, n=253 infants	**Dexiprom 1999; Parsons 1988	253
Fetal death	Amorim 1999; Block 1977; Collaborative 1981; Dexiprom 1999; Doran 1980; Gamsu 1989; Garite 1992; Kari 1994; Liggins 1972; Parsons 1988; Qublan 2001; Schutte 1980; Taeusch 1979	3627	RR 0.98 (0.73 to 1.30), 13 trials	Block 1977; Collaborative 1981; Dexiprom 1999; Doran 1980; Liggins 1972; Parsons 1988; Qublan 2001; Schutte 1980	2748	RR 0.95 (0.69 to 1.30), 8 trials, n=2748 infants	Collaborative 1981; Dexiprom 1999; Liggins 1972; Parsons 1988	950
				**Dexiprom 1999; Parsons 1988	253	RR 0.20 (0.01 to 4.04), 2 trials, n=253 infants	**Dexiprom 1999; Parsons 1988	253
Neonatal death	Amorim 1999; Block 1977; Collaborative 1981; Dexiprom 1999; Doran 1980; Fekih 2002; Gamsu 1989; Garite 1992; Goodner 1979; Kari 1994; Lewis 1996; Liggins 1972; Lopez 1989; Morales 1989; Nelson 1985; Parsons 1988; Porto 2011; Qublan 2001; Schutte 1980; Silver 1996; Taeusch 1979	4408	RR 0.68 (0.58 to 0.80), 21 trials	Block 1977; Collaborative 1981; Dexiprom 1999; Doran 1980; Lewis 1996; Liggins 1972; Lopez 1989; Morales 1989; Nelson 1985; Parsons 1988; Porto 2011; Qublan 2001; Schutte 1980; Silver 1996	3348	RR 0.69 (0.57 to 0.84), 14 trials, n=3348 infants	Collaborative 1981; Dexiprom 1999; Liggins 1972; Lopez 1989; Morales 1989; Nelson 1985; Parsons 1988; Porto 2011; Silver 1996	1037
				**Dexiprom 1999; Lopez 1989; Morales 1989; Nelson 1985; Parsons 1988	501	RR 0.72 (0.41 to 1.26), 5 trials, n=501 infants	**Dexiprom 1999; Lopez 1989; Morales 1989; Nelson 1985; Parsons 1988	501
Respiratory distress syndrome	Amorim 1999; Balci 2010; Block 1977; Cararach 1991; Carlan 1991; Collaborative 1981; Dexiprom 1999; Doran 1980; Fekih 2002;	4590	RR 0.65 (0.58 to 0.73), 25 trials	Block 1977; Cararach 1991; Carlan 1991; Collaborative 1981; Dexiprom 1999; Doran	3348	RR 0.68 (0.60 to 0.78), 16 trials, n=3348 infants	Cararach 1991; Carlan 1991; Collaborative 1981; Dexiprom 1999;	1332

	Gamsu 1989; Garite 1992; Goodner 1979; Kari 1994; Lewis 1996; Liggins 1972; Lopez 1989; Morales 1989; Nelson 1985; Parsons 1988; Porto 2011; Qublan 2001; Schutte 1980; Silver 1996; Taeusch 1979; Teramo 1980			1980; Lewis 1996; Liggins 1972; Lopez 1989; Morales 1989; Nelson 1985; Parsons 1988; Porto 2011; Qublan 2001; Schutte 1980; Silver 1996			Liggins 1972; Lopez 1989; Morales 1989; Nelson 1985; Parsons 1988; Porto 2011; Silver 1996	
				** Cararach 1991; Carlan 1991; Dexiprom 1999; Lopez 1989; Morales 1989; Nelson 1985; Parsons 1988;	538	RR 0.80 (0.57 to 1.14); 7 trials, n=538 infants	** Cararach 1991; Carlan 1991; Dexiprom 1999; Lopez 1989; Morales 1989; Nelson 1985; Parsons 1988;	538

*Source: Roberts CPG version 2015 ; ^meta-analyses conducted for these Clinical Practice Guidelines; ; **Trials specifying preterm prelabour rupture of membranes as entry criteria

Summary of evidence for use of single course of antenatal corticosteroids for preterm prelabour rupture of membranes at trial entry

Sixteen of 26 trials included in the Roberts CPG version 2015 systematic review reported they included a proportion of women who had preterm prelabour rupture of membranes at trial entry. The proportion of women recruited with preterm prelabour rupture of membranes at trial entry ranged from 23% to 100%, where reported.

For the mother

Overall, where reported in 26 trials, no differences were seen between women treated with a single course of antenatal corticosteroids and women with no corticosteroids in the risk for chorioamnionitis, pyrexia after trial entry, intrapartum pyrexia, postnatal pyrexia or puerperal sepsis.

Sixteen trials reported including a proportion of women with preterm prelabour rupture of membranes at trial entry.

- For chorioamnionitis, intrapartum pyrexia, postnatal pyrexia and puerperal sepsis the size of the treatment effect was similar to the overall effect and there was no difference between groups;
- For pyrexia after trial entry the direction of the treatment effect was opposite to the overall effect, showing reduced risk, but there was no difference between groups;

Seven trials reported only including women with preterm prelabour rupture of membranes at trial entry.

- For chorioamnionitis and postnatal pyrexia the size of the treatment effect was similar to the overall effect and there was no difference between groups;
- For pyrexia after trial entry, postnatal pyrexia and puerperal sepsis the direction of the treatment effect was opposite to the overall effect, showing reduced risk, but there was no difference between groups.

No data were reported for maternal quality of life from any of the trials included in the Roberts CPG version 2015 systematic review.

For the infant

Overall, where reported in 26 trials, there was a significant reduction in the risks for perinatal death, neonatal death and respiratory distress syndrome. No difference was seen in the risk for fetal death between infants exposed to a single course of antenatal corticosteroids and infants with no exposure.

Sixteen trials reported including a proportion of women with preterm prelabour rupture of membranes at trial entry.

- For perinatal death, neonatal death and respiratory distress syndrome the size of the treatment effect was similar to the overall effect and the difference was statistically significant for infants exposed to a single course of antenatal corticosteroids compared with no exposure.
- For fetal death, the size of the treatment effect was similar to the overall effect and there was no difference between groups;

Seven trials reported only including women with preterm prelabour rupture of membranes at trial entry.

- For perinatal death, neonatal death and respiratory distress syndrome the size of the treatment effect was similar to the overall effect but there was no significant difference between groups;
- For fetal death, the size of the treatment effect was similar to the overall effect and there was no difference between groups.

The lack of statistical effect for those trials that only included women with preterm prelabour rupture of membranes is probably due to the smaller number of babies.

No data were reported for a composite of serious infant outcomes in any of the trials included in the Roberts CPG version 2015 systematic review.

Evidence is based on a subset of data from trials that reported they included a proportion of women with preterm prelabour rupture of membranes. This level of evidence cannot be used to form a clinical recommendation.

See Appendix M17 – Evidence Summary (Page 376)

What is the safety for the mother, fetus, infant, child, adult of administering a single course of antenatal corticosteroids to women with preterm prelabour rupture of membranes (at trial entry) at risk of preterm birth?

Practice point:
• Use a single course of antenatal corticosteroids for women with preterm prelabour rupture of membranes.

What is the safety for the mother of administering repeat antenatal corticosteroids to women with preterm prelabour rupture of membranes (at trial entry) at risk of preterm birth?

What is the safety for the fetus, infant, child, adult of administering repeat antenatal corticosteroids to women with preterm prelabour rupture of membranes (at trial entry) at risk of preterm birth?

Repeat antenatal corticosteroids

Six of 10 trials from the Cochrane systematic review of *Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes* (Crowther 2011) stated that they included a proportion of women with preterm prelabour rupture of membranes at trial entry in their trials (**Table 41**):

- Aghajafari (2002) 34%
- Crowther (2006) 34%
- Guinn (2002) 24%
- McEvoy (2010) proportion not reported
- Murphy (2008) 16%
- Peltoniemi (2007) 39%

Two trials did not report if women with preterm prelabour rupture of membranes were included in their trials (Mazumder 2008, McEvoy 2002). Women with preterm prelabour rupture of membranes were not eligible for two trials (Garite 2009, Wapner 2006). All of the trials included in the Crowther (2011) systematic review included women who had already been treated with a single course of antenatal corticosteroids seven days or more previously and remained at risk for preterm birth (Appendix K). No additional trials were identified in the Crowther CPG version 2015 systematic review.

In the summary of the evidence we report the overall treatment effects from all trials with available data, for the primary outcomes of these Clinical Practice Guidelines, for repeat antenatal corticosteroids. We then report on the subset of six trials that specifically reported that they included a proportion of women recruited into their trial with *preterm prelabour rupture of membranes at trial entry.*

Maternal primary outcomes for these Clinical Practice Guidelines:

Maternal infection -

Chorioamnionitis - Overall no difference was seen in the risk for chorioamnionitis between women who had been treated with repeat antenatal corticosteroids and those with no repeat treatment (RR 1.16, 95%CI 0.92 to 1.46; 6 trials, n=4261 women).

- Four trials reported they included a proportion of women with preterm prelabour rupture of membranes at trial entry (16% to 34%) and provided data for chorioamnionitis (Aghajafari 2002, Crowther 2006, Guinn 2001, Murphy 2008). The size of the treatment effect was similar to the overall effect and there was no significant difference between groups (RR 1.19, 95%CI 0.94 to 1.52; 4 trials, n=3332 women) (**Table 52**).

Puerperal sepsis - Overall no difference was seen in the risk for puerperal sepsis between women who had been treated with repeat antenatal corticosteroids and those with no repeat treatment (RR 1.15, 95%CI 0.83 to 1.60; 5 trials, n=3091 women).

- Four trials reported they included a proportion of women with preterm prelabour rupture of membranes at trial entry (16% to 39%) and provided data for puerperal sepsis (Aghajafari 2002, Guinn 2001, Murphy 2008, Peltoniemi 2007). The size of the treatment effect was similar to the

overall effect and there was no significant difference between groups (RR 1.26, 95%CI 0.89 to 1.80; 4 trials, n=2599 women) (**Table 52**).

Postnatal pyrexia - Overall no difference was seen in the risk for postnatal pyrexia requiring treatment between women who had been treated with repeat antenatal corticosteroids and those with no repeat treatment (RR 0.87, 95%CI 0.55 to 1.38; 1 trial, n=982 women). This single trial (Crowther 2006) reported that 34% of the women included had preterm prelabour rupture of membranes at trial entry (**Table 52**).

Other maternal infection outcomes - There were no randomised controlled trial data reported for pyrexia after trial entry requiring treatment or intrapartum pyrexia requiring treatment in the Crowther systematic review (Crowther 2011) (**Table 52**).

Other maternal primary outcomes for these Clinical Practice Guidelines - No data on quality of life were reported in the subgroup of trials that reported they included a proportion of the women in their trial with preterm prelabour rupture of membranes at trial entry.

Infant primary outcomes for these Clinical Practice Guidelines:

Fetal, neonatal or later death -

Perinatal death - Overall no difference was seen in the risk for perinatal death between infants who had been exposed to repeat antenatal corticosteroids and those with no repeat exposure (RR 0.94, 95%CI 0.71 to 1.23; 9 trials, n=5554 infants).

- Six trials reported they had included a proportion of women with preterm prelabour rupture of membranes at trial entry (range 16% to 34% where detailed) and provided data for perinatal death (Aghajafari 2002, Crowther 2006, Guinn 2001, McEvoy 2010, Murphy 2008, Peltoniemi 2007). The size of the treatment effect was similar to the overall effect and there was no significant difference between groups (RR 1.03, 95%CI 0.77 to 1.39; 6 trials, n=4406 infants) (**Table 53**).

Fetal death - Overall no difference was seen in the risk for fetal death between infants who had been exposed to repeat antenatal corticosteroids and those with no repeat exposure (RR 0.82, 95%CI 0.24 to 2.84; 7 trials, n=2755 infants).

- Five trials reported they had included a proportion of women with preterm prelabour rupture of membranes at trial entry (range 24% to 39% where detailed) and provided data for fetal death (Aghajafari 2002, Crowther 2006, Guinn 2001, McEvoy 2010, Peltoniemi 2007). The size of the treatment effect was similar to the overall effect and there was no significant difference between groups (RR 1.10, 95%CI 0.20 to 4.98; 5 trials, n=2102 infants) (**Table 53**).

Neonatal death - Overall no difference was seen in the risk for neonatal death between infants who had been exposed to repeat antenatal corticosteroids and those with no repeat exposure (RR 0.91, 95%CI 0.62 to 1.34; 7 trials, n=2713 infants).

- Five trials reported they had included a proportion of women with preterm prelabour rupture of membranes at trial entry (range 24% to 39%, where detailed) and provided data for neonatal death (Aghajafari 2002, Crowther 2006, Guinn 2001, McEvoy 2010 (proportion not reported), Peltoniemi 2007). The size of the treatment effect was similar to the overall effect and there was no significant difference between groups (RR 1.01, 95%CI 0.66 to 1.56; 5 trials, n=2081 infants) (**Table 53**).

Respiratory distress syndrome - Overall there was a significant reduction for the risk of respiratory distress syndrome for infants who had been exposed to repeat antenatal corticosteroids compared with no repeat exposure (RR 0.83, 95%CI 0.75 to 0.91; 8 trials, n=3206 infants).

- Five trials reported they had included a proportion of women with preterm prelabour rupture of membranes at trial entry (range 24% to 39%, where detailed) and provided data for respiratory distress syndrome (Aghajafari 2002, Crowther 2006, Guinn 2001, McEvoy 2010, Peltoniemi 2007). The treatment effect was similar to the overall treatment effect and was statistically significant (RR 0.86, 95%CI 0.77 to 0.97; 5 trials, n=2081 infants) (**Table 53**).

Composite of serious infant outcomes - Overall there was a significant reduction in the risk for a composite of serious infant outcomes for infants who had been exposed to repeat antenatal corticosteroids compared with no repeat exposure (RR 0.84, 95%CI 0.75 to 0.94; 7 trials, n=5094).

- Four trials reported they included a proportion of women with preterm prelabour rupture of membranes at trial entry (range 16% to 34%) and provided data for a composite of serious infant outcomes (Aghajafari 2002, Crowther 2006, Guinn 2001, Murphy 2008). The size of the treatment effect was similar to the overall effect but there was no significant difference between groups (RR 0.88, 95%CI 0.77 to 1.01; 4 trials, n=3966 infants) (**Table 53**).

Table 52: Comparison of the overall effect estimate for use of repeat antenatal corticosteroids with trials that reported including a proportion of women with preterm prelabour rupture of membranes at trial entry – Maternal primary outcomes

	Repeat course of antenatal corticosteroid*			Trials known to have included women with preterm prelabour rupture of membranes at trial entry^				
Primary outcome	**Trials contributing data**	**Number of women**	**Risk ratio (RR) (95% Confidence Interval)**	**Trials contributing data**	**Number of women**	**Risk ratio (RR) (95% Confidence Interval)**	**Actual proportion detailed in trials**	**Actual number of women**
Chorioamnionitis	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Mazumder 2008; McEvoy 2010; Murphy 2008; Wapner 2006	4261	RR 1.16 (0.92 to 1.46), 6 trials	Aghajafari 2002; Crowther 2006; Guinn 2001; Murphy 2008	3332	RR 1.19 (0.94 to 1.52), 4 trials, n=3332 women	Aghajafari 2002; Crowther 2006; Guinn 2001; Murphy 2008	751
Puerperal sepsis	Aghajafari 2002; Guinn 2001; Murphy 2008; Peltoniemi 2007; Wapner 2006	3091	RR 1.15 (0.83 to 1.60), 5 trials	Aghajafari 2002; Guinn 2001; Murphy 2008; Peltoniemi 2007	2599	RR 1.26 (0.89 to 1.80), 4 trials, n=2599 women	Aghajafari 2002; Guinn 2001; Murphy 2008; Peltoniemi 2007	514
Pyrexia after trial entry requiring treatment	-	-	NR	-	-	NR	-	-
Intrapartum pyrexia requiring treatment	-	-	NR	-	-	NR	-	-
Postnatal pyrexia requiring treatment	Crowther 2006	982	RR 0.87 (0.55 to 1.38), 1 trial	Crowther 2006	982	RR 0.87 (0.55 to 1.38), 1 trial, n=982 women	Crowther 2006	334

*Source: Crowther (2011); ^meta-analyses conducted for these Clinical Practice Guidelines

Table 53: Comparison of the overall effect estimate for use of repeat antenatal corticosteroids with trials that reported including a proportion of women with preterm prelabour rupture of membranes at trial entry – Infant primary outcomes

	Repeat course of antenatal corticosteroid*			Trials known to have included women with preterm prelabour rupture of membranes at trial entry^				
Primary outcome	**Trials contributing data**	**Number of infants**	**Risk ratio (RR) (95% Confidence Interval)**	**Trials contributing data**	**Number of infants**	**Risk ratio (RR) (95% Confidence Interval)**	**Actual proportion detailed in trials**	**Actual number of infants**
Perinatal death	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Mazumder 2008; McEvoy 2010; Murphy 2008; Peltoniemi 2007; Wapner 2006	5554	RR 0.94 (0.71 to 1.23), 9 trials	Aghajafari 2002; Crowther 2006; Guinn 2001; McEvoy 2010; Murphy 2008; Peltoniemi 2007	4406	RR 1.03 (0.77 to 1.39), 6 trials, n=4406 infants	Aghajafari 2002; Crowther 2006; Guinn 2001; Murphy 2008; Peltoniemi 2007	1012
Fetal death	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Mazumder 2008; McEvoy 2010; Peltoniemi 2007	2755	RR 0.82 (0.24 to 2.84), 7 trials	Aghajafari 2002; Crowther 2006; Guinn 2001; McEvoy 2010; Peltoniemi 2007	2102	RR 1.10 (0.20 to 4.98), 5 trials, n=2102 infants	Aghajafari 2002; Crowther 2006; Guinn 2001; Peltoniemi 2007	643
Neonatal death	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Mazumder 2008; McEvoy 2010; Peltoniemi 2007	2713	RR 0.91 (0.62 to 1.34), 7 trials	Aghajafari 2002; Crowther 2006; Guinn 2001; McEvoy 2010; Peltoniemi 2007	2081	RR 1.01 (0.66 to 1.56), 5 trials, n=2081 infants	Aghajafari 2002; Crowther 2006; Guinn 2001; Peltoniemi 2007	627
Respiratory distress syndrome	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Mazumder 2008; McEvoy 2010; Peltoniemi 2007; Wapner 2006	3206	RR 0.83 (0.75 to 0.91), 8 trials	Aghajafari 2002; Crowther 2006; Guinn 2001; McEvoy 2010; Peltoniemi 2007	2081	RR 0.86 (0.77 to 0.97), 5 trials, n=2081 infants	Aghajafari 2002; Crowther 2006; Guinn 2001; Peltoniemi 2007	627
Composite outcome of serious infant outcomes	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Mazumder 2008; Murphy 2008; Wapner 2006	5094	RR 0.84 (0.75 to 0.94), 7 trials	Aghajafari 2002; Crowther 2006; Guinn 2001; Murphy 2008	3966	RR 0.88 (0.77 to 1.01), 4 trials, n=3966 infants	Aghajafari 2002; Crowther 2006; Guinn 2001; Murphy 2008	869

*Source: Crowther (2011); ^meta-analyses conducted for these Clinical Practice Guidelines

Summary of evidence for use of repeat antenatal corticosteroids for preterm prelabour rupture of membranes at trial entry

Six of ten trials included in the Crowther (2011) systematic review reported they included a proportion of women who had preterm prelabour rupture of membranes at trial entry (range 16% to 39%, where reported).

For the mother

Overall, where reported in 10 trials, no differences were seen between women treated with repeat antenatal corticosteroids and women with no repeat corticosteroids in the risk for chorioamnionitis, postnatal pyrexia or puerperal sepsis.

Six trials reported including a proportion of women with preterm prelabour rupture of membranes at trial entry. The evidence is consistent with the overall treatment effect:

- For chorioamnionitis, postnatal pyrexia and puerperal sepsis, the size of the treatment effect was the same or similar to the overall effect and there was no difference between groups.

No data were reported for pyrexia after trial entry, intrapartum pyrexia or maternal quality of life from these six trials.

For the infant

Overall, where reported in 10 trials, there was a significant reduction in the risks for respiratory distress syndrome and a composite of serious infant outcomes. No differences were seen in the risks for perinatal death, fetal death, neonatal death or severe respiratory distress syndrome between infants exposed to a repeat antenatal corticosteroids and infants with no repeat exposure.

Six trials reported including a proportion of women in preterm labour. The evidence is consistent with the overall treatment effect:

- For respiratory distress syndrome the size of the treatment effect was similar to the overall effect and there was a significant reduction in risk for infants exposed to a repeat antenatal corticosteroids compared with no repeat exposure;
- For a composite of serious infant outcomes the size of the treatment effect was similar to the overall effect but there was no significant difference between groups;
- For perinatal death, fetal death and neonatal death the size of the treatment effect was similar to the overall effect and there was no significant difference between groups.

Evidence is based on a subset of data from trials that reported they included a proportion of women with preterm prelabour rupture of membranes. This level of evidence cannot be used to form a clinical recommendation.

See Appendix M18 – Evidence Summary (Page 380)

What is the safety for the mother, fetus, infant, child, adult of administering repeat antenatal corticosteroids to women with preterm prelabour rupture of membranes (at trial entry) at risk of preterm birth?

Practice points:
• Repeat antenatal corticosteroids for a woman with preterm prelabour rupture of membranes.

14.4 Women with chorioamnionitis at risk of preterm birth

What is the safety for the mother of administering a single course of antenatal corticosteroids to women with chorioamnionitis at risk of preterm birth?

What is the safety for the fetus, infant, child, adult of administering a single course of antenatal corticosteroids to women with chorioamnionitis at risk of preterm birth?

Single course of antenatal corticosteroids

Four of 26 trials included in the Roberts CPG version 2015 systematic review reported that they included a proportion, although very small, of women with chorioamnionitis in their trial (at trial entry). Not all of the trials reported the proportion (**Table 40**):

- Carlan (1991) 14%
- Fekih (2001) 2%
- Silver (1996) 33%
- Qublan (2001) proportion not reported

Women with chorioamnionitis were not eligible for inclusion in fourteen of the remaining trials (Balci 2010, Cararach 1991, Collaborative Group on Antenatal Steroid Therapy 1981, Dexiprom 1999, Gamsu 1989, Garite 1992, Kari 1994, Lewis 1996, Lopez 1989, Morales 1989, Nelson 1985, Parsons 1988, Porto 2011, Schutte 1980) (Appendix J).

In the summary of the evidence we report the overall treatment effects from all trials with available data, for the primary outcomes of these Clinical Practice Guidelines, for a single course of antenatal corticosteroids. We then report on the subset of four trials that specifically reported that they included a proportion of women recruited into their trial with *chorioamnionitis at trial entry*.

Maternal primary outcomes for these Clinical Practice Guidelines:

Maternal infection -

Puerperal sepsis - Overall no difference was seen in the risk for puerperal sepsis requiring treatment between women who had been treated with a single course of antenatal corticosteroids and those who received no antenatal corticosteroids (RR 1.35, 95%CI 0.93 to 1.95; 8 trials, n=1003 women).

- Two trials reported they included a proportion of women with chorioamnionitis at trial entry (2% where reported) and provided data for puerperal sepsis (Qublan 2001, Silver 1996). The treatment effect was in the same direction as the overall effect and was statistically significant (RR 2.65, 95%CI 1.18 to 5.91; 2 trials, n=214 women). Caution is suggested in interpreting the data as the numbers of participants are small and there is evidence of imprecision with wide confidence intervals that overlap with those for the overall treatment effect that showed no significant difference (**Table 54**).

Postnatal pyrexia - Overall no difference was seen in the risk for postnatal pyrexia requiring treatment between women who had been treated with a single course of antenatal corticosteroids and those who received no antenatal corticosteroids (RR 0.92, 95%CI 0.64 to 1.33; 5 trials, n=1323 women).

- One trial (Fekih 2002) reported including 2% of women with chorioamnionitis at trial entry. The treatment effect was similar to the overall treatment effect and there was no significant difference between groups (RR 1.00, 95%CI 0.15 to 6.87; 1 trial, n=118 women) (**Table 54**).

Other maternal infection outcomes - No data were reported for other maternal infection outcomes including pyrexia after trial entry or intrapartum pyrexia requiring treatment in those trials that reported that they included a proportion of women with chorioamnionitis at trial entry (**Table 54**).

Other maternal primary outcomes for these Clinical Practice Guidelines - No data on quality of life were reported in trials of a single course of antenatal corticosteroids that recruited and reported a proportion of the women in their trial had chorioamnionitis at trial entry.

Infant primary outcomes for these Clinical Practice Guidelines:

Fetal, neonatal or later death -

Perinatal death - Overall there was a significant reduction in the risk for perinatal death for infants who were exposed to a single course of antenatal corticosteroids compared with no exposure (RR 0.77, 95%CI 0.67 to 0.89; 13 trials, n=3627 infants).

- Only one trial (Qublan 2001) reported including a proportion of women with chorioamnionitis at trial entry (proportion not reported) and provided data for perinatal death. The size of the treatment effect was similar to the overall effect and was statistically significant (RR 0.48, 95%CI 0.32 to 0.72; 1 trial, n=139 infants) (**Table 55**).

Fetal death - Overall no difference was seen in the risk for fetal death between infants who were exposed to a single course of antenatal corticosteroids and those with no exposure (RR 0.98, 95%CI 0.73 to 1.30; 13 trials, n=3627 infants).

- Only one trial (Qublan 2001) reported that it included a proportion of women with chorioamnionitis at trial entry (proportion not reported) and provided data for fetal death. The size of the treatment effect was similar to the overall effect and there was no significant difference between groups (RR 0.93, 95%CI 0.13 to 6.42; 1 trial, n=139 infants) (**Table 55**).

Neonatal death - Overall there was a significant reduction in the risk for neonatal death for infants who were exposed to a single course of antenatal corticosteroids compared with no exposure (RR 0.68, 95%CI 0.58 to 0.80; 21 trials, n=4408 infants).

- Three trials reported that they included a proportion of women with chorioamnionitis at trial entry (2% to 33% where reported) and provided data for neonatal death (Fekih 2002, Qublan 2001, Silver 1996). The size of the treatment effect was similar to the overall effect and was statistically significant (RR 0.48, 95%CI 0.34 to 0.68; 3 trials, n=362 infants) (**Table 55**).

Respiratory distress syndrome - Overall there was a significant reduction in the risk for respiratory distress syndrome for infants who were exposed to a single course of antenatal corticosteroids compared with no exposure (RR 0.65, 95%CI 0.58 to 0.73; 25 trials, n=4590 infants).

- Three trials reported they included a proportion of women with chorioamnionitis at trial entry (2% to 33% where reported) and provided data for respiratory distress syndrome (Fekih 2002, Qublan 2001, Silver 1996). The size of the treatment effect was similar to the overall effect and was statistically significant (RR 0.67, 95%CI 0.53 to 0.84; 3 trials, n=386 infants) (**Table 55**).

Composite of serious infant outcomes - This outcome was not reported in any of the trials of a single course of antenatal corticosteroids.

Table 54: Comparison of the overall effect estimate for use of a single course of antenatal corticosteroids with trials that reported including a proportion of women with chorioamnionitis at trial entry – Maternal primary outcomes

Primary outcome	Single course of antenatal corticosteroid*			Trials known to have included women with chorioamnionitis at trial entry^				
	Trials contributing data	Number of women	Risk ratio (RR) (95% Confidence Interval)	Trials contributing data	Number of women	Risk ratio (RR) (95% Confidence Interval)	Actual proportion detailed in trials	Actual number of women
Puerperal sepsis	Amorim 1999; Dexiprom 1999; Garite 1992; Lewis 1996; Qublan 2001; Schutte 1980; Silver 1996; Taeusch 1979	1003	RR 1.35 (0.93 to 1.95), 8 trials	Qublan 2001; Silver 1996	214	RR 2.65 (1.18 to 5.91) 2 trials, n=214 women	Silver 1996	25
Pyrexia after trial entry requiring treatment	Amorim 1999; Nelson 1985; Schutte 1980; Taeusch 1979	481	RR 1.11 (0.67 to 1.67), 4 trials	No trials	-	-	-	-
Intrapartum pyrexia requiring treatment	Amorim 1999; Schutte 1980	319	RR 0.60 (0.15 to 2.49), 2 trials	No trials	-	-	-	-
Postnatal pyrexia requiring treatment	Amorim 1999; Collaborative 1981; Dexiprom 1999; Fekih 2002; Schutte 1980	1323	RR 0.92 (0.64 to 1.33), 5 trials	Fekih 2002	118	RR 1.00 (0.15 to 6.87) 1 trial, n=118 women	Fekih 2002	2

*Source: Roberts CPG version 2015; ^meta-analyses conducted for these Clinical Practice Guidelines

Table 55: Comparison of the overall effect estimate for use of a single course of antenatal corticosteroids with trials that reported including a proportion of women with chorioamnionitis at trial entry – Infant primary outcomes

	Single course of antenatal corticosteroid*			Trials known to have included women with chorioamnionitis at trial entry^				
Primary outcome	**Trials contributing data**	**Number of infants**	**Risk ratio (RR) (95% Confidence Interval)**	**Trials contributing data**	**Number of infants**	**Risk ratio (RR) (95% Confidence Interval)**	**Actual proportion detailed in trials**	**Actual number of infants**
Perinatal death	Amorim 1999; Block 1977; Collaborative 1981; Dexiprom 1999; Doran 1980; Gamsu 1989; Garite 1992; Kari 1994; Liggins 1972; Parsons 1988; Qublan 2001; Schutte 1980; Taeusch 1979	3627	RR 0.77 (0.67 to 0.89), 13 trials	Qublan 2001	139	RR 0.48 (0.32 to 0.72) 1 trial, n=139 infants	-	-
Fetal death	Amorim 1999; Block 1977; Collaborative 1981; Dexiprom 1999; Doran 1980; Gamsu 1989; Garite 1992; Kari 1994; Liggins 1972; Parsons 1988; Qublan 2001; Schutte 1980; Taeusch 1979	3627	RR 0.98 (0.73 to 1.30), 13 trials	Qublan 2001	139	RR 0.93 (0.13 to 6.42) 1 trial, n=139 infants	-	-
Neonatal death	Amorim 1999; Block 1977; Collaborative 1981; Dexiprom 1999; Doran 1980; Fekih 2002; Gamsu 1989; Garite 1992; Goodner 1979; Kari 1994; Lewis 1996; Liggins 1972; Lopez 1989; Morales 1989; Nelson 1985; Parsons 1988; Porto 2011; Qublan 2001; Schutte 1980; Silver 1996; Taeusch 1979	4408	RR 0.68 (0.58 to 0.80), 21 trials	Fekih 2002; Qublan 2001; Silver 1996	362	RR 0.48 (0.34 to 0.68) 3 trials, n=362 infants	Fekih 2002; Silver 1996	35
Respiratory distress syndrome	Amorim 1999; Balci 2010; Block 1977; Cararach 1991; Carlan 1991; Collaborative 1981; Dexiprom 1999; Doran 1980; Fekih 2002; Gamsu 1989; Garite 1992; Goodner 1979; Kari 1994; Lewis 1996; Liggins 1972; Lopez 1989; Morales 1989; Nelson 1985; Parsons 1988; Porto 2011; Qublan 2001; Schutte 1980; Silver 1996; Taeusch 1979; Teramo 1980	4590	RR 0.65 (0.58 to 0.73), 25 trials	Fekih 2002; Qublan 2001; Silver 1996	386	RR 0.67 (0.53 to 0.84) 3 trials, n=386 infants	Fekih 2002; Silver 1996	35

*Source: Roberts CPG version 2015; ^meta-analyses conducted for these Clinical Practice Guidelines

Evidence summary for use of a single course of antenatal corticosteroids for women with chorioamnionitis

Four of 26 trials included in the Roberts CPG version 2015 systematic review reported they included a proportion of women who had chorioamnionitis at trial entry. The proportion of women included with chorioamnionitis ranged from 2% to 33% for the trials of a single course of antenatal corticosteroids, where reported.

For the mother

Overall, where reported in 26 trials, no differences were seen between women treated with a single course of antenatal corticosteroids and women with no corticosteroids in the risk for pyrexia after trial entry, intrapartum pyrexia, postnatal pyrexia or puerperal sepsis.

Four trials reported including a proportion of women with chorioamnionitis at trial entry.

- For postnatal pyrexia, the size of the treatment effect was similar to the overall effect and there was no difference between groups;
- For puerperal sepsis the direction of the treatment effect was similar to the overall effect and was statistically significant. However the confidence intervals overlap with the overall effect which was not statistically significant.

No data were reported for pyrexia after trial entry, intrapartum pyrexia or maternal quality of life in these four trials.

For the infant

Overall, where reported in 26 trials, there was a significant reduction in the risks for perinatal death, neonatal death and respiratory distress syndrome. No difference was seen in the risk for fetal death between infants exposed to a single course of antenatal corticosteroids and infants with no exposure.

Four trials reported including a proportion of women with chorioamnionitis at trial entry and the data are consistent with the overall treatment effect.

- For perinatal death, neonatal death and respiratory distress syndrome the size of the treatment effect was similar to the overall effect and the difference was statistically significant for infants exposed to a single course of antenatal corticosteroids compared with no exposure.
- For fetal death, the size of the treatment effect was similar to the overall effect and there was no difference between groups.

Evidence is based on a subset of data from trials that reported they included a proportion of women with chorioamnionitis at trial entry. This level of evidence cannot be used to form a clinical recommendation.

See Appendix M19 – Evidence Summary (Page 384)

What is the safety for the mother, fetus, infant, child, adult of administering a single course of antenatal corticosteroids to women with chorioamnionitis at risk of preterm birth?

Practice Points

- Use a single course of antenatal corticosteroids for women with chorioamnionitis at risk of preterm birth.
- Do not delay birth in women with chorioamnionitis to administer a single course of antenatal corticosteroids.
- Where appropriate, monitor women with chorioamnionitis for signs of puerperal sepsis when antenatal corticosteroids have been given.

What is the safety for the mother of administering repeat antenatal corticosteroids to women with chorioamnionitis at risk of preterm birth?

What is the safety for the fetus, infant, child, adult of administering repeat antenatal corticosteroids to women with chorioamnionitis at risk of preterm birth?

Repeat antenatal corticosteroids

For eight of the 10 trials included in the Crowther (2011) Cochrane systematic review '*Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes*' chorioamnionitis was an exclusion criterion (Aghajafari 2002, Crowther 2006, Garite 2009, Mazumder 2008, McEvoy 2010, Murphy 2008, Peltoniemi 2007, Wapner 2006) (Appendix K). Two trials (Guinn 2001, McEvoy 2002) did not provide information on whether a proportion of women with chorioamnionitis were included in their trials (**Table 41**).

Therefore there were no randomised trials included in the Crowther (2011) systematic review of repeat antenatal corticosteroids where women with chorioamnionitis were known to be included in the trial. No additional relevant trials were identified in the Crowther CPG version 2015 systematic review.

See Appendix M20 – Evidence Summary (Page 388)

What is the safety for the mother, fetus, infant, child, adult of administering repeat antenatal corticosteroids to women with chorioamnionitis at risk of preterm birth?

Practice Points:

- Repeat antenatal corticosteroids for a woman with chorioamnionitis at risk of preterm birth.
- Do not delay birth in women with chorioamnionitis to administer repeat antenatal corticosteroids.
- Use repeat antenatal corticosteroids in women with chorioamnionitis at the discretion of the attending physician.
- Where appropriate, monitor women with chorioamnionitis for signs of puerperal sepsis when antenatal corticosteroids have been given.

Research recommendation:

- Randomised trials are needed to investigate if antenatal corticosteroids should be repeated in women at risk of preterm birth who had antenatal corticosteroids 7 days previously and then present with chorioamnionitis.

14.5 Women with antepartum haemorrhage at risk of preterm birth

What is the safety for the mother of administering a single course of antenatal corticosteroids to women with antepartum haemorrhage at risk of preterm birth?

What is the safety for the fetus, infant, child, adult of administering a single course of antenatal corticosteroids to women with antepartum haemorrhage at risk of preterm birth?

Single course of antenatal corticosteroids

Six of 26 trials included in the Roberts CPG version 2015 systematic review reported that they included a small proportion of women with an antepartum haemorrhage in their trials (**Table 40**):

- Gamsu (1989) 12%
- Garite (1992) 20%
- Kari (1994) 36%
- Qublan (2001) 4%
- Silver (1996) 12%
- Taeusch (1979) 20%

Antepartum haemorrhage was not an inclusion criterion for recruitment to any of the trials. The main inclusion criterion for the trials was spontaneous, threatened or planned preterm birth.
Women with an antepartum haemorrhage were not eligible for three trials (Balci 2010, Cararach 1991, Dexiprom 1999) (Appendix J).
The remaining 16 trials did not state if they included a proportion women with antepartum haemorrhage at risk of preterm birth (Amorim 1999, Block 1977, Carlan 1991, Collaborative 1981, Doran 1989, Fekih 2002, Goodner 1979, Lewis 1996, Liggins 1972, Lopez 1989, Morales 1989, Nelson 1985, Parsons 1988, Porto 2011, Schutte 1980, Shanks 2010, Teramo 1980).

In the summary of the evidence we report the overall treatment effects from all trials with available data, for the primary outcomes of these Clinical Practice Guidelines, for a single course of antenatal corticosteroids. We then report on the subset of six trials that specifically reported that they included a proportion of women recruited into their trial with *antepartum haemorrhage at trial entry*.

Maternal primary outcomes for these Clinical Practice Guidelines

Maternal infection -

Chorioamnionitis - Overall no difference was seen in the risk for chorioamnionitis between women who had been treated with a single course of antenatal corticosteroids and those who received no antenatal corticosteroids (RR 0.90, 95%CI 0.69 to 1.17; 13 trials, n=2525 women).

- Four trials reported they included a proportion of women with an antepartum haemorrhage (range 4% to 36%) and provided data for chorioamnionitis (Garite 1992, Kari 1994, Qublan 2001; Silver 1996). The size of the treatment effect was similar to the overall effect and there was no significant difference between groups (RR 1.29, 95%CI 0.81 to 2.05; 4 trials, n=442 women) (**Table 56**).

Puerperal sepsis - Overall no difference was seen in the risk for puerperal sepsis between women who had been treated with a single course of antenatal corticosteroids and those who received no antenatal corticosteroids (RR 1.35, 95%CI 0.93 to 1.95; 8 trials, n=1003 women).

- Four trials reported they included a proportion of women with an antepartum haemorrhage (range 4% to 20%) and provided data for puerperal sepsis (Garite 1992, Qublan 2001, Silver 1996, Taeusch 1979). The treatment effect was similar to the overall effect but was statistically significant

(RR 2.34, 95%CI 1.41 to 3.87; 4 trials, n=403 women). Three of the trials (Qublan 2001, Taeusch 1979, Silver 1996) used dexamethasone as the antenatal corticosteroid. Caution is needed when interpreting these data. The numbers of participants are small, confidence intervals are wide and overlap with those of the overall treatment effect which was not statistically significant. (**Table 56**).

Pyrexia after trial entry - Overall no difference was seen in the risk for pyrexia after trial entry requiring treatment between women who had been treated with a single course of antenatal corticosteroids and those who received no antenatal corticosteroids (RR 1.11, 95%CI 0.67 to 1.67; 4 trials, n=481 women).

- One trial (Taeusch 1979) reported including 20% of women with an antepartum haemorrhage and provided data for pyrexia after trial entry requiring treatment. The treatment effect was similar to the overall effect but was statistically significant (RR 2.05, 95%CI 1.14 to 3.69, 1 trial, n=118 women) (**Table 56**). This trial used dexamethasone as the antenatal corticosteroid. Caution is needed when interpreting these data. The numbers of participants are small, confidence intervals are wide and overlap with those of the overall treatment effect which was not statistically significant.

Other maternal infection outcomes - None of the trials that reported they included a proportion of women with an antepartum haemorrhage at trial entry reported data for intrapartum pyrexia or postnatal pyrexia requiring treatment (**Table 56**).

Other primary maternal outcomes for these Clinical Practice Guidelines **-** No data on quality of life were reported in the trials that reported that they included a proportion of the women in their trial with an antepartum haemorrhage.

Infant primary outcomes for these Clinical Practice Guidelines

Fetal, neonatal or later death -

Perinatal death - Overall there was a significant reduction in the risk for perinatal death for infants who were exposed to a single course of antenatal corticosteroids compared with no exposure (RR 0.77, 95%CI 0.67 to 0.89; 13 trials, n=3627 infants).

- Five trials reported they included a proportion of women with an antepartum haemorrhage (4% to 36%) and provided data for perinatal death (Gamsu 1989, Garite 1992, Kari 1994, Qublan 2001, Taeusch 1979). The treatment effect was similar to the overall effect and was statistically significant (RR 0.70, 95%CI 0.54 to 0.92; 5 trials, n=800 infants) (**Table 57**).

Fetal death - Overall no difference was seen in the risk for fetal death between infants who were exposed to a single course of antenatal corticosteroids and those with no exposure (RR 0.98, 95%CI 0.73 to 1.30; 13 trials, n= 3627 infants).

- Five trials reported they included a proportion of women with an antepartum haemorrhage (4% to 36%) and provided data for fetal death (Gamsu 1989; Garite 1992; Kari 1994; Qublan 2001; Taeusch 1979). The size of the treatment effect was similar to the overall effect and there was no significant difference between groups (RR 0.97, 95%CI 0.41 to 2.30; 5 trials, n=800 infants) (**Table 57**).

Neonatal death - Overall there was a significant reduction in the risk for neonatal death for infants who were exposed to a single course of antenatal corticosteroids compared with no exposure (RR 0.68, 95%CI 0.58 to 0.80; 21 trials, n=4408 infants).

- Six trials reported they included a proportion of women with an antepartum haemorrhage (4% to 36%) and provided data for neonatal death (Gamsu 1989, Garite 1992, Kari 1994, Qublan 2001, Silver 1996, Taeusch 1979). The size of the treatment effect was similar to the overall effect and was statistically significant (RR 0.67, 95%CI 0.51 to 0.89; 6 trials, n=868 infants) (**Table 57**).

Respiratory distress syndrome - Overall there was a significant reduction in the risk for respiratory distress syndrome for infants who were exposed to a single course of antenatal corticosteroids compared with no exposure (RR 0.65, 95%CI 0.58 to 0.73; 25 trials, n=4590 infants).

- Six trials reported they included a proportion of women with an antepartum haemorrhage (4% to 36%) and provided data for respiratory distress syndrome (Gamsu 1989, Garite 1992, Kari 1994, Qublan 2001, Silver 1996, Taeusch 1979). The size of the treatment effect was similar to the overall effect and was statistically significant (RR 0.75, 95%CI 0.64 to 0.89; 6 trials, n=870 infants) (**Table 57**).

Composite of serious infant outcomes - This outcome was not reported in any of the trials of a single course of antenatal corticosteroids.

Table 56: Comparison of the overall effect estimate for use of a single course of antenatal corticosteroids with trials that reported including a proportion of women with antepartum haemorrhage at risk of preterm birth – Maternal primary outcomes

Primary outcome	Single course of antenatal corticosteroids*			Trials known to have included a proportion of women with antepartum haemorrhage^				
	Trials contributing data	Number of women	Risk ratio (RR) (95% Confidence Interval)	Trials contributing data	Number of women	Risk ratio (RR) (95% Confidence Interval)	Actual proportion detailed in trials	Actual number of women
Chorioamnionitis	Amorim 1999; Carlan 1991; Dexiprom 1999; Fekih 2002; Garite 1992; Kari 1994; Lewis 1996; Liggins 1972; Lopez 1989; Morales 1989; Qublan 2001; Schutte 1980; Silver 1996	2525	RR 0.90 (0.69 to 1.17), 13 trials	Garite 1992; Kari 1994; Qublan 2001; Silver 1996	442	RR 1.29 (0.81 to 2.05) 4 trials, n=442 women	Garite 1992; Kari 1994; Qublan 2001; Silver 1996	86
Puerperal sepsis	Amorim 1999; Dexiprom 1999; Garite 1992; Lewis 1996; Qublan 2001; Schutte 1980; Silver 1996; Taeusch 1979	1003	RR 1.35 (0.93 to 1.95), 8 trials	Garite 1992; Qublan 2001; Silver 1996; Taeusch 1979	403	RR 2.34 (1.41 to 3.87) 4 trials, n=403 women	Garite 1992; Qublan 2001; Silver 1996; Taeusch 1979	53
Pyrexia after trial entry requiring treatment	Amorim 1999; Nelson 1985; Schutte 1980; Taeusch 1979	481	RR 1.11 (0.67 to 1.67), 4 trials	Taeusch 1979	118	RR 2.05 (1.14 to 3.69) 1 trial, n=118 women	Taeusch 1979	24
Intrapartum pyrexia requiring treatment	Amorim 1999; Schutte 1980	319	RR 0.60 (0.15 to 2.49), 2 trials	No trials	-	-	-	-
Postnatal pyrexia requiring treatment	Amorim 1999; Collaborative 1981; Dexiprom 1999; Fekih 2002; Schutte 1980	1323	RR 0.92 (0.64 to 1.33), 5 trials	No trials	-	-	-	-

*Source: Roberts CPG version 2015; ^meta-analyses conducted for these Clinical Practice Guidelines

Table 57: Comparison of the overall effect estimate for use of a single course of antenatal corticosteroids with trials that reported including a proportion of women with antepartum haemorrhage at risk of preterm birth – Infant primary outcomes

Primary outcome	Single course of antenatal corticosteroids			Trials known to have included a proportion of women with antepartum haemorrhage				
	Trials contributing data	Number of infants	Risk ratio (RR) (95% Confidence Interval)	Trials contributing data	Number of infants	Risk ratio (RR) (95% Confidence Interval)	Actual proportion detailed in trials	Actual number of infants
Perinatal death	Amorim 1999; Block 1977; Collaborative 1981; Dexiprom 1999; Doran 1980; Gamsu 1989; Garite 1992; Kari 1994; Liggins 1972; Parsons 1988; Qublan 2001; Schutte 1980; Taeusch 1979	3627	RR 0.77 (0.67 to 0.89), 13 trials	Gamsu 1989; Garite 1992; Kari 1994; Qublan 2001; Taeusch 1979	800	RR 0.70 (0.54 to 0.92) 5 trials, n=800 infants	Gamsu 1989; Garite 1992; Kari 1994; Qublan 2001; Taeusch 1979	146
Fetal death	Amorim 1999; Block 1977; Collaborative 1981; Dexiprom 1999; Doran 1980; Gamsu 1989; Garite 1992; Kari 1994; Liggins 1972; Parsons 1988; Qublan 2001; Schutte 1980;Taeusch 1979	3627	RR 0.98 (0.73 to 1.30), 13 trials	Gamsu 1989; Garite 1992; Kari 1994; Qublan 2001; Taeusch 1979	800	RR 0.97 (0.41 to 2.30) 5 trials, n=800 infants	Gamsu 1989; Garite 1992; Kari 1994; Qublan 2001; Taeusch 1979	146
Neonatal death	Amorim 1999; Block 1977; Collaborative 1981; Dexiprom 1999; Doran 1980; Fekih 2002; Gamsu 1989; Garite 1992; Goodner 1979; Kari 1994; Lewis 1996; Liggins 1972; Lopez 1989; Morales 1989; Nelson 1985; Parsons 1988; Porto 2011; Qublan 2001; Schutte 1980; Silver 1996; Taeusch 1979	4408	RR 0.68 (0.58 to 0.80), 21 trials	Gamsu 1989; Garite 1992; Kari 1994; Qublan 2001; Silver 1996; Taeusch 1979	868	RR 0.67 (0.51 to 0.89) 6 trials, n=868 infants	Gamsu 1989; Garite 1992; Kari 1994; Qublan 2001; Silver 1996; Taeusch 1979	152
Respiratory distress syndrome	Amorim 1999; Balci 2010; Block 1977; Cararach 1991; Carlan 1991; Collaborative 1981; Dexiprom 1999; Doran 1980; Fekih 2002; Gamsu 1989; Garite 1992; Goodner 1979; Kari 1994; Lewis 1996; Liggins 1972; Lopez 1989; Morales 1989; Nelson 1985; Parsons 1988; Porto 2011; Qublan 2001; Schutte 1980; Silver 1996; Taeusch 1979; Teramo 1980	4590	RR 0.65 (0.58 to 0.73), 25 trials	Gamsu 1989; Garite 1992; Kari 1994; Qublan 2001; Silver 1996; Taeusch 1979	870	RR 0.75 (0.64 to 0.89) 6 trials, n=870 infants	Gamsu 1989; Garite 1992; Kari 1994; Qublan 2001; Silver 1996; Taeusch 1979	153

*Source: Roberts CPG version 2015 ; ^meta-analyses conducted for these Clinical Practice Guidelines

Evidence summary for a single course of antenatal corticosteroids and women with antepartum haemorrhage

Six of 26 trials included in the Roberts CPG version 2015 systematic review reported they included a proportion of women who had an antepartum haemorrhage (range 4% to 36%, where reported).

For the mother

Overall, where reported in 26 trials, no differences were seen between women treated with a single course of antenatal corticosteroids and women with no corticosteroids in the risk for chorioamnionitis, pyrexia after trial entry, intrapartum pyrexia, postnatal pyrexia or puerperal sepsis.

Six trials reported including a proportion of women with an antepartum haemorrhage.

- For chorioamnionitis the size of the treatment effect was similar to the overall effect and there was no difference between groups;
- For pyrexia after trial entry and puerperal sepsis the direction of the treatment effect was similar to the overall effect and was statistically significant. However the number of participants are small and the confidence intervals overlap with the overall effect which was not statistically significant.

No data were reported for intrapartum pyrexia, postnatal pyrexia or maternal quality of life in these six trials.

For the infant

Overall, where reported in 26 trials, there was a significant reduction in the risks for perinatal death, neonatal death and respiratory distress syndrome. No difference was seen in the risk for fetal death between infants exposed to a single course of antenatal corticosteroids and infants with no exposure.

Six trials reported including a proportion of women with an antepartum haemorrhage. The evidence is consistent with the overall treatment effect:

- For perinatal death, neonatal death and respiratory distress syndrome the size of the treatment effect was similar to the overall effect and the difference was statistically significant for infants exposed to a single course of antenatal corticosteroids compared with no exposure.
- For fetal death the size of the treatment effect was similar to the overall effect and there was no difference between groups.

No data were reported for a composite of serious infant outcomes in any of the trials included in the Roberts CPG version 2015 systematic review.

Evidence is based on a subset of data from trials that reported they included a proportion of women with an antepartum haemorrhage. This level of evidence cannot be used to form a clinical recommendation.

See Appendix M21 – Evidence Summary (Page 392)

What is the safety for the mother, fetus, infant, child, adult of administering a single course of antenatal corticosteroids to women with antepartum haemorrhage at risk of preterm birth?

Practice points:

- Use a single course of antenatal corticosteroids for women with an ante-partum haemorrhage at risk of preterm birth.
- Where appropriate, monitor for signs of puerperal sepsis in women with an antepartum haemorrhage when antenatal corticosteroids have been given.

What is the safety for the mother of administering repeat antenatal corticosteroids to women with antepartum haemorrhage at risk of preterm birth?

What is the safety for the fetus, infant, child, adult of administering repeat antenatal corticosteroids to women with antepartum haemorrhage at risk of preterm birth?

Repeat course of antenatal corticosteroids

Seven of the ten trials included in the Crowther (2011) systematic review '*Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes*' reported that they included a small proportion of women with an antepartum haemorrhage in their trials (**Table 41**):

- Aghajafari (2002) 17%
- Crowther (2006) 29%
- Garite (2009) 4%
- McEvoy (2002) 19%
- McEvoy (2010) 22%
- Murphy (2008) 14%
- Wapner (2006) 11%

No trials of repeat antenatal corticosteroids stated that women with antepartum haemorrhage were not eligible. Antepartum haemorrhage was not an inclusion criterion for any trial. The main inclusion criteria for trial entry were that the women had already received a single course of antenatal corticosteroids and that there was a risk of preterm birth. (Appendix K). No new relevant trials were identified in the CPG version 2015 systematic review.

In the summary of the evidence we report the overall treatment effects from all trials with available data, for the primary outcomes of these Clinical Practice Guidelines, for repeat antenatal corticosteroids. We then report on the subset of seven trials that specifically reported that they included a proportion of women recruited into their trial with *antepartum haemorrhage at trial entry*.

Maternal primary outcomes for these Clinical Practice Guidelines

Maternal infection -

Chorioamnionitis - Overall no difference was seen in the risk for chorioamnionitis between women who had been treated with repeat antenatal corticosteroids and those with no repeat treatment (RR 1.16, 95%CI 0.92 to 1.46; 6 trials, n=4261 women).

- Five trials reported they had included a proportion of women with an antepartum haemorrhage (4% to 29%) and provided data for chorioamnionitis (Aghajafari 2002, Crowther 2006, Garite 2009, Murphy 2008, Wapner 2006). The size of the treatment effect was similar to the overall effect and there was no significant difference between the groups (RR 1.04, 9%%CI 0.77 to 1.42; 5 trials, n=3776 women) (**Table 58**).

Puerperal sepsis - Overall no difference was seen in the risk for puerperal sepsis between women who had been treated with repeat antenatal corticosteroids and those with no repeat treatment (RR 1.15, 95%CI 0.83 to 1.60; 5 trials, n=3091 women).

- Three trials reported they included a proportion of women with an antepartum haemorrhage (11% to 17%) and provided data for puerperal sepsis (Aghajafari 2002, Murphy 2008, Wapner 2006). The

size of the treatment effect was similar to the overall effect and there was no significant difference between groups (RR 1.12, 9%%CI 0.72 to 1.75; 3 trials, n=2357 women) (**Table 58**).

Postnatal pyrexia - Overall no difference was seen in the risk for postnatal pyrexia requiring treatment between women who had been treated with repeat antenatal corticosteroids and those with no repeat treatment (RR 0.87, 95%CI 0.55 to 1.38; 1 trial, n=982 women). Evidence is based on a single trial (Crowther 2006) that included 29% of women with an antepartum haemorrhage (**Table 58**).

Other maternal infection outcomes - No data were reported for pyrexia after trial entry or intrapartum pyrexia requiring treatment in the trials that reported including a proportion of women with an antepartum haemorrhage.

Other primary maternal outcomes for these Clinical practice Guidelines - No other data on quality of life was reported in the subgroup of trials that reported that they included a proportion of the women with an antepartum haemorrhage.

Infant primary outcomes for these Clinical Practice Guidelines:

Fetal, neonatal or later death -

Perinatal death - Overall no difference was seen in the risk for perinatal death between women who had been treated with repeat antenatal corticosteroids and those with no repeat treatment (RR 0.94, 95%CI 0.71 to 1.23; 9 trials, n=5554 women).

- Six trials reported they included a proportion of women with an antepartum haemorrhage (4% to 29%) and provided data for perinatal death (Aghajafari 2002, Crowther 2006, Garite 2009, McEvoy 2010, Murphy 2008, Wapner 2006). The size of the treatment effect was similar to the overall effect and there was no significant difference between groups (RR 0.96, 95%CI 0.71 to 1.29; 6 trials, n=4650 infants) (**Table 59**).

Fetal death - Overall no difference was seen in the risk for fetal death between women who had been treated with repeat antenatal corticosteroids and those with no repeat treatment (RR 0.82, 95%CI 0.24 to 2.84; 7 trials, n=2755 women).

- Four trials reported they included a proportion of women with an antepartum haemorrhage (4% to 29%) and provided data for fetal death (Aghajafari 2002, Crowther 2006 Garite 2009, McEvoy 2010). The size of the treatment effect was similar to the overall effect and there was no significant difference between groups (RR 1.01, 95%CI 0.14 to 7.13; 4 trials, n=1851 infants) (**Table 59**).

Neonatal death - Overall no difference was seen in the risk for neonatal death between women who had been treated with repeat antenatal corticosteroids and those with no repeat treatment (RR 0.91, 95%CI 0.62 to 1.34; 7 trials, n=2713 women).

- Four trials reported they included a proportion of women with an antepartum haemorrhage (4% to 29%) and provided data for neonatal death (Aghajafari 2002, Crowther 2006, Garite 2009, McEvoy 2010). The size of the treatment effect was similar to the overall effect and there was no significant difference between groups (RR 0.93, 95%CI 0.58 to 1.49; 4 trials, n=1828 infants) (**Table 59**).

Respiratory distress syndrome - Overall there was a significant reduction in the risk for respiratory distress syndrome for infants exposed to repeat antenatal corticosteroids compared with no repeat exposure (RR 0.83, 95%CI 0.75 to 0.91; 8 trials, n=3206 infants).

- Five trials reported they included a proportion of women with an antepartum haemorrhage (4% to 29%) and provided data for respiratory distress syndrome (Aghajafari 2002, Crowther 2006, Garite

2009, McEvoy 2010, Wapner 2006). The treatment effect was similar to the overall effect and was statistically significant (RR 0.76, 95%CI 0.68 to 0.86; 5 trials, n=2323 infants) (**Table 59**).

Composite of serious infant outcomes - Overall there was a significant reduction in the risk for a composite of serious infant outcomes for infants exposed to repeat antenatal corticosteroids compared with no repeat exposure (RR 0.84, 95%CI 0.75 to 0.94; 7 trials, n=5094 infants).

- Five trials reported they included a proportion of women with an antepartum haemorrhage (4% to 29%) and provided data for a composite of serious infant outcomes (Aghajafari 2002, Crowther 2006, Garite 2009, Murphy 2008, Wapner 2006). The treatment effect was similar to the overall effect and was statistically significant (RR 0.85, 95%CI 0.76 to 0.96; 5 trials, n=4517 infants) (**Table 59**).

Table 58: Comparison of the overall effect estimate for use of repeat antenatal corticosteroids with trials that reported including a proportion of women with antepartum haemorrhage at risk of preterm birth – Maternal primary outcomes

Primary outcome	Repeat antenatal corticosteroids*			Trials known to have included a proportion of women with antepartum haemorrhage^				
	Trials contributing data	Number of women	Risk ratio (RR) (95% Confidence Interval)	Trials contributing data	Number of women	Risk ratio (RR) (95% Confidence Interval)	Actual proportion detailed in trials	Actual number of women
Chorioamnionitis	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Murphy 2008; Wapner 2006	4261	RR 1.16 (0.92 to 1.46), 6 trials	Aghajafari 2002; Crowther 2006; Garite 2009; Murphy 2008; Wapner 2006	3776	RR 1.04 (0.77 to 1.42) 5 trials, n=3776 women	Aghajafari 2002; Crowther 2006; Garite 2009; Murphy 2008; Wapner 2006	618
Puerperal sepsis	Aghajafari 2002; Guinn 2001; Murphy 2008; Peltoniemi 2007; Wapner 2006	3091	RR 1.15 (0.83 to 1.60), 5 trials	Aghajafari 2002; Murphy 2008; Wapner 2006	2357	RR 1.12 (0.72 to 1.75) 3 trials, n=2357 women	Aghajafari 2002; Murphy 2008; Wapner 2006	315
Pyrexia after trial entry requiring treatment	-	-	Not reported	-	-	Not reported	-	-
Intrapartum pyrexia requiring treatment	-	-	Not reported	-	-	Not reported	-	-
Postnatal pyrexia requiring treatment	Crowther 2006	982	RR 0.87 (0.55 to 1.38), 1 trial	Crowther 2006	982	RR 0.87 (0.55 to 1.38), 1 trial, n=982 women	Crowther 2006	285

*Source: Crowther (2011); ^meta-analyses conducted for these Clinical Practice Guidelines

Table 59: Comparison of the overall effect estimate for use of repeat antenatal corticosteroids with trials that reported including a proportion of women with antepartum haemorrhage at risk of preterm birth – Infant primary outcomes

Primary outcome	Repeat antenatal corticosteroids*			Trials known to have included a proportion of women with antepartum haemorrhage^				
	Trials contributing data	Number of infants	Risk ratio (RR) (95% Confidence Interval)	Trials contributing data	Number of infants	Risk ratio (RR) (95% Confidence Interval)	Actual proportion detailed in trials	Actual number of infants
Perinatal death	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Mazumder 2008; McEvoy 2010; Murphy 2008; Peltoniemi 2007; Wapner 2006	5554	RR 0.94 (0.71 to 1.23), 9 trials	Aghajafari 2002; Crowther 2006; Garite 2009; McEvoy 2010; Murphy 2008; Wapner 2006	4650	RR 0.96 (0.71 to 1.29) 6 trials, n=4650 infants	Aghajafari 2002; Crowther 2006; Garite 2009; McEvoy 2010; Murphy 2008; Wapner 2006	761
Fetal death	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Mazumder 2008; McEvoy 2010; Peltoniemi 2007	2755	RR 0.82 (0.24 to 2.84), 7 trials	Aghajafari 2002; Crowther 2006; Garite 2009; McEvoy 2010	1851	RR 1.01 (0.14 to 7.13) 4 trials, n=1851 infants	Aghajafari 2002; Crowther 2006; Garite 2009; McEvoy 2010	383
Neonatal death	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Mazumder 2008; McEvoy 2010; Peltoniemi 2007	2713	RR 0.91 (0.62 to 1.34), 7 trials	Aghajafari 2002; Crowther 2006; Garite 2009; McEvoy 2010	1828	RR 0.93 (0.58 to 1.49) 4 trials, n=1828 infants	Aghajafari 2002; Crowther 2006; Garite 2009; McEvoy 2010	382
Respiratory distress syndrome	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Mazumder 2008; McEvoy 2010; Peltoniemi 2007; Wapner 2006	3206	RR 0.83 (0.75 to 0.91), 8 trials	Aghajafari 2002; Crowther 2006; Garite 2009; McEvoy 2010; Wapner 2006	2323	RR 0.76 (0.68 to 0.86) 5 trials, n=2323 infants	Aghajafari 2002; Crowther 2006; Garite 2009; McEvoy 2010; Wapner 2006	437
Composite outcome of serious infant outcomes	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Mazumder 2008; Murphy 2008; Wapner 2006	5094	RR 0.84 (0.75 to 0.94), 7 trials	Aghajafari 2002; Crowther 2006; Garite 2009; Murphy 2008; Wapner 2006	4517	RR 0.85 (0.76 to 0.96) 5 trials, n=4517 infants	Aghajafari 2002; Crowther 2006; Garite 2009; Murphy 2008; Wapner 2006	732

*Source: Crowther (2011); ^meta-analyses conducted for these Clinical Practice Guidelines

Evidence summary for repeat antenatal corticosteroids and women with antepartum haemorrhage

Seven of ten trials included in the Crowther (2011) systematic review reported they included a proportion of women who had antepartum haemorrhage at trial entry (range 4% to 29% for the trials of a repeat antenatal corticosteroids, where reported).

For the mother

Overall, where reported in 10 trials, no differences were seen between women treated with repeat antenatal corticosteroids and women with no repeat corticosteroids in the risk for chorioamnionitis, postnatal pyrexia or puerperal sepsis.

Seven trials reported including a proportion of women with an antepartum haemorrhage. The evidence is consistent with the overall treatment effect:

- For chorioamnionitis, postnatal pyrexia and puerperal sepsis, the size of the treatment effect was the same or similar to the overall effect and there was no difference between groups.

No data were reported for pyrexia after trial entry, intrapartum pyrexia or maternal quality of life from these seven trials.

For the infant

Overall, where reported in 10 trials, there was a significant reduction in the risks for respiratory distress syndrome and a composite of serious infant outcomes. No differences were seen in the risks for perinatal death, fetal death or neonatal death between infants exposed to a repeat antenatal corticosteroids and infants with no repeat exposure.

Seven trials reported including a proportion of women with an antepartum haemorrhage. The evidence is consistent with the overall treatment effect:

- For respiratory distress syndrome and a composite of serious infant outcomes the size of the treatment effect was similar to the overall effect and there was a significant reduction in risk for infants exposed to a repeat antenatal corticosteroids compared with no repeat exposure;
- For perinatal death, fetal death and neonatal death the size of the treatment effect was similar to the overall effect and there was no difference between groups.

Evidence is based on a subset of data from trials that reported they included a proportion of women with an antepartum haemorrhage. This level of evidence cannot be used to form a clinical recommendation.

See Appendix M22– Evidence Summary (Page 396)

What is the safety for the mother, fetus, infant, child, adult of administering repeat antenatal corticosteroids to women with antepartum haemorrhage at risk of preterm birth?

Practice points:

- Repeat antenatal corticosteroids for a woman with an antepartum haemorrhage at risk of preterm birth.
- Where appropriate, monitor for signs of puerperal sepsis in women with an antepartum haemorrhage when antenatal corticosteroids have been given.

14.6 Women with a multiple pregnancy (twins and higher order)

What is the safety for the mother and fetus, infant, child, adult of administering a single course of antenatal corticosteroids to women with a multiple pregnancy (twins and higher order) with an additional risk factor(s) for preterm birth?

Single course of antenatal corticosteroids

Twelve of 26 trials in the Roberts CPG version 2015 systematic review reported that they included a small proportion of women with a multiple pregnancy (twins and higher). Not all of the trials reported the proportion (**Table 40**):

- Block (1977) proportion not reported
- Collaborative (1981) 16%
- Dexiprom (1999) 2%
- Doran (1980) 5%
- Fekih (2002) 9%
- Gamsu (1989) 12%
- Garite (1992) 8%
- Kari (1994) 20%
- Liggins (1972) 12%
- Schutte (1980) 11%
- Silver (1996) 23%
- Taeusch (1979) 11%

Women with a multiple pregnancy were not eligible for eight trials (Amorim 1999, Balci 2010, Cararach 1991, Lewis 1996, Morales 1989, Porto 2011, Qublan 2001, Shanks 2010). Having a multiple pregnancy was not a specific inclusion criterion for the trials included in the systematic review. These trials recruited women at risk of preterm birth or women, including spontaneous or planned preterm birth (Appendix J).

In the summary of the evidence we report the overall treatment effects from all trials with available data, for the primary outcomes of these Clinical Practice Guidelines, for a single course of antenatal corticosteroids. We then report on the subset of 12 trials that specifically reported that they included a proportion of women recruited into their trial with *a multiple pregnancy at risk of preterm birth.*

Maternal primary outcomes for these Clinical Practice Guidelines:

Maternal infection -

Chorioamnionitis - Overall no difference was seen in the risk for chorioamnionitis between women who had been treated with a single course of antenatal corticosteroids and those who received no antenatal corticosteroids (RR 0.90, 95%CI 0.69 to 1.17; 13 trials, n=2525 women).

- Seven trials reported they included a proportion of women with a multiple pregnancy (2% to 23%) and provided data for chorioamnionitis (Dexiprom 1999, Fekih 2002, Garite 1992, Kari 1994, Liggins 1972, Schutte 1980, Silver 1996). The size of the treatment effect was similar to the overall effect and there was no significant difference between groups (RR 0.97, 95%CI 0.71 to 1.33; 7 trials, n=1862 women) (**Table 60**).

Puerperal sepsis - Overall no difference was seen in the risk for puerperal sepsis between women who had been treated with a single course of antenatal corticosteroids and those who received no antenatal corticosteroids (RR 1.35, 95%CI 0.93 to 1.95; 8 trials, n=1003 women).

- Five trials reported they included a proportion of women with a multiple pregnancy (2% to 23%) and provided data for puerperal sepsis (Dexiprom 1999, Garite 1992, Schutte 1980, Silver 1996, Taeusch 1979). The treatment effect was similar to the overall effect but was statistically significant (RR 1.61, 95%CI 1.01 to 2.56; 5 trials, n=569 women). Three of these trials (Dexiprom 1999, Silver 1996, Taeusch 1979) used dexamethasone as the antenatal corticosteroid (**Table 60**). The confidence intervals overlap with those of the overall treatment effect which was not statistically significant.

Pyrexia after trial entry - Overall no difference was seen in the risk for pyrexia after trial entry requiring treatment between women who had been treated with a single course of antenatal corticosteroids and those who received no antenatal corticosteroids (RR 1.11, 95%CI 0.67 to 1.67; 4 trials, n=481 women).

- Two trials reported they included 11% of women with a multiple pregnancy and provided data for pyrexia after trial entry (Schutte 1980, Taeusch 1979). The size of the treatment effect was similar to the overall effect and there was no significant difference between groups (RR 1.58, 95%CI 0.94 to 2.65; 2 trials, n=219 women) (**Table 60**).

Intrapartum pyrexia - Overall no difference was seen in the risk for intrapartum pyrexia requiring treatment between women who had been treated with a single course of antenatal corticosteroids and those who received no antenatal corticosteroids (RR 0.60, 95%CI 0.15 to 2.49; 2 trials, n=319 women).

- One trial (Schutte 1980) reported that it included 11% of women with a multiple pregnancy and provided data for intrapartum pyrexia requiring treatment. The size of the treatment effect was similar to the overall effect and there was no significant difference between groups (RR 0.26, 95%CI 0.03 to 2.20; 1 trial, n=101 women) (**Table 60**).

Postnatal pyrexia - Overall no difference was seen in the risk for postnatal pyrexia requiring treatment between women who had been treated with a single course of antenatal corticosteroids and those who received no antenatal corticosteroids (RR 0.92, 95%CI 0.64 to 1.33; 5 trials, n=1323 women).

- Four trials reported they included a proportion of women with a multiple pregnancy (2% to 16%) and provided data for postnatal pyrexia requiring treatment (Collaborative 1989, Dexiprom 1999, Fekih 2002, Schutte 1980). The size of the treatment effect was similar to the overall effect and there was no significant difference between groups (RR 1.00, 95%CI 0.66 to 1.51; 4 trials, n=1105 women) (**Table 60**).

Other primary maternal outcomes for these Clinical Practice Guidelines - No data on quality of life were reported in trials of a single course of antenatal corticosteroids that reported they included a proportion of the women with a multiple pregnancy.

Infant primary outcomes for these Clinical Practice Guidelines:

Fetal, neonatal or later death -

Perinatal death - Overall there was a significant reduction in the risk for perinatal death for infants who were exposed to a single course of antenatal corticosteroids compared with no exposure (RR 0.77, 95%CI 0.67 to 0.89; 13 trials, n=3627 infants).

- Ten trials reported they included a proportion of women with a multiple pregnancy (2% to 20%, where reported) and provided data for perinatal death (Block 1977, Collaborative 1981, Dexiprom 1999, Doran 1980, Gamsu 1989, Garite 1992, Kari 1994, Liggins 1972, Schutte 1980, Taeusch 1979). The size of the treatment effect was similar to the overall effect and was statistically significant (RR 0.84, 95%CI 0.71 to 0.98; 10 trials, n=3225 infants) (**Table 61**).

Fetal death - Overall no difference was seen in the risk for fetal death between infants who were exposed to a single course of antenatal corticosteroids and those with no exposure (RR 0.98, 95%CI 0.73 to 1.30; 13 trials, n=3627 infants).

- Eleven trials reported they included a proportion of women with a multiple pregnancy (2% to 20%, where reported) and provided data for fetal death (Block 1977, Collaborative 1981, Dexiprom 1999, Doran 1980, Gamsu 1989, Garite 1992, Kari 1994, Liggins 1972, Schutte 1980, Taeusch 1979). The size of the treatment effect was similar to the overall effect and there was no significant difference between groups (RR 0.95, 95%CI 0.70 to 1.29; 10 trials, n=3225 infants) (**Table 61**).

Neonatal death - Overall there was a significant reduction in the risk for neonatal death for infants who were exposed to a single course of antenatal corticosteroids compared with no exposure (RR 0.68, 95%CI 0.58 to 0.80; 21 trials, n=4408 infants).

- Twelve trials reported they included a proportion of women with a multiple pregnancy (2% to 23%, where reported) and provided data for neonatal death (Block 1977, Collaborative 1981, Dexiprom 1999, Doran 1980, Fekih 2002, Gamsu 1989, Garite 1992, Kari 1994, Liggins 1972, Schutte 1980, Silver 1996, Taeusch 1979). The size of the treatment effect was similar to the overall effect and was statistically significant (RR 0.75, 95%CI 0.62 to 0.91; 12 trials, n=3290 infants) (**Table 61**).

Respiratory distress syndrome - Overall there was a significant reduction in the risk for respiratory distress syndrome for infants who were exposed to a single course of antenatal corticosteroids compared with no exposure (RR 0.65, 95%CI 0.58 to 0.73; 25 trials, n=4590 infants).

- Twelve trials reported they included a proportion of women with a multiple pregnancy (2% to 23%, where reported) and provided data for respiratory distress syndrome (Block 1977, Collaborative 1981, Dexiprom 1999, Doran 1980, Fekih 2002, Gamsu 1989, Garite 1992, Kari 1994, Liggins 1972, Schutte 1980, Silver 1996, Taeusch 1979). The size of the treatment effect was similar to the overall effect and was statistically significant (RR 0.69, 95%CI 0.61 to 0.79; 12 trials, n=3250 infants) (**Table 61**).

Composite of serious infant outcomes - This outcome was not reported in any of the trials of a single course of antenatal corticosteroids included in the Roberts CPG version 2015 systematic review.

Table 60: Comparison of the overall effect estimate for use of a single course of antenatal corticosteroids with trials that reported including a proportion of women with a multiple pregnancy at risk of preterm birth – Maternal primary outcomes

Primary outcome	Single course of antenatal corticosteroids			Trials known to have included a proportion of women with a multiple pregnancy at risk of preterm birth				
	Trials contributing data	Number of women	Risk ratio (RR) (95% Confidence Interval)	Trials contributing data	Number of women	Risk ratio (RR) (95% Confidence Interval)	Actual proportion detailed in trials	Actual number of women
Chorioamnionitis	Amorim 1999; Carlan 1991; Dexiprom 1999; Fekih 2002; Garite 1992; Kari 1994; Lewis 1996; Liggins 1972; Lopez 1989; Morales 1989; Qublan 2001; Schutte 1980; Silver 1996	2525	RR 0.90 (0.69 to 1.17), 13 trials	Dexiprom 1999; Fekih 2002; Garite 1992; Kari 1994; Liggins 1972; Schutte 1980; Silver 1996	1862	RR 0.97 (0.71 to 1.33) 7 trials, n=1862 women	Dexiprom 1999; Fekih 2002; Garite 1992; Kari 1994; Liggins 1972; Schutte 1980; Silver 1996	219
Puerperal sepsis	Amorim 1999; Dexiprom 1999; Garite 1992; Lewis 1996; Qublan 2001; Schutte 1980; Silver 1996; Taeusch 1979	1003	RR 1.35 (0.93 to 1.95), 8 trials	Dexiprom 1999; Garite 1992; Schutte 1980; Silver 1996; Taeusch 1979	569	RR 1.61 (1.01 to 2.56), 5 trials, n=569 women	Dexiprom 1999; Garite 1992; Schutte 1980; Silver 1996; Taeusch 1979	54
Pyrexia after trial entry requiring treatment	Amorim 1999; Nelson 1985; Schutte 1980; Taeusch 1979	481	RR 1.11 (0.67 to 1.67), 4 trials	Schutte 1980; Taeusch 1979	219	RR 1.58 (0.94 to 2.65) 2 trials, n=219 women	Schutte 1980; Taeusch 1979	24
Intrapartum pyrexia requiring treatment	Amorim 1999; Schutte 1980	319	RR 0.60 (0.15 to 2.49), 2 trials	Schutte 1980	101	RR 0.26 (0.03 to 2.20) 1 trial, n=101 women	Schutte 1980	11
Postnatal pyrexia requiring treatment	Amorim 1999; Collaborative 1981; Dexiprom 1999; Fekih 2002; Schutte 1980	1323	RR 0.92 (0.64 to 1.33), 5 trials	Collaborative 1989; Dexiprom 1999; Fekih 2002; Schutte 1980	1105	RR 1.00 (0.66 to 1.51) 4 trials, n=1105 women	Collaborative 1989; Dexiprom 1999; Fekih 2002; Schutte 1980	135

*Source: Roberts CPG version 2015 ; ^meta-analyses conducted for these Clinical Practice Guidelines

Table 61: Comparison of the overall effect estimate for use of a single course of antenatal corticosteroids with trials that reported including a proportion of women with a multiple pregnancy at risk of preterm birth – Infant primary outcomes

	Single course of antenatal corticosteroids			Trials known to have included a proportion of women with a multiple pregnancy at risk of preterm birth				
Primary outcome	**Trials contributing data**	**Number of infants**	**Risk ratio (RR) (95% Confidence Interval)**	**Trials contributing data**	**Number of infants**	**Risk ratio (RR) (95% Confidence Interval)**	**Actual proportion detailed in trials**	**Actual number of infants**
Perinatal death	Amorim 1999; Block 1977; Collaborative 1981; Dexiprom 1999; Doran 1980; Gamsu 1989; Garite 1992; Kari 1994; Liggins 1972; Parsons 1988; Qublan 2001; Schutte 1980; Taeusch 1979	3627	RR 0.77 (0.67 to 0.89), 13 trials	Block 1977; Collaborative 1981; Dexiprom 1999; Doran 1980; Gamsu 1989; Garite 1992; Kari 1994; Liggins 1972; Schutte 1980; Taeusch 1979	3225	RR 0.84 (0.71 to 0.98), 10 trials, n=3225 infants	Collaborative 1981; Dexiprom 1999; Doran 1980; Gamsu 1989; Garite 1992; Kari 1994; Liggins 1972; Schutte 1980; Taeusch 1979	382
Fetal death	Amorim 1999; Block 1977; Collaborative 1981; Dexiprom 1999; Doran 1980; Gamsu 1989; Garite 1992; Kari 1994; Liggins 1972; Parsons 1988; Qublan 2001; Schutte 1980; Taeusch 1979	3627	RR 0.98 (0.73 to 1.30), 13 trials	Block 1977; Collaborative 1981; Dexiprom 1999; Doran 1980; Gamsu 1989; Garite 1992; Kari 1994; Liggins 1972; Schutte 1980; Taeusch 1979	3225	RR 0.95 (0.70 to 1.29), 10 trials, n=3225 infants	Collaborative 1981; Dexiprom 1999; Doran 1980; Gamsu 1989; Garite 1992; Kari 1994; Liggins 1972; Schutte 1980; Taeusch 1979	382
Neonatal death	Amorim 1999; Block 1977; Collaborative 1981; Dexiprom 1999; Doran 1980; Fekih 2002; Gamsu 1989; Garite 1992; Goodner 1979; Kari 1994; Lewis 1996; Liggins 1972; Lopez 1989; Morales 1989; Nelson 1985; Parsons 1988; Porto 2011; Qublan 2001; Schutte 1980; Silver 1996; Taeusch 1979	4408	RR 0.68 (0.58 to 0.80), 21 trials	Block 1977; Collaborative 1981; Dexiprom 1999; Doran 1980; Fekih 2002; Gamsu 1989; Garite 1992; Kari 1994; Liggins 1972; Schutte 1980; Silver 1996; Taeusch 1979	3290	RR 0.75 (0.62 to 0.91), 12 trials, n=3290 infants	Collaborative 1981; Dexiprom 1999; Doran 1980; Fekih 2002; Gamsu 1989; Garite 1992; Kari 1994; Liggins 1972; Schutte 1980; Silver 1996; Taeusch 1979	397
Respiratory distress syndrome	Amorim 1999; Balci 2010; Block 1977; Cararach 1991; Carlan 1991; Collaborative 1981; Dexiprom 1999; Doran 1980; Fekih 2002; Gamsu 1989; Garite 1992; Goodner 1979; Kari 1994; Lewis 1996; Liggins 1972; Lopez 1989; Morales 1989; Nelson 1985; Parsons 1988; Porto 2011; Qublan 2001; Schutte 1980; Silver 1996; Taeusch 1979; Teramo 1980	4590	RR 0.65 (0.58 to 0.73), 25 trials	Block 1977; Collaborative 1981; Dexiprom 1999; Doran 1980; Fekih 2002; Gamsu 1989; Garite 1992; Kari 1994; Liggins 1972; Schutte 1980; Silver 1996; Taeusch 1979	3250	RR 0.69 (0.61 to 0.79), 12 trials, n=3250 infants	Collaborative 1981; Dexiprom 1999; Doran 1980; Fekih 2002; Gamsu 1989; Garite 1992; Kari 1994; Liggins 1972; Schutte 1980; Silver 1996; Taeusch 1979;	391

*Source: Roberts CPG version 2015 ; ^meta-analyses conducted for these Clinical Practice Guidelines

Evidence summary for the use of a single course of antenatal corticosteroids for women with a multiple pregnancy with an additional risk factor(s) for preterm birth

Twelve of the 26 trials included in the Roberts CPG version 2015 systematic review reported including a proportion of women with a multiple pregnancy in their trials (range 2% to 23%) who were at risk of imminent preterm birth.

For the mother

Overall, where reported in 26 trials, no differences were seen between women treated with a single course of antenatal corticosteroids and women with no corticosteroids in the risk for chorioamnionitis, pyrexia after trial entry, intrapartum pyrexia, postnatal pyrexia or puerperal sepsis.

Twelve trials reported including a proportion of women with a multiple pregnancy at risk of preterm birth.

- For chorioamnionitis, pyrexia after trial entry, intrapartum pyrexia and postnatal pyrexia the size of the treatment effect was similar to the overall effect and there was no difference between groups;
- For puerperal sepsis the direction of the treatment effect was similar to the overall effect and was statistically significant. However, the confidence intervals overlap with those of the overall treatment effect which was not statistically significant.

No data were reported for maternal quality of life in any of the 26 trials included in the Roberts CPG version 2015 systematic review.

For the infant

Overall, where reported in 26 trials, there was a significant reduction in the risks for perinatal death, neonatal death and respiratory distress syndrome. No difference was seen in the risk for fetal death between infants exposed to a single course of antenatal corticosteroids and infants with no exposure.

Twelve trials reported including a proportion of women with a multiple pregnancy at risk of preterm birth. The evidence is consistent with the overall treatment effect:

- For perinatal death, neonatal death and respiratory distress syndrome the size of the treatment effect was similar to the overall effect and the difference was statistically significant for infants exposed to a single course of antenatal corticosteroids compared with no exposure.
- For fetal death the size of the treatment effect was similar to the overall effect and there was no difference between groups.

No data were reported for a composite of serious infant outcomes in any of the trials included in the Roberts CPG version 2015 systematic review.

Evidence is based on a subset of data from trials that reported they included a proportion of women with a multiple pregnancy at risk of preterm birth. This level of evidence cannot be used to form clinical recommendations.

See Appendix M23- Evidence Summary (Page 400)

What is the safety for the mother and fetus, infant, child, adult of administering a single course of antenatal corticosteroids to women with a multiple pregnancy (twins and higher order) with an additional risk factor(s) for preterm birth?

Practice points:

- Use a single course of antenatal corticosteroids for women with a multiple pregnancy with an additional risk factor(s) for preterm birth.
- Where appropriate, estimate the risk of preterm birth by considering the use of adjunct prediction tests including fetal fibronectin and assessment of cervical length. Where appropriate, monitor women with a multiple pregnancy at risk of preterm birth for signs of puerperal sepsis when antenatal corticosteroids have been given.

What is the safety for the mother and fetus, infant, child, adult of administering repeat antenatal corticosteroids to women with a multiple pregnancy (twins and higher order) with an additional risk factor(s) for preterm birth?

Repeat antenatal corticosteroids

Nine of ten trials in the Crowther (2011) systematic review of repeat antenatal corticosteroids '*Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes*' reported that they included a proportion of women with a multiple pregnancy (**Table 41**):

- Aghajafari (2002) 34%
- Crowther (2006) 16%
- Garite (2009) 32%
- Guinn (2001) 7%
- Mazumder (2008) proportion not reported
- McEvoy (2010) 33%
- Murphy (2008) 11%
- Peltoniemi (2007) 29%
- Wapner (2006) 20%

Garite (2009) and McEvoy (2010) included a twin pregnancy but triplets and higher order pregnancies were not eligible for inclusion. Women with a multiple pregnancy were not eligible for the McEvoy (2002) trial. McEvoy (2002) excluded women with a multiple pregnancy (Appendix K). No additional new trials were identified in the Crowther CPG version 2015.

Having a multiple pregnancy was not a specific inclusion criterion for the trials reported in the Crowther (2011) systematic review. The inclusion criteria included having previously received a single course of antenatal corticosteroids with a continued risk of preterm birth.

In the summary of the evidence we report the overall treatment effects from all trials with available data, for the primary outcomes of these Clinical Practice Guidelines, for repeat antenatal corticosteroids. We then report on the subset of nine trials that specifically reported that they included a proportion of women recruited into their trial with *a multiple pregnancy at risk of preterm birth.*

Maternal primary outcomes for these Clinical Practice Guidelines:

Maternal infection -

Chorioamnionitis - Overall no difference was seen in the risk for chorioamnionitis between women who had been treated with repeat antenatal corticosteroids and those with no repeat treatment (RR 1.16, 95%CI 0.92 to 1.46; 6 trials, n=4261 women). These trials all reported including a proportion of women with a multiple pregnancy (11% to 34%) with an additional risk factor of preterm birth (**Table 62**).

Puerperal sepsis - Overall no difference was seen in the risk for puerperal sepsis between women who had been treated with repeat antenatal corticosteroids and those with no repeat treatment (RR 1.15, 95%CI 0.83 to 1.60; 5 trials, n=3091 women). All these trials reported including a proportion of women with a multiple pregnancy (11% to 34%) with an additional risk factor of preterm birth (**Table 62**).

Postnatal pyrexia - Overall no difference was seen in the risk for postnatal pyrexia requiring treatment between women who had been treated with repeat antenatal corticosteroids and those with no repeat treatment (RR 0.87, 95%CI 0.55 to 1.38; 1 trial, n=982 women). Evidence is based on a single trial

(Crowther 2006) that included 16% of women with a multiple pregnancy with an additional risk factor of preterm birth (**Table 62**).
No data were reported for pyrexia after trial entry or intrapartum pyrexia requiring treatment.

Other primary maternal outcomes for these Clinical Practice Guidelines - No data on quality of life were reported in the trials included in the Crowther (2011) systematic review that recruited and reported a proportion of the women with a multiple pregnancy with an additional risk of preterm birth.

Infant primary outcomes for these Clinical Practice Guidelines

Fetal, neonatal or later death -

Perinatal death - Overall no difference was seen in the risk for perinatal death between women who had been treated with repeat antenatal corticosteroids and those with no repeat treatment (RR 0.94, 95%CI 0.71 to 1.23; 9 trials, n=5554 women). All these trials reported including a proportion of women with a multiple pregnancy (7% to 34%) with an additional risk factor of preterm birth (**Table 63**).

Fetal death - Overall no difference was seen in the risk for fetal death between women who had been treated with repeat antenatal corticosteroids and those with no repeat treatment (RR 0.82, 95%CI 0.24 to 2.84; 7 trials, n=2755 women). All these trials reported including a proportion of women with a multiple pregnancy (7% to 34%) with an additional risk factor of preterm birth (**Table 63**).

Neonatal death - Overall no difference was seen in the risk for neonatal death between women who had been treated with repeat antenatal corticosteroids and those with no repeat treatment (RR 0.91, 95%CI 0.62 to 1.34; 7 trials, n=2713 women). All these trials reported including a proportion of women with a multiple pregnancy (7% to 34%) with an additional risk factor of preterm birth (**Table 63**).

Respiratory distress syndrome - Overall there was a significant reduction in the risk for respiratory distress syndrome for infants exposed to repeat antenatal corticosteroids compared with no repeat exposure (RR 0.83, 95%CI 0.75 to 0.91; 8 trials, n=3206 infants). All these trials reported including a proportion of women with a multiple pregnancy (7% to 34%) with an additional risk factor of preterm birth (**Table 63**).

Composite of serious infant outcomes - Overall there was a significant reduction in the risk for a composite of serious infant outcomes for infants exposed to repeat antenatal corticosteroids compared with no repeat exposure (RR 0.84, 95%CI 0.75 to 0.94; 7 trials, n=3959 infants). All these trials reported including a proportion of women with a multiple pregnancy (7% to 34%) with an additional risk factor of preterm birth (**Table 63**).

Table 62: Comparison of the overall effect estimate for use of repeat antenatal corticosteroids with trials that reported including a proportion of women with multiple pregnancy at risk of preterm birth – Maternal primary outcomes

Primary outcome	Repeat course of antenatal corticosteroids and trials known to have included a proportion of women with a multiple pregnancy at risk of preterm birth*				
	Trials contributing data	Number of women	Risk ratio (RR) (95% Confidence Interval)	Actual proportion detailed in trials	Actual number of women
Chorioamnionitis	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Murphy 2008; Wapner 2006	4261	RR 1.16 (0.92 to 1.46), 6 trials, n=4261 women	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Murphy 2008; Wapner 2006	637
Puerperal sepsis	Aghajafari 2002; Guinn 2001; Murphy 2008; Peltoniemi 2007; Wapner 2006	3091	RR 1.15 (0.83 to 1.60), 5 trials, n=3091 women	Aghajafari 2002; Guinn 2001; Murphy 2008; Peltoniemi 2007; Wapner 2006	412
Pyrexia after trial entry requiring treatment	NR	NR	NR	-	-
Intrapartum pyrexia requiring treatment	NR	NR	NR	-	-
Postnatal pyrexia requiring treatment	Crowther 2006	982	RR 0.87 (0.55 to 1.38), 1 trial, n=982 women	Crowther 2006	157

*Source: Crowther (2011)

Table 63: Comparison of the overall effect estimate for use of repeat antenatal corticosteroids with trials that reported including a proportion of women with multiple pregnancy at risk of preterm birth – Infant primary outcomes

Primary outcome	Repeat course of antenatal corticosteroids and trials that included a proportion of women with a multiple pregnancy at risk of preterm birth*				
	Trials contributing data	Number of infants	Risk ratio (RR) (95% Confidence Interval)	Actual proportion detailed in trials	Actual number of infants
Perinatal death	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Mazumder 2008; McEvoy 2010; Murphy 2008; Peltoniemi 2007; Wapner 2006	5554	RR 0.94 (0.71 to 1.23), 9 trials, n=5554 infants	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; McEvoy 2010; Murphy 2008; Peltoniemi 2007; Wapner 2006	865
Fetal death	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Mazumder 2008; McEvoy 2010; Peltoniemi 2007	2755	RR 0.82 (0.24 to 2.84), 7 trials, n=2755 infants	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; McEvoy 2010; Peltoniemi 2007	513
Neonatal death	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Mazumder 2008; McEvoy 2010; Peltoniemi 2007	2713	RR 0.91 (0.62 to 1.34), 7 trials, n=2713 infants	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; McEvoy 2010; Peltoniemi 2007	505
Respiratory distress syndrome	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Mazumder 2008; McEvoy 2010; Peltoniemi 2007; Wapner 2006	3206	RR 0.83 (0.75 to 0.91), 8 trials , n=3206 infants	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; McEvoy 2010; Peltoniemi 2007; Wapner 2006	604
Composite outcome of serious infant outcomes	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Mazumder 2008; Murphy 2008; Wapner 2006	3959	RR 0.84 (0.75 to 0.94), 7 trials, n=3959 infants	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Murphy 2008; Wapner 2006	754

*Source: (Crowther 2011)

Evidence summary for the use of repeat antenatal corticosteroids for women with a multiple pregnancy at risk of imminent preterm birth

Nine of 10 trials in the Crowther (2011) systematic review reported including a proportion of women in their trials who had a multiple pregnancy at risk of preterm birth (range 7% to 34% where reported).

For the mother

Overall, where reported in 10 trials, no differences were seen between women treated with repeat antenatal corticosteroids and women with no repeat corticosteroids in the risk for chorioamnionitis, postnatal pyrexia or puerperal sepsis.

Nine trials reported including a proportion of women with a multiple pregnancy at risk of preterm birth. The evidence is consistent with the overall treatment effect:

- For chorioamnionitis, postnatal pyrexia and puerperal sepsis, the size of the treatment effect was the same or similar to the overall effect and there was no difference between groups.

No data were reported for pyrexia after trial entry, intrapartum pyrexia or maternal quality of life from these seven trials.

For the infant

Overall, where reported in 10 trials, there was a significant reduction in the risks for respiratory distress syndrome and a composite of serious infant outcomes. No differences were seen in the risks for perinatal death, fetal death and neonatal death between infants exposed to a repeat antenatal corticosteroids and infants with no repeat exposure.

Nine trials reported including a proportion of women with a multiple pregnancy at risk of preterm birth. The evidence is consistent with the overall treatment effect:

- For respiratory distress syndrome and a composite of serious infant outcomes the size of the treatment effect was similar to the overall effect and there was a significant reduction in risk for infants exposed to a repeat antenatal corticosteroids compared with no repeat exposure;
- For perinatal death, fetal death and neonatal death the size of the treatment effect was similar to the overall effect and there was no difference between groups.

Evidence is based on a subset of data from trials that reported they included a proportion of women with a multiple pregnancy at risk of preterm birth. This level of evidence cannot be used to form a clinical recommendation.

See Appendix M24 – Evidence Summary (Page 404)

What is the safety for the mother and fetus, infant, child, adult of administering repeat antenatal corticosteroids to women with a multiple pregnancy (twins and higher order) with an additional risk factor(s) for preterm birth?

Practice points:

- Repeat antenatal corticosteroids for a woman with a multiple pregnancy with an additional risk factor(s) for preterm birth
- Where appropriate, estimate the risk of preterm birth by considering the use of adjunct prediction tests including fetal fibronectin and assessment of cervical length. Where appropriate, monitor women with a multiple pregnancy at risk of preterm birth for signs of puerperal sepsis when antenatal corticosteroids have been given.

What is the safety for the mother and fetus, infant, child, adult of administering a single course of antenatal corticosteroids to women with a multiple pregnancy (twins and higher order) prophylactically (with no additional risk factor(s) for preterm birth)?

Single course of antenatal corticosteroids

Maternal primary outcomes for these Clinical Practice Guidelines:

There was no randomised controlled trial evidence reported for maternal primary outcomes for these Clinical Practice Guidelines for the use of prophylactic antenatal corticosteroids in women with a multiple pregnancy with no additional risk of preterm birth. These women were not eligible for inclusion in the randomised trials included in the Roberts CPG version 2015 systematic review (Appendix J).

Infant primary outcomes for these Clinical Practice Guidelines:

There was no randomised controlled trial evidence reported for infant primary outcomes for these Clinical Practice Guidelines for exposure to prophylactic antenatal corticosteroids where the mother had a multiple pregnancy with no additional risk of preterm birth. These women were not eligible for inclusion in the randomised trials included in Roberts CPG version 2015 systematic review (Appendix J).

Evidence summary for the use of a single course of prophylactic antenatal corticosteroids for women with a multiple pregnancy with no additional risk of preterm birth

There was no randomised controlled trial evidence for prophylactic antenatal corticosteroids in women with a multiple pregnancy with no additional risk of preterm birth.

There is an absence of both short and long term neonatal and childhood follow-up data reported for exposure prophylactic use of antenatal corticosteroids in a multiple pregnancy where there is no additional risk of preterm birth.

See Appendix M25 Evidence Summary (Page 408)

What is the safety for the mother and fetus, infant, child, adult of administering a single course of antenatal corticosteroids to women with a multiple pregnancy (twins and higher order) prophylactically (with no additional risk factor(s) for preterm birth)?

Practice Point:

- Do not use a single course of antenatal corticosteroids in women with a multiple pregnancy where there is no other identified risk of preterm birth.

Research recommendation:

- In settings where prophylactic antenatal corticosteroids are being used in women with a multiple pregnancy, with no other identified risk of preterm birth, there is a need for a randomised trial.

What is the safety for the mother and fetus, infant, child, adult of administering a single course or a repeat course(s) of antenatal corticosteroids to women with a multiple pregnancy (twins and higher order) prophylactically (with no additional risk factor(s) for preterm birth)?

Repeat antenatal corticosteroids

Maternal primary outcomes for these Clinical Practice Guidelines:

There was no randomised controlled trial evidence reported for maternal primary outcomes for these Clinical Practice Guidelines for the use of prophylactic antenatal corticosteroids in women with a multiple pregnancy with no additional risk of preterm birth. These women were not eligible for inclusion in the randomised trials included in the Crowther (2011) systematic review (Appendix K).

Infant primary outcomes for these Clinical Practice Guidelines:

There was no randomised controlled trial evidence reported for infant primary outcomes for these Clinical Practice Guidelines for the use of prophylactic antenatal corticosteroids in women with a multiple pregnancy with no additional risk of preterm birth. These women were not eligible for inclusion in the randomised trials included in the Crowther (2011) systematic review (Appendix K).

Evidence summary for the use of repeat prophylactic antenatal corticosteroids for women with a multiple pregnancy with no additional risk of preterm birth

There was no randomised controlled trial evidence for prophylactic antenatal corticosteroids in women with a multiple pregnancy with no additional risk of preterm birth.

There is an absence of both short and long term neonatal and childhood follow-up data reported for exposure prophylactic use of antenatal corticosteroids in a multiple pregnancy where there is no additional risk of preterm birth.

See Appendix M26 – Evidence Summary (Page 412)

What is the safety for the mother and fetus, infant, child, adult of administering a single course or a repeat course(s) of antenatal corticosteroids to women with a multiple pregnancy (twins and higher order) prophylactically (with no additional risk factor(s) for preterm birth)?

Practice Point:

- Do not use repeat antenatal corticosteroids in women with a multiple pregnancy where there is no other identified risk of preterm birth.

Research recommendation:

- In settings where prophylactic antenatal corticosteroids are being used in women with a multiple pregnancy, with no other identified risk of preterm birth, there is a need for a randomised trial.

14.7 Women with diabetes mellitus or gestational diabetes at risk of preterm birth

What is the safety for the mother of administering a single course of antenatal corticosteroids to women with diabetes mellitus or gestational diabetes at risk of preterm birth?

What is the safety for the fetus, infant, child, adult of administering a single course of antenatal corticosteroids to women with diabetes mellitus or gestational diabetes at risk of preterm birth?

Single course of antenatal corticosteroids –

Five trials in the Roberts CPG version 2015 systematic review reported they had included a very small proportion of women with diabetes in pregnancy (**Table 40**):

- Amorim (1999) 18%
- Doran (1980) 4%
- Porto (2011) 2%
- Shanks (2010) 16%
- Taeusch (1979) 5%

Four of these trials did not specify details on the type of diabetes (Doran 1980, Porto 2011, Shanks 2010, Taeusch 1979). One trial (Amorim 1999) recruited and reported women with gestational diabetes (18%).

Women with diabetes mellitus were not eligible for two trials (Amorim 1999, Balci 2010), women with insulin treated diabetes were not eligible for one trial (Kari 1994), and women with gestational diabetes were not eligible for one trial (Fekih 2002). The remaining trials in which women with diabetes pre-specified as not being eligible did not specify the type of diabetes (Fekih 2002, Gamsu 1989, Garite 1992, Schutte 1980, Teramo 1980). Diabetes was not an inclusion criterion for participation in these trials of a single course of antenatal corticosteroids. The main criterion for inclusion was risk of preterm birth (Appendix J).

In the summary of the evidence we report the overall treatment effects from all trials with available data, for the primary outcomes of these Clinical Practice Guidelines, for a single course of antenatal corticosteroids. We then report on the subset of five trials that specifically reported that they included a proportion of women recruited into their trial with *diabetes in pregnancy*.

Maternal primary outcomes for these Clinical Practice Guidelines -

Maternal infection -

Chorioamnionitis - Overall no difference was seen in the risk for chorioamnionitis between women who had been treated with a single course of antenatal corticosteroids and those who received no antenatal corticosteroids (RR 0.90, 95%CI 0.69 to 1.17; 13 trials, n=2525 women).

- One trial (Amorim 1999) reported that it included 18% of women with gestational diabetes and provided data for chorioamnionitis. The treatment effect was in the opposite direction to the overall effect but there was no significant difference between groups (RR 1.96, 95%CI 0.18 to 21.34; 1 trial, n=218 women) (**Table 64**).

Puerperal sepsis - Overall no difference was seen in the risk for puerperal sepsis between women who had been treated with a single course of antenatal corticosteroids and those who received no antenatal corticosteroids (RR 1.35, 95%CI 0.93 to 1.95; 8 trials, n=1003 women).

- Two trials reported including a proportion of women with diabetes in pregnancy (5% to 18%) and provided data for puerperal sepsis (Amorim 1999, Taeusch 1979). The size of the treatment

effect was similar to the overall effect and there was no significant difference between groups (RR 1.10, 95%CI 0.62 to 1.95; 2 trials, n=336 women) (**Table 64**).

Pyrexia after trial entry - Overall no difference was seen in the risk for pyrexia after trial entry requiring treatment between women who had been treated with a single course of antenatal corticosteroids and those who received no antenatal corticosteroids (RR 1.11, 95%CI 0.67 to 1.67; 4 trials, n=481 women).

- Two trials reported including a proportion of women with diabetes in pregnancy (5% to 18%) and provided data for pyrexia after trial entry (Amorim 1999, Taeusch 1979). The size of the treatment effect was similar to the overall effect and there was no significant difference between groups (RR 1.34, 95%CI 0.86 to 2.11; 2 trials, n=336 women) (**Table 64**).

Intrapartum pyrexia - Overall no difference was seen in the risk for intrapartum pyrexia requiring treatment between women who had been treated with a single course of antenatal corticosteroids and those who received no antenatal corticosteroids (RR 0.60, 95%CI 0.15 to 2.49; 2 trials, n= 319 women).

- One trial (Amorim 1999) reported that it included 18% of women with gestational diabetes and provided data for intrapartum pyrexia. The direction of the treatment effect was opposite to the overall effect and there was no significant difference between groups (RR 1.96, 95%CI 0.18 to 21.34; 1 trial, n=218 women) (**Table 64**).

Postnatal pyrexia - Overall no difference was seen in the risk for postnatal pyrexia requiring treatment between women who had been treated with a single course of antenatal corticosteroids and those who received no antenatal corticosteroids (RR 0.92, 95%CI 0.64 to 1.33; 5 trials, n=1323 women).

- One trial (Amorim 1999) reported that it included 18% of women with gestational diabetes and provided data for postnatal pyrexia. The size of the treatment effect was similar to the overall effect and there was no significant difference between groups (RR 0.68, 95%CI 0.30 to 1.52; 1 trial, n=218 women) (**Table 64**).

Other primary maternal outcomes for these Clinical Practice Guidelines - No data on quality of life were reported in the trials included in the Roberts CPG version 2015 systematic review.

Other relevant secondary outcomes of these Clinical Practice Guidelines - These Clinical Practice Guidelines provided additional data for maternal hyperglycaemia following treatment with antenatal corticosteroids.

As detailed in Chapter 3 of these Clinical Practice Guidelines, only one of 26 trials included in the Roberts CPG version 2015 systematic review reported on glucose intolerance in women with severe preeclampsia following a single course of antenatal corticosteroids (Amorim 1999). The trial included 18% of women had gestational diabetes and reported a significant increase in maternal blood glucose (RR 2.71, 95%CI 1.14 to 6.46, 1 trial, n=123). Only 62% of women randomised had blood glucose concentrations assessed. No analysis was conducted to compare outcomes for women with gestational diabetes and those without gestational diabetes. The evidence is based on a single trial with a small number of women with a major comorbidity (severe preeclampsia). The analysis should be interpreted with caution due to wide confidence intervals suggesting imprecision.

Infant primary outcomes for these Clinical Practice Guidelines:

Fetal, neonatal or later death -

Perinatal death - Overall there was a significant reduction in the risk for perinatal death for infants who were exposed to a single course of antenatal corticosteroids compared with no exposure (RR 0.77, 95%CI 0.67 to 0.89; 13 trials, n=3627 infants).

- Three trials reported they included a proportion of women with diabetes in pregnancy (4% to 18%) and provided data for perinatal death (Amorim 1999, Doran 1980, Taeusch 1979). The size of the treatment effect was similar to the overall effect and was statistically significant (RR 0.63, 95%CI 0.44 to 0.89; 3 trials, n=489 infants) (**Table 65**).

Fetal death - Overall no difference was seen in the risk for fetal death between infants who were exposed to a single course of antenatal corticosteroids and those with no exposure (RR 0.98, 95%CI 0.73 to 1.30; 13 trials, n=3627 infants).

- Three trials reported they included a proportion of women with diabetes in pregnancy (4% to 18%) and provided data for perinatal death (Amorim 1999, Doran 1980, Taeusch 1979). The size of the treatment effect was similar to the overall effect and there was no significant difference between groups (RR 0.99, 95%CI 0.47 to 2.06; 3 trials, n=489 infants) (**Table 65**).

Neonatal death - Overall there was a significant reduction in the risk for neonatal death for infants who were exposed to a single course of antenatal corticosteroids compared with no exposure (RR 0.68, 95%CI 0.58 to 0.80; 21 trials, n=4408 infants).

- Four trials reported they included a proportion of women with diabetes in pregnancy (2% to 18%) and provided data for neonatal death. The size of the treatment effect was similar to the overall effect and was statistically different (RR 0.52, 95%CI 0.34 to 0.79; 4 trials, n=783 infants) (**Table 65**).

***Respiratory distress syndrome* -** Overall there was a significant reduction in the risk for respiratory distress syndrome for infants who were exposed to a single course of antenatal corticosteroids compared with no exposure (RR 0.65, 95%CI 0.58 to 0.73; 25 trials, n=4590 infants).

- Four trials reported they included a proportion of women with diabetes in pregnancy (2% to 18%) and provided data for respiratory distress syndrome. The size of the treatment effect was similar to the overall effect and was statistically significant (RR 0.54, 95%CI 0.38 to 0.76; 4 trials, n=783 infants) (**Table 65**).

***Composite of serious infant outcomes* -** This outcome was not reported in any of the trials of a single course of antenatal corticosteroids.

Table 64: Comparison of the overall effect estimate for use of a single course of antenatal corticosteroids with trials that reported including a proportion of women with diabetes mellitus or gestational diabetes – Maternal primary outcomes*

Primary outcome	Single course of antenatal corticosteroids			Trials known to have included a proportion of women with diabetes mellitus or gestational diabetes^				
	Trials contributing data	Number of women	Risk ratio (RR) (95% Confidence Interval)	Trials contributing data	Number of women	Risk ratio (RR) (95% Confidence Interval)	Actual proportion detailed in trials	Actual number of women
Chorioamnionitis	Amorim 1999; Carlan 1991; Dexiprom 1999; Fekih 2002; Garite 1992; Kari 1994; Lewis 1996; Liggins 1972; Lopez 1989; Morales 1989; Qublan 2001; Schutte 1980; Silver 1996	2525	RR 0.90 (0.69 to 1.17), 13 trials	Amorim 1999	218	RR 1.96 (0.18 to 21.34) 1 trial, n=218 women	Amorim 1999	39
Puerperal sepsis	Amorim 1999; Dexiprom 1999; Garite 1992; Lewis 1996; Qublan 2001; Schutte 1980; Silver 1996; Taeusch 1979	1003	RR 1.35 (0.93 to 1.95), 8 trials	Amorim 1999; Taeusch 1979	336	RR 1.10 (0.62 to 1.95) 2 trials, n=336 women	Amorim 1999; Taeusch 1979	45
Pyrexia after trial entry requiring treatment	Amorim 1999; Nelson 1985; Schutte 1980; Taeusch 1979	481	RR 1.11 (0.67 to 1.67), 4 trials	Amorim 1999; Taeusch 1979	336	RR 1.34 (0.86 to 2.11) 2 trials, n=336 women	Amorim 1999; Taeusch 1979	45
Intrapartum pyrexia requiring treatment	Amorim 1999; Schutte 1980	319	RR 0.60 (0.15 to 2.49), 2 trials	Amorim 1999	218	RR 1.96 (0.18 to 21.34) 1 trial, n=218 women	Amorim 1999	39
Postnatal pyrexia requiring treatment	Amorim 1999; Collaborative 1981; Dexiprom 1999; Fekih 2002; Schutte 1980	1323	RR 0.92 (0.64 to 1.33), 5 trials	Amorim 1999	218	RR 0.68 (0.30 to 1.52) 1 trial, n=218 women	Amorim 1999	39

*Source : Roberts CPG version 2015; ^meta-analyses conducted for these Clinical Practice Guidelines

Table 65: Comparison of the overall effect estimate for use of a single course of antenatal corticosteroids with trials that reported including a proportion of women with diabetes mellitus or gestational diabetes – Infant primary outcomes*

Primary outcome	Single course of antenatal corticosteroids			Trials known to have included a proportion of women with diabetes mellitus or gestational diabetes^				
	Trials contributing data	Number of infants	Risk ratio (RR) (95% Confidence Interval)	Trials contributing data	Number of infants	Risk ratio (RR) (95% Confidence Interval)	Actual proportion detailed in trials	Actual number of infants
Perinatal death	Amorim 1999; Block 1977; Collaborative 1981; Dexiprom 1999; Doran 1980; Gamsu 1989; Garite 1992; Kari 1994; Liggins 1972; Parsons 1988; Qublan 2001; Schutte 1980; Taeusch 1979	3627	RR 0.77 (0.67 to 0.89), 13 trials	Amorim 1999; Doran 1980; Taeusch 1979	489	RR 0.63 (0.44 to 0.89) 3 trials, n=489 infants	Amorim 1999; Doran 1980; Taeusch 1979	51
Fetal death	Amorim 1999; Block 1977; Collaborative 1981; Dexiprom 1999; Doran 1980; Gamsu 1989; Garite 1992; Kari 1994; Liggins 1972; Parsons 1988; Qublan 2001; Schutte 1980; Taeusch 1979	3627	RR 0.98 (0.73 to 1.30), 13 trials	Amorim 1999; Doran 1980; Taeusch 1979	489	RR 0.99 (0.47 to 2.06) 3 trials, n=489 infants	Amorim 1999; Doran 1980; Taeusch 1979	51
Neonatal death	Amorim 1999; Block 1977; Collaborative 1981; Dexiprom 1999; Doran 1980; Fekih 2002; Gamsu 1989; Garite 1992; Goodner 1979; Kari 1994; Lewis 1996; Liggins 1972; Lopez 1989; Morales 1989; Nelson 1985; Parsons 1988; Porto 2011; Qublan 2001; Schutte 1980; Silver 1996; Taeusch 1979	4408	RR 0.68 (0.58 to 0.80), 21 trials	Amorim 1999; Doran 1980; Porto 2011; Taeusch 1979	783	RR 0.52 (0.34 to 0.79) 4 trials, n=783 infants	Amorim 1999; Doran 1980; Porto 2011; Taeusch 1979	51
Respiratory distress syndrome	Amorim 1999; Balci 2010; Block 1977; Cararach 1991; Carlan 1991; Collaborative 1981; Dexiprom 1999; Doran 1980; Fekih 2002; Gamsu 1989; Garite 1992; Goodner 1979; Kari 1994; Lewis 1996; Liggins 1972; Lopez 1989; Morales 1989; Nelson 1985; Parsons 1988; Porto 2011; Qublan 2001; Schutte 1980; Silver 1996; Taeusch 1979; Teramo 1980	4590	RR 0.65 (0.58 to 0.73), 25 trials	Amorim 1999; Doran 1980; Porto 2011; Taeusch 1979	783	RR 0.54 (0.38 to 0.76) 4 trials n=783 infants	Amorim 1999; Doran 1980; Porto 2011; Taeusch 1979	51

*Source: Roberts CPG version 2015; ^meta-analyses conducted for these Clinical Practice Guidelines

Evidence Summary for the use of a single course of antenatal corticosteroids in women with diabetes mellitus or gestational diabetes at risk of preterm birth

Five of 26 trials included in the Roberts CPG version 2015 systematic review reported including a proportion of women in their trials who had diabetes in pregnancy and were at risk of preterm birth. The proportion of women recruited with diabetes in pregnancy ranged from 2% to 18% for the trials of a single course of antenatal corticosteroids, where reported.

For the mother

Overall, where reported in 26 trials, no differences were seen between women treated with a single course of antenatal corticosteroids and women with no corticosteroids in the risk for chorioamnionitis, pyrexia after trial entry, intrapartum pyrexia, postnatal pyrexia or puerperal sepsis.

Five trials reported including a proportion of women with diabetes in pregnancy.

- For pyrexia after trial entry, postnatal pyrexia and puerperal sepsis the size of the treatment effect was similar to the overall effect and there was no significant difference between groups;
- For chorioamnionitis and intrapartum pyrexia the treatment effect was in the opposite direction to the overall effect but there was no significant difference between groups;
- There was a significant increase in maternal blood glucose ≥72 hours following administration of antenatal corticosteroids in a single trial of women with severe pre-eclampsia.

No data were reported for maternal quality of life in any of the 26 trials included in the Roberts CPG version 2015 systematic review.

For the infant

Overall, where reported in 26 trials, there was a significant reduction in the risks for perinatal death, neonatal death and respiratory distress syndrome. No difference was seen in the risk for fetal death between infants exposed to a single course of antenatal corticosteroids and infants with no exposure.

Five trials reported including a proportion of women with diabetes in pregnancy. The evidence is consistent with the overall treatment effect:

- For perinatal death, neonatal death and respiratory distress syndrome the size of the treatment effect was similar to the overall effect and the difference was statistically significant for infants exposed to a single course of antenatal corticosteroids compared with no exposure.
- For fetal death the size of the treatment effect was similar to the overall effect and there was no difference between groups.

No data were reported for a composite of serious infant outcomes in any of the trials included in the Roberts CPG version 2015 systematic review.

The presence of maternal diabetes in pregnancy is not a reason to withhold antenatal corticosteroids where there is a risk of preterm birth. These women will require blood glucose monitoring and management of hyperglycaemia as per local protocols.

Evidence is based on a subset of data from trials that reported they included a proportion of women with diabetes in pregnancy. This level of evidence cannot be used to form a clinical recommendation.

See Appendix M27 - Evidence Summary (Page 416)

What is the safety for the mother, fetus, infant, child, adult of administering a single course of antenatal corticosteroids to women with diabetes mellitus or gestational diabetes at risk of preterm birth?

Practice Points:

- Use a single course of antenatal corticosteroids for women with diabetes in pregnancyor gestational diabetes at risk of preterm birth.
- Where appropriate, monitor women with diabetes in pregnancy or gestational diabetes at risk of preterm birth for signs of puerperal sepsis when antenatal corticosteroids have been given.

Research recommendation:

- Future randomised trials of antenatal corticosteroids should review the effect on maternal glucose tolerance.

What is the safety for the mother of administering repeat antenatal corticosteroids to women with diabetes mellitus or gestational diabetes at risk of preterm birth?

What is the safety for the fetus, infant, child, adult of administering repeat antenatal corticosteroids to women with diabetes mellitus or gestational diabetes at risk of preterm birth?

Repeat antenatal corticosteroids

Four of ten trials included in the in the Crowther (2011) Cochrane systematic review '*Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes*' reported they had included a very small proportion of women with diabetes in pregnancy (**Table 41**):

- Guinn (2002) 0% (no women had diabetes in pregnancy)
- McEvoy (2010) 9%
- Murphy (2008) 5%
- Peltoniemi (2007) 10%

McEvoy (2010) included women with gestational diabetes, Murphy (2008) included women with diet controlled and insulin dependent diabetes and Peltoniemi (2007) included women with gestational diabetes and insulin dependent diabetes.

Women with insulin dependent diabetes were not eligible for three trials (McEvoy 2002, McEvoy 2010, Wapner 2006). Diabetes was not an inclusion criterion for participation in these trials of a repeat course of antenatal corticosteroids. The main criterion for inclusion was having already received a single course of antenatal corticosteroids and continued risk of preterm birth (Appendix K). No additional trials were identified in the Crowther CPG version 2015.

In the summary of the evidence we report the overall treatment effects from all trials with available data, for the primary outcomes of these Clinical Practice Guidelines, for repeat antenatal corticosteroids. We then report on the subset of four trials that specifically reported that they included a proportion of women recruited into their trial with *diabetes in pregnancy*.

Maternal primary outcomes for these Clinical Practice Guidelines -

Maternal infection -

Chorioamnionitis - Overall no difference was seen in the risk for chorioamnionitis between women who had been treated with repeat antenatal corticosteroids and those with no repeat treatment (RR 1.16, 95%CI 0.92 to 1.46; 6 trials, n=4261 women).

- Only one trial reported including a proportion of women with diabetes in pregnancy (5%) and provided data for chorioamnionitis (Murphy 2008). The size of the treatment effect was similar to the overall effect and there was no significant difference between groups (RR 1.08, 95%CI 0.59 to 1.97; 1 trial, n=1853 women) (**Table 66**). Murphy (2008) included insulin and diet controlled diabetes (no further details).

Puerperal sepsis - Overall no difference was seen in the risk for puerperal sepsis between women who had been treated with repeat antenatal corticosteroids and those with no repeat treatment (RR 1.15, 95%CI 0.83 to 1.60; 5 trials, n=3091 women).

- Two trials reported they included a proportion of women with diabetes in pregnancy (5% to 10%) and provided data for puerperal sepsis (Murphy 2008, Peltoniemi, 2007). The size of the treatment effect was similar to the overall effect and there was no significant difference between groups (RR 1.41, 95%CI 0.94 to 2.12; 2 trials, n=2102 women) (**Table 66**). Peltoniemi (2007) included women

with gestational diabetes and insulin dependent diabetes (no further details). Murphy (2008) included insulin and diet controlled diabetes (no further details).

Other maternal infection outcomes for these Clinical Practice Guidelines - No data were reported for pyrexia after trial entry or intrapartum pyrexia or postnatal pyrexia requiring treatment in the trials that reported including a proportion of women with diabetes in pregnancy.

Other primary maternal outcomes for these Clinical practice Guidelines - No data on quality of life was reported in trials that were included in the Crowther (2011) systematic review.

Other relevant secondary outcomes of these Clinical Practice Guidelines - These Clinical Practice Guidelines have provided further details for maternal hyperglycaemia following treatment with antenatal corticosteroids.

None of the trials that recruited and reported that a proportion of women had diabetes in pregnancy provided outcome data for maternal glucose intolerance. As detailed in Chapter 6 of these Clinical Practice Guidelines, one trial (Wapner 2006) that did not specify if women with diabetes in pregnancy were eligible for recruitment reported no difference in maternal hyperglycaemia between women who had received repeat antenatal corticosteroids and those with no repeat treatment (RR 1.31, 95%CI 0.89 to 1.93; 1 trial, n=492 women).

Infant primary outcomes for these Clinical Practice Guidelines:

Fetal, neonatal or later death -

Perinatal death - Overall no difference was seen in the risk for perinatal death between women who had been treated with repeat antenatal corticosteroids and those with no repeat treatment (RR 0.94, 95%CI 0.71 to 1.23; 9 trials, n=5554 women).

- Three trials reported they included a proportion of women with diabetes in pregnancy (5% to 10%) and provided data for perinatal death (McEvoy 2010, Murphy 2008, Peltoniemi 2007). The size of the treatment effect was similar to the overall effect and there was no significant difference between groups (RR 1.19, 95%CI 0.80 to 1.77; 3 trials, n=2742 infants) (**Table 67**).

Fetal death - Overall no difference was seen in the risk for fetal death between women who had been treated with repeat antenatal corticosteroids and those with no repeat treatment (RR 0.82, 95%CI 0.24 to 2.84; 7 trials, n=2755 women).

- Two trials reported they included a proportion of women with diabetes in pregnancy (9% to 10%) and provided data for fetal death (McEvoy 2010, Peltoniemi 2007). The size of the treatment effect was similar to the overall effect and there was no significant difference between groups (RR 1.05, 95%CI 0.07 to 16.65; 2 trials, n=438 infants) (**Table 67**).

Neonatal death - Overall no difference was seen in the risk for neonatal death between women who had been treated with repeat antenatal corticosteroids and those with no repeat treatment (RR 0.91, 95%CI 0.62 to 1.34; 7 trials, n=2713 women).

- Two trials reported they included a proportion of women with diabetes in pregnancy (9% to 10%) and provided data for neonatal death (McEvoy 2010, Peltoniemi 2007). The size of the treatment effect was similar to the overall effect and there was no significant difference between groups (RR 2.83, 95%CI 0.76 to 10.37; 2 trials, n=438 infants) (**Table 67**).

Respiratory distress syndrome - Overall there was a significant reduction in the risk for respiratory distress syndrome for infants exposed to repeat antenatal corticosteroids compared with no repeat exposure (RR 0.83, 95%CI 0.75 to 0.91; 8 trials, n=3206 infants).

- Two trials reported they included a proportion of women with diabetes in pregnancy (0% to 10%) and provided data for respiratory distress syndrome (McEvoy 2010, Peltoniemi 2007). The size of the treatment effect was similar to the overall effect and there was no significant difference between groups (RR 0.98, 95%CI 0.80 to 1.20; 2 trials, n=438 infants) (**Table 67**).

Composite of serious infant outcomes - Overall there was a significant reduction in the risk for a composite of serious infant outcomes for infants exposed to repeat antenatal corticosteroids compared with no repeat exposure (RR 0.84, 95%CI 0.75 to 0.94; 7 trials, n=3959 infants).

- Only one trial reported including a proportion of women with diabetes in pregnancy (5%) and provided data for a composite of serious infant outcomes (Murphy 2008). The size of the treatment effect was similar to the overall effect and there was no difference between groups (RR 1.03, 95%CI 0.83 to 1.27; 1 trial, n=2304 infants) (**Table 67**).

Table 66: Comparison of the overall effect estimate for use of repeat antenatal corticosteroids with trials that reported including a proportion of women with diabetes mellitus or gestational diabetes – Maternal primary outcomes

Primary outcome	Repeat antenatal corticosteroids			Trials known to have included a proportion of women with diabetes mellitus or gestational diabetes^				
	Trials contributing data	Number of women	Risk ratio (RR) (95% Confidence Interval)	Trials contributing data	Number of women	Risk ratio (RR) (95% Confidence Interval)	Actual proportion detailed in trials	Actual number of women
Chorioamnionitis	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Murphy 2008; Wapner 2006	4261	RR 1.16 (0.92 to 1.46), 6 trials	Murphy 2008	1853	RR 1.08 (0.59 to 1.97) 1 trial, n=1853 women	Murphy 2008	93
Puerperal sepsis	Aghajafari 2002; Guinn 2001; Murphy 2008; Peltoniemi 2007; Wapner 2006	3091	RR 1.15 (0.83 to 1.60), 5 trials	Murphy 2008; Peltoniemi 2007	2102	RR 1.41 (0.94 to 2.12) 2 trials, n=2102 women	Murphy 2008; Peltoniemi 2007	118
Pyrexia after trial entry requiring treatment	-	-	Not reported	-	-	Not reported	-	-
Intrapartum pyrexia requiring treatment	-	-	Not reported	-	-	Not reported	-	-
Postnatal pyrexia requiring treatment	Crowther 2006	982	RR 0.87 (0.55 to 1.38), 1 trial	-	-	Not reported	-	-

Source: Crowther (2011); ^meta-analyses conducted for these Clinical Practice Guidelines

Table 67: Comparison of the overall effect estimate for use of repeat antenatal corticosteroids with trials that reported including a proportion of women with diabetes mellitus or gestational diabetes – Infant primary outcomes

	Repeat antenatal corticosteroids			**Trials known to have included a proportion of women with diabetes mellitus or gestational diabetes^**				
Primary outcome	**Trials contributing data**	**Number of infants**	**Risk ratio (RR) (95% Confidence Interval)**	**Trials contributing data**	**Number of infants**	**Risk ratio (RR) (95% Confidence Interval)**	**Actual proportion detailed in trials**	**Actual number of infants**
Perinatal death	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Mazumder 2008; McEvoy 2010; Murphy 2008; Peltoniemi 2007; Wapner 2006	5554	RR 0.94 (0.71 to 1.23), 9 trials	McEvoy 2010; Murphy 2008; Peltoniemi 2007	2742	RR 1.19 (0.80 to 1.77) 3 trials, n=2742 infants	McEvoy 2010; Murphy 2008; Peltoniemi 2007	158
Fetal death	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Mazumder 2008; McEvoy 2010; Peltoniemi 2007	2755	RR 0.82 (0.24 to 2.84), 7 trials	McEvoy 2010; Peltoniemi 2007	438	RR 1.05 (0.07 to 16.65) 2 trials, n=438 infants	McEvoy 2010; Peltoniemi 2007	43
Neonatal death	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Mazumder 2008; McEvoy 2010; Peltoniemi 2007	2713	RR 0.91 (0.62 to 1.34), 7 trials	McEvoy 2010; Peltoniemi 2007	438	RR 2.83 (0.76 to 10.37) 2 trials, n=438 infants	McEvoy 2010; Peltoniemi 2007	43
Respiratory distress syndrome	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Mazumder 2008; McEvoy 2010; Peltoniemi 2007; Wapner 2006	3206	RR 0.83 (0.75 to 0.91), 8 trials	McEvoy 2010; Peltoniemi 2007	438	RR 0.98 (0.80 to 1.20) 2 trials, n=438 infants	McEvoy 2010; Peltoniemi 2007	43
Composite outcome of serious infant outcomes	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Mazumder 2008; Murphy 2008; Wapner 2006	3959	RR 0.84 (0.75 to 0.94), 7 trials	Murphy 2008	2304	RR 1.03 (0.83 to 1.27) 1 trial, n=2304 infants	Murphy 2008	115

Source: (Crowther 2011); ^meta-analyses conducted for these Clinical Practice Guidelines

Evidence Summary for the use of repeat antenatal corticosteroids in women with diabetes mellitus or gestational diabetes at risk of preterm birth

Four of ten trials included in the Crowther (2011) systematic review reported including a very small proportion of women in their trials who had diabetes in pregnancy and were at risk of preterm birth. The proportion of women recruited with diabetes in pregnancy ranged from 0% to 10% for the trials of repeat antenatal corticosteroids, where reported.

For the mother
Overall, where reported in 10 trials, no differences were seen between women treated with repeat antenatal corticosteroids and women with no repeat corticosteroids in the risk for chorioamnionitis, postnatal pyrexia or puerperal sepsis.

Three trials reported including a proportion of women with diabetes in pregnancy. The evidence is consistent with the overall treatment effect:

- For chorioamnionitis and puerperal sepsis, the size of the treatment effect was similar to the overall effect and there was no difference between groups.

No data were reported for pyrexia after trial entry, postnatal pyrexia, intrapartum pyrexia or maternal quality of life from these seven trials.

For the infant
Overall, where reported in 10 trials, there was a significant reduction in the risks for respiratory distress syndrome and a composite of serious infant outcomes. No differences were seen in the risks for perinatal death, fetal death or neonatal death between infants exposed to a repeat antenatal corticosteroids and infants with no repeat exposure.

Three trials reported including a proportion of women with diabetes in pregnancy.

- For perinatal death, fetal death, neonatal death, respiratory distress syndrome and a composite of serious infant outcomes the size of the treatment effect was similar to the overall effect and there was no significant difference between groups.

The presence of maternal diabetes in pregnancy is not a reason to withhold antenatal corticosteroids where there is a risk of preterm birth. These women will require blood glucose monitoring and management of hyperglycaemia as per local protocols.

Evidence is based on a subset of data from trials that reported they included a proportion of women with diabetes in pregnancy. This level of evidence cannot be used to form a clinical recommendation.

See Appendix M28 – Evidence Summary (Page 420)

What is the safety for the mother, fetus, infant, child, adult of administering repeat antenatal corticosteroids to women with diabetes mellitus or gestational diabetes at risk of preterm birth?

Practice points:

- Repeat antenatal corticosteroids for a woman with diabetes in pregnancy or gestational diabetes at risk of preterm birth.
- Women with diabetes in pregnancy or gestational diabetes at risk of preterm birth and receiving antenatal corticosteroids will require blood glucose monitoring and management of any hyperglycaemia.
- Where appropriate, monitor women with diabetes in pregnancy or gestational diabetes for signs of puerperal sepsis when antenatal corticosteroids have been given.
- Where appropriate, estimate the risk of preterm birth by considering the use of adjunct prediction tests including fetal fibronectin and assessment of cervical length.

Research recommendations:

- Any future randomised trials of repeat antenatal corticosteroids should report their effect on maternal glucose tolerance.
- Identify the best management of women with diabetes in pregnancy given repeat antenatal corticosteroids.

14.8 Women with systemic infection at trial entry at risk of preterm birth

What is the safety for the mother of administering a single course of antenatal corticosteroids to women with systemic infection at trial entry at risk of preterm birth?

What is the safety for the fetus, infant, child, adult of administering a single course of antenatal corticosteroids to women with systemic infection at trial entry at risk of preterm birth?

Given there is some concern about anti-inflammatory characteristics of antenatal corticosteroids in women with systemic infection such as tuberculosis or sepsis (Royal College of Obstetricians and Gynaecologists 2012) we explored the evidence for this specific obstetric population.

Women with infection at trial entry were not eligible for a total of eight trials included in the Roberts CPG version 2015 systematic review (**Table 40**). Women with active tuberculosis were not eligible for one trial (Collaborative 1981). Women with evidence of infection (no details) were not eligible for five randomised trials (Dexiprom 1999, Lewis 1996, Qublan 2001, Schutte 1980, Silver 1996) and women with existing infection (no details) were not eligible for two randomised controlled trials (Nelson 1985, Parsons 1988) (Appendix J).

Evidence summary for the use of a single course of antenatal corticosteroids in women with systemic infection at trial entry at risk of preterm birth

Eight of 26 randomised trials of a single course of antenatal corticosteroids included in the Roberts CPG version 2015 systematic review stated that women with systemic infection at trial entry were not eligible for inclusion. The remaining 18 trials did not state if a proportion of the women included in their trials had systemic infection at trial entry.

Therefore there is no evidence for maternal or infant primary outcomes of these Clinical Practice Guidelines for women with systemic infection at trial entry in the trials included in the Roberts CPG version 2015 systematic review.

See Appendix M29 – Evidence Summary (Page 424)

What is the safety for the mother, fetus, infant, child, adult of administering a single course of antenatal corticosteroids to women with systemic infection at trial entry at risk of preterm birth?

Practice Points:

- Use a single course of antenatal corticosteroids for women with a systemic infection at risk of preterm birth.
- Do not delay birth in women with a systemic infection to administer a single course antenatal corticosteroids if at risk of preterm birth.

Research recommendation:

- In future randomised trials of antenatal corticosteroids there is a need to assess the impact, if any, of a single course of antenatal corticosteroids in women with systemic infection at risk of preterm birth.

What is the safety for the mother of administering repeat antenatal corticosteroids to women with systemic infection at trial entry at risk of preterm birth?

What is the safety for the fetus, infant, child, adult of administering repeat antenatal corticosteroids to women with systemic infection at trial entry at risk of preterm birth?

Repeat antenatal corticosteroids

Given there is some concern about anti-inflammatory characteristics of antenatal corticosteroids in women with systemic infection such as tuberculosis or sepsis (Royal College of Obstetricians and Gynaecologists 2012) we explored the evidence for this specific obstetric population.

Women with active tuberculosis or human immunodeficiency virus were not eligible for two trials (Garite 2009, Guinn 2001) in the Cochrane systematic review '*Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes*' (Crowther 2011) (Appendix K). No additional trials were identified in the Crowther CPG version 2015.

There was insufficient detail in the remaining trials to ascertain if women with a known systemic infection were included (Aghajafari 2002, Crowther 2006, Mazumder 2008, McEvoy 2002, McEvoy 2010, Murphy 2008, Peltoniemi 2007, Wapner 2006) (**Table 41**).

Evidence summary for the use of repeat antenatal corticosteroids in women with systemic infection (eg. tuberculosis/sepsis) at trial entry at risk of preterm birth

Two of ten randomised trials of a repeat antenatal corticosteroids included in the Crowther (2011) systematic review stated that women with systemic infection at trial entry were not eligible for inclusion. The remaining eight trials did not state if a proportion of the women included in their trials had systemic infection at trial entry.

Therefore there is no evidence for maternal or infant primary outcomes of these Clinical Practice Guidelines for women with systemic infection at trial entry in the trials included in the Crowther (2011) systematic review.

See Appendix M30 – Evidence Summary (Page 428)

What is the safety for the mother, fetus, infant, child, adult of administering repeat antenatal corticosteroids to women with systemic infection at trial entry at risk of preterm birth?

Practice Points

- Repeat antenatal corticosteroids for women with a systemic infection at risk of preterm birth.
- Do not delay birth in women with a systemic infection to administer repeat antenatal corticosteroids if at risk of preterm birth.
- Where appropriate, monitor women with systemic infection at risk of preterm birth for signs of puerperal sepsis when antenatal corticosteroids have been given

Research recommendation:

- In future randomised trials of repeat antenatal corticosteroids there is a need to assess the impact, if any, on women with systemic infection at risk of preterm birth.

14.9 Women with pregnancy associated hypertension/pre-eclampsia at risk of preterm birth

What is the safety for the mother of administering a single course of antenatal corticosteroids to women with pregnancy associated hypertension/pre-eclampsia at risk of preterm birth?

What is the safety for the fetus, infant, child, adult of administering a single course of antenatal corticosteroids to women with pregnancy associated hypertension/pre-eclampsia at risk of preterm birth?

Single course of antenatal corticosteroids

Ten of 26 trials in the Roberts CPG version 2015 systematic review reported that they included a small proportion of women in their trial with pregnancy associated hypertension (**Table 40**):

- Amorim (1999) 100%
- Collaborative (1981) 11%
- Fekih (2002) 16%
- Gamsu (1989) 7%
- Garite (1992) 10%
- Kari (1994) 31%
- Liggins (1972) 7%
- Porto (2011) 26%
- Shanks (2010) 12%
- Silver (1996) 5%.

For the remaining 16 trials, women with pre-eclampsia were not eligible for five trials (Balci 2010, Doran 1980, Taeusch 1979, Teramo 1980) and women with severe hypertension were not eligible for one trial (Schutte 1980). Twelve trials did not specify if women with pregnancy associated hypertension were eligible for recruitment (Block 1977, Cararach 1991, Carlan 1991, Dexiprom 1999, Goodner 1979, Lewis 1996, Lopez 1989, Morales 1989, Nelson 1985, Parsons 1988, Qublan) (Appendix J).

All of the trials required that the women be at risk of preterm birth. One trial (Amorim 1999) had severe pre-eclampsia as a specified inclusion criterion. Amorim (1999) defined severe preeclampsia according to the criteria proposed by the National High Blood Pressure Working Group. Not all women had severe hypertension (systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥110 mm Hg), but all had ≥ ominous sign (proteinuria ≥3^+ by dipstick, creatinine >1.2 mg/dL, platelet count <100,000 cells/mm3, epigastric pain, visual disturbances). All subjects had ≥2^+ proteinuria by dipstick.

In the summary of the evidence we report the overall treatment effects from all trials with available data, for the primary outcomes of these Clinical Practice Guidelines, for a single course of antenatal corticosteroids. We then report on the subset of 10 trials that specifically reported that they included a proportion of women recruited into their trial with *pregnancy associated hypertension.*

Maternal primary outcomes for these Clinical Practice Guidelines:

Maternal infection -

Chorioamnionitis - Overall no difference was seen in the risk for chorioamnionitis between women who had been treated with a single course of antenatal corticosteroids and those who received no antenatal corticosteroids (RR 0.90, 95%CI 0.69 to 1.17; 13 trials, n=2525 women).

- Six trials reported they included a proportion of women with pregnancy associated hypertension (5% to 100%) and provided data for chorioamnionitis (Amorim 1999, Fekih 2002, Garite 1992,

Kari 1994, Liggins 1972, Silver 1996). The treatment effect was similar to the overall effect and there was no significant difference between groups (RR 0.98, 95%CI 0.70 to 1.38; 6 trials, n=1775 women) (**Table 68**).

Puerperal sepsis - Overall no difference was seen in the risk for puerperal sepsis between women who had been treated with a single course of antenatal corticosteroids and those who received no antenatal corticosteroids (RR 1.35, 95%CI 0.93 to 1.95; 8 trials, n=1003 women).

- Three trials reported including a proportion of women with pregnancy associated hypertension (5% to 100%) and provided data for puerperal sepsis (Amorim 1999, Garite 1992, Silver 1996). The size of the treatment effect was similar to the overall effect and there was no significant difference between groups (RR 1.31, 95%CI 0.80 to 2.17; 3 trials, n=364 women) (**Table 68**).

Pyrexia after trial entry - Overall no difference was seen in the risk for pyrexia after trial entry requiring treatment between women who had been treated with a single course of antenatal corticosteroids and those who received no antenatal corticosteroids (RR 1.11, 95%CI 0.67 to 1.67; 4 trials, n=481 women).

- One trial reported it included 100% of women with pregnancy associated hypertension (severe pre-eclampsia) (Amorim 1999) and provided data for pyrexia after trial entry. The direction of the treatment effect was opposite to the overall effect but there was no significant difference between groups (RR 0.77, 95%CI 0.37 to 1.62; 1 trial, n=218 women) (**Table 68**).

Intrapartum pyrexia - Overall no difference was seen in the risk for intrapartum pyrexia requiring treatment between women who had been treated with a single course of antenatal corticosteroids and those who received no antenatal corticosteroids (RR 0.60, 95%CI 0.15 to 2.49; 2 trials, n=319 women).

- One trial reported that it included 100% of women with pregnancy associated hypertension (severe pre-eclampsia) (Amorim 1999) and provided data for intrapartum pyrexia. The treatment effect was in the opposite direction to the overall effect but there was no significant difference between groups (RR 1.96, 95%CI 0.18 to 21.34, 1 trial, n=218 women) (**Table 68**).

Postnatal pyrexia - Overall no difference was seen in the risk for postnatal pyrexia requiring treatment between women who had been treated with a single course of antenatal corticosteroids and those who received no antenatal corticosteroids (RR 0.92, 95%CI 0.64 to 1.33; 5 trials, n=1323 women).

- Three trials reported that they included a proportion of women with pregnancy associated hypertension (11% to 100%) and provided data for postnatal pyrexia (Amorim 1999, Collaborative Group on Antenatal Steroid Therapy 1981, Fekih 2002). The size of the effect was similar to the overall effect and there was no significant difference between groups (RR 0.86, 95%CI 0.57 to 1.30; 3 trials, n=1018 women) (**Table 68**).

Other primary maternal outcomes for these Clinical Practice Guidelines - No data on quality of life were reported in the trials included in the Roberts CPG version 2015 systematic review.

Infant primary outcomes for these Clinical Practice Guidelines:

Fetal, neonatal and later death -

Perinatal death - Overall there was a significant reduction in the risk for perinatal death for infants who were exposed to a single course of antenatal corticosteroids compared with no exposure (RR 0.77, 95%CI 0.67 to 0.89; 13 trials, n=3627 infants).

- Six trials reported they included a proportion of women with an pregnancy associated hypertension (7% to 100%) and provided data for perinatal death (Amorim 1999, Collaborative Group on Antenatal Steroid Therapy 1981, Gamsu 1989, Gaite 1992, Kari 1994, Liggins 1972). The size of the

treatment effect was similar to the overall effect but there was no significant difference between groups (RR 0.88, 95%CI 0.75 to 1.04; 6 trials, n=2727 infants) (**Table 69**).

Fetal death - Overall no difference was seen in the risk for fetal death between infants who were exposed to a single course of antenatal corticosteroids and those with no exposure (RR 0.98, 95%CI 0.73 to 1.30; 13 trials, n=3627 infants).

- Six trials reported they included a proportion of women with pregnancy associated hypertension (7% to 100%) and provided data for fetal death (Amorim 1999, Collaborative Group on Antenatal Steroid Therapy 1981, Gamsu 1989, Garite 1992, Kari 1994, Liggins 1972). The size of the treatment effect was similar to the overall effect and there was no significant difference between groups (RR 0.97, 95%CI 0.71 to 1.31, 6 trials, n=2727 infants) (**Table 69**).

Neonatal death - Overall there was a significant reduction in the risk for neonatal death for infants who were exposed to a single course of antenatal corticosteroids compared with no exposure (RR 0.68, 95%CI 0.58 to 0.80; 21 trials, n=4408 infants).

- Nine trials reported they included a proportion of women with pregnancy associated hypertension (5% to 100%) and provided data for neonatal death (Amorim 1999, Collaborative Group on Antenatal Steroid Therapy 1981, Fekih 2002, Gamsu 1989, Garite 1992, Kari 1994, Liggins 1972, Porto 2011, Silver 1996)The size of the treatment effect was similar to the overall effect and was statistically significant (RR 0.78, 95%CI 0.64 to 0.95; 9 trials, n=3111 infants) (**Table 69**).

Respiratory distress syndrome - Overall there was a significant reduction in the risk for respiratory distress syndrome for infants who were exposed to a single course of antenatal corticosteroids compared with no exposure (RR 0.65, 95%CI 0.58 to 0.73; 25 trials, n=4590 infants).

- Nine trials reported they included a proportion of women with pregnancy associated hypertension (5% to 100%) and provided data for respiratory distress syndrome (Amorim 1999, Collaborative Group on Antenatal Steroid Therapy 1981, Fekih 2002, Gamsu 1989, Garite 1992, Kari 1994, Liggins 1972, Porto 2011, Silver 1996). The size of the treatment effect was similar to the overall effect and was statistically significant (RR 0.68, 95%CI 0.53 to 0.88; 9 trials, n=3075 infants) (**Table 69**).

Composite of serious infant outcomes - This outcome was not reported in any of the trials of a single course of antenatal corticosteroids included in the Roberts CPG version 2015 systematic review.

Table 68: Comparison of the overall effect estimate for use of a single course of antenatal corticosteroids with trials that reported including a proportion of women with hypertension – Maternal primary outcomes*

Primary outcome	Single course of antenatal corticosteroids			Trials known to have included a proportion of women with pregnancy associated hypertension^				
	Trials contributing data	Number of women	Risk ratio (RR) (95% Confidence Interval)	Trials contributing data	Number of women	Risk ratio (RR) (95% Confidence Interval)	Actual proportion detailed in trials	Actual number of women
Chorioamnionitis	Amorim 1999; Carlan 1991; Dexiprom 1999; Fekih 2002; Garite 1992; Kari 1994; Lewis 1996; Liggins 1972; Lopez 1989; Morales 1989; Qublan 2001; Schutte 1980; Silver 1996	2525	RR 0.90 (0.69 to 1.17), 13 trials	Amorim 1999; Fekih 2002; Garite 1992; Kari 1994; Liggins 1972; Silver 1996	1775	RR 0.98 (0.70 to 1.38) 6 trials, n=1775 women	Amorim 1999; Fekih 2002; Garite 1992; Kari 1994; Liggins 1972; Silver 1996	377
Puerperal sepsis	Amorim 1999; Dexiprom 1999; Garite 1992; Lewis 1996; Qublan 2001; Schutte 1980; Silver 1996; Taeusch 1979	1003	RR 1.35 (0.93 to 1.95), 8 trials	Amorim 1999; Garite 1992; Silver 1996	364	RR 1.31 (0.80 to 2.17) 3 trials, n=364 women	Amorim 1999; Garite 1992; Silver 1996	229
Pyrexia after trial entry requiring treatment	Amorim 1999; Nelson 1985; Schutte 1980; Taeusch 1979	481	RR 1.11 (0.67 to 1.67), 4 trials	Amorim 1999	218	RR 0.77 (0.37 to 1.62) 1 trial, n=218 women	Amorim 1999	218
Intrapartum pyrexia requiring treatment	Amorim 1999; Schutte 1980	319	RR 0.60 (0.15 to 2.49), 2 trials	Amorim 1999	218	RR 1.96 (0.18 to 21.34) 1 trial, n=218 women	Amorim 1999	218
Postnatal pyrexia requiring treatment	Amorim 1999; Collaborative 1981; Dexiprom 1999; Fekih 2002; Schutte 1980	1323	RR 0.92 (0.64 to 1.33), 5 trials	Amorim 1999; Collaborative 1981; Fekih 2002	1018	RR 0.86 (0.57 to 1.30) 3 trials, n=1018 women	Amorim 1999; Collaborative 1981; Fekih 2002	312

*Source: Roberts CPG version 2015; ^meta-analyses conducted for these Clinical Practice Guidelines

Table 69: Comparison of the overall effect estimate for use of a single course of antenatal corticosteroids with trials that reported including a proportion of women with hypertension – Infant primary outcomes*

Primary outcome	Single course of antenatal corticosteroids			Trials known to have included a proportion of women with pregnancy associated hypertension^				
	Trials contributing data	Number of infants	Risk ratio (RR) (95% Confidence Interval)	Trials contributing data	Number of infants	Risk ratio (RR) (95% Confidence Interval)	Actual proportion detailed in trials	Actual number of infants
Perinatal death	Amorim 1999; Block 1977; Collaborative 1981; Dexiprom 1999; Doran 1980; Gamsu 1989; Garite 1992; Kari 1994; Liggins 1972; Parsons 1988; Qublan 2001; Schutte 1980; Taeusch 1979	3627	RR 0.77 (0.67 to 0.89), 13 trials	Amorim 1999; Collaborative 1981; Gamsu 1989; Garite 1992; Kari 1994; Liggins 1972	2727	RR 0.88 (0.75 to 1.04) 6 trials, n=2727 infants	Amorim 1999; Collaborative 1981; Gamsu 1989; Garite 1992; Kari 1994; Liggins 1972	476
Fetal death	Amorim 1999; Block 1977; Collaborative 1981; Dexiprom 1999; Doran 1980; Gamsu 1989; Garite 1992; Kari 1994; Liggins 1972; Parsons 1988; Qublan 2001; Schutte 1980; Taeusch 1979	3627	RR 0.98 (0.73 to 1.30), 13 trials	Amorim 1999; Collaborative 1981; Gamsu 1989; Garite 1992; Kari 1994; Liggins 1972	2727	RR 0.97 (0.71 to 1.31) 6 trials, n=2727 infants	Amorim 1999; Collaborative 1981; Gamsu 1989; Garite 1992; Kari 1994; Liggins 1972	476
Neonatal death	Amorim 1999; Block 1977; Collaborative 1981; Dexiprom 1999; Doran 1980; Fekih 2002; Gamsu 1989; Garite 1992; Goodner 1979; Kari 1994; Lewis 1996; Liggins 1972; Lopez 1989; Morales 1989; Nelson 1985; Parsons 1988; Porto 2011; Qublan 2001; Schutte 1980; Silver 1996; Taeusch 1979	4408	RR 0.68 (0.58 to 0.80), 21 trials	Amorim 1999; Collaborative 1981; Fekih 2002; Gamsu 1989; Garite 1992; Kari 1994; Liggins 1972; Porto 2011; Silver 1996	3111	RR 0.78 (0.64 to 0.95) 9 trials, n=3111 infants	Amorim 1999; Collaborative 1981; Fekih 2002; Gamsu 1989; Garite 1992; Kari 1994; Liggins 1972; Porto 2011; Silver 1996	549
Respiratory distress syndrome	Amorim 1999; Balci 2010; Block 1977; Cararach 1991; Carlan 1991; Collaborative 1981; Dexiprom 1999; Doran 1980; Fekih 2002; Gamsu 1989; Garite 1992; Goodner 1979; Kari 1994; Lewis 1996; Liggins 1972; Lopez 1989; Morales 1989; Nelson 1985; Parsons 1988; Porto 2011; Qublan 2001; Schutte 1980; Silver 1996; Taeusch 1979; Teramo 1980	4590	RR 0.65 (0.58 to 0.73), 25 trials	Amorim 1999; Collaborative 1981; Fekih, 2002; Gamsu 1989; Garite 1992; Kari 1994; Liggins 1972; Porto 2011; Silver 1996	3075	RR 0.68 (0.53 to 0.88)# 9 trials, n=3075 infants	Amorim 1999; Collaborative 1981; Fekih, 2002; Gamsu 1989; Garite 1992; Kari 1994; Liggins 1972; Porto 2011; Silver 1996	545

*Source: Roberts CPG version 2015; ^ meta-analyses conducted for these Clinical Practice Guidelines; #random effects model

Evidence summary for the use of a single course of antenatal corticosteroids for women with pregnancy associated hypertension at risk of preterm birth

Ten of 26 trials included in the Roberts CPG version 2015 systematic review reported including a proportion of women in their trials who had pregnancy associated hypertension and were at risk of preterm birth. The proportion of women recruited with pregnancy associated hypertension ranged from 5% to 100% for the trials of a single course of antenatal corticosteroids. All of the women included in the Amorim (1999) trial had severe pre-eclampsia.

For the mother

Overall, where reported in 26 trials, no differences were seen between women treated with a single course of antenatal corticosteroids and women with no corticosteroids in the risk for chorioamnionitis, pyrexia after trial entry, intrapartum pyrexia, postnatal pyrexia or puerperal sepsis.

Ten trials reported including a proportion of women with pregnancy associated hypertension. The evidence is consistent with the overall treatment effect:

- For chorioamnionitis, postnatal pyrexia and puerperal sepsis, the size of the treatment effect was similar to the overall effect and there was no difference between groups;
- For pyrexia after trial entry and intrapartum pyrexia the direction of the treatment effect was opposite to the overall effect but there was no difference between groups.

No data were reported for maternal quality of life in the trials included in the Roberts (2006) systematic review.

For the infant

Overall, where reported in 26 trials, there was a significant reduction in the risks for perinatal death, neonatal death and respiratory distress syndrome. No difference was seen in the risk for fetal death between infants exposed to a single course of antenatal corticosteroids and infants with no exposure.

Ten trials reported including a proportion of women with pregnancy associated hypertension. The evidence is consistent with the overall treatment effect:

- For neonatal death and respiratory distress syndrome the size of the treatment effect was similar to the overall effect and there was also a significant reduction in risk for infants exposed to a single course of antenatal corticosteroids compared with no exposure;
- For fetal death and perinatal death the size of the treatment effect was similar to the overall effect and there was no difference between groups.

Evidence is based on a subset of data from trials that reported they included a proportion of women with pregnancy associated hypertension. This level of evidence cannot be used to form a clinical recommendation.

See Appendix M31 – Evidence Summary (Page 432)

What is the safety for the mother, fetus, infant, child, adult of administering a single course of antenatal corticosteroids to women with pregnancy associated hypertension/pre-eclampsia at risk of preterm birth?

Practice points:

- Use a single course of antenatal corticosteroids for women with pregnancy associated hypertension at risk of preterm birth.

What is the safety for the mother of administering repeat antenatal corticosteroids to women with pregnancy associated hypertension/pre-eclampsia at risk of preterm birth?

What is the safety for the fetus, infant, child, adult of administering a repeat antenatal corticosteroids to women with pregnancy associated hypertension/pre-eclampsia at risk of preterm birth?

Repeat antenatal corticosteroids

Seven of 10 trials in the Cochrane systematic review '*Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes*' (Crowther 2011) reported that they included a small proportion women in their trial with pregnancy associated hypertension (**Table 41**):

- Crowther (2006) 10%
- Garite (2009) 6%
- Guinn (2002) (proportion not reported)
- McEvoy (2002) 14%
- McEvoy (2010) 6%
- Murphy (2008) 14%
- Peltoniemi (2007) 5%

Pregnancy associated hypertension was not specific inclusion criterion for any of the trials included in the Crowther (2011) systematic review. None of the trials included in the Cochrane systematic review '*Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes*' (Crowther 2011) excluded women with pregnancy associated hypertension or pre-eclampsia at risk of preterm birth (Appendix K). No additional trials were identified in the Crowther CPG version 2015 systematic review.

In the summary of the evidence we report the overall treatment effects from all trials with available data, for the primary outcomes of these Clinical Practice Guidelines, for repeat antenatal corticosteroids. We then report on the subset of seven trials that specifically reported that they included a proportion of women recruited into their trial with *pregnancy associated hypertension.*

Maternal primary outcomes for these Clinical Practice Guidelines:

Maternal infection -

Chorioamnionitis - Overall no difference was seen in the risk for chorioamnionitis between women who had been treated with repeat antenatal corticosteroids and those with no repeat treatment (RR 1.16, 95%CI 0.92 to 1.46; 6 trials, n=4261 women).

- Four trials reported they included a proportion of women with pregnancy associated hypertension (6% to 14%, where reported) and provided data for chorioamnionitis (Crowther 2006; Garite 2002; Guinn 2001; Murphy 2008). The size of the treatment effect was similar to the overall effect and there was no significant difference between groups (RR 1.15, 95%CI 0.91 to 1.46; 4 trials, n=3757 women) (**Table 70**).

Puerperal sepsis - Overall no difference was seen in the risk for puerperal sepsis between women who had been treated with repeat antenatal corticosteroids and those with no repeat treatment (RR 1.15, 95%CI 0.83 to 1.60; 5 trials, n=3091 women).

- Three trials reported they included a proportion of women with pregnancy associated hypertension (5% to 14%, where reported) and provided data for puerperal sepsis (Guinn 2001; Murphy 2008; Peltoniemi, 2007). The size of the treatment effect was similar to the overall effect and there was no significant difference between groups (RR 1.26, 95%CI 0.89 to 1.80; 3 trials, n=2587 women) (**Table 70**).

Postnatal pyrexia - Overall no difference was seen in the risk for postnatal pyrexia between women who had been treated with repeat antenatal corticosteroids and those with no repeat treatment (RR 0.87, 95%CI 0.55 to 1.38; 1 trial, n=982 women). This single trial (Crowther 2006) included 10% of women with pregnancy associated hypertension.

Other maternal infection outcomes for these Clinical Practice Guidelines - No data were reported for pyrexia after trial entry or intrapartum pyrexia or postnatal pyrexia requiring treatment in the trials that reported including a proportion of women with diabetes in pregnancy.

Other primary maternal outcomes for these Clinical practice Guidelines - No data on quality of life were reported in trials that were included in the Crowther (2011) systematic review.

Infant primary outcomes for these Clinical Practice Guidelines:

Fetal, neonatal or later death -

Perinatal death - Overall no difference was seen in the risk for perinatal death between women who had been treated with repeat antenatal corticosteroids and those with no repeat treatment (RR 0.94, 95%CI 0.71 to 1.23; 9 trials, n=5554 women).

- Six trials reported they included a proportion of women with pregnancy associated hypertension (5% to 14%, where reported) and provided data for perinatal death (Crowther 2006, Garite 2009, Guinn 2001, McEvoy 2010, Murphy 2008, Peltoniemi 2007). The size of the treatment effect was similar to the overall effect and there was no significant difference between groups (RR 1.01, 95%CI 0.75 to 1.34; 6 trials, n=4967 infants) (**Table 71**).

Fetal death - Overall no difference was seen in the risk for fetal death between women who had been treated with repeat antenatal corticosteroids and those with no repeat treatment (RR 0.82, 95%CI 0.24 to 2.84; 7 trials, n=2755 women).

- Five trials reported they included a proportion of women with pregnancy associated hypertension (5% to 10%, where reported) and provided data for fetal death (Crowther 2006, Garite 2009, Guinn 2001, McEvoy 2010, Peltoniemi 2007). The size of the treatment effect was similar to the overall effect and there was no significant difference between groups (RR 1.01, 95%CI 0.25 to 4.01; 5 trials, n=2663 infants) (**Table 71**).

Neonatal death - Overall no difference was seen in the risk for neonatal death between women who had been treated with repeat antenatal corticosteroids and those with no repeat treatment (RR 0.91, 95%CI 0.62 to 1.34; 7 trials, n=2713 women).

- Five trials reported they included a proportion of women with pregnancy associated hypertension (5% to 10%, where reported) and provided data for neonatal death (Crowther 2006, Garite 2009, Guinn 2001, McEvoy 2010, Peltoniemi 2007). The size of the treatment effect was similar to the overall effect and there was no significant difference between groups (RR 0.97, 95%CI 0.64 to 1.45; 5 trials, n=2621 infants) (**Table 71**).

Respiratory distress syndrome - Overall there was a significant reduction in the risk for respiratory distress syndrome for infants exposed to repeat antenatal corticosteroids compared with no repeat exposure (RR 0.83, 95%CI 0.75 to 0.91; 8 trials, n=3206 infants).

- Five trials reported they included a proportion of women with pregnancy associated hypertension (5% to 10%, where reported) and provided data for respiratory distress syndrome (Crowther 2006, Garite 2009, Guinn 2001, McEvoy 2010, Peltoniemi 2007). The size of the treatment effect was

similar to the overall effect and the difference was statistically significant (RR 0.84, 95%CI 0.76 to 0.92; 5 trials, n=2663 infants) (**Table 71**).

Composite of serious infant outcomes - Overall there was a significant reduction in the risk for a composite of serious infant outcomes for infants exposed to repeat antenatal corticosteroids compared with no repeat exposure (RR 0.84, 95%CI 0.75 to 0.94; 7 trials, n=5094 infants).

- Four trials reported that they included a proportion of women with pregnancy associated hypertension (6% to 14%, where reported) and provided data for a composite of serious infant outcomes (Crowther 2006, Garite 2009, Guinn 2001, Murphy 2008). The size of the treatment effect was similar to the overall effect and there was a significant difference between groups (RR 0.85, 95%CI 0.76 to 0.95; 4 trials, n=4508 infants) (**Table 71**).

Table 70: Comparison of the overall effect estimate for use of repeat antenatal corticosteroids with trials that reported including a proportion of women with hypertension – Maternal primary outcomes*

Primary outcome	Repeat course of antenatal corticosteroids			Trials known to have included a proportion of women with pregnancy associated hypertension^				
	Trials contributing data	Number of women	Risk ratio (RR) (95% Confidence Interval)	Trials contributing data	Number of women	Risk ratio (RR) (95% Confidence Interval)	Actual proportion detailed in trials	Actual number of women
Chorioamnionitis	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Murphy 2008; Wapner 2006	4261	RR 1.16 (0.92 to 1.46), 6 trials	Crowther 2006; Garite 2009; Guinn 2001; Murphy 2008;	3757	RR 1.15 (0.91 to 1.46) 4 trials, n=3757 women	Crowther 2006; Garite 2009; Murphy 2008;	383
Puerperal sepsis	Aghajafari 2002; Guinn 2001; Murphy 2008; Peltoniemi 2007; Wapner 2006	3091	RR 1.15 (0.83 to 1.60), 5 trials	Guinn 2001; Murphy 2008; Peltoniemi 2007	2587	RR 1.26 (0.89 to 1.80) 3 trials, n=2587 women	Guinn 2001; Murphy 2008; Peltoniemi 2007	272
Pyrexia after trial entry requiring treatment	-	-	Not reported	-	-	Not reported	-	-
Intrapartum pyrexia requiring treatment	-	-	Not reported	-	-	Not reported	-	-
Postnatal pyrexia requiring treatment	Crowther 2006	982	RR 0.87 (0.55 to 1.38), 1 trial	Crowther 2006	982	RR 0.87 (0.55 to 1.38), 1 trial, n=982 women	Crowther 2006	98

*Source: Crowther (2011); ^meta-analyses conducted for these Clinical Practice Guidelines

Table 71: Comparison of the overall effect estimate for use of repeat antenatal corticosteroids with trials that reported including a proportion of women with hypertension – Infant primary outcomes*

Primary outcome	Repeat course of antenatal corticosteroids			Trials known to have included a proportion of women with pregnancy associated hypertension^				
	Trials contributing data	Number of infants	Risk ratio (RR) (95% Confidence Interval)	Trials contributing data	Number of infants	Risk ratio (RR) (95% Confidence Interval)	Actual proportion detailed in trials	Actual number of infants
Perinatal death	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Mazumder 2008; McEvoy 2010; Murphy 2008; Peltoniemi 2007; Wapner 2006	5554	RR 0.94 (0.71 to 1.23), 9 trials	Crowther 2006; Garite 2009; Guinn 2001; McEvoy 2010; Murphy 2008; Peltoniemi 2007	4967	RR 1.01 (0.75 to 1.34), 6 trials, n=4967 infants	Crowther 2006; Garite 2009; McEvoy 2010; Murphy 2008; Peltoniemi 2007	496
Fetal death	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Mazumder 2008; McEvoy 2010; Peltoniemi 2007	2755	RR 0.82 (0.24 to 2.84), 7 trials	Crowther 2006; Garite 2009; Guinn 2001; McEvoy 2010; Peltoniemi 2007	2663	RR 1.01 (0.25 to 4.01), 5 trials, n=2663 infants	Crowther 2006; Garite 2009; McEvoy 2010; Peltoniemi 2007	173
Neonatal death	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Mazumder 2008; McEvoy 2010; Peltoniemi 2007	2713	RR 0.91 (0.62 to 1.34), 7 trials	Crowther 2006; Garite 2009; Guinn 2001; McEvoy 2010; Peltoniemi 2007	2621	RR 0.97 (0.64 to 1.45), 5 trials, n=2621 infants	Crowther 2006; Garite 2009; McEvoy 2010; Peltoniemi 2007	170
Respiratory distress syndrome	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Mazumder 2008; McEvoy 2010; Peltoniemi 2007; Wapner 2006	3206	RR 0.83 (0.75 to 0.91), 8 trials	Crowther 2006; Garite 2009; Guinn 2001; McEvoy 2010; Peltoniemi 2007	2663	RR 0.84 (0.76 to 0.92), 5 trials, n=2663 infants	Crowther 2006; Garite 2009; McEvoy 2010; Peltoniemi 2007	170
Composite outcome of serious infant outcomes	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Mazumder 2008; Murphy 2008; Wapner 2006	5094	RR 0.84 (0.75 to 0.94), 7 trials	Crowther 2006; Garite 2009; Guinn 2001; Murphy 2008	4508	RR 0.85 (0.76 to 0.95), 4 trials, n=4508 infants	Crowther 2006; Garite 2009; Murphy 2008	371

*Source: (Crowther 2011); ^meta-analyses conducted for these Clinical Practice Guidelines

Evidence summary for the use of repeat antenatal corticosteroids for women with pregnancy associated hypertension at risk of preterm birth

Seven of 10 trials included in the Crowther (2011) systematic review reported including a proportion of women in their trials who had pregnancy associated hypertension and were at risk of preterm birth. The proportion of women recruited with pregnancy associated hypertension ranged from 5% to 14%, where reported.

For the mother
Overall, where reported in 10 trials, no differences were seen between women treated with repeat antenatal corticosteroids and women with no repeat corticosteroids in the risk for chorioamnionitis, postnatal pyrexia or puerperal sepsis.

Seven trials reported including a proportion of women with pregnancy associated hypertension. The evidence is consistent with the overall treatment effect:

- For chorioamnionitis, postnatal pyrexia and puerperal sepsis, the size of the treatment effect was similar to the overall effect and there was no difference between groups;

No data were reported for pyrexia after trial entry, intrapartum pyrexia or maternal quality of life.

For the infant
Overall, where reported in 10 trials, there was a significant reduction in the risks for respiratory distress syndrome and a composite of serious infant outcomes. No differences were seen in the risks for perinatal death, fetal death or neonatal death between infants exposed to a repeat antenatal corticosteroids and infants with no repeat exposure.

Seven trials reported including a proportion of women with pregnancy associated hypertension. The evidence is consistent with the overall treatment effect:

- For respiratory distress syndrome and a composite of serious infant outcomes the size of the treatment effect was similar to the overall effect and there was also a significant reduction in risk for infants exposed to a repeat antenatal corticosteroids compared with no repeat exposure;
- For perinatal death, fetal death and neonatal death the size of the treatment effect was similar to the overall effect and there was no difference between groups.

See Appendix M32– Evidence Summary (Page 436)

14.9 What is the safety for the mother, fetus, infant, child, adult of administering repeat antenatal corticosteroids to women with pregnancy associated hypertension/pre-eclampsia at risk of preterm birth?

Practice point:

- Repeat antenatal corticosteroids for a woman with pregnancy associated hypertension at risk of preterm birth.

14.10 Women with a fetus with intrauterine growth restriction at risk of preterm birth

What is the safety for the mother of administering a single course of antenatal corticosteroids to women with a fetus with intrauterine growth restriction at risk of preterm birth?

What is the safety for the fetus, infant, child, adult of administering a single course of antenatal corticosteroids to women with a fetus with intrauterine growth restriction at risk of preterm birth?

Single course of antenatal corticosteroids

Three of 26 trials in the Roberts CPG version 2015 systematic review reported that they included a very small proportion of women in their trial with a fetus with intrauterine growth restriction at risk of preterm birth (**Table 40**):

- Garite (1992) 6%
- Porto (2011) 1%
- Silver (1996) 9%

Of the remaining 23 trials, women with a fetus with intrauterine growth restriction were not eligible for two trials (Balci 2010, Schutte 1980). Twenty-one trials did not provide details of whether women with intrauterine growth restriction were eligible for and included in their trials (Appendix J).

In the summary of the evidence we report the overall treatment effects from all trials with available data, for the primary outcomes of these Clinical Practice Guidelines, for a single course of antenatal corticosteroids. We then report on the subset of three trials that specifically reported that they included a proportion of women recruited into their trial with *a fetus with intrauterine growth restriction.*

Maternal primary outcomes for these Clinical Practice Guidelines:

Maternal infection -

Chorioamnionitis - Overall no difference was seen in the risk for chorioamnionitis between women who had been treated with a single course of antenatal corticosteroids and those who received no antenatal corticosteroids (RR 0.90, 95%CI 0.69 to 1.17; 13 trials, n=2525 women).

- Two trials reported they included a proportion of women with a fetus with intrauterine growth restriction (6% to 9%) and provided data for chorioamnionitis (Garite 1992, Silver 1996). The treatment effect was similar to the overall effect and there was no significant difference between groups (RR 0.94, 95%CI 0.51 to 1.76; 2 trials, n=146 women) (**Table 72**).

Puerperal sepsis - Overall no difference was seen in the risk for puerperal sepsis between women who had been treated with a single course of antenatal corticosteroids and those who received no antenatal corticosteroids (RR 1.35, 95%CI 0.93 to 1.95; 8 trials, n=1003 women).

- Two trials reported including a proportion of women with a fetus with intrauterine growth restriction (6% to 9%) and provided data for puerperal sepsis (Garite 1992, Silver 1996). The direction of the treatment effect was similar to the overall effect but reached statistical significance (RR 2.16, 95%CI 1.09 to 4.26; 2 trials, n=146 women). Caution is required when interpreting these data as there is imprecision associated with wide confidence intervals that overlap with those of the overall treatment effect that was not statistically significant (**Table 72**).

Other maternal infection outcomes - No data were reported for pyrexia after trial entry, intrapartum pyrexia or postnatal pyrexia in trials that reported including a proportion of women with a fetus with intrauterine growth restriction.

Other primary maternal outcomes for these Clinical Practice Guidelines - No data on quality of life were reported in the trials included in the Roberts CPG version 2015 systematic review.

Infant primary outcomes for these Clinical Practice Guidelines:

Fetal, neonatal and later death -

Perinatal death - Overall there was a significant reduction in the risk for perinatal death for infants who were exposed to a single course of antenatal corticosteroids compared with no exposure (RR 0.77, 95%CI 0.67 to 0.89; 13 trials, n=3627 infants).

- Only one small trial reported including 6% of women with a fetus with intrauterine growth restriction and provided data for perinatal death (Garite 1992). The direction of the treatment effect was opposite to the overall effect but there was no significant difference between groups, probably due to fewer infants (RR 1.14, 95%CI 0.59 to 2.21; 1 trial, n=77 infants) (**Table 73**).

Fetal death - Overall no difference was seen in the risk for fetal death between infants who were exposed to a single course of antenatal corticosteroids and those with no exposure (RR 0.98, 95%CI 0.73 to 1.30; 13 trials, n=3627 infants).

- Only one small trial reported including 6% of women with a fetus with intrauterine growth restriction and provided data for fetal death (Garite 1992). The direction of the treatment effect was opposite to the overall effect and there was no significant difference between groups (RR 3.42, 95%CI 0.37 to 31.41, 1 trial, n=77 infants) (**Table 73**).

Neonatal death - Overall there was a significant reduction in the risk for neonatal death for infants who were exposed to a single course of antenatal corticosteroids compared with no exposure (RR 0.68, 95%CI 0.58 to 0.80; 21 trials, n=4408 infants).

- Three trials reported they included a proportion of women with a fetus with intrauterine growth restriction (1% to 9%) and provided data for neonatal death (Garite 1992, Porto 2011, Silver 1996). The size of the treatment effect was similar to the overall effect but there was no significant difference between groups, probably due to fewer infants (RR 0.77, 95%CI 0.43 to 1.35; 3 trials, n=489 infants) (**Table 73**).

Respiratory distress syndrome - Overall there was a significant reduction in the risk for respiratory distress syndrome for infants who were exposed to a single course of antenatal corticosteroids compared with no exposure (RR 0.65, 95%CI 0.58 to 0.73; 25 trials, n=4590 infants).

- Three trials reported they included a proportion of women with a fetus with intrauterine growth restriction (1% to 9%) and provided data for respiratory distress syndrome (Garite 1992, Porto 2011, Silver 1996). The size of the treatment effect was similar to the overall effect but there was no significant difference between groups, probably due to fewer infants (RR 0.97, 95%CI 0.81 to 1.16; 3 trials, n=489 infants) (**Table 73**).

Composite of serious infant outcomes - This outcome was not reported in any of the trials of a single course of antenatal corticosteroids included in the Roberts CPG version 2015 systematic review.

Table 72: Comparison of the overall effect estimate for use of a single course of antenatal corticosteroids with trials that reported including a proportion of women with a fetus with intrauterine growth restriction– Maternal primary outcomes*

Primary outcome	Single course of antenatal corticosteroids			Trials known to have included a proportion of women with a fetus with intrauterine growth restriction^				
	Trials contributing data	Number of women	Risk ratio (RR) (95% Confidence Interval)	Trials contributing data	Number of women	Risk ratio (RR) (95% Confidence Interval)	Actual proportion detailed in trials	Actual number of women
Chorioamnionitis	Amorim 1999; Carlan 1991; Dexiprom 1999; Fekih 2002; Garite 1992; Kari 1994; Lewis 1996; Liggins 1972; Lopez 1989; Morales 1989; Qublan 2001; Schutte 1980; Silver 1996	2525	RR 0.90 (0.69 to 1.17), 13 trials	Garite 1992; Silver 1996	146	RR 0.94 (0.51 to 1.76), 2 trials, n=146 women	Garite 1992; Silver 1996	11
Puerperal sepsis	Amorim 1999; Dexiprom 1999; Garite 1992; Lewis 1996; Qublan 2001; Schutte 1980; Silver 1996; Taeusch 1979	1003	RR 1.35 (0.93 to 1.95), 8 trials	Garite 1992; Silver 1996	146	RR 2.16 (1.09 to 4.26) 2 trials, n=146 women	Garite 1992; Silver 1996	11
Pyrexia after trial entry requiring treatment	Amorim 1999; Nelson 1985; Schutte 1980; Taeusch 1979	481	RR 1.11 (0.67 to 1.67), 4 trials	-	-	Not reported	-	-
Intrapartum pyrexia requiring treatment	Amorim 1999; Schutte 1980	319	RR 0.60 (0.15 to 2.49), 2 trials	-	-	Not reported	-	-
Postnatal pyrexia requiring treatment	Amorim 1999; Collaborative 1981; Dexiprom 1999; Fekih 2002; Schutte 1980	1323	RR 0.92 (0.64 to 1.33), 5 trials	-	-	Not reported	-	-

* Source: Roberts CPG version 2015; ^meta-analyses conducted for these Clinical Practice Guidelines

Table 73 Comparison of the overall effect estimate for use of a single course of antenatal corticosteroids with trials that reported including a proportion of women with a fetus with intrauterine growth restriction– Infant primary outcomes*

Primary outcome	Single course of antenatal corticosteroids			Trials known to have included a proportion of women with a fetus with intrauterine growth restriction^				
	Trials contributing data	Number of infants	Risk ratio (RR) (95% Confidence Interval)	Trials contributing data	Number of infants	Risk ratio (RR) (95% Confidence Interval)	Actual proportion detailed in trials	Actual number of infants
Perinatal death	Amorim 1999; Block 1977; Collaborative 1981; Dexiprom 1999; Doran 1980; Gamsu 1989; Garite 1992; Kari 1994; Liggins 1972; Parsons 1988; Qublan 2001; Schutte 1980; Taeusch 1979	3627	RR 0.77 (0.67 to 0.89), 13 trials	Garite 1992	77	RR 1.14 (0.59 to 2.21), 1 trial, n=77 infants	Garite 1992	5
Fetal death	Amorim 1999; Block 1977; Collaborative 1981; Dexiprom 1999; Doran 1980; Gamsu 1989; Garite 1992; Kari 1994; Liggins 1972; Parsons 1988; Qublan 2001; Schutte 1980; Taeusch 1979	3627	RR 0.98 (0.73 to 1.30), 13 trials	Garite 1992	77	RR 3.42(0.37 to 31.41), 1 trial, n=77 infants	Garite 1992	5
Neonatal death	Amorim 1999; Block 1977; Collaborative 1981; Dexiprom 1999; Doran 1980; Fekih 2002; Gamsu 1989; Garite 1992; Goodner 1979; Kari 1994; Lewis 1996; Liggins 1972; Lopez 1989; Morales 1989; Nelson 1985; Parsons 1988; Porto 2011; Qublan 2001; Schutte 1980; Silver 1996; Taeusch 1979	4408	RR 0.68 (0.58 to 0.80), 21 trials	Garite 1992; Porto 2011; Silver 1996	489	RR 0.77 (0.43 to 1.35), 3 trials, n=489 infants	Garite 1992; Porto 2011; Silver 1996	16
Respiratory distress syndrome	Amorim 1999; Balci 2010; Block 1977; Cararach 1991; Carlan 1991; Collaborative 1981; Dexiprom 1999; Doran 1980; Fekih 2002; Gamsu 1989; Garite 1992; Goodner 1979; Kari 1994; Lewis 1996; Liggins 1972; Lopez 1989; Morales 1989; Nelson 1985; Parsons 1988; Porto 2011; Qublan 2001; Schutte 1980; Silver 1996; Taeusch 1979; Teramo 1980	4590	RR 0.65 (0.58 to 0.73), 25 trials	Garite 1992; Porto 2011; Silver 1996	489	RR 0.97 (0.81 to 1.16), 3 trials, n=489 infants	Garite 1992; Porto 2011; Silver 1996	16

*Source: Roberts CPG version 2015; ^meta-analyses conducted for these Clinical Practice Guidelines

Evidence summary for use of a single course of antenatal corticosteroids for women with a fetus with intrauterine growth restriction at risk of preterm birth

Three of 26 trials included in the Roberts CPG version 2015 systematic review reported including a very small proportion of women with a fetus with intrauterine growth restriction at risk of preterm birth. The proportion of women recruited with a fetus with intrauterine growth restriction at risk of preterm birth ranged from 1% to 9% for the trials of a single course of antenatal corticosteroids.

For the mother

Overall, where reported in 26 trials, no differences were seen between women treated with a single course of antenatal corticosteroids and women with no corticosteroids in the risk for chorioamnionitis, pyrexia after trial entry, intrapartum pyrexia, postnatal pyrexia or puerperal sepsis.

Three trials reported including a proportion of women with a fetus with intrauterine growth restriction.

- For chorioamnionitis the size of the treatment effect was similar to the overall effect and there was no difference between groups;
- For puerperal sepsis the treatment effect was in the same direction as the overall effect but reached statistical significance. Caution is required when interpreting these data as there is imprecision associated with wide confidence intervals that overlap with those of the overall treatment effect that was not statistically significant.

No data were reported for pyrexia after trial entry, intrapartum pyrexia, postnatal pyrexia or maternal quality of life.

For the infant

Overall, where reported in 26 trials, there was a significant reduction in the risks for perinatal death, neonatal death and respiratory distress syndrome. No difference was seen in the risk for fetal death between infants exposed to a single course of antenatal corticosteroids and infants with no exposure.

Three trials reported including a proportion of women with a fetus with intrauterine growth restriction.

- For perinatal death and fetal death the treatment effect was in the opposite direction to the overall effect but there was no difference in groups
- For neonatal death and respiratory distress syndrome the size of the treatment effect was similar to the overall effect but there was no difference between groups.

The differences are probably due to the small numbers of infants in the trials that reported including a proportion of women with a fetus with intrauterine growth restriction.

See Appendix M33 – Evidence Summary (Page 440)

What is the safety for the mother, fetus, infant, child, adult of administering a single course of antenatal corticosteroids to women with a fetus with intrauterine growth restriction at risk of preterm birth?

Practice points:

- Use a single course of antenatal corticosteroids for women with a fetus with intrauterine growth restriction at risk of preterm birth.
- Where appropriate, monitor women with intrauterine fetal growth restriction for signs of puerperal sepsis when antenatal corticosteroids have been given.

Research recommendations:

- What are the haemodynamic effects of antenatal corticosteroids on the growth restricted fetus?
- What is the optimal timing of birth following administration of antenatal corticosteroids for women with a fetus with intrauterine growth restriction?

What is the safety for the mother of administering repeat antenatal corticosteroids to women with a fetus with intrauterine growth restriction at risk of preterm birth?

What is the safety for the fetus, infant, child, adult of administering repeat antenatal corticosteroids to women with a fetus with intrauterine growth restriction/fetal compromise at risk of preterm birth?

Repeat antenatal corticosteroids

Six of 10 trials in the Cochrane systematic review '*Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes'* (Crowther 2011) reported that they included a very small proportion women in their trial with a fetus with intrauterine growth restriction (**Table 41**):

- Aghajafari (2002) 0%
- Crowther (2006) 7%
- Garite (2009) 2%
- Guinn (2002) 7%
- McEvoy (2002) 19%
- Murphy (2008) 9%

Of the remaining four trials, women with a fetus with growth restriction were not eligible for one trial (Wapner 2006) and three trials did not report if women with a fetus with growth restriction were eligible for inclusion (Mazumder 2008, McEvoy 2010, Peltoniemi 2007) (Appendix K). The eligibility criterion for the trials included in the Crowther (2011) systematic review was that all women had already received a single course of antenatal corticosteroids and were at considered to be at continued risk of preterm birth. No additional trials were identified in the Crowther CPG version 2015 systematic review.

In the summary of the evidence we report the overall treatment effects from all trials with available data, for the primary outcomes of these Clinical Practice Guidelines, for repeat antenatal corticosteroids. We then report on the subset of six trials that specifically reported that they included a proportion of women recruited into their trial with *a fetus with intrauterine growth restriction.*

Maternal primary outcomes for these Clinical Practice Guidelines:

Maternal infection -

Chorioamnionitis - Overall no difference was seen in the risk for chorioamnionitis between women who had been treated with repeat antenatal corticosteroids and those with no repeat treatment (RR 1.16, 95%CI 0.92 to 1.46; 6 trials, n=4261 women).

- Five trials reported they included a proportion of women with a fetus with growth restriction (0% to 9%) and provided data for chorioamnionitis (Aghajafari 2002, Crowther 2006, Garite 2009, Guinn 2001, Murphy 2008). The size of the treatment effect was similar to the overall effect and there was no significant difference between groups (RR 1.15, 95%CI 0.91 to 1.46; 5 trials, n=3769 women) (**Table 74**).

Puerperal sepsis - Overall no difference was seen in the risk for puerperal sepsis between women who had been treated with repeat antenatal corticosteroids and those with no repeat treatment (RR 1.15, 95%CI 0.83 to 1.60; 5 trials, n=3091 women).

- Three trials reported they included a proportion of women with a fetus with growth restriction (0% to 9%) and provided data for puerperal sepsis (Aghajafari 2002, Guinn 2001, Murphy 2008). The

size of the treatment effect was similar to the overall effect and there was no significant difference between groups (RR 1.17, 95%CI 0.77 to 1.77; 3 trials, n=2350 women) (**Table 74**).

Postnatal pyrexia - Overall no difference was seen in the risk for postnatal pyrexia between women who had been treated with repeat antenatal corticosteroids and those with no repeat treatment (RR 0.87, 95%CI 0.55 to 1.38; 1 trial, n=982 women). This single trial (Crowther 2006) included 7% of women with a fetus with growth restriction.

Other maternal infection outcomes for these Clinical Practice Guidelines - No data were reported for pyrexia after trial entry or intrapartum pyrexia or postnatal pyrexia requiring treatment in the trials that reported including a proportion of women with a fetus with growth restriction.

Other primary maternal outcomes for these Clinical practice Guidelines - No data on quality of life were reported in trials that were included in the Crowther (2011) systematic review.

Infant primary outcomes for these Clinical Practice Guidelines:

Fetal, neonatal or later death -

Perinatal death - Overall no difference was seen in the risk for perinatal death between women who had been treated with repeat antenatal corticosteroids and those with no repeat treatment (RR 0.94, 95%CI 0.71 to 1.23; 9 trials, n=5554 women).

- Five trials reported they included a proportion of women with a fetus with growth restriction (0% to 9%) and provided data for perinatal death (Aghajafari 2002, Crowther 2006, Garite 2009, Guinn 2001, Murphy 2008). The size of the treatment effect was similar to the overall effect and there was no significant difference between groups (RR 0.93, 95%CI 0.69 to 1.26; 5 trials, n=4545 infants) (**Table 75**).

Fetal death - Overall no difference was seen in the risk for fetal death between women who had been treated with repeat antenatal corticosteroids and those with no repeat treatment (RR 0.82, 95%CI 0.24 to 2.84; 7 trials, n=2755 women).

- Four trials reported they included a proportion of women with a fetus with growth restriction (0% to 7%) and provided data for fetal death (Aghajafari 2002, Crowther 2006, Garite 2009, Guinn 2001). The size of the treatment effect was similar to the overall effect and there was no significant difference between groups (RR 0.99, 95%CI 0.20 to 4.90; 4 trials, n=2241 infants) (**Table 75**).

Neonatal death - Overall no difference was seen in the risk for neonatal death between women who had been treated with repeat antenatal corticosteroids and those with no repeat treatment (RR 0.91, 95%CI 0.62 to 1.34; 7 trials, n=2713 women).

- Four trials reported they included a proportion of women with a fetus with growth restriction (0% to 7%) and provided data for neonatal death (Aghajafari 2002, Crowther 2006, Garite 2009, Guinn 2001). The size of the treatment effect was similar to the overall effect and there was no significant difference between groups (RR 0.82, 95%CI 0.52 to 1.27; 4 trials, n=2199 infants) (**Table 75**).

Respiratory distress syndrome - Overall there was a significant reduction in the risk for respiratory distress syndrome for infants exposed to repeat antenatal corticosteroids compared with no repeat exposure (RR 0.83, 95%CI 0.75 to 0.91; 8 trials, n=3206 infants).

- Four trials reported they included a proportion of women with a fetus with growth restriction (0% to 7%) and provided data for respiratory distress syndrome (Aghajafari 2002, Crowther 2006, Garite 2009, Guinn 2001). The size of the treatment effect was similar to the overall effect and the

difference was statistically significant (RR 0.80, 95%CI 0.71 to 0.90; 4 trials, n=2199 infants) (**Table 75**).

Composite of serious infant outcomes - Overall there was a significant reduction in the risk for a composite of serious infant outcomes for infants exposed to repeat antenatal corticosteroids compared with no repeat exposure (RR 0.84, 95%CI 0.75 to 0.94; 7 trials, n=5094 infants).

- Five trials reported that they included a proportion of women with a fetus with growth restriction (0% to 9%) and provided data for a composite of serious infant outcomes (Aghajafari 2002, Crowther 2006, Garite 2009, Guinn 2001, Murphy 2008). The size of the treatment effect was similar to the overall effect and was statistically significant (RR 0.85, 95%CI 0.76 to 0.95; 5 trials, n=4524 infants) (**Table 75**).

Other relevant outcomes for these Clinical Practice Guidelines - These Clinical Practice Guidelines have provided some additional data for birthweight.

Overall birthweight was significantly reduced following exposure to repeat antenatal corticosteroids compared with no repeat exposure (MD -75.79 grams, 95%CI -117.63 to -33.96; 9 trials, n=5626 infants). There was no difference in birthweight z score between exposure to repeat antenatal corticosteroids and no repeat exposure (MD -0.11 grams, 95%CI 0.23 to 0.00; 2 trials, n=1256 infants).

- Five trials reported that they included a proportion of women with a fetus with growth restriction (0% to 9%) and provided data for a composite of serious infant outcomes (Aghajafari 2002, Crowther 2006, Garite 2009, Guinn 2001, Murphy 2008). The mean difference (MD) in birthweight was -68.85 grams (95%CI -119.46 to -18.24; 5 trials, n=4524 infants). This is similar to the overall birthweight and was also statistically different.

Table 74: Comparison of the overall effect estimate for use of repeat antenatal corticosteroids with trials that reported including a proportion of women with a fetus with intrauterine growth restriction– Maternal primary outcomes*

Primary outcome	Repeat antenatal corticosteroids			Trials known to have included a proportion of women with a fetus with intrauterine growth restriction^				
	Trials contributing data	Number of women	Risk ratio (RR) (95% Confidence Interval)	Trials contributing data	Number of women	Risk ratio (RR) (95% Confidence Interval)	Actual proportion detailed in trials	Actual number of women
Chorioamnionitis	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Murphy 2008; Wapner 2006	4261	RR 1.16 (0.92 to 1.46), 6 trials	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Murphy 2008	3769	RR 1.15 (0.91 to 1.46) 5 trials, n=3769 women	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Murphy 2008	279
Puerperal sepsis	Aghajafari 2002; Guinn 2001; Murphy 2008; Peltoniemi 2007; Wapner 2006	3091	RR 1.15 (0.83 to 1.60), 5 trials	Aghajafari 2002; Guinn 2001; Murphy 2008;	2587	RR 1.17 (0.77 to 1.77), 3 trials, n=2350 women	Aghajafari 2002; Guinn 2001; Murphy 2008;	201
Pyrexia after trial entry requiring treatment	NR	NR	NR	-	-	-	-	-
Intrapartum pyrexia requiring treatment	NR	NR	NR	-	-	-	-	-
Postnatal pyrexia requiring treatment	Crowther 2006	982	RR 0.87 (0.55 to 1.38), 1 trial	Crowther 2006	982	RR 0.87 (0.55 to 1.38), 1 trial, n=982 women	Crowther 2006	69

*Source: Crowther (2011); ^meta-analyses conducted for these Clinical Practice Guidelines

Table 75: Comparison of the overall effect estimate for use of repeat antenatal corticosteroids with trials that reported including a proportion of women with a fetus with intrauterine growth restriction – Infant primary outcomes*

Primary outcome	Repeat antenatal corticosteroids			Trials known to have included a proportion of women with a fetus with intrauterine growth restriction				
	Trials contributing data	Number of infants	Risk ratio (RR) (95% Confidence Interval)	Trials contributing data	Number of infants	Risk ratio (RR) (95% Confidence Interval)	Actual proportion detailed in trials	Actual number of infants
Perinatal death	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Mazumder 2008; McEvoy 2010; Murphy 2008; Peltoniemi 2007; Wapner 2006	5554	RR 0.94 (0.71 to 1.23), 9 trials	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Murphy 2008	4545	RR 0.93 (0.69 to 1.26), 5 trials, n=4545 infants	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Murphy 2008	334
Fetal death	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Mazumder 2008; McEvoy 2010; Peltoniemi 2007	2755	RR 0.82 (0.24 to 2.84), 7 trials	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001	2241	RR 0.99 (0.20 to 4.90) 4 trials, n=2241 infants	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001	127
Neonatal death	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Mazumder 2008; McEvoy 2010; Peltoniemi 2007	2713	RR 0.91 (0.62 to 1.34), 7 trials	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001	2199	RR 0.82 (0.52 to 1.27) 4 trials, n=2199 infants	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001	125
Respiratory distress syndrome	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Mazumder 2008; McEvoy 2010; Peltoniemi 2007; Wapner 2006	3206	RR 0.83 (0.75 to 0.91), 8 trials	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001	2199	RR 0.80 (0.71 to 0.90) 4 trials, n=2199 infants	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001	125
Composite outcome of serious infant outcomes	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Mazumder 2008; Murphy 2008; Wapner 2006	5094	RR 0.84 (0.75 to 0.94), 7 trials	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Murphy 2008;	4524	RR 0.85 (0.76 to 0.95) 5 trials, n=4524 infants	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Murphy 2008;	332

*Source: (Crowther 2011); ^meta-analyses conducted for these Clinical Practice Guidelines

Evidence summary for use of antenatal corticosteroids for women with a fetus with intrauterine growth restriction at risk of preterm birth

Five of 10 trials included in the Crowther (2011) systematic review reported including a proportion of women in their trials who had a fetus with intrauterine growth restriction at risk of preterm birth The proportion of women recruited with a fetus with intrauterine growth restriction ranged from 0% to 9%, where reported.

For the mother

Overall, where reported in 10 trials, no differences were seen between women treated with repeat antenatal corticosteroids and women with no repeat corticosteroids in the risk for chorioamnionitis, postnatal pyrexia or puerperal sepsis.

Five trials reported including a proportion of women with a fetus with intrauterine growth restriction. The evidence is consistent with the overall treatment effect:

- For chorioamnionitis, postnatal pyrexia and puerperal sepsis, the size of the treatment effect was similar to the overall effect and there was no difference between groups.

No data were reported for pyrexia after trial entry, intrapartum pyrexia or maternal quality of life.

For the infant

Overall, where reported in 10 trials, there was a significant reduction in the risks for respiratory distress syndrome and a composite of serious infant outcomes. No differences were seen in the risks for perinatal death, fetal death and neonatal death between infants exposed to a repeat antenatal corticosteroids and infants with no repeat exposure. Birthweight was also significantly reduced in infants who had been exposed to repeat antenatal corticosteroids.

Five trials reported including a proportion of women with a fetus with intrauterine growth restriction. The evidence is consistent with the overall treatment effect:

- For respiratory distress syndrome and a composite of serious infant outcomes the size of the treatment effect was similar to the overall effect and there was also a significant reduction in risk for infants exposed to a repeat antenatal corticosteroids compared with no repeat exposure;
- For perinatal death, fetal death and neonatal death the size of the treatment effect was similar to the overall effect and there was no difference between groups.
- Birthweight was similar to the overall birthweight and there was also a significant difference.

See Appendix M34 – Evidence Summary (Page 444)

What is the safety for the mother, fetus, infant, child, adult of administering repeat antenatal corticosteroids to women with a fetus with intrauterine growth restriction at risk of preterm birth?

Practice point:

- Repeat antenatal corticosteroids for a woman with a fetus with intrauterine growth restriction at risk of preterm birth.

14.11 Women with ultrasound evidence of cervical shortening /funnelling

What is the safety for the mother of administering a single course or a repeat dose(s) of antenatal corticosteroids to women with ultrasound evidence of cervical shortening/funnelling at risk of preterm birth?

What is the safety for the fetus, infant, child, adult of administering a single course or a repeat dose(s) of antenatal corticosteroids to women with ultrasound evidence of cervical shortening/funnelling at risk of preterm birth?

None of the trials in the updated systematic reviews (Roberts CPG version 2015; Brownfoot CPG version 2015; Crowther CPG version 2015; Sotiriadis CPG version 2015) detailed the proportion of women randomised with ultrasound evidence of cervical shortening.

Cervical shortening may be partly explained by normal biologic variance. Other reasons for cervical shortening include pathologic processes such as inflammation, haemorrhage, premature uterine contractions, or uterine over-distension all of which may lead to preterm birth (Lee 2009). Transvaginal assessment of the cervix is an easily reproducible and safe technique (Heath 1998a) that has been widely introduced to aid prediction of those at highest risk of preterm birth. A number of parameters of cervical assessment have been studied including funnel length and width and cervical index, however, closed length of cervix is the most reproducible and accepted measure used.

Iams (1996) used ultrasound to determine cervical length in 2915 women at approximately 24 weeks' gestation and 2531 of these women again at approximately 28 weeks'. This demonstrated a normal distribution of cervical length in the general population but with the relative risk of preterm birth increasing as the length of the cervix decreased.

Subsequent studies in larger general populations have confirmed the increased risk of preterm birth in asymptomatic women with a short cervix (<15 mm) in the late second or early third trimester (Heath 1998b, Hassan 2000). However, these studies identify risk of birth before 34 weeks' and do not provide data for risk of birth within 48 hours or less than seven days to allow assessment of effect and safety of antenatal corticosteroid use or when the timing of use should occur.

Transvaginal assessment of cervical length has been used in asymptomatic women with identified risk factors for preterm birth to predict those at highest risk of preterm birth (Andrews 2000, Owen 2001, Guzman 2001). These tests have been performed mid trimester and have estimated risk of preterm birth at various gestational ages before 35 weeks' gestation. In the largest study of 'high risk' women (n=469) a shorter cervix (≤25 mm) at 15 to 24 weeks' gestation had a negative predictive value of 99% but only a 10% positive predictive value for birth at less than 28 weeks' (Guzman 2001). No data were provided on the risk of birth within 48 hours or less than seven days and ultrasound was performed at gestational ages when antenatal corticosteroids are not usually indicated (less than 24 weeks'). Although ultrasound assessment of cervical length in asymptomatic women with pre-existing risk factors for preterm birth may be useful to consider other therapeutic options such as cerclage (Berghella 2010) and progesterone (Romero 2012) it is not useful in identifying those who may benefit from antenatal corticosteroids.

Conversely in a diagnostic accuracy systematic review of symptomatic women (Boots 2014) cervical length has a diagnostic value as a predictor of birth within 48 hours and within 7 days of testing (**Table 76**). Where there was a 10% chance of preterm birth predicted to occur within 48 hours before the test,

the post-test probability increased to 42% when the test was positive and decreased to 3% for a negative test. Where there was a 20% chance of preterm birth predicted to occur within 7 days before the test, the post-test probability increased to 63% when the test was positive and decreased to 7% for a negative test.

Table 76: Diagnostic accuracy of ultrasound determined cervical length for predicting preterm birth*.

	Birth within 48 hours of testing	Birth within 7 days of testing
Sensitivity (95% confidence interval)	0.77 (0.54 to 0.90)	0.74 (0.58 to 0.85)
Specificity (95% confidence interval)	0.88 (0.84 to 0.91)	0.89 (0.85 to 0.92)

*Source: Boots (2014)

On searching the literature for these Clinical Practice Guidelines, one randomised trial was identified using cervical length to target antenatal corticosteroid use in women symptomatic for preterm birth (Alfirevic 2007). This trial did not report on any of the primary maternal or neonatal outcomes for these Clinical Practice Guidelines. The trial randomised 41 women with a singleton pregnancy who were having uterine contractions prior to 34 weeks' gestation and where a clinical decision had been made to use tocolytics and antenatal corticosteroids. The trial compared routine care (tocolytics and antenatal corticosteroids) in 20 women to 21 women with a transvaginal ultrasound scan to determine cervical length and if <15 mm they received tocolytics and antenatal corticosteroids.

The primary outcome of the trial was the proportion of women still pregnant after 7 days from the last injection of antenatal corticosteroids and to assess 'appropriate' treatment (defined as preterm birth with corticosteroids given within one week of birth). Seven women (33%) in the ultrasound group had a cervical length <15 mm and received tocolytics and antenatal corticosteroids. Fourteen percent of the ultrasound group were considered to have been treated inappropriately (gave birth more than one week after antenatal corticosteroid administration) compared with the routine care group where 90% received antenatal corticosteroids inappropriately (RR 0.16, 95%CI 0.05 to 0.39) (Alfirevic 2007). There were no babies in either group who were born preterm without receiving a full course of antenatal corticosteroids. No neonatal outcomes were reported.

The issue of the safety of withholding antenatal corticosteroids warrants further study. The authors acknowledge this study was not large enough to exclude the possibility that withholding antenatal corticosteroids if the cervix is not short (≥15 mm) may result in some babies being born without adequate antenatal corticosteroid treatment.

Evidence Summary for the use of antenatal corticosteroids in women with ultrasound evidence of cervical shortening/funnelling

There were no randomised controlled trial data for women with a ultrasound evidence of a short cervix at risk of preterm birth identified in the Roberts CPG version 2015 systematic review for a single course of antenatal corticosteroids or repeat antenatal corticosteroids. Compared with women with no cervical shortening, women with a short cervix, determined by transvaginal ultrasound, have an increased risk of a preterm birth.

See Appendix M35 - – Evidence Summary (Page 448)

What is the safety for the mother, fetus, infant, child, adult of administering a single course or a repeat dose(s) of antenatal corticosteroids to women with ultrasound evidence of cervical shortening/funnelling at risk of preterm birth?

Practice Points:

- Use a single course of antenatal corticosteroids for a woman presenting with symptoms of preterm

labour and with ultrasound evidence of cervical shortening (<15mm) and at risk of preterm birth.

- Repeat antenatal corticosteroids for a woman presenting with symptoms of preterm labour with ultrasound evidence of cervical shortening (<15mm) at risk of preterm birth.

14.12 Fetal fibronectin test and the use of antenatal corticosteroids in women at risk of preterm birth

What is the safety for the mother of administering a single course or a repeat dose(s) of antenatal corticosteroids to women having undergone fetal fibronectin testing?

What is the safety for the fetus, infant, child, adult of administering a single course or a repeat dose(s) of antenatal corticosteroids to women having undergone fetal fibronectin testing?

Fetal fibronectin is a fetal glycoprotein found at the interface between the maternal decidua and the fetal amniochorion (Lee 2009). It is released through mechanical or inflammatory mediated damage to the placenta or fetal membranes prior to birth and an elevated level in the cervico-vaginal fluid (>50 ng/mL) has been identified as a predictor of preterm birth in the presence of intact membranes (Goldenberg 1996).

None of the trials in the updated systematic reviews (Roberts CPG version 2015; Brownfoot CPG version 2015; Crowther CPG version 2015; Sotiriadis CPG version 2015) detailed the proportion of women randomised with results of a fetal fibronectin test.

The result of a fetal fibronectin test was not an eligibility criterion for any trial included in the CPG version 2015 systematic reviews (Appendix J; Appendix K).

A large systematic review including 64 observational studies investigated the use of fetal fibronectin screening in symptomatic and asymptomatic women in a combined total of 26,876 women (Honest 2002). In 28 studies of asymptomatic women a positive fetal fibronectin test was associated with an increase in the risk of preterm birth at less than 34 weeks' and less than 37 weeks' gestation. However in a general population it had a low sensitivity with only 18% of those with a positive test giving birth at less than 34 weeks' and likely to be a much smaller proportion giving birth within seven days (data not provided). In a similar way to ultrasound assessment of cervical length, fetal fibronectin in asymptomatic women is unlikely to be a helpful adjunct to determine which women and their fetuses that would benefit from antenatal corticosteroids.

However, this review also identified that in symptomatic women fetal fibronectin has a very high negative predictive value. Approximately 99% of women presenting with symptoms of preterm labour and a negative fetal fibronectin test did not give birth within 7 days. The review estimated that if antenatal corticosteroids were administered to all symptomatic women at 31 weeks' gestation in the absence of fetal fibronectin testing, the number needed to treat (NNT) to prevent 1 case of respiratory distress syndrome would be 109 versus only 17 if only those with positive fetal fibronectin were targeted (Honest 2002).

The review concluded that the excellent negative predictive value has the ability to facilitate decision making regarding, amongst a variety of factors, the administration of corticosteroids. The improved prediction of preterm birth can prevent unnecessary healthcare expenditure without compromising outcomes (Chandiramani 2011).

Evidence summary for the use of antenatal corticosteroids following a fetal fibronectin test in women at risk of preterm birth

There was no randomised controlled trial evidence that addressed the use of antenatal corticosteroids in the presence of a positive or negative fetal fibronectin test.

The fetal fibronectin test has a very high negative predicative value and therefore women with a negative test are unlikely to be at imminent risk of preterm birth.

See Appendix M36 – Evidence Summary (Page 452)

What is the safety for the mother, fetus/infant/child/adult of administering a single course or a repeat dose(s) of antenatal corticosteroids to women having undergone fetal fibronectin testing?

Practice Points:
• Use a single course of antenatal corticosteroids for a woman presenting with symptoms of preterm labour with a positive fetal fibronectin test and at risk of preterm birth. • Repeat antenatal corticosteroids for a woman presenting with symptoms of preterm labour with a positive fetal fibronectin test at risk of preterm birth. • Do not use antenatal corticosteroids in a woman where a fetal fibronectin test is negative due to the high negative predictive value of the test.

14.13 Women for whom preterm birth is medically indicated for other reasons

What is the safety for the mother of administering a single course of antenatal corticosteroids to women for whom preterm birth is medically indicated?

What is the safety for the fetus, infant, child, adult of administering a single course of antenatal corticosteroids to women for whom preterm birth is medically indicated?

In previous sections of Chapter 14 these Clinical Practice Guidelines have included some of the more common reasons for medical indications for preterm birth such as pre-eclampsia and intrauterine growth restriction. Other reasons for medically indicated preterm birth include maternal cardiac disease, chronic asthma, renal disease, cancer or cholestasis. None of the randomised trials included in the Roberts CPG version 2015 systematic review detailed if women with these conditions were eligible for inclusion.

We were unable to obtain any data on the maternal or infant primary outcomes for these Clinical Practice Guidelines in women for whom preterm birth was medically indicated for maternal cardiac disease, chronic asthma, renal disease, cancer or cholestasis.

Evidence summary for the use of a single course of antenatal corticosteroids in women for whom preterm birth is medically indicated

No randomised controlled trial evidence was reported for the use of a single course of antenatal corticosteroids for a variety of maternal conditions where preterm birth may be medically indicated.

Based on the benefits observed in the overall treatment effect (Chapters 3 to 5) it is likely that there would be benefit to the fetus of exposure to a single course of antenatal corticosteroids for fetal lung development with no health harms for the mother.

The benefits and harms of a single course of antenatal corticosteroids in cases where preterm birth is medically indicated has not been fully explored in randomised trials. Further research is required to explore the value of antenatal corticosteroids in these subgroups of women and their infants.

See Appendix M37 – Evidence Summary (Page 456)

What is the safety for the mother, fetus, infant, child, adult of administering a single course of antenatal corticosteroids to women for whom preterm birth is medically indicated?

Practice Points:

- Use a single course of antenatal corticosteroids for women with other medical indications for preterm birth.
- Do not delay birth to administer antenatal corticosteroids if preterm birth is medically indicated.

What is the safety for the mother of administering repeat antenatal corticosteroids to women for whom preterm birth is medically indicated?

What is the safety for the fetus, infant, child, adult of administering repeat antenatal corticosteroids to women for whom preterm birth is medically indicated?

In previous sections of Chapter 14 these Clinical Practice Guidelines have included some of the more common reasons for medical indications for preterm birth such as pre-eclampsia and intrauterine growth restriction. Other reasons for medically indicated preterm birth include maternal cardiac disease, chronic asthma, renal disease, cancer or cholestasis. None of the randomised trials included in the Crowther (2011) systematic review detailed if women with these conditions were eligible for inclusion.

We were unable to obtain any data on the maternal or infant primary outcomes for these Clinical Practice Guidelines for women for whom preterm birth was medically indicated for maternal cardiac disease, chronic asthma, renal disease, cancer or cholestasis.

Evidence summary for the use of repeat antenatal corticosteroids in women for whom preterm birth is medically indicated

No randomised controlled trial evidence was reported for the use of repeat antenatal corticosteroids for a variety of maternal conditions where preterm birth may be medically indicated. Based on the benefits observed in the overall treatment effect (Chapters 6 to 8) it is likely that there would be benefit to the fetus of exposure to repeat antenatal corticosteroids for fetal lung development with no health harms for the mother.

The benefits and harms of repeat antenatal corticosteroids in cases where preterm birth is medically indicated has not been fully explored in randomised trials. Further research is required to explore the value of antenatal corticosteroids in these subgroups of women and their infants.

See Appendix M38 – Evidence Summary (Page 460)

What is the safety for the mother, fetus, infant, child, adult of administering repeat antenatal corticosteroids to women for whom preterm birth is medically indicated?

Practice Point:
• Repeat antenatal corticosteroids for a woman with other medical indications for preterm birth.

Chapter 15: Use of antenatal corticosteroids for women with diabetes in pregnancy or gestational diabetes at term

What are the benefits and harms for the mother of administering antenatal corticosteroids for fetal lung maturation to women with diabetes mellitus or gestational diabetes at term?

What are the benefits and harms for the fetus, infant, child and adult of administering antenatal corticosteroids for fetal lung maturation to women with diabetes mellitus or gestational diabetes at term?

Summary of evidence for use of antenatal corticosteroids in women with diabetes in pregnancy or gestational diabetes.

The updated systematic reviews (Roberts CPG version 2015; Brownfoot CPG version 2015; Crowther CPG version 2015; Sotiriadis CPG version 2015) found no data from randomised trials for maternal or neonatal outcomes associated with the use of antenatal corticosteroids in women with diabetes or gestational diabetes at term.

See Appendix M39 –Evidence Summary (Page 464)

Practice points:

- There is insufficient evidence currently to make a recommendation for antenatal corticosteroids at term (≥37 weeks' gestation) for women with diabetes in pregnancy.
- Use antenatal corticosteroids 48 hours prior to caesarean birth planned beyond 34 weeks' and 6 days gestation if there is known fetal lung immaturity.
- Monitor maternal blood glucose concentrations and treat if elevated.

Research recommendation:

- Randomised trials are needed to investigate the effects, if any, of using antenatal corticosteroids at term gestation in women with diabetes in pregnancy.

Chapter 16: Are antenatal corticosteroids cost effective?

Are antenatal corticosteroids cost effective?

Antenatal corticosteroids are listed as a priority intervention prior to preterm birth (PMNCH 2011). Both dexamethasone and betamethasone are identified on the WHO priority medicines list for the purpose of reducing mortality in preterm babies (Lawn 2012). Despite the wealth of evidence from well conducted randomised controlled trials only New Zealand, Australia and Argentina have registration of antenatal corticosteroids for the indication of fetal lung maturation (Lawn 2012). In many other countries the indication for use for fetal lung maturation is a standard of care by implication.

The risk ratio for significant health outcomes and health resources for a single course of antenatal corticosteroids versus no corticosteroids and for repeat dose(s) of antenatal corticosteroids versus no repeat dose(s) are summarised in **Table 77**

A single course of antenatal corticosteroids compared to no antenatal corticosteroids reduces the risk of perinatal deaths by 23%. Respiratory distress syndrome is reduced by 35% with a single course and further repeat antenatal corticosteroids reduced respiratory distress syndrome by 17%. A composite outcome of serious neonatal adverse events was reduced by 16% with administration of repeat antenatal corticosteroids.

There were no significant differences in admission to neonatal intensive care which probably reflects the gestational age at birth. However, the risk for the need for mechanical ventilation is reduced by 27% in the single course of antenatal corticosteroids and by 11% when repeat antenatal corticosteroids are administered. Other respiratory outcomes including duration of mechanical ventilation and requirement for oxygen supplementation were also significantly reduced.

Economic evaluation - Early preterm

Earlier cost-benefit evaluations undertaken in the 1990's suggested a net saving for a single course of antenatal corticosteroids versus no corticosteroids for infants of <35 weeks' (Mugford 1991), <31 weeks' (Egberts 1992) and low birthweight (<2000g) (Simpson 1995). Simpson (1995) calculated that for each 100 low birthweight infants (<2000 g) who were exposed to a complete course of antenatal corticosteroids

- For the group that received antenatal corticosteroids the total estimated cost of their hospitalisation was US$1.72 million (based on Crowley (Crowley 1990) and the state of Maryland data).
- For the group that received antenatal corticosteroids there were an estimated seven deaths and 25 cases of respiratory distress syndrome.
- In the group that did not received antenatal corticosteroids, the estimated cost of hospitalisation was US$2.05 million
- In the group that did not received antenatal corticosteroids there were an estimated 12 deaths and 37 cases of respiratory distress syndrome.

Simpson (1995) found similar results when they examined data from hospitals within the National Institute of Child Health and Human Development Neonatal Research Network Centers.

- Based on 1992 costs a saving of US$500,000 per 100 infants treated with antenatal corticosteroids at <28 weeks' gestational age was calculated.

- The antenatal corticosteroid group was also estimated to have 17 fewer deaths, nine additional cases of respiratory distress syndrome and seven additional survivors without respiratory distress syndrome per 100 exposed infants.

Economic evaluation later preterm

A decision analytic and economic analysis was conducted (Bastek 2012) examining if antenatal corticosteroids had health benefits for late preterm infants (34 to 36 weeks' gestation). The authors included data from the Cochrane review of *Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth* (Roberts 2006) to estimate the probabilities of selected neonatal outcomes that included mortality, respiratory distress syndrome, neurodevelopmental delay and health with or without antenatal corticosteroids. They identified other population based data from observational studies. The costs were all calculated in US$.

- At 34, 35 and 36 weeks' the use of antenatal corticosteroids to women at risk of imminent preterm birth was the most cost-effective strategy (Incremental cost-effectiveness ratio - ICER $/QALY 62,888.25 at 34 weeks', 64,425.67 at 35 weeks' and 64,793.71 at 36 weeks') (Bastek 2012).

Further modelling suggested that if all late preterm infants received antenatal corticosteroids the rate of respiratory distress syndrome would be reduced by almost half for infants with gestational age of 34 and 35 weeks' and by 40% in infants with a gestational age of 36 weeks'. The estimated savings for infants of 34 and 35 weeks' was US$ 32 million.

However there was an estimated cost of US$3.4 million for infants with a gestational age of 36 weeks' and this was associated with increased hospitalisation compared with savings due to reduced respiratory distress syndrome in the 34 and 35 weeks' groups. Respiratory distress syndrome was assumed to be relatively less common from 36 weeks' gestational age. It was also estimated that an additional US$166.2 million per annum could be saved as a result of reduced chronic respiratory disease, neurodevelopmental delay and death in childhood (Bastek 2012).

Table 77: Significant health outcomes and resource use following administration of antenatal corticosteroids for women at risk of preterm birth*

Outcome	Single Course antenatal corticosteroids		Repeat Course/s antenatal corticosteroids	
	RR (95%CI)	Authors	RR (95%CI)	Authors
Perinatal death	0.77 (0.67 to 0.89) 13 trials, 3627 infants	Amorim 1999; Block 1977; Collaborative 1981; Dexiprom 1999; Doran 1980; Gamsu 1989; Garite 1992; Kari 1994; Liggins 1972; Parsons 1988; Qublan 2001; Schutte 1980; Taeusch 1979	0.94 (0.71 to 1.23) 9 trials, 5554 infants	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Mazumder 2008; McEvoy 2010; Murphy 2008; Peltoniemi 2007; Wapner 2006
Respiratory distress syndrome	0.65 (0.58 to 0.73); 25 trials, 4590 infants	Amorim 1999; Balci 2010; Block 1977; Cararach 1991; Carlan 1991; Collaborative 1981; Dexiprom 1999; Doran 1980; Fekih 2002; Gamsu 1989; Garite 1992; Goodner 1979; Kari 1994; Lewis 1996; Liggins 1972; Lopez 1989; Morales 1989; Nelson 1985; Parsons 1988; Porto 2011; Qublan 2001; Schutte 1980; Silver 1996; Taeusch 1979; Teramo 1980	0.83 (0.75 to 0.91) 8 trials, 3206 infants	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Mazumder 2008; McEvoy 2010; Peltoniemi 2007; Wapner 2006
Composite outcome	N/R	N/R	0.84 (0.75 to 0.94) 7 trials, 5094 infants	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Mazumder 2008; Murphy 2008; Wapner 2006
Admission to neonatal intensive care	0.88 (0.73 to 1.06) 4 trials, 629 infants	Amorim 1999; Lewis 1996; Porto 2011; Shanks 2010	1.01 (0.95 to 1.07) 2 trials, 3448 infants	Crowther 2006; Murphy 2008
Need for mechanical ventilation	0.73 (0.59 to 0.92) 7 trials, 1021 infants	Amorim 1999; Balci 2010; Block 1977; Dexiprom 1999; Garite 1992; Porto 2011; Shanks 2010	0.84 (0.71 to 0.99) 6 trials, 4918 infants	Crowther 2006; Garite 2009; McEvoy 2010; Murphy 2008; Peltoniemi 2007; Wapner 2006
Duration of mechanical ventilation (mean difference)	-1.42 (-2.28 to -0.56) 3 trials, 518 infants	Garite 1992; Morales 1989; Porto 2011	0.30 (-0.90 to 1.50) 1 trial, 37 infants	McEvoy 2002
Duration of oxygen supplementation (mean difference)	-2.86 (-5.51 to -0.21) 1 trial, 73 infants	Amorim 1999	3.30 (-2.31 to 8.91) 1 trial, 3 7 infants	McEvoy 2002
Developmental delay in childhood	0.49 (0.24 to 1.00); 2 trials, 518 infants	2 trials, 518 infants Amorim 1999; Collaborative 1981	0.97 (0.84 to 1.13); 3 trials, 3202 infants	Crowther 2006; Murphy 2008; Peltoniemi 2007

*Source: Roberts CPG version 2015; Crowther (2011)

Summary for cost-effectiveness of antenatal corticosteroids

Single course of antenatal corticosteroids

The costs of administering a single, complete course of antenatal betamethasone or dexamethasone to women at risk of preterm labour, up to 36 weeks' gestation, results in significant savings for infant health outcomes (primarily by reducing the risk of respiratory distress syndrome).

Repeat antenatal corticosteroids

As repeat antenatal corticosteroids reduce respiratory distress syndrome and serious infant morbidities their use is likely to have economic benefits. No decision analysis or economic analysis for repeat antenatal corticosteroids has been conducted to date.

Research recommendation:
• Conduct a decision analysis / economic analysis for repeat antenatal corticosteroids

Chapter 17: Implementation of these Clinical Practice Guidelines

Clinical practice guideline recommendations can aid clinicians, policymakers and consumers in determining the best treatment options for prevention or treatment of a particular disease. However, there is no single "ideal" or most effective intervention to promote the uptake of guideline recommendations.

We propose that implementation of the 'Antenatal corticosteroids given to women prior to birth to improve fetal, child and adult health' clinical practice guideline will include:

- raising awareness of key audiences and stakeholders to the new guideline recommendations and best practice;
- identification of processes and systems that will support the uptake or adoption of the guideline recommendations;
- an assessment of local barriers and enablers to the implementation of the guideline recommendations which will identify characteristics of the individual, organisation and political environment;
- identification of key factors that can be measured and reviewed to assess changes in practice and adherence to the guideline recommendations and effect on health outcomes.

Resources that have been found to be useful in implementation of clinical practice guideline recommendations (Flodgren 2010, Forsetlund 2009, Giguere 2012, Ivers 2012) include:

- a Powerpoint presentation describing the key recommendations of the guideline/ guidance for use by health professionals;
- supporting resources such as checklists or summary cards;
- incorporation of the guideline recommendations into conference programmes, journal articles, continuing education programmes and online quizzes;
- incorporation of the guideline recommendations into local care pathways;
- measures for determining the extent to which the key recommendations have been implemented (clinical and process outcomes);
- an evaluation strategy to assess the extent to which the recommendations have been selected or developed and then adopted into routine clinical practice.

It is anticipated that the implementation of this guideline will:

- provide clear, evidence-based advice for all health care workers, policy makers and women at risk of imminent preterm birth;
- improve outcomes for mothers and babies by reducing fetal and neonatal death, respiratory distress syndrome, intraventricular haemorrhage, systemic infection within 48 hours of birth and need for respiratory support;
- provide a benchmark for clinical practice in the treatment of women at risk of preterm birth.

It is recommended that these key messages be actively promoted as part of the dissemination and education strategy for these guidelines.

The key stakeholders

- *Women who are at risk of preterm birth and their family:* Women at risk of imminent preterm birth need to be provided with information about the use of antenatal corticosteroids. This includes how they can improve fetal lung development and reduce the risk of death and other morbidities for their baby. This information needs to take account of different levels of health knowledge, individual issues and concerns, cultural, social, financial circumstances and womens' views and preferences.

- *Health service providers:* Each local health service provider should ensure that services for pregnant women at risk of preterm birth are configured to reflect best practice and are designed around the needs of the women and the safe birth of her baby.

- *Health care professionals:* Health care professionals including midwives, obstetricians, maternal fetal medicine subspecialists and neonatologists have a crucial role in providing evidence based professional care, health information about the care and supporting women at risk of preterm birth and their families.

- *Pharmacists*: Pharmacists can play a role in advising on the appropriate use of single and repeat antenatal corticosteroids.

- *Consumer organisations:* Relevant consumer groups will be encouraged to promote the clinical and research recommendations and practice points in these guidelines to their membership

- *Professional colleges and organisations:* Professional colleges and organisations will be encouraged to actively promote the uptake of the guidelines clinical and research recommendations and practice points and provide and promote education about the guidelines to their members.

Dissemination of the guideline

The full guideline will be published in electronic format on the Liggins Institute, University of Auckland website. The guideline will be officially launched in 2015 at The Perinatal Society of Australia and New Zealand Annual Conference with promotion of the recommendations by key opinion leaders at relevant conferences in 2015.

A multifaceted implementation approach is recommended to ensure that there is sufficient opportunity

- to raise awareness of the guidelines;
- promote and encourage adoption of the recommendations by health care practitioners, policy makers and consumers.

Table 78 shows suggested stages of change for the implementation of the 'Antenatal corticosteroids given to women prior to birth for improving fetal, child and adult health' clinical practice guideline.

Table 78: Stages of change for implementation of the 'Antenatal corticosteroids given to women prior to birth to improve fetal, child and adult health' clinical practice guidelines.

Methods/ Stages of change	Awareness	Agreement	Adoption	Adherence
Predisposing	Launch of the guideline Ensure health practitioners have access to the guideline in both New Zealand and Australia.	Using key opinion leaders/champions to promote the guidelines at conference and in newsletters and journals . Offering training to health practitioners in the new guideline.	Undertake a current practice review in a select number of units to identify the gap between existing practice and the guidelines.	Collect data on the dissemination of the guideline and supporting tools and resources.
Enabling	Provide website access to a downloadable version of the guideline. Ensure health practitioners have access to the guideline in both New Zealand and Australia.	Development of resources to explain the appropriate use of antenatal corticosteroids.	Design local care pathways for women at risk of preterm birth if required.	Conduct qualitative research with consumers and health professionals to understand whether the new guidelines have met their needs. Incorporate the collection of clinical and process outcomes into routine data collection systems to evaluate the impact of the guidelines recommendations.
Reinforcing		Supporting peer review group discussion of the guideline.	Offer professional development points for practitioners competing education modules.	Offer clinical audit tools to assess performance. Development of and participation in randomised trials and other research activities on the use of antenatal corticosteroids .

Adapted from the Pathman/PRECEDE Model (David 2003)

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Appendix A: Guideline Panel Membership

Members	Expertise	Affiliation	Role on the panel
Caroline Crowther	Maternal fetal medicine subspecialist.	Liggins Institute, The University of Auckland	Chairperson of the Guideline Panel
Julie Brown	Research Synthesis and Clinical Guideline Development	The Liggins Institute, University of Auckland	Member of the Executive Group, member for the Guideline Panel and Project Officer
Jane Alsweiler	Neonatologist	Senior Lecturer, Department of Paediatrics: Child and Youth Health, University of Auckland Consultant Neonatologist, NICU, National Women's Health, Auckland City Hospital Honorary Senior Lecturer, Liggins Institute, University of Auckland	Member of the Executive Group, member for the Guideline Panel
Philippa Middleton	Perinatal Epidemiologist, Research Methodologist	Executive Director of ARCH within Robinson Institute, University of Adelaide	Member of the Executive Group, member for the Guideline Panel
Katie Groom	Maternal fetal medicine subspecialist.	Consultant Obstetrician and Gynaecologist at National Women's Health, Auckland City Hospital Senior Lecturer in Department of Obstetrics and Gynaecology, University of Auckland	Royal Australian and New Zealand College of Obstetrics and Gynaecology
Euan Wallace*	Obstetrician and Gynaecologist	Director of Obstetric Services for Southern Health, Department of Obstetrics & Gynaecology Monash University, Director of the Ritchie Centre, Monash University	Perinatal Society of Australia and New Zealand
Dell Horey*	Consumer Advocate	Faculty of Health Sciences, School of Health Sciences Research, Melbourne University	Consumer representative
Liz van Dort	Consumer	Australia	Consumer representative
Cara Wasywich	Consumer	New Zealand	Consumer representative
Christine East	Midwifery	Co-Director of Maternity Services, Southern Health Professor of Midwifery, School of Nursing and Midwifery, Monash University	Perinatal Society of Australia and New Zealand

		Associate Editor for the Cochrane Pregnancy and Childbirth Group	
Vicki Flenady	Perinatal Epidemiologist	Director, Translational Health, Mater Institute, International Stillbirth Alliance, WHO Research Network	Chair of Perinatal Society of Australia and New Zealand Policy Group
Kay Gamble	Midwifery Diabetes Nurse Specialist	Delivery Unit, National Women's Health, Auckland City Hospital	College of Midwives New Zealand
Brenda Hughes	Specialist Paediatric Pharmacist	Auckland City Hospital	Pharmacists
Bill Jeffries	General Physician, Endocrinologist	Head of Department of Medicine, Lyell McEwin Hospital, Head of Obstetric Medicine at Flinders University	Expert in obstetric medicine
Mahia Winder	Maori Midwifery Advisor, Auckland District Health Board	Regional Committee of the New Zealand College of Midwives, Auckland University of Technology Midwifery Advisory Board, Auckland District Health Board's Child and Youth Mortality Review Panel, Ministry of Health's Mother and Baby Workforce Development Committee	Māori (New Zealand)
Annie Marshall	Neonatal Nurse,	Chairperson of the Neonatal Nurses College of Aotearoa (NNCA)	Neonatal Nurses College of Aotearoa
Sally Jeston	Neonatal Nurse	Australian College of Neonatal Nurses	Australian College of Neonatal Nurses
Chris McKinlay	Neonatologist	Liggins Institute, University of Auckland. New Zealand	Expert on antenatal corticosteroids
Tineke Crawford	Research Officer	Liggins Institute, University of Auckland. New Zealand	Management Group
Emma McGoldrick	Doctoral Student	Liggins Institute, University of Auckland. New Zealand	Management Group
Elaine Fyfe	Research Officer	Liggins Institute, University of Auckland. New Zealand	Management Group

*Resigned from Panel due to time constraints

Antenatal Corticosteroid Clinical Practice Guideline Panel Declarations of Competing Interest

Name	Declarations of Competing Interest
Caroline Crowther	Named author on following publications related to the topic of focus: 1. Brownfoot FC, Gagliardi DI, Bain E, Middleton P, **Crowther CA**. Different corticosteroids and regimens for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev 2013;8:CD006764. 2. **Crowther C**, Harding JE, Middleton PF, Andersen CC, Ashwood P, Robinson JS; A*STEROID Study Group. Australasian randomized trial to evaluate the role of maternal intramuscular dexamethasone versus betamethasone prior to preterm birth to increase survival free of childhood neurosensory disability (A*STEROID): study protocol. BMC Pregnancy Childbirth 2013;13:104. 3. **Crowther C**, Aghajafari F, Askie L, Asztalos E, Brochlehurst P, Bubner T, PRECISE Study Group. Repeat prenatal corticosteroid prior to preterm birth: a systematic review and individual participant data meta-analysis for the PRECISE study group (prenatal repeat corticosteroid international IPD study group: assessing the effects using the best level of evidence) – study protocol. Systematic Review 2012;1(12). 4. **Crowther CA**, McKinlay CJ, Middleton P, Harding, JE. Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes. Cochrane Database Syst Rev 2011;6:CD003935. 5. **Crowther CA**, Doyle LW, Haslam RR, Hiller JE, Harding JE, Robinson JS for the ACTORDS Study Group. Outcomes at 2 years of age after repeat doses of antenatal corticosteroids. N Engl J Med 2007;357(12):1179-89. 6. **Crowther C**, Haslam R, Hiller J, Doyle L, Robinson J & Australasian Collaborative Trials of Repeat Doses of Steroids (ACTORDS) Study Group. Neonatal respiratory distress syndrome after repeat exposure to antenatal corticosteroids: a randomized trial. Lancet 2006;367(9526):1913-9.
Chris McKinlay	1. Named author on following publications related to the topic of focus:**McKinlay CJD**, Cutfield WS, Battin MR, dalziel SR, Crowther CAC, Harding JE on behalf of the ACTORDS Study Group. Cardiovascular risk factors in children after repeat doses of antenatal glucorticoids: An RCT. Pediatrics 2015; 135(2): e405-15 2. **McKinlay CJD**, Crowther CA, Middleton P, Harding JE. Repeat antenatal glucocorticoids for women at risk of preterm birth: a Cochrane systematic review. Am J Obstet Gynecol. 2012;206(3):187-94. 3. Crowther CA, **McKinlay CJD**, Middleton P, Harding JE. Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes. Cochrane Database Sys Rev. 2011;6:CD003935.
Katie Groom	Funding from Hologic to attend the Australian fFN (fetal fibronectin) Advisory Panel Meeting (one day consultation meeting).
Philippa Middleton	Named author on following publications related to the topic of focus: 1. Crowther C, Harding JE, **Middleton PF**, Andersen CC, Ashwood P, Robinson JS; A*STEROID Study Group. Australasian randomized trial to evaluate the role of maternal intramuscular dexamethasone versus betamethasone prior to preterm birth to increase survival free of childhood neurosensory disability (A*STEROID): study protocol. BMC Pregnancy Childbirth 2013;13:104. 2. Brownfoot FC, Gagliardi DI, Bain E, **Middleton P**, Crowther CA. Different corticosteroids and regimens for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev 2013;8:CD006764. 3. Crowther C, Aghajafari F, Askie L, Asztalos E, Brochlehurst P, Bubner T, Doyle LW, Dutta S, Garite TJ, Guinn DA, Hallman M, Hannah ME, Hardy P, Maurel K, Mazumder P, McEvoy C, **Middleton PF**, Murphy KE, Peltoniemi OM, Peters D, Sullivan L, Thom EA, Voysey M, Wapner RJ, Yellans L, Zhang S. Repeat prenatal corticosteroid prior to preterm birth: a systematic review and individual participant data meta-analysis for the PRECISE study group (prenatal repeat corticosteroid international IPD study group: assessing the effects using the best level of evidence) – study protocol. Systematic Review 2012;1(12). 4. McKinlay CJD, Crowther CA, **Middleton P**, Harding JE. Repeat antenatal glucocorticoids for women at risk of preterm birth: a Cochrane systematic review. Am J Obstet Gynecol. 2012;206(3):187-94. 5. Crowther CA, McKinlay CJD, **Middleton P**, Harding JE. Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes. Cochrane Database Sys Rev. 2011;6:CD003935.
No conflicts declared	Jane Alsweiler; Julie Brown; Tineke Crawford; Christine East; Vicki Flenady; Kay Gamble; Bill Jeffries; Brenda Hughes; Sally Jeston; Annie Marshall; Emma McGoldrick; Mahia Winder; Elizabeth Van Dort; Cara Wasysich

Appendix B: Health Outcomes for these Clinical Practice Guidelines

Maternal outcomes for these Clinical Practice Guidelines

Maternal outcomes	Roberts 2006	Crowther 2011	Brownfoot 2013	Sotriadis 2009
Pyrexia after entry into trial requiring antibiotics *	√	√	√	
Chorioamnionitis*	√	√	√	
Intrapartum fever requiring antibiotics*	√	√	√	
Post-natal pyrexia*	√	√	√	
Puerperal sepsis*	√	√	√	
Quality of life*		√		
Glucose tolerance*	√		√	
Mortality	√	√	√	
Hypertension	√	√	√	
Mode of birth		√		
Post-partum haemorrhage (PPH)				
Breastfeeding at hospital discharge and at 6 months		√		
Post-natal depression symptoms		√		
Mental anxiety				
Adverse effects of antenatal corticosteroid therapy (Gastrointestinal upset, glucose intolerance, insomnia, pain at injection site, bruising at injection site, infection at injection site, weight gain, Cushing syndrome)	√	√	√	
Gestational diabetes mellitus diagnosis post trial after antenatal corticosteroid treatment				
Insulin use after antenatal corticosteroid treatment				
Maternal outcomes in women with diabetes in pregnancy				
Use of insulin or an increase in insulin use after antenatal corticosteroid treatment				
Elevated HbA1C post-partum				
Elevated fasting plasma glucose				
Change in diabetes associated treatment regimen after antenatal corticosteroid treatment				
Hospital admission for glucose control				
Maternal hyperglycaemia				
Maternal hypoglycaemia				

*primary outcomes for these Guidelines

Fetal, Neonatal and Infant outcomes for these Clinical Practice Guidelines

Fetal, Neonatal and Infant outcomes	Roberts 2006	Crowther 2011	Brownfoot 2013	Sotriadis 2009
Fetal, neonatal or later death*	√	√	√	
Respiratory distress syndrome*	√	√	√	√
Composite serious outcome (may include fetal, neonatal or later death, severe respiratory distress, severe IVH (Grade 3 or 4), chronic lung disease, necrotising enterocolitis, retinopathy of prematurity, cystic periventricular leukomalacia, patent ductus arteriosus, neonatal encephalopathy)*		√		
Intraventricular haemorrhage (IVH) any grade	√	√	√	
Severe IVH (Grade 3 or 4)	√	√	√	
Cystic periventricular leucomalacia/white matter injury		√	√	
Neonatal encephalopathy in term babies				
Patent ductus arteriosus as defined, requiring treatment		√	√	
Transient tachypnoea of the neonate (term)				
Hypoglycaemia requiring treatment				
Hyperglycaemia requiring treatment				
Chronic lung disease	√	√	√	
Necrotising enterocolitis	√	√	√	
Retinopathy of prematurity		√	√	
Gestational age at birth		√		
Interval between antenatal corticosteroid exposure and birth	√	√	√	
Small for gestational age as defined	√	√	√	
Birthweight	√	√	√	
Birth length	√	√	√	
Birth head circumference	√	√	√	
Placental weight	√	√	√	
Low Apgar (<7 at 5 minutes)	√	√	√	
Use and duration of respiratory support	√	√	√	√
Use and duration of oxygen supplementation	√	√	√	
Use of surfactant	√	√	√	
Air leak syndrome	√	√	√	
Pulmonary hypertension				
Inotropic support	√	√	√	
Use of nitric oxide for respiratory support		√		
Early neonatal infection (< 48 hours)	√	√	√	
Late neonatal infection (≥ 48 hours)		√	√	
Use of post-natal corticosteroids		√		
Neonatal blood pressure	√	√	√	
Anthropometry at hospital discharge		√		
HPA axis suppression, including cortisol	√	√	√	

*primary outcomes for these Guidelines

Child outcomes for these Clinical Practice Guidelines

Child outcomes	Roberts 2006	Crowther 2011	Brownfoot 2013	Sotriadis 2009
Survival free of neurosensory disability*		√		
Neurosensory disability (composite of impairments: cerebral palsy, blindness, deafness, developmental delay)*	√	√	√	
Total mortality	√	√	√	
Cerebral palsy	√	√	√	
Developmental delay / IQ	√	√	√	
Visual impairment	√	√	√	
Hearing impairment	√	√	√	
Motor dysfunction		√		
Anthropometry	√	√	√	
Child behaviour	√	√	√	
Respiratory disease/lung function	√	√	√	
Blood pressure	√	√	√	
Impairment of insulin / glucose axis or insulin sensitivity	√	√	√	
Cognitive ability	√	√	√	
Learning disability	√	√	√	
Hypothalamic pituitary adrenal axis suppression	√	√	√	
Child as adult outcomes				
Survival free of metabolic disease*		√	√	
Mortality	√	√		
Diabetes				
Obesity				
Cardiovascular disease			√	
Age at puberty	√	√	√	
Educational attainment	√	√	√	
IQ		√	√	
Cognitive ability		√	√	
Learning disability		√	√	
Visual impairment	√	√	√	
Hearing impairment	√	√	√	
Bone density	√	√	√	
Respiratory function	√	√	√	
Anthropometry	√	√	√	
Blood pressure	√	√	√	
Hypothalamic pituitary adrenal axis suppression	√	√		

*primary outcomes for these Guidelines

Health service use outcomes for these Clinical Practice Guidelines

Health service use outcomes	Roberts 2006	Crowther 2011	Brownfoot 2013	Sotriadis 2009
Duration of respiratory support*				
Length of neonatal hospitalisation	√	√	√	
Length of stay in NICU		√		√
Admission to NICU		√		√
Maternal admission to ICU		√		
Length of postnatal hospitalisation for the women	√	√	√	
Length of antenatal hospitalisation for the women	√	√	√	

*primary outcomes for these Guidelines

Appendix C: Clinical Practice Guidelines Process and Methods

The following section details the methodology used for the development of these Clinical Practice Guidelines.

Electronic searching

Search strategies were developed by an information specialist in conjunction with the research team (search strings are at the end of this Appendix).

Electronic searches were not date limited and the databases searched were:

- Medline
- Embase
- CENTRAL
- Cochrane Database of Systematic Reviews
- HTA database
- National Guideline Clearing House
- Guidelines International Network Database
- Clinical Trials Register
- Specialised register of the Pregnancy and Childbirth Cochrane Group

Searches took place in October 2012 and were re-run in September 2014.

Population

The target population were women who received antenatal corticosteroids (any regimen, drug type or number of courses) for fetal lung maturation.

Type of studies

Where possible we used the highest possible level of evidence to inform clinical practice recommendations. Where possible evidence was restricted to clinical guidelines, systematic reviews and randomised controlled trials. We acknowledge that in some areas there may be a lack of high quality evidence and a lower level of evidence will be accepted.

Where studies were identified within existing systematic reviews or guidelines, they were not critically appraised nor an evidence table created.

Only evidence published in peer reviewed journals were included in the systematic reviews.

The following types of publication were excluded: case series studies, editorials and commentaries, book chapters, personal communications or news items.

Analyses

These Clinical Practice Guidelines have presented some of the original data from the sentinel Cochrane systematic reviews (Roberts 2006; Crowther 2011; Brownfoot 2013; Sotriadis 2009). For the purpose of the Clinical Practice Guidelines the reviews were updated, additional analyses were undertaken including meta-analyses and subgroup interaction tests (Roberts CPG version 2015; Crowther CPG version 2015; Brownfoot CPG version 2015). Where there was evidence of substantial clinical heterogeneity ($I^2 \geq 30\%$) a random effects model was used. All data are presented as effect estimates with 95% confidence intervals for continuous data or mean differences with 95% confidence intervals for continuous data.

Evidence tables

Evidence was summarised in risk of bias or evidence tables depending on the level of evidence.

Assessment of quality of included studies

A number of internationally recognised tools are available to critically appraise studies. Evidence was appraised using an adapted NHMRC and GRADE methods (Appendix M).

Search strategies for antenatal corticosteroids

CENTRAL RCT search
Database: EBM Reviews - Cochrane Central Register of Controlled Trials <Sept 2014>
Search Strategy:

1 exp obstetric labor, premature/ or exp premature birth/ (707)
2 pre-term birth$.tw. (8)
3 preterm birth$.tw. (382)
4 (prematur$ adj3 birth$).tw. (338)
5 (prematur$ adj3 labo?r$).tw. (244)
6 (preterm adj3 deliver$).tw. (454)
7 (prematur$ adj3 deliver$).tw. (136)
8 (pre-term adj3 deliver$).tw. (9)
9 (preterm adj3 labo?r).tw. (533)
10 (pre-term adj3 labo?r).tw. (12)
11 early birth$.tw. (5)
12 early delivery.tw. (16)
13 early labo?r.tw. (127)
14 immature labo?r.tw. (0)
15 immature deliver$.tw. (0)
16 immature birth$.tw. (1)
17 exp Infant, Premature/ (2071)
18 (Premature adj3 infant$).tw. (1446)
19 premature newborn$.tw. (110)
20 (preterm adj3 infant$).tw. (2312)
21 pre-term newborn$.tw. (5)
22 preterm newborn$.tw. (112)
23 prematurity.tw. (745)
24 pre-term infant$.tw. (40)
25 exp Respiratory Distress Syndrome, Newborn/ or exp Infant, Premature, Diseases/ (1732)
26 (neonatal adj3 respiratory distress syndrome).tw. (149)
27 (newborn$ adj3 respiratory distress syndrome).tw. (48)
28 or/1-27 (6387)
29 exp Prenatal Care/ (732)
30 prenatal.tw. (1038)
31 antenatal.tw. (1037)
32 antepartum.tw. (181)
33 or/29-32 (2405)
34 or/28,33 (8307)
35 exp Adrenal Cortex Hormones/ or exp Steroids/ or exp Betamethasone/ or exp Glucocorticoids/ (35183)

36 exp Dexamethasone/ (2044)
37 Adrenal Cortex Hormone$.tw. (5)
38 Steroid$.tw. (9538)
39 Betamethasone.tw. (1037)
40 Glucocorticoid$.tw. (1550)
41 glucorticoid$.tw. (6)
42 celestona.tw. (3)
43 celeston.tw. (5)
44 celestone.tw. (9)
45 Dexamethasone.tw. (3095)
46 corticosteroid$.tw. (6945)
47 "rescue course".tw. (16)
48 exp Hydrocortisone/ (4204)
49 Hydrocortisone.tw. (1181)
50 or/35-49 (45069)
51 34 and 50 (781)

MEDLINE RCT search
Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:
---
1 exp obstetric labor, premature/ or exp premature birth/ (16250)
2 pre-term birth$.tw. (201)
3 preterm birth$.tw. (7160)
4 (prematur$ adj3 birth$).tw. (5059)
5 (prematur$ adj3 labo?r$).tw. (3243)
6 (preterm adj3 deliver$).tw. (7839)
7 (prematur$ adj3 deliver$).tw. (3587)
8 (pre-term adj3 deliver$).tw. (330)
9 (preterm adj3 labo?r).tw. (5524)
10 (pre-term adj3 labo?r).tw. (192)
11 early birth$.tw. (113)
12 early delivery.tw. (379)
13 early labo?r.tw. (394)
14 immature labo?r.tw. (5)
15 immature deliver$.tw. (14)
16 immature birth$.tw. (18)
17 exp Infant, Premature/ (38247)
18 (Premature adj3 infant$).tw. (16371)
19 premature newborn$.tw. (1771)
20 (preterm adj3 infant$).tw. (15391)
21 pre-term newborn$.tw. (79)
22 preterm newborn$.tw. (1353)
23 prematurity.tw. (12795)
24 pre-term infant$.tw. (436)
25 exp Respiratory Distress Syndrome, Newborn/ or exp Infant, Premature, Diseases/ (34726)
26 (neonatal adj3 respiratory distress syndrome).tw. (757)
27 (newborn$ adj3 respiratory distress syndrome).tw. (511)

28 or/1-27 (99820)
29 exp Prenatal Care/ (19041)
30 Prenatal.tw. (61639)
31 antenatal.tw. (20284)
32 antepartum.tw. (4131)
33 or/29-32 (93014)
34 or/28,33 (184058)
35 exp Adrenal Cortex Hormones/ or exp Steroids/ or exp Betamethasone/ or exp Glucocorticoids/ (734374)
36 exp Dexamethasone/ (42402)
37 Adrenal Cortex Hormone$.tw. (534)
38 Steroid$.tw. (172037)
39 Betamethasone.tw. (3682)
40 Glucocorticoid$.tw. (48189)
41 glucorticoid$.tw. (129)
42 celestona.tw. (3)
43 celeston.tw. (12)
44 celestone.tw. (61)
45 Dexamethasone.tw. (41716)
46 corticosteroid$.tw. (70550)
47 "rescue course".tw. (18)
48 exp Hydrocortisone/ (60760)
49 Hydrocortisone.tw. (13614)
50 or/35-49 (856085)
51 randomized controlled trial.pt. (339845)
52 controlled clinical trial.pt. (85435)
53 randomized.ab. (255169)
54 placebo.tw. (144626)
55 clinical trials as topic.sh. (163098)
56 randomly.ab. (186586)
57 trial.ti. (109757)
58 (crossover or cross-over or cross over).tw. (55119)
59 or/51-58 (832816)
60 exp animals/ not humans.sh. (3796335)
61 59 not 60 (768262)
62 34 and 50 and 61 (1044)

Appendix D: Single course of antenatal corticosteroids - maternal outcomes (Roberts CPG version 2015)

Outcome	Effect Size	95%CI	P	No of studies	n
Maternal infection requiring treatment including:					
Pyrexia after entry into trial	RR 1.11	0.74 to 1.67	0.61	4	481
Sub group analysis for fever in women after trial entry requiring antibiotics:					
Intact membranes at 1st dose	*0.77*	*0.37 to 1.62*	*0.49*	*1*	*218*
Premature ROM at 1st dose	*0.25*	*0.03 to 2.06*	*0.20*	*1*	*44*
Chorioamnionitis	RR 0.91	0.70 to 1.18	0.48	12	2485
Sub group analysis for Chorioamnionitis:					
Singleton pregnancies	*0.82*	*0.58 to 1.18*	*0.28*	*5*	*1661*
Multiple pregnancies	*0.43*	*0.04 to 4.49*	*0.48*	*1*	*74*
Delivery <28 weeks'	*0.93*	*0.44 to 1.97*	*0.85*	*1*	*91*
Delivery <30 weeks'	*1.08*	*0.61 to 1.92*	*0.80*	*1*	*184*
Delivery <32 weeks'	*0.78*	*0.46 to 1.34*	*0.37*	*1*	*319*
Delivery <34 weeks'	*0.69*	*0.42 to 1.12*	*0.13*	*1*	*547*
Delivery <36 weeks'	*0.71*	*0.44 to 1.15*	*0.16*	*1*	*793*
Delivery at least at 34 weeks'	*0.58*	*0.20 to 1.68*	*0.32*	*1*	*728*
Delivery at least at 36 weeks'	*1.19*	*0.17 to 8.36*	*0.86*	*1*	*442*
Delivery <24 hours after 1st dose	*0.92*	*0.38 to 2.27*	*0.86*	*2*	*239*
Delivery <48 hours after 1st dose	*0.78*	*0.38 to 1.60*	*0.49*	*1*	*341*
Delivery 1-7 days after 1st dose	*0.55*	*0.27 to 1.11*	*0.096*	*1*	*482*
Delivery >7 days after 1st dose	*1.59*	*0.63 to 4.03*	*0.33*	*1*	*461*
Intact membranes at 1st dose	*0.83*	*0.50 to 1.40*	*0.49*	*4*	*1243*
Premature ROM at 1st dose	*1.00*	*0.70 to 1.43*	*0.99*	*6*	*919*
ROM >24 hours	*1.16*	*0.71 to 1.89*	*0.55*	*2*	*483*
ROM >48 hours	*0.82*	*0.42 to 1.60*	*0.56*	*1*	*236*
Pregnancies with hypertension syndromes	*2.36*	*0.36 to 15.73*	*0.37*	*2*	*311*
Dexamethasone	*1.35*	*0.89 to 2.05*	*0.16*	*4*	*575*
Betamethasone	*0.71*	*0.50 to 1.01*	*0.053*	*8*	*1910*
<26 weeks' at 1st dose	*2.18*	*0.62 to 7.69*	*0.22*	*1*	*46*
Between 26 and <30 weeks' at 1st dose	*1.06*	*0.55 to 2.06*	*0.85*	*1*	*242*
Between 30 and <33 weeks' at 1st dose	*0.19*	*0.04 to 0.86*	*0.031*	*1*	*294*
Between 33 and <35 weeks' at 1st dose	*0.47*	*0.12 to 1.80*	*0.27*	*1*	*333*
Between 35 and <37 weeks' at 1st dose	*0.18*	*0.01 to 3.36*	*0.25*	*1*	*181*
Single courses only	*0.89*	*0.60 to 1.33*	*0.57*	*3*	*1394*
Courses including weekly repeats	*0.84*	*0.57 to 1.25*	*0.39*	*8*	*887*
Intrapartum fever requiring antibiotics	RR 0.60	0.15 to 2.49	0.48	2	319
Post-natal pyrexia	RR 0.92	0.64 to 1.33	0.66	5	1323
Sub group analysis for postnatal fever in woman:					
Intact membranes at 1st dose	*0.68*	*0.30 to 1.52*	*0.35*	*1*	*218*
Premature ROM at 1st dose	*1.00*	*0.36 to 2.75*	*1.00*	*1*	*204*
Puerperal sepsis	RR 1.35	0.93 to 1.95	0.11	8	1003
Sub group analysis for Puerperal sepsis:					
Delivery <24 hours after 1st dose	*0.13*	*0.01 to 2.58*	*0.18*	*1*	*46*
Intact membranes at 1st dose	*1.10*	*0.61 to 2.00*	*0.74*	*2*	*289*

Premature ROM at 1st dose	*1.11*	*0.55 to 2.25*	*0.77*	*4*	*477*
ROM >24 hours	*0.76*	*0.22 to 2.58*	*0.66*	*1*	*158*
Pregnancies with hypertension syndromes	*0.68*	*0.30 to 1.52*	*0.35*	*1*	*218*
Dexamethasone	*1.74*	*1.04 to 2.89*	*0.033*	*4*	*536*
Betamethasone	*1.00*	*0.58 to 1.72*	*0.99*	*4*	*467*
Single courses only	*1.02*	*0.07 to 15.86*	*0.99*	*1*	*101*
Courses including weekly repeats	*1.41*	*0.90 to 2.20*	*0.13*	*5*	*580*
Mortality	RR 0.98	0.06 to 15.50	0.99	3	365
Sub group analysis for mortality:					
Intact membranes at 1st dose	*0.98*	*0.06 to 15.50*	*0.99*	*1*	*218*
Premature ROM at 1st dose	*No events*			*2*	*103*
Pregnancies with hypertension syndromes	*0.98*	*0.06 to 15.50*	*0.99*	*1*	*218*
Hypertension	RR 1.00	0.36 to 2.76	1.00	1	220
Mode of birth	Not reported				
Postpartum haemorrhage (PPH)	Not reported				
Breastfeeding at hospital discharge	Not reported				
Breastfeeding at 6 months	Not reported				
Postnatal depression symptoms	Not reported				
Mental anxiety	Not reported				
Quality of life	Not reported				
Adverse effects of therapy (GI upset, glucose intolerance, insomnia, pain at injection site, bruising at injection site, infection at injection site, weight gain, Cushing syndrome)	No events			1	101
Glucose intolerance	RR 2.71	1.14 to 6.46	0.025	1*	123
GDM diagnosis post trial entry	Not reported				
Insulin use	Not reported				

* conducted in women with severe pre-eclampsia

In women with Gestational Diabetes Mellitus (GDM) / Diabetics

Outcome	Effect Size
Increase in insulin use after antenatal corticosteroid treatment	Not reported
HbA1c post partum	Not reported
Fasting plasma glucose (FPG)	Not reported
Change in GDM/diabetes treatment regimen after antenatal corticosteroid treatment	Not reported
Hospital admission for glucose control	Not reported
Maternal hyperglycaemia	Not reported
Maternal hypoglycaemia	Not reported

Appendix E: Single course of antenatal corticosteroids - Fetal, Neonatal and Infant Outcomes (Roberts CPG version 2015)

Outcome	Effect Size	95%CI	P	No of studies	n
Fetal, neonatal or later death	RR 0.77	0.67 to 0.89	0.00035	13	3627
Sub group analysis for fetal & neonatal death:					
Singleton pregnancies	*0.79*	*0.65 to 0.96*	*0.016*	*3*	*1425*
Multiple pregnancies	*0.71*	*0.41 to 1.22*	*0.22*	*2*	*252*
Delivery <28 weeks'	*0.81*	*0.65 to 1.01*	*0.065*	*2*	*129*
Delivery <30 weeks'	*0.86*	*0.70 to 1.05*	*0.14*	*1*	*201*
Delivery <32 weeks'	*0.71*	*0.57 to 0.88*	*0.0018*	*3*	*453*
Delivery <34 weeks'	*0.73*	*0.58 to 0.91*	*0.0063*	*1*	*598*
Delivery <36 weeks'	*0.75*	*0.61 to 0.94*	*0.012*	*2*	*969*
Delivery at least at 34 weeks'	*1.13*	*0.66 to 1.96*	*0.66*	*1*	*770*
Delivery at least at 36 weeks'	*3.25*	*0.99 to 10.66*	*0.052*	*2*	*498*
Delivery <24 hours after 1st dose	*0.60*	*0.39 to 0.94*	*0.024*	*3*	*293*
Delivery <48 hours after 1st dose	*0.59*	*0.41 to 0.86*	*0.0061*	*1*	*373*
Delivery 1-7 days after 1st dose	*0.81*	*0.60 to 1.09*	*0.16*	*3*	*606*
Delivery >7 days after 1st dose	*1.42*	*0.91 to 2.23*	*0.12*	*3*	*598*
Intact membranes at 1st dose	*0.87*	*0.70 to 1.08*	*0.21*	*4*	*1332*
Premature ROM at 1st dose	*0.62*	*0.46 to 0.82*	*0.00091*	*4*	*733*
ROM >24 hours	*0.77*	*0.51 to 1.17*	*0.22*	*2*	*508*
ROM >48 hours	*0.93*	*0.57 to 1.51*	*0.77*	*1*	*255*
Pregnancies with hypertension syndromes	*0.83*	*0.57 to 1.20*	*0.32*	*2*	*313*
Dexamethasone	*0.75*	*0.59 to 0.96*	*0.024*	*5*	*1420*
Betamethasone	*0.78*	*0.65 to 0.93*	*0.0054*	*8*	*2207*
<26 weeks' at 1st dose	*1.00*	*0.66 to 1.50*	*0.99*	*1*	*49*
Between 26 and <30 weeks' at 1st dose	*0.80*	*0.59 to 1.08*	*0.14*	*1*	*261*
Between 30 and <33 weeks' at 1st dose	*0.59*	*0.35 to 1.01*	*0.052*	*1*	*319*
Between 33 and <35 weeks' at 1st dose	*1.10*	*0.59 to 2.05*	*0.76*	*1*	*353*
Between 35 and <37 weeks' at 1st dose	*1.23*	*0.25 to 5.94*	*0.80*	*1*	*194*
Single courses only	*0.79*	*0.64 to 0.96*	*0.018*	*6*	*2056*
Courses including weekly repeats	*0.63*	*0.48 to 0.82*	*0.00067*	*4*	*479*
Fetal death	RR 0.98	0.73 to 1.30	0.87	13	3627
Sub group analysis for fetal death:					
Singleton pregnancies	*1.12*	*0.78 to 1.61*	*0.55*	*3*	*1425*
Multiple pregnancies	*0.53*	*0.20 to 1.40*	*0.20*	*2*	*252*
Delivery <28 weeks'	*0.65*	*0.39 to 1.09*	*0.10*	*2*	*129*
Delivery <30 weeks'	*0.85*	*0.53 to 1.36*	*0.49*	*1*	*201*
Delivery <32 weeks'	*0.92*	*0.62 to 1.38*	*0.70*	*3*	*453*
Delivery <34 weeks'	*0.81*	*0.54 to 1.21*	*0.31*	*1*	*598*
Delivery <36 weeks'	*0.85*	*0.59 to 1.23*	*0.38*	*2*	*969*
Delivery at least at 34 weeks'	*0.81*	*0.36 to 1.80*	*0.60*	*1*	*770*
Delivery at least at 36 weeks'	*5.92*	*0.29 to 122.63*	*0.25*	*2*	*498*
Delivery <24 hours after 1st dose	*0.68*	*0.34 to 1.38*	*0.29*	*3*	*293*
Delivery <48 hours after 1st dose	*0.78*	*0.40 to 1.51*	*0.46*	*1*	*373*
Delivery 1-7 days after 1st dose	*1.01*	*0.58 to 1.76*	*0.98*	*3*	*606*
Delivery >7 days after 1st dose	*1.36*	*0.73 to 2.53*	*0.34*	*3*	*598*
Intact membranes at 1st dose	*1.09*	*0.73 to 1.64*	*0.66*	*4*	*1332*
Premature ROM at 1st dose	*0.86*	*0.46 to 1.61*	*0.63*	*5*	*790*
ROM >24 hours	*1.23*	*0.62 to 2.44*	*0.55*	*2*	*508*
ROM >48 hours	*1.10*	*0.52 to 2.32*	*0.81*	*1*	*255*
Pregnancies with hypertension syndromes	*1.73*	*0.91 to 3.28*	*0.096*	*3*	*331*

Dexamethasone	*0.92*	*0.56 to 1.50*	*0.73*	*5*	*1420*
Betamethasone	*1.01*	*0.73 to 1.39*	*0.96*	*8*	*2207*
<26 weeks' at 1st dose	*0.65*	*0.33 to 1.25*	*0.20*	*1*	*49*
Between 26 and <30 weeks' at 1st dose	*1.23*	*0.65 to 2.34*	*0.52*	*1*	*261*
Between 30 and <33 weeks' at 1st dose	*0.67*	*0.31 to 1.46*	*0.31*	*1*	*319*
Between 33 and <35 weeks' at 1st dose	*1.10*	*0.39 to 3.07*	*0.85*	*1*	*353*
Between 35 and <37 weeks' at 1st dose	*2.46*	*0.23 to 26.68*	*0.46*	*1*	*194*
Single courses only	*0.96*	*0.67 to 1.36*	*0.81*	*6*	*2056*
Courses including weekly repeats	*1.36*	*0.64 to 2.87*	*0.42*	*4*	*479*
Neonatal death	RR 0.68	0.58 to 0.80	<0.00001	21	4408
Sub group analysis for neonatal death:					
Singleton pregnancies	*0.67*	*0.53 to 0.85*	*0.0013*	*7*	*1925*
Multiple pregnancies	*0.79*	*0.39 to 1.61*	*0.52*	*2*	*236*
Delivery <28 weeks'	*0.79*	*0.56 to 1.12*	*0.19*	*2*	*89*
Delivery <30 weeks'	*0.82*	*0.60 to 1.11*	*0.19*	*1*	*150*
Delivery <32 weeks'	*0.59*	*0.43 to 0.80*	*0.000863*	*3*	*378*
Delivery <34 weeks'	*0.69*	*0.52 to 0.92*	*0.011*	*2*	*715*
Delivery <36 weeks'	*0.68*	*0.50 to 0.92*	*0.013*	*2*	*869*
Delivery at least at 34 weeks'	*1.58*	*0.71 to 3.50*	*0.26*	*2*	*808*
Delivery at least at 36 weeks'	*2.62*	*0.77 to 8.96*	*0.12*	*3*	*514*
Delivery <24 hours after 1st dose	*0.53*	*0.29 to 0.96*	*0.035*	*4*	*295*
Delivery <48 hours after 1st dose	*0.49*	*0.30 to 0.81*	*0.0057*	*1*	*339*
Delivery 1-7 days after 1st dose	*0.74*	*0.51 to 1.07*	*0.11*	*3*	*563*
Delivery >7 days after 1st dose	*1.45*	*0.75 to 2.80*	*0.27*	*3*	*561*
Intact membranes at 1st dose	*0.77*	*0.58 to 1.03*	*0.077*	*4*	*1236*
Premature ROM at 1st dose	*0.61*	*0.46 to 0.83*	*0.001*	*8*	*1024*
ROM >24 hours	*0.56*	*0.31 to 1.01*	*0.053*	*2*	*477*
ROM >48 hours	*0.81*	*0.40 to 1.64*	*0.56*	*1*	*230*
Pregnancies with hypertension syndromes	*0.50*	*0.29 to 0.87*	*0.013*	*2*	*278*
Dexamethasone	*0.72*	*0.55 to 0.94*	*0.015*	*6*	*1468*
Betamethasone	*0.67*	*0.54 to 0.81*	*<0.0001*	*15*	*2940*
<26 weeks' at 1st dose	*1.87*	*0.61 to 5.72*	*0.27*	*1*	*27*
Between 26 and <30 weeks' at 1st dose	*0.67*	*0.45 to 0.99*	*0.046*	*1*	*227*
Between 30 and <33 weeks' at 1st dose	*0.51*	*0.23 to 1.11*	*0.090*	*1*	*295*
Between 33 and <35 weeks' at 1st dose	*1.11*	*0.49 to 2.48*	*0.81*	*1*	*339*
Between 35 and <37 weeks' at 1st dose	*0.62*	*0.06 to 6.76*	*0.70*	*1*	*191*
Single courses only	*0.71*	*0.55 to 0.90*	*0.006*	*9*	*2336*
Courses including weekly repeats	*0.55*	*0.43 to 0.72*	*<0.00001*	*8*	*922*
Respiratory distress syndrome (RDS)	RR 0.65	0.58 to 0.73	<0.00001	25	4590
Sub group analysis for RDS:					
Singleton pregnancies	*0.60*	*0.51 to 0.70*	*<0.00001*	*12*	*2907*
Multiple pregnancies	*0.85*	*0.60 to 1.20*	*0.35*	*4*	*320*
Delivery <28 weeks'	*0.79*	*0.53 to 1.18*	*0.25*	*4*	*102*
Delivery <30 weeks'	*0.67*	*0.52 to 0.87*	*0.0022*	*4*	*218*
Delivery <32 weeks'	*0.56*	*0.45 to 0.71*	*<0.00001*	*6*	*583*
Delivery <34 weeks'	*0.58*	*0.47 to 0.72*	*<0.00001*	*5*	*1177*
Delivery <36 weeks'	*0.52*	*0.40 to 0.69*	*<0.00001*	*4*	*1022*
Delivery at least at 34 weeks'	*0.66*	*0.38 to 1.16*	*0.15*	*5*	*1261*
Delivery at least at 36 weeks'	*0.30*	*0.03 to 2.67*	*0.28*	*5*	*557*
Delivery <24 hours after 1st dose	*0.87*	*0.66 to 1.15*	*0.33*	*9*	*517*
Delivery <48 hours after 1st dose	*0.67*	*0.49 to 0.93*	*0.017*	*3*	*374*
Delivery 1-7 days after 1st dose	*0.46*	*0.35 to 0.60*	*<0.00001*	*9*	*1110*
Delivery >7 days after 1st dose	*0.82*	*0.53 to 1.28*	*0.39*	*8*	*988*
Intact membranes at 1st dose	*0.62*	*0.51 to 0.74*	*<0.00001*	*5*	*1527*
Premature ROM at 1st dose	*0.68*	*0.57 to 0.83*	*<0.0001*	*12*	*1129*
ROM >24 hours	*0.68*	*0.51 to 0.90*	*0.0067*	*6*	*626*
ROM >48 hours	*0.71*	*0.36 to 1.41*	*0.33*	*2*	*247*

Pregnancies with hypertension syndromes	*0.50*	*0.35 to 0.72*	*0.00014*	*5*	*382*
Dexamethasone	*0.80*	*0.68 to 0.93*	*0.0050*	*6*	*1457*
Betamethasone	*0.56*	*0.48 to 0.65*	*<0.00001*	*18*	*3115*
<26 weeks' at 1st dose	*2.86*	*0.37 to 21.87*	*0.31*	*1*	*24*
Between 26 and <30 weeks' at 1st dose	*0.49*	*0.34 to 0.72*	*0.00026*	*2*	*242*
Between 30 and <33 weeks' at 1st dose	*0.56*	*0.36 to 0.87*	*0.011*	*2*	*361*
Between 33 and <35 weeks' at 1st dose	*0.53*	*0.31 to 0.91*	*0.021*	*2*	*434*
Between 35 and <37 weeks' at 1st dose	*0.61*	*0.11 to 3.26*	*0.56*	*1*	*189*
Single courses only	*0.63*	*0.52 to 0.76*	*<0.00001*	*9*	*2309*
Courses including weekly repeats	*0.61*	*0.52 to 0.72*	*<0.00001*	*9*	*946*
Moderate / severe RDS	RR 0.55	0.43 to 0.71	<0.00001	6	1686
Sub group analysis for moderate/severe RDS:					
Delivery <24 hours after 1st dose	*0.69*	*0.37 to 1.27*	*0.24*	*1*	*182*
Delivery <48 hours after 1st dose	*0.45*	*0.27 to 0.73*	*0.0014*	*1*	*326*
Delivery 1-7 days after 1st dose	*0.37*	*0.22 to 0.62*	*0.00020*	*1*	*462*
Delivery >7 days after 1st dose	*1.83*	*0.69 to 4.87*	*0.22*	*1*	*446*
Transient tachypnoea of the neonate (term)	Not reported				
Hypoglycaemia requiring treatment	Not reported				
Hyperglycaemia requiring treatment	Not reported				
Intraventricular haemorrhage (IVH) any grade	RR 0.54	0.43 to 0.69	<0.00001	13	2872
Severe IVH (Grade 3 or 4)	RR 0.28	0.16 to 0.50	0.000017	5	572
Sub group analysis for IVH:					
In babies diagnosed by autopsy	*0.48*	*0.29 to 0.79*	*0.0042*	*5*	*1846*
In babies diagnosed by ultrasound scan	*0.58*	*0.44 to 0.77*	*0.00011*	*7*	*889*
Singleton pregnancies	*0.49*	*0.33 to 0.71*	*0.00023*	*5*	*1561*
Multiple pregnancies	*0.39*	*0.07 to 2.06*	*0.27*	*1*	*137*
Delivery <28 weeks'	*0.34*	*0.14 to 0.86*	*0.022*	*1*	*62*
Delivery <30 weeks'	*0.56*	*0.29 to 1.10*	*0.094*	*1*	*150*
Delivery <32 weeks'	*0.52*	*0.28 to 0.99*	*0.046*	*1*	*277*
Delivery <34 weeks'	*0.53*	*0.29 to 0.95*	*0.034*	*1*	*515*
Delivery <36 weeks'	*0.56*	*0.31 to 1.02*	*0.060*	*1*	*767*
Delivery at least at 34 weeks'	*1.13*	*0.07 to 17.92*	*0.93*	*1*	*746*
Delivery at least at 36 weeks'	*No events*			*1*	*459*
Delivery <24 hours after 1st dose	*0.54*	*0.21 to 1.36*	*0.19*	*3*	*264*
Delivery <48 hours after 1st dose	*0.26*	*0.09 to 0.75*	*0.012*	*1*	*339*
Delivery 1-7 days after 1st dose	*0.51*	*0.23 to 1.13*	*0.096*	*1*	*482*
Delivery >7 days after 1st dose	*2.01*	*0.37 to 10.86*	*0.42*	*1*	*453*
Intact membranes at 1st dose	*0.50*	*0.35 to 0.72*	*0.00017*	*4*	*1200*
Premature ROM at 1st dose	*0.47*	*0.28 to 0.79*	*0.0040*	*5*	*895*
ROM >24 hours	*0.55*	*0.16 to 1.84*	*0.33*	*2*	*477*
ROM >48 hours	*0.87*	*0.18 to 4.22*	*0.86*	*1*	*230*
Pregnancies with hypertension syndromes	*0.38*	*0.17 to 0.87*	*0.022*	*2*	*278*
Dexamethasone	*0.63*	*0.43 to 0.91*	*0.015*	*5*	*703*
Betamethasone	*0.50*	*0.37 to 0.68*	*<0.00001*	*8*	*2169*
<26 weeks' at 1st dose	*1.20*	*0.24 to 6.06*	*0.83*	*1*	*27*
Between 26 and <30 weeks' at 1st dose	*0.45*	*0.21 to 0.95*	*0.036*	*2*	*229*
Between 30 and <33 weeks' at 1st dose	*0.23*	*0.03 to 2.00*	*0.18*	*1*	*295*
Between 33 and <35 weeks' at 1st dose	*1.11*	*0.23 to 5.40*	*0.90*	*1*	*339*
Between 35 and <37 weeks' at 1st dose	*No events*			*1*	*191*
Single courses only	*0.48*	*0.31 to 0.75*	*0.0013*	*4*	*1666*
Courses including weekly repeats	*0.59*	*0.45 to 0.78*	*0.00022*	*7*	*877*
Chronic lung disease	RR 0.86	0.42 to 1.79	0.70	6	818
Sub group analysis for chronic lung disease:					
Intact membranes at 1st dose	*1.13*	*0.27 to 4.74*	*0.65*	*3*	*434*
Premature ROM at 1st dose	*0.50*	*0.33 to 0.76*	*0.00099*	*1*	*165*
Pregnancies with hypertension syndromes	*0.20*	*0.02 to 1.68*	*0.14*	*1*	*200*

Dexamethasone	*1.81*	*0.44 to 7.46*	*0.41*	*3*	*380*
Betamethasone	*0.63*	*0.29 to 1.35*	*0.0025*	*3*	*438*
Single courses only	*5.36*	*0.66 to 43.56*	*0.12*	*1*	*161*
Courses including weekly repeats	*0.77*	*0.42 to 1.44*	*0.42*	*4*	*534*
Necrotising enterocolitis (NEC)	RR 0.46	0.29 to 0.74	0.0012	8	1675
Sub group analysis for NEC:					
Intact membranes at 1st dose	*0.61*	*0.15 to 2.48*	*0.49*	*2*	*257*
Premature ROM at 1st dose	*0.39*	*0.18 to 0.86*	*0.020*	*4*	*583*
ROM >24 hours	*0.55*	*0.17 to 1.74*	*0.31*	*1*	*157*
Pregnancies with hypertension syndromes	*0.50*	*0.09 to 2.67*	*0.42*	*1*	*200*
Retinopathy of prematurity	Not reported				
Cystic periventricular leucomalacia	Not reported				
White matter injury	Not reported				
Patent ductus arteriosus as defined, requiring treatment	Not reported				
Neonatal encephalopathy in term babies	Not reported				
Composite serious outcome (may include fetal, neonatal or later death, severe respiratory distress, severe IVH (Grade 3 or 4), chronic lung disease, necrotising enterocolitis, retinopathy of prematurity, cystic periventricular leucomalacia, patent ductus arteriosus, neonatal encephalopathy)	Not reported				
Gestational age at birth	Not reported				
Interval between trial entry and birth	MD 0.23	-1.86 to 2.32	0.83	3	1513
Small for gestational age (as defined)	RR 1.05	0.78 to 1.42	0.75	4	698
Mean Birthweight (grams)	MD -6.93	-39.41 to 25.55	0.68	13	2961
Sub group analysis for mean birthweight:					
Singleton pregnancies	*-16.61*	*-55.45 to 22.23*	*0.40*	*6*	*1727*
Multiple pregnancies	*82.36*	*-146.23 to 310.95*	*0.48*	*1*	*150*
Delivery <28 weeks'	*71.20*	*-42.54 to 184.94*	*0.22*	*1*	*100*
Delivery <30 weeks'	*0.89*	*-98.17 to 99.95*	*0.99*	*1*	*201*
Delivery <32 weeks'	*1.15*	*-91.77 to 94.07*	*0.98*	*1*	*347*
Delivery <34 weeks'	*-30.28*	*-115.06 to 54.50*	*0.48*	*1*	*598*
Delivery <36 weeks'	*-8.32*	*-51.31 to 34.67*	*0.70*	*3*	*1044*
Delivery at least at 34 weeks'	*-12.00*	*-107.48 to 83.48*	*0.81*	*1*	*770*
Delivery at least at 36 weeks'	*-34.84*	*-117.23 to 47.55*	*0.41*	*1*	*757*
Delivery <24 hours after 1st dose	*46.52*	*-94.26 to 187.29*	*0.52*	*2*	*242*
Delivery <48 hours after 1st dose	*-5.90*	*-131.95 to 120.15*	*0.93*	*1*	*373*
Delivery 1-7 days after 1st dose	*-105.92*	*-212.52 to 0.68*	*0.051*	*1*	*520*
Delivery >7 days after 1st dose	*-147.01*	*-291.97 to -2.05*	*0.047*	*1*	*486*
Intact membranes at 1st dose	*-59.09*	*-157.84 to 39.67*	*0.24*	*3*	*1107*
Premature ROM at 1st dose	*-42.68*	*-108.91 to 23.55*	*0.21*	*5*	*835*
ROM >24 hours	*-196.46*	*-335.19 to -57.73*	*0.0055*	*1*	*349*
ROM >48 hours	*-201.79*	*-363.30 to -40.28*	*0.014*	*1*	*255*
Pregnancies with hypertension syndromes	*-131.72*	*-319.68 to 56.24*	*0.17*	*1*	*95*
Dexamethasone	*-25.49*	*-97.63 to 46.65*	*0.49*	*3*	*492*
Betamethasone	*-2.21*	*-38.59 to 34.17*	*0.91*	*10*	*2469*
<26 weeks' at 1st dose	*63.14*	*-607.37 to 733.65*	*0.85*	*1*	*49*
Between 26 and <30 weeks' at 1st dose	*26.41*	*-215.55 to 268.37*	*0.83*	*1*	*261*
Between 30 and <33 weeks' at 1st dose	*-190.64*	*-359.98 to -21.30*	*0.027*	*1*	*319*
Between 33 and <35 weeks' at 1st dose	*-38.72*	*-172.29 to 94.85*	*0.57*	*1*	*353*
Between 35 and <37 weeks' at 1st dose	*-13.57*	*-175.45 to 148.31*	*0.87*	*1*	*194*
Single courses only	*-10.08*	*-68.96 to 48.79*	*0.74*	*7*	*2244*
Courses including weekly repeats	*-20.10*	*-83.79 to 43.60*	*0.54*	*4*	*409*

Birth length	Not reported				
Birth head circumference	Not reported				
Placental weight	Not reported				
Low Apgar:					
Apgar <7 at five minutes	RR 0.84	0.69 to 1.01	0.06	8	2072
Use and duration of respiratory support:					
Use of respiratory support *mechanical ventilation/CPAP	RR 0.73	0.59 to 0.92	0.006	7	1021
Sub group analysis for need for mechanical ventilation/CPAP:					
Intact membranes at 1st dose	*0.70*	*0.52 to 0.93*	*0.016*	*2*	*253*
Premature ROM at 1st dose	*0.90*	*0.47 to 1.73*	*0.75*	*1*	*206*
ROM >24 hours	*0.67*	*0.30 to 1.53*	*0.35*	*1*	*157*
Pregnancies with hypertension syndromes	*0.62*	*0.42 to 0.91*	*0.015*	*1*	*200*
Duration of respiratory support (days) *mechanical ventilation/CPAP	MD -1.42	-2.28 to -0.56	0.16	3	518
Sub group analysis for duration of mechanical ventilation/CPAP:					
Intact membranes at 1st dose	*3.80*	*-20.79 to 28.39*	*0.76*	*1*	*33*
Premature ROM at 1st dose	*-3.50*	*-5.12 to -1.88*	*0.000022*	*1*	*165*
Use and duration of oxygen supplementation					
Use of oxygen supplementation	Not reported				
Duration of oxygen supplementation (days)	MD -2.86	-5.51 to -0.21	0.035	1	73
Use of surfactant	RR 0.74	0.52 to 1.05	0.10	4	776
Air leak syndrome	RR 0.69	0.19 to 2.47	0.57	1	138
Pulmonary hypertension	Not reported				
Inotropic support	Not reported				
Use of nitric oxide for respiratory support	Not reported				
Early neonatal infection (<48 hours)	RR 0.57	0.38 to 0.86	0.007	6	1359
Sub group analysis for infection in first 48 hours of life:					
Intact membranes at 1st dose	*0.46*	*0.26 to 0.84*	*0.012*	*1*	*200*
Premature ROM at 1st dose	*0.97*	*0.45 to 2.06*	*0.93*	*3*	*291*
ROM >24 hours	*0.97*	*0.40 to 2.39*	*0.95*	*1*	*157*
Pregnancies with hypertension syndromes	*0.46*	*0.26 to 0.84*	*0.012*	*1*	*200*
Late neonatal infection (≥48 hours):					
Proven infection while in the neonatal intensive care unit	RR 0.82	0.66 to 1.02	0.07	12	2927
Sub group analysis for infection in first 48 hours of life:					
Intact membranes at 1st dose	*0.69*	*0.51 to 0.95*	*0.023*	*3*	*1057*
Premature ROM at 1st dose	*1.26*	*0.86 to 1.85*	*0.23*	*7*	*796*
ROM >24 hours	*1.34*	*0.82 to 2.21*	*0.24*	*2*	*363*
ROM >48 hours	*1.15*	*0.68 to 1.95*	*0.61*	*2*	*258*
Pregnancies with hypertension syndromes	*0.55*	*0.34 to 0.87*	*0.012*	*2*	*278*
Use of post-natal corticosteroids	Not reported				
Neonatal blood pressure	Not reported				
Anthropometry at hospital discharge	Not reported				
HPA axis suppression, including cortisol:					
Mean infant HPA axis function (cortisol)	MD 3.94	-3.12 to 11.00	0.27	1	27
Sub group analysis for Mean infant HPA axis function (cortisol):					
Delivery <24 hours after 1st dose	9.00	-11.93 to 29.93	0.40	1	6

Delivery 24 – 48 hours after 1st dose	0.00	-8.68 to 8.68	1.00	1	10
Delivery >48 hours after 1st dose	13.00	-1.90 to 27.90	0.087	1	11

Appendix F: Single course of antenatal corticosteroids - Child/adult (follow up) (Roberts CPG version 2015)

Childhood Outcome	Effect Size	95%CI	P	No of studies	n
Total mortality	RR 0.68	0.36 to 1.27	0.22	4	1010
Neurosensory disability (composite of impairments: cerebral palsy, blindness, deafness, developmental delay)	Not reported				
Cerebral palsy	RR 0.60	0.34 to 1.03	0.065	5	904
Sub group analysis for cerebral palsy in childhood:					
Pregnancies with hypertension syndromes	*0.28*	*0.03 to 3.01*	*0.30*	*1*	*94*
Developmental delay / IQ	RR 0.49	0.24 to 1.00	0.048	2	518
Neurodevelopmental delay	RR 0.64	1.14 to 2.98	0.57	1	82
Visual impairment	RR 0.55	0.24 to 1.23	0.15	2	166
Hearing impairment	RR 0.64	0.04 to 9.87	0.75	2	166
Motor dysfunction	Not reported				
Survival free of neurosensory disability	Not reported				
Anthropometry:					
Mean childhood weight (kg)	MD 0.30	-0.39 to 1.00	0.39	2	333
Mean childhood height (cm)	MD 1.02	-0.26 to 2.29	0.12	2	334
Mean childhood head circumference (cm)	MD 0.27	-0.08 to 0.63	0.13	2	328
Child behaviour	Not reported				
Respiratory disease:					
Mean childhood VC (% predicted)	MD -1.68	-5.12 to 1.75	0.34	2	150
Mean childhood FEV1 (% predicted)	MD -4.73	-10.13 to 0.67	0.086	1	75
Mean childhood FEV1/VC	MD -1.06	-3.23 to 1.11	0.34	2	150
Blood pressure:					
Mean childhood systolic blood pressure (mmHg)	MD -1.60	-4.06 to 0.86	0.20	1	223
Impairment of insulin / glucose axis	Not reported				
Insulin sensitivity	Not reported				
Cognitive ability	Not reported				
Learning disability:					
Intellectual impairment in childhood	RR 0.86	0.44 to 1.69	0.67	3	778
Behavioural / learning difficulties in childhood	RR 0.86	0.35 to 2.09	0.74	1	90

Adult Outcome	Effect Size	95%CI	P	No of studies	n
Diabetes:					
Mean adult glucose (mmol/L) – fasting	MD 0.01	-0.09 to 0.11	0.84	1	432
Mean adult glucose (mmol/L) – 30 minutes following 75g oral GTT	MD 0.19	-0.14 to 0.52	0.25	1	413
Mean adult glucose (mmol/L) – 120 minutes following 75g oral GTT	MD -0.27	-0.52 to -0.02	0.038	1	410
Mean adult insulin (log values) – fasting	MD 0.08	-0.03 to 0.19	0.16	1	435
Mean adult insulin (log values) – 30 minutes following 75g oral GTT	MD 0.16	0.04 to 0.28	0.0083	1	412
Mean adult insulin (log values) – 120 minutes following 75g oral GTT	MD -0.10	-0.27 to 0.07	0.25	1	428
Obesity	Not reported				
Cardiovascular disease:					
Mean cholesterol in adulthood (mmol/L)	MD -0.11	-0.28 to 0.06	0.20	1	445
Age at puberty (mean years)	MD 0.00	-0.94 to 0.94	1.00	1	38
Educational attainment (university or polytechnic education)	RR 0.94	0.80 to 1.10	0.45	1	534
IQ	Not reported				
Cognitive ability	Not reported				
Learning disability:					
Intellectual impairment	RR 0.24	0.01 to 4.95	0.36	2	273
Survival free of metabolic disease	Not reported				

Use of Health Services

Outcome	Effect Size	95%CI	P	No of studies	n
Length of antenatal hospitalisation for the woman (days)	MD 0.50	-1.40 to 2.40	0.61	1	218
Length of postnatal hospitalisation for the woman (days)	MD 0.00	-1.72 to 1.72	1.00	1	218
Maternal admission to ICU	RR 0.74	0.26 to 2.05	0.56	2	319
Admission to NICU	RR 0.88	0.73 to 1.06	0.18	4	629
Length of stay in NICU	Not reported				
Length of neonatal hospitalisation (days)	MD 0.00	-1.08 to 1.09	1.00	4	641
Duration of respiratory support (days)	MD -1.42	-2.28 to -0.56	0.001	3	518

Appendix G: Repeat antenatal corticosteroids - Maternal outcomes (Crowther 2011)

Outcome	Effect Size	95%CI	P	No of studies	n
Maternal infection requiring treatment including:					
Pyrexia after entry into trial	Not reported				
Chorioamnionitis	RR 1.16	0.92 to 1.46	0.22	6	4261
Sub group analysis for chorioamnionitis:					
Preterm prelabour rupture of membranes	*1.56*	*1.05 to 2.31*	*0.026*	*1*	*160*
Repeat corticosteroids as betamethasone	*1.16*	*0.92 to 1.46*	*0.22*	*6*	*4261*
Repeat doses at a minimum interval of 7 days or less	*1.23*	*0.95 to 1.59*	*0.12*	*4*	*1971*
A minimum interval of 14 days or more	*0.94*	*0.56 to 1.57*	*0.82*	*2*	*2290*
One repeat course	*0.64*	*0.23 to 1.77*	*0.39*	*1*	*437*
Planned dose per treatment course 12 mg or less	*1.08*	*0.72 to 1.62*	*0.70*	*1*	*982*
Planned dose per treatment course >12 to 24 mg	*1.20*	*0.90 to 1.58*	*0.21*	*5*	*3279*
Planned repeat drug exposure was 12 mg or less/week	*1.08*	*0.77 to 1.51*	*0.65*	*2*	*2835*
Planned repeat drug exposure was >12 mg/week to 24 mg/week	*1.35*	*0.96 to 1.88*	*0.081*	*3*	*989*
Intrapartum fever requiring antibiotics	Not reported				
Post-natal pyrexia	RR 0.87	0.55 to 1.38	0.56	1	982
Puerperal sepsis	RR 1.15	0.83 to 1.60	0.40	5	3091
Sub group analysis for puerperal sepsis:					
Preterm prelabour rupture of membranes	*0.65*	*0.19 to 2.22*	*0.49*	*1*	*160*
Repeat corticosteroids as betamethasone	*1.15*	*0.83 to 1.60*	*0.40*	*5*	*3091*
Repeat doses at a minimum interval of 7 days or less	*1.02*	*0.66 to 1.59*	*0.91*	*4*	*1238*
A minimum interval of 14 days or more	*1.34*	*0.80 to 2.22*	*0.26*	*1*	*1853*
One repeat course	*1.57*	*0.80 to 3.10*	*0.19*	*1*	*249*
Planned dose per treatment course 12 mg or less	*1.57*	*0.80 to 3.10*	*0.19*	*1*	*249*
Planned dose per treatment course >12 to 24 mg	*1.05*	*0.72 to 1.54*	*0.80*	*4*	*2842*
Planned repeat drug exposure was 12 mg or less/week	*1.34*	*0.80 to 2.22*	*0.26*	*1*	*1853*
Planned repeat drug exposure was >12 mg/week to 24 mg/week	*0.76*	*0.42 to 1.36*	*0.35*	*3*	*989*
Mortality	Not reported				
Hypertension	RR 1.08	0.87 to 1.32	0.49	3	3327
Mode of birth:					
Vaginal	RR 0.93	0.87 to 1.00	0.060	7	4062
Caesarean	RR 1.05	0.99 to 1.10	0.090	7	4062
Postpartum haemorrhage	RR 0.60	0.33 to 1.07	0.081	1	485
Breastfeeding at hospital discharge	Not reported				
Breastfeeding at 6 months	Not reported				
Postnatal depression symptoms	Not reported				

Mental anxiety	Not reported				
Quality of life	Not reported				
Adverse effects of therapy (Gastrointestinal upset, glucose intolerance, insomnia, pain at injection site, bruising at injection site, infection at injection site, weight gain, Cushing syndrome)	RR 0.97	0.24 to 3.90	0.96	2	1474
Gastrointestinal upset	Not reported				
Insomnia	RR 2.63	1.10 to 6.30	0.029	3	1486
Pain at injection site	RR 0.73	0.11 to 5.05	0.75	2	1474
Bruising at injection site	RR 0.38	0.21 to 0.71	0.0022	1	492
Infection at injection site	Not reported				
Weight gain	Not reported				
Cushing syndrome	Not reported				
Glucose intolerance:	Not reported				
Maternal hyperglycaemia	RR 1.31	0.89 to 1.93	0.17	1	492
GDM diagnosis post trial entry	Not reported				
Insulin use	Not reported				

In women with Gestational Diabetes Mellitus (GDM) / Diabetics

Outcome	Effect Size
Increase in insulin use after antenatal corticosteroid treatment	Not reported
HbA1c post partum	Not reported
Fasting plasma glucose	Not reported
Change in GDM / diabetes treatment regimen after antenatal corticosteroid treatment	Not reported
Hospital admission for glucose control	Not reported
Maternal hyperglycaemia	Not reported
Maternal hypoglycaemia	Not reported

Appendix H: Repeat antenatal corticosteroids - Fetal, Neonatal and Infant Outcomes (Crowther 2011)

Outcome	Effect Size	95%CI	P	No of studies	n
Fetal, neonatal or later death	RR 0.94	0.71 to 1.23	0.63	9	5554
Sub group analysis for fetal & neonatal death:					
Preterm prelabour rupture of membranes	*0.49*	*0.13 to 1.88*	*0.30*	*1*	*160*
Repeat corticosteroids as betamethasone	*0.94*	*0.71 to 1.23*	*0.63*	*9*	*5554*
Repeat doses at a minimum interval of 7 days or less	*0.96*	*0.67 to 1.37*	*0.82*	*6*	*2871*
A minimum interval of 14 days or more	*1.02*	*0.69 to 1.51*	*0.91*	*3*	*2993*
One repeat course	*1.41*	*0.64 to 3.08*	*0.39*	*3*	*1015*
Planned dose per treatment course 12 mg or less	*1.12*	*0.70 to 1.79*	*0.64*	*2*	*1472*
Planned dose per treatment course >12 to 24 mg	*0.85*	*0.61 to 1.19*	*0.36*	*7*	*4082*
Planned dose per treatment course >24 mg					
Planned repeat drug exposure was 12 mg or less/week	*1.01*	*0.73 to 1.40*	*0.96*	*2*	*3450*
Planned repeat drug exposure was >12 mg/week to 24 mg/week	*0.51*	*0.26 to 1.00*	*0.050*	*4*	*1089*
Fetal death	RR 0.82	0.24 to 2.84	0.76	7	2755
Sub group analysis for fetal death:					
Repeat corticosteroids as betamethasone	*0.82*	*0.24 to 2.84*	*0.76*	*7*	*2755*
Repeat doses at a minimum interval of 7 days or less	*0.71*	*0.14 to 3.57*	*0.68*	*4*	*1740*
A minimum interval of 14 days or more	*1.00*	*0.06 to 15.86*	*1.00*	*2*	*689*
One repeat course	*1.02*	*0.14 to 7.23*	*0.98*	*3*	*1015*
Planned dose per treatment course 12 mg or less	*1.03*	*0.15 to 7.31*	*0.97*	*2*	*1472*
Planned dose per treatment course >12 to 24 mg	*0.70*	*0.14 to 3.55*	*0.67*	*5*	*1283*
Planned repeat drug exposure was 12 mg or less/week	*1.02*	*0.06 to 16.23*	*0.99*	*1*	*1146*
Planned repeat drug exposure was >12 mg/week to 24 mg/week	*0.59*	*0.08 to 4.42*	*0.61*	*3*	*594*
Neonatal death	RR 0.91	0.62 to 1.34	0.65	7	2713
Sub group analysis for neonatal death:					
Repeat corticosteroids as betamethasone	*0.91*	*0.62 to 1.34*	*0.65*	*7*	*2713*
Repeat doses at a minimum interval of 7 days or less	*0.92*	*0.61 to 1.38*	*0.70*	*5*	*2045*
A minimum interval of 14 days or more	*0.86*	*0.28 to 2.66*	*0.80*	*2*	*668*
One repeat course	*1.47*	*0.65 to 3.33*	*0.36*	*3*	*994*
Planned dose per treatment course 12 mg or less	*1.12*	*0.70 to 1.80*	*0.64*	*2*	*1470*
Planned dose per treatment course >12 to 24 mg	*0.62*	*0.32 to 1.20*	*0.16*	*5*	*1243*
Planned dose per treatment course >24 mg					

Planned repeat drug exposure was 12 mg or less/week	*0.94*	*0.56 to 1.59*	*0.83*	*1*	*1144*
Planned repeat drug exposure was >12 mg/week to 24 mg/week	*0.52*	*0.23 to 1.18*	*0.12*	*3*	*575*
Respiratory distress syndrome (RDS)	RR 0.83	0.75 to 0.91	0.00016	8	3206
Sub group analysis for RDS:					
Preterm prelabour rupture of membranes	*0.87*	*0.60 to 1.24*	*0.44*	*1*	*160*
Repeat corticosteroids as betamethasone	*0.83*	*0.75 to 0.91*	*0.00016*	*8*	*3206*
Repeat doses at a minimum interval of 7 days or less	*0.86*	*0.77 to 0.96*	*0.0094*	*6*	*2538*
A minimum interval of 14 days or more	*0.72*	*0.58 to 0.89*	*0.0019*	*2*	*668*
One repeat course	*0.85*	*0.73 to 0.99*	*0.033*	*3*	*994*
Planned dose per treatment course 12 mg or less	*0.86*	*0.76 to 0.98*	*0.021*	*2*	*1470*
Planned dose per treatment course >12 to 24 mg	*0.78*	*0.67 to 0.92*	*0.0023*	*6*	*1736*
Planned repeat drug exposure was 12 mg or less/week	*0.79*	*0.68 to 0.92*	*0.0027*	*1*	*1144*
Planned repeat drug exposure was >12 mg/week to 24 mg/week	*0.86*	*0.68 to 1.10*	*0.22*	*4*	*1068*
Transient tachypnoea of the neonate (term)	Not reported				
Hypoglycaemia requiring treatment	Not reported				
Hyperglycaemia requiring treatment	Not reported				
Intraventricular haemorrhage (IVH) any grade	RR 0.94	0.75 to 1.18	0.61	6	3065
Sub group analysis for IVH:					
Repeat corticosteroids as betamethasone	*0.94*	*0.75 to 1.18*	*0.61*	*6*	*3065*
Repeat doses at a minimum interval of 7 days or less	*0.98*	*0.77 to 1.26*	*0.89*	*5*	*2519*
A minimum interval of 14 days or more	*0.77*	*0.43 to 1.36*	*0.36*	*1*	*546*
One repeat course	*0.99*	*0.69 to 1.42*	*0.96*	*2*	*872*
Planned dose per treatment course 12 mg or less	*1.02*	*0.74 to 1.40*	*0.92*	*2*	*1470*
Planned dose per treatment course >12 to 24 mg	*0.88*	*0.64 to 1.21*	*0.43*	*4*	*1595*
Planned repeat drug exposure was 12 mg or less/week	*0.89*	*0.57 to 1.38*	*0.60*	*1*	*1144*
Planned repeat drug exposure was >12 mg/week to 24 mg/week	*0.95*	*0.64 to 1.40*	*0.79*	*3*	*1017*
Severe IVH (Grade 3 or 4)	RR 1.13	0.69 to 1.86	0.63	6	4819
Chronic lung disease	RR 1.06	0.87 to 1.30	0.54	8	5393
Sub group analysis for chronic lung disease:					
Preterm prelabour rupture of membranes	*0.77*	*0.42 to 1.41*	*0.39*	*1*	*160*
Repeat corticosteroids as betamethasone	*1.06*	*0.87 to 1.30*	*0.54*	*8*	*5393*
Repeat doses at a minimum interval of 7 days or less	*0.97*	*0.78 to 1.21*	*0.78*	*6*	*2538*
A minimum interval of 14 days or more	*1.49*	*0.96 to 2.32*	*0.078*	*2*	*2855*
One repeat course	*1.27*	*0.83 to 1.96*	*0.27*	*2*	*877*
Planned dose per treatment course 12 mg or less	*0.97*	*0.74 to 1.27*	*0.82*	*2*	*1470*
Planned dose per treatment course >12 to 24 mg	*1.18*	*0.88 to 1.59*	*0.27*	*6*	*3923*
Planned repeat drug exposure was 12 mg	*1.03*	*0.79 to 1.35*	*0.81*	*2*	*3448*

or less/week					
Planned repeat drug exposure was >12 mg/week to 24 mg/week	*0.97*	*0.65 to 1.44*	*0.87*	*4*	*1068*
Necrotising enterocolitis	RR 0.74	0.51 to 1.08	0.12	8	5394
Retinopathy of prematurity	RR 1.02	0.81 to 1.28	0.86	7	4883
Cystic periventricular leucomalacia	RR 0.77	0.43 to 1.37	0.37	7	4888
White matter injury	Not reported				
Patent ductus arteriosus as defined, requiring treatment	RR 0.80	0.64 to 0.98	0.036	6	4356
Neonatal encephalopathy in term babies	Not reported				
Composite serious outcome (may include fetal, neonatal or later death, severe respiratory distress, severe IVH (Grade 3 or 4), chronic lung disease, necrotising enterocolitis, retinopathy of prematurity, cystic periventricular leucomalacia, patent ductus arteriosus, neonatal encephalopathy)	RR 0.84	0.75 to 0.94	0.0022	7	5094
Sub group analysis for composite serious outcome:					
Repeat corticosteroids as betamethasone	*0.84*	*0.75 to 0.94*	*0.0022*	*7*	*5094*
Repeat doses at a minimum interval of 7 days or less	*0.78*	*0.66 to 0.91*	*0.0022*	*5*	*2232*
A minimum interval of between 8 and <14 days					
A minimum interval of 14 days or more	*0.90*	*0.77 to 1.05*	*0.19*	*2*	*2862*
One repeat course	*0.75*	*0.60 to 0.93*	*0.0099*	*1*	*558*
Planned dose per treatment course 12 mg or less	*0.77*	*0.62 to 0.96*	*0.019*	*1*	*1144*
Planned dose per treatment course >12 to 24 mg	*0.87*	*0.76 to 0.99*	*0.032*	*6*	*3950*
Planned dose per treatment course >24 mg					
Planned repeat drug exposure was 12 mg or less/week	*0.90*	*0.77 to 1.05*	*0.17*	*2*	*3448*
Planned repeat drug exposure was >12 mg/week to 24 mg/week	*0.78*	*0.60 to 1.00*	*0.050*	*4*	*1088*
Gestational age at birth	MD -0.09	-0.33 to 0.15	0.48	8	3179
Interval between trial entry and birth	Not reported				
Small for gestational age (as defined)	RR 1.18	0.97 to 1.43	0.10	7	3975
Sub group analysis for small for gestational age:					
Repeat corticosteroids as betamethasone	*1.18*	*0.97 to 1.43*	*0.10*	*7*	*3975*
Repeat doses at a minimum interval of 7 days or less	*1.38*	*1.04 to 1.82*	*0.025*	*4*	*1006*
A minimum interval of between 8 and <14 days					
A minimum interval of 14 days or more	*1.03*	*0.79 to 1.35*	*0.82*	*3*	*2969*
One repeat course	*1.16*	*0.87 to 1.54*	*0.31*	*3*	*991*
Four or more repeat courses	*2.00*	*1.07 to 3.73*	*0.030*	*1*	*368*
Planned dose per treatment course 12 mg or less	*1.33*	*0.92 to 1.94*	*0.13*	*1*	*326*
Planned dose per treatment course >12 to	*1.13*	*0.90 to 1.42*	*0.29*	*6*	*3649*

24 mg					
Planned repeat drug exposure was 12 mg or less/week	*1.06*	*0.75 to 1.50*	*0.73*	*1*	*2304*
Planned repeat drug exposure was >12 mg/week to 24 mg/week	*1.29*	*0.88 to 1.90*	*0.20*	*4*	*792*
Mean birthweight (grams)	MD -75.79	-117.63 to 33.96	0.00038	9	5626
Sub group analysis for mean birthweight (grams):					
Repeat corticosteroids as betamethasone	*-75.79*	*-117.63 to -33.96*	*0.00038*	*9*	*5626*
Repeat doses at a minimum interval of 7 days or less	*-63.68*	*-128.59 to 1.24*	*0.055*	*5*	*2328*
A minimum interval of 14 days or more	*-79.61*	*-143.23 to -16.00*	*0.014*	*3*	*2972*
One repeat course	*-57.20*	*-132.99 to 18.59*	*0.14*	*3*	*994*
Four or more repeat courses	*-161.00*	*-290.52 to -31.48*	*0.015*	*1*	*368*
Planned dose per treatment course 12 mg or less	*-48.72*	*-119.84 to 22.40*	*0.18*	*2*	*1470*
Planned dose per treatment course >12 to 24 mg	*-90.12*	*-141.85 to -38.39*	*0.00064*	*7*	*4156*
Planned repeat drug exposure was 12 mg or less/week	*-54.00*	*-126.19 to 18.19*	*0.14*	*2*	*3448*
Planned repeat drug exposure was >12 mg/week to 24 mg/week	*-110.62*	*-199.49 to -21.74*	*0.015*	*4*	*1184*
Birthweight z score	MD -0.11	0.23 to 0.00	0.060	2	1256
Sub group analysis for birthweight z score:					
Repeat corticosteroids as betamethasone	*-0.11*	*-0.23 to 0.00*	*0.060*	*2*	*1256*
Repeat doses at a minimum interval of 7 days or less	*-0.13*	*-0.26 to 0.00*	*0.045*	*1*	*1144*
A minimum interval of 14 days or more	*0.00*	*-0.34 to 0.34*	*1.0*	*1*	*112*
One repeat course	*0.00*	*-0.34 to 0.34*	*1.0*	*1*	*112*
Planned dose per treatment course 12 mg or less	*-0.13*	*-0.26 to 0.00*	*0.045*	*1*	*1144*
Planned dose per treatment course >12 to 24 mg	*0.0*	*-0.34 to 0.34*	*1.0*	*1*	*112*
Planned repeat drug exposure was 12 mg or less/week	*-0.13*	*-0.26 to 0.00*	*0.045*	*1*	*1144*
Mean birth length(cm)	MD -0.56	-0.89 to -0.23	0.00094	6	4550
Birth length z score	MD -0.05	-0.19 to 0.09	0.47	2	1256
Mean birth head circumference	MD -0.32	-0.49 to -0.15	0.00030	9	5625
Birth head circumference z score	MD -0.14	-0.27 to 0.00	0.044	2	1256
Placental weight	Not reported				
Low Apgar (<7 at five minutes)	RR 0.84	0.64 to 1.10	0.20	3	4004
Use and duration of respiratory support:					
Use of respiratory support	RR 0.84 (mechanical ventilation)	0.71 to 0.99	0.033	6	4918
Duration of respiratory support (days)	MD 0.30	-0.09 to 1.50	0.62	1	37
Use and duration of oxygen supplementation:					

Use of oxygen supplementation	RR 0.92	0.85 to 0.99	0.025	2	3448
Duration of oxygen supplementation (days)	MD 3.30	-2.31 to 8.91	0.25	1	37
Use of surfactant	RR 0.78	0.65 to 0.95	0.014	9	5525
Air leak syndrome	RR 0.76	0.29 to 1.97	0.57	3	2192
Pulmonary hypertension	Not reported				
Inotropic support	RR 0.80	0.66 to 0.97	0.023	2	1470
Use of nitric oxide for respiratory support	RR 0.58	0.29 to 1.17	0.13	1	1144
Early neonatal infection (<48 hours)	RR 0.93	0.79 to 1.11	0.43	3	1544
Late neonatal infection (≥48 hours)					
Proven infection while in the NICU	RR 1.00	0.83 to 1.20	0.99	6	5002
Use of post-natal corticosteroids	RR 1.38	0.99 to 1.93	0.058	3	3931
Neonatal blood pressure:					
Mean neonatal blood pressure first day after birth	MD 0.70	-2.47 to 3.87	0.67	1	175
Mean neonatal blood pressure 6 weeks' after birth	MD -1.40	-5.06 to 2.26	0.45	1	175
Anthropometry at hospital discharge:					
Mean weight at primary hospital discharge (grams)	MD -1.00	-77.15 to 75.15	0.98	1	1090
Weight z score at primary hospital discharge	MD -0.05	-0.16 to 0.06	0.38	2	1195
Mean head circumference at primary hospital discharge (cm)	MD 0.12	-0.10 to 0.35	0.27	2	1195
Head circumference z score at primary hospital discharge	MD -0.03	-0.15 to 0.10	0.68	2	1195
Mean length at primary hospital discharge (cm)	MD 0.02	-0.44 to 0.47	0.94	2	1189
Length z score at primary hospital discharge	MD -0.06	-0.23 to 0.10	0.46	2	1189
HPA axis suppression, including cortisol:					
Mean basal cortisol concentrations (nmol/L) at birth	MD -44.90	-78.41 to -11.39	0.0086	1	67

Appendix I: Repeat antenatal corticosteroids - Child/adult (follow up) (Crowther 2011)

Childhood Outcome	Effect Size	95%CI	P	No of studies	n
Total mortality	RR 1.06	0.80 to 1.41	0.66	4	4370
Sub group analysis for total mortality up to early childhood follow up:					
Repeat corticosteroids as betamethasone	*1.06*	*0.80 to 1.41*	*0.66*	*4*	*4370*
Repeat doses at a minimum interval of 7 days or less	*1.11*	*0.74 to 1.67*	*0.60*	*3*	*2066*
A minimum interval of 14 days or more	*1.02*	*0.69 to 1.51*	*0.92*	*1*	*2304*
One repeat course	*2.31*	*0.82 to 6.50*	*0.11*	*1*	*326*
Planned dose per treatment course 12 mg or less	*1.11*	*0.72 to 1.71*	*0.65*	*2*	*1472*
Planned dose per treatment course >12 to 24 mg	*1.04*	*0.72 to 1.50*	*0.85*	*2*	*2898*
Planned repeat drug exposure was 12 mg or less/week	*0.98*	*0.72 to 1.33*	*0.90*	*2*	*3450*
Planned repeat drug exposure was >12 mg/week to 24 mg/week	*1.15*	*0.39 to 3.38*	*0.80*	*1*	*594*
Neurosensory disability (composite of impairments: cerebral palsy, blindness, deafness, developmental delay)	RR 1.08	0.31 to 3.76	0.90	2	1256
Sub group analysis for neurosensory disability at early childhood follow up:					
Repeat corticosteroids as betamethasone	*1.08*	*0.31 to 3.76*	*0.90*	*2*	*1256*
Repeat doses at a minimum interval of 7 days or less	*1.08*	*0.31 to 3.76*	*0.90*	*2*	*1256*
One repeat course	*3.53*	*0.37 to 33.52*	*0.27*	*1*	*257*
Planned dose per treatment course 12 mg or less	*1.08*	*0.31 to 3.76*	*0.90*	*2*	*1256*
Planned repeat drug exposure was 12 mg or less/week	*0.77*	*0.55 to 1.08*	*0.13*	*1*	*999*
Cerebral palsy	RR 1.03	0.71 to 1.50	0.88	4	3800
Developmental delay / IQ	RR 0.97	0.84 to 1.13	0.72	3	3202
Visual impairment	RR 1.17	0.65 to 2.10	0.61	2	3151
Hearing impairment	RR 0.85	0.29 to 2.52	0.77	3	3405
Motor dysfunction:					
Psychomotor developmental index at early childhood follow up	MD 0.40	-1.75 to 2.55	0.72	1	958
Survival free of neurosensory disability	RR 1.01	0.92 to 1.11	0.84	2	1317
Sub group analysis for survival free of neurosensory disability to early childhood follow up:					
Repeat corticosteroids as betamethasone	*1.01*	*0.92 to 1.11*	*0.84*	*2*	*1317*
Repeat doses at a minimum interval of 7 days or less	*1.01*	*0.92 to 1.11*	*0.84*	*2*	*1317*
One repeat course	*0.98*	*0.95 to 1.01*	*0.26*	*1*	*257*
Planned dose per treatment course 12 mg or less	*1.01*	*0.92 to 1.11*	*0.84*	*2*	*1317*
Planned repeat drug exposure was 12 mg	*1.04*	*0.99 to 1.10*	*0.15*	*1*	*1060*

or less/week					
Anthropometry:					
Mean weight at early childhood follow up	MD -0.03	-0.21 to 0.15	0.75	3	1776
Weight z score at early childhood follow up	MD -0.03	-0.19 to 0.13	0.71	1	1047
Weight small for age at early childhood follow up	RR 0.92	0.71 to 1.19	0.52	2	1448
Mean height at early childhood follow up	MD -0.13	-0.55 to 0.30	0.56	3	1776
Height z score at early childhood follow up	MD -0.04	-0.17 to 0.09	0.59	2	1290
Height small for age at early childhood follow up	RR 1.12	0.63 to 2.02	0.69	2	1441
Mean head circumference at early childhood follow up	MD -0.05	-0.22 to 0.11	0.53	3	1776
Head circumference z score at early childhood follow up	MD 0.04	-0.09 to 0.18	0.51	2	1290
Head circumference small for age at early childhood follow up	RR 1.10	0.77 to 1.56	0.60	2	1442
Child behaviour:					
Behaviour score within clinical range at early childhood follow up	RR 1.09	0.79 to 1.51	0.58	1	1045
Respiratory disease:					
Asthma / wheeze at early childhood follow up	RR 0.89	0.63 to 1.27	0.53	3	1720
Blood pressure:					
Mean systolic blood pressure	MD -2.90	-5.40 to -0.40	0.023	1	486
Mean diastolic blood pressure	MD -1.00	-2.86 to 0.86	0.29	1	486
Hypertension at early childhood follow up	RR 0.97	0.77 to 1.23	0.80	1	628
Impairment of insulin / glucose axis	Not reported				
Insulin sensitivity	Not reported				
Cognitive ability					
Mental developmental index at early childhood follow up	MD 1.23	-0.65 to 3.11	0.20	2	1162
Learning disability	Not reported				

Adult Outcome	Effect Size
Diabetes	Not reported
Obesity	Not reported
Cardiovascular disease	Not reported
Age at puberty	Not reported
Educational attainment	Not reported
IQ	Not reported
Cognitive ability	Not reported
Learning disability	Not reported
Survival free of metabolic disease	Not reported

Use of Health Services

Outcome	Effect Size	95%CI	P	No of studies	n
Length of antenatal hospitalisation for the woman	Not reported				
Length of postnatal hospitalisation for the woman	MD 0.0	-0.22 to 0.22	1.00	1	483
Maternal admission to ICU	Not reported				
Admission to NICU	RR 1.01	0.95 to 1.07	0.82	2	3448
Length of stay in NICU	Not reported				
Length of neonatal hospitalisation	Not reported				
Duration of respiratory support (days)	MD 0.30	-0.09 to 1.50	0.62	1	37

Appendix J: Eligibility criteria for inclusion/exclusion criteria in trials included in the Roberts (2006) systematic review and Roberts CPG version 2015 systematic review

Author/year	Inclusion criteria	Exclusion criteria
Amorim 1999	Women with severe pre-eclampsia Singleton pregnancy with a live fetus Gestational age between 26 and 34 weeks' Likely minimal interval of 24 hours between drug administration and delivery	Indication for immediate delivery Diabetes PROM Maternal disease Congenital malformations Perinatal haemolytic disease Group B streptococcal infection
Balci 2010	34 to 36 weeks' gestation based on LMP or fetal biometric measurements on ultrasonography The mother had had at least two contractions lasting more than 30 seconds in 10 minutes on cardiotocography, and cervical dilatation >3 cm with 80% effacement.	Obstetric complications (severe IUGR, pre-eclampsia, placental abruption, placenta praevia) Multiple pregnancy Women who had already received antenatal corticosteroid therapy Women with early rupture of membranes Suspicion of chorioamnionitis Fetal anomaly Fetal distress Severe systemic disease (heart disease, hyperthyroidism, hypothyroidism, renal disease, diabetes mellitus)
Block 1977	Women with preterm labour and PROM	Not stated
Cararach 1991	Women with PROM Gestational age 28 to 30 weeks'	Not stated
Carlan 1991	Women with PROM 24 to 34 weeks'	Not stated
Collaborative 1981	Women at high risk of preterm delivery L/S ratio <2.0 in cases of uncertain gestation Hyperthyroidism Hypertension Placental insufficiency Drug addiction, methadone use Gestation >34 weeks'	>5 cm of cervical dilatation Anticipated delivery <24 hours or >7 days Intrauterine infection Previous glucocorticoid treatment History of peptic ulcer Active tuberculosis Viral keratitis Severe fetal Rh sensitisation Infant unlikely to be available for follow up
Dexiprom 1999	Women with PROM 28 to 34 weeks' gestation (or estimated fetal weight of 1000 g to	Cervical dilatation >4 cm Evidence of infection

	2000 g if gestational age unknown)	Evidence of antepartum haemorrhage <19 years of age
Doran 1980	Women with PROM, spontaneous preterm labour or planned elective preterm delivery 24 to 34 weeks' gestation	Women with preeclampsia Women for whom steroids are contraindicated on medical grounds.
Fekih 2002	Women in preterm labour 26 to 34 weeks'	Gestational diabetes >4 cm cervical dilatation Fetal abnormalities Contraindication to corticosteroids Delivery elsewhere or after 34 weeks' (post randomisation exclusions)
Gamsu 1989	Women with spontaneous or planned preterm delivery <34 weeks' gestation	Contraindication to corticosteroids Contraindications to postponing delivery Diabetes Suspected intrauterine infection
Garite 1992	Women likely to deliver between 24 hours and 7 days with spontaneous preterm labour or planned preterm delivery 24 to 27 weeks' and 6 days gestation	PROM Clinical or laboratory evidence of infection Contraindication to previously given corticosteroids Diabetes
Goodner 1979	Any pregnant woman expected to deliver prior to 34 weeks' gestation	Not stated
Kari 1994	Women with preterm labour or threatened preterm delivery due to pre eclampsia	Rupture of membranes Chorioamnionitis Congenital abnormalities Proven lung maturity Insulin treated diabetes Previously treated with corticosteroids
Lewis 1996	Singleton pregnancy PROM 24 to 34 weeks' gestation	Evidence of infection Vaginal examination Cerclage Allergic to penicillin Contraindication to expectant management Lung maturity confirmed by L/S ratio if 32 weeks' or more
Liggins 1972	Women with threatened or planned preterm delivery 24 to 36 weeks'	Imminent delivery Contraindication to corticosteroids
Lopez 1989	27 to 35 weeks' Premature rupture of membranes (confirmed using speculoscopy and ultrasound) No signs of infection Not in labour at time of hospitalisation	Not stated

Morales 1989	PROM Singleton pregnancy 26 to 34 weeks' gestation	PROM <12 hours before onset of labour Uterine tenderness Foul smelling lochia Fetal tachycardia Allergy to penicillin Congential abnormalities L/S ratio 2 or more Unable to obtain an L/S ratio Dubowitz assigned gestational age different from obstetric assessment by 3 weeks' (post randomisation exclusion)
Nelson 1985	PROM 28 to 34 weeks' gestation	Fetal distress Active labour Cervical dilatation >3 cm Sensitivity to tocolytics PROM >24 hours Existing infection
Parsons 1988	PROM and <4 cm of cervical dilatation 25 to 32 weeks' gestation	Infection Fetal distress Fetal anomalies Contraindication to tocolysis
Porto 2011	34 to 36 weeks' and 6 days gestation At risk of imminent premature delivery (either spontaneously or if early delivery is recommended as a result of problems with mother or fetus)	Multiple pregnancy Major congenital malformations Haemorrhage symptoms with active bleeding Clinical evidence of chorioamnionitis Previous use of antenatal corticosteroids Need for immediate resolution of pregnancy for maternal or fetal reasons
Qublan 2001	PROM Singleton pregnancy 27 to 34 weeks' gestation	Lethal congenital abnormality Fetal death Infection Expected delivery within 12 hours
Schutte 1980	Women with preterm labour in whom it was possible to delay delivery by at least 12 hours 26 to 32 weeks' gestation	No contraindications to the use of corticosteroids or ociprenaline (insulin treated diabetes, hyperthyroidism, infection, severe hypertension, cardiac disease, marked fetal growth retardation or fetal distress)
Shanks 2010	Singleton pregnancy 34 to 36 weeks' and 6 days gestation Immature TDx-FLM-II test (<45 mg/g) (surfactant to albumin ratio) after clinically indicated amniocentesis to test for fetal lung maturity	Multiple gestation Ruptured membranes Uncertain gestational ages Previous steroid treatment in current pregnancy Delivery before completing the steroid course Those unwilling or unable to comply with study protocol

Silver 1996	Women at risk of delivery between 24 to 29 weeks'	Infection Maternal or fetal indications for urgent delivery
Taeusch 1979	Women with preterm labour, PROM or with cervical dilatation <5cm at 33 weeks' or less Women with an L/S ratio <2 if >33 weeks' or who had a previous infant with RDS	Indication for immediate delivery Obstetrician objection Pre eclampsia Previously received corticosteroids
Teramo 1980	Women with preterm labour and cervical dilatation <4 cm without progression of labour upon initial observation of up to 12 hours. 28 to 35 weeks' gestation	Pre eclampsia Diabetes

PROM Prelabour rupture of membranes, IUGR intrauterine growth restriction; RDS respiratory distress syndrome

Appendix K: Eligibility criteria for inclusion/exclusion criteria in trials included in the Crowther (2011) systematic review

Author/year	Inclusion criteria	Exclusion criteria
Aghajafari 2002	24 to 30 weeks' gestation; At continued risk of preterm birth who remained undelivered 7 or more days following a single course of antenatal corticosteroids (defined at 2 doses of 12 mg/dose intramuscular betamethasone given at 12 or 24 hour intervals, or 4 doses of 5-6 mg/dose intramuscular dexamethasone, given at 12 hour intervals); One or more of the following risk factors for preterm birth: regular uterine contractions; shortened cervical length or cervical dilatation; preterm prelabour rupture of membranes; antepartum bleeding secondary to placental separation or placenta praevia; history of preterm birth; maternal hypertension; other medical condition increasing the risk of preterm delivery or intrauterine growth restriction; other fetal conditions increasing the risk of preterm delivery.	Women who required chronic doses of corticosteroids secondary to medical conditions; Contra-indication to corticosteroids; Clinical evidence of chorioamnionitis; Known lethal fetal congenital anomaly;
Crowther 2006	Less than 32 weeks' gestation; Had received an initial treatment of corticosteroids 7 or more days previously; Deemed to be at continued risk of preterm birth by their responsible clinician; No contraindication to further corticosteroid therapy; Single, twin or triplet pregnancy.	In second stage of labour; Chorioamnionitis requiring urgent delivery; If further corticosteroid therapy was judged to be essential.
Garite 2009	25 to less than 33 weeks' gestation; Received a course of betamethasone 14 or more days previously and judged to have recurrent or continued risk of preterm birth; Single or twin pregnancy.	Major fetal anomaly; Cervical dilatation of 5cm or more; Higher order multiples; Ruptured membranes; Documented lung maturity; Receiving corticosteroids for other indications; Human immunodeficiency virus infection or active tuberculosis.
Guinn 2001	24 to less than 33 weeks' gestation; At high risk of preterm birth and who remained undelivered 1 weeks' following an initial course of antenatal corticosteroids (defined as 2 doses of 12 mg/dose intramuscular betamethasone, repeated at 24 hours; or 4 doses of 6 mg/dose intramuscular dexamethasone, given at 12 hour intervals); One or more of the following risk factors for preterm birth: preterm labour with intact membranes; preterm premature rupture of membranes (rupture of membranes occurring >1 hour prior to the onset of preterm labour); maternal medical illness (pre-eclampsia, hypertension, diabetes, renal disease, systemic lupus erythematosus, trauma); suspected fetal jeopardy (intrauterine growth	Women who required immediate delivery; Fetal anomalies incompatible with life; Documented fetal lung maturity; Maternal active tuberculosis or human immunodeficiency virus infection.

	restriction <10th percentile, oligohydramnios, abnormal antepartum testing, progression of fetal anomaly compatible with life; twin to twin transfusion syndrome).	
Mazumder 2008	26 to 33 weeks' gestation; At risk of preterm birth and had received a course of betamethasone 7 or more days previously; Available for follow up every week until birth.	Unreliable gestational age; Frank chorioamnionitis; Major fetal malformation.
McEvoy 2002	25 to 33 weeks' gestation; Undelivered one week after a single course of antenatal corticosteroids (defined at 2 doses of 12 mg/dose intramuscular betamethasone) given because of increased risk of preterm birth.	Insulin dependent diabetes; Drug addiction; Known lethal fetal congenital anomaly.
McEvoy 2010	26 to less than 34 weeks' gestation; At least 14 days after first course of antenatal corticosteroids; At continued risk of preterm birth as judged by their care provider; Provided informed consent.	Insulin dependent diabetics; Major documented fetal or chromosomal abnormality; Multiple pregnancy greater than twins; Clinical chorioamnionitis; Initial course of antenatal corticosteroids given <24 weeks' gestation; Chronic steroid use during pregnancy for clinical care.
Murphy 2008	25 to 32 weeks' gestation; Remained undelivered 14-21 days after an initial course of antenatal corticosteroids and continued to be at high risk of preterm birth; Single, twin or triplet pregnancy.	Contraindication to corticosteroid use; Required chronic doses of corticosteroids; Evidence of chorioamnionitis; Known lethal fetal congenital abnormality; Initial course of antenatal corticosteroids given <23 weeks' gestation; Previously participated in MACS; Women with a multiple pregnancy with a fetal death after 13 weeks'.
Peltoniemi 2007	Less than 34 weeks' gestation; Received a single course of betamethasone less than 7 days previously; To have an elective delivery within 48 hours, or were at very high risk of spontaneous delivery within 48 hours (cervical opening 3cm or more and regular contractions at 5 to 10 minute intervals).	Long term maternal corticosteroid use; Clinical chorioamnionitis; Lethal disease of the fetus.
Wapner 2006	23 weeks' and 0 days to 31 weeks' and 6 days gestation; Intact membranes; Received a single full course of antenatal corticosteroid between 7 and 10 days earlier; Remained at high risk of spontaneous preterm birth or had the diagnosis of placenta praevia or chronic abruption.	Preterm premature rupture of membranes prior to randomisation; Confirmed fetal lung maturity; Chorioamnionitis; Major fetal anomaly; Non-reassuring fetal status; Systemic corticosteroid use during current pregnancy; Insulin dependent diabetes.

Appendix L: Eligibility criteria for inclusion/exclusion criteria in trials included in the Brownfoot (2013) systematic review and Brownfoot CPG version 2015 systematic review

Author/year	Inclusion criteria	Exclusion criteria
Chen 2005	Preterm prelabour rupture of membranes between 24 and 32 weeks'; Preterm labour between 24 and 34 weeks' (Preterm prelabour rupture of membranes was diagnosed in the presence of a gush of fluid from the vagina followed by persistent, uncontrolled leakage or pooling of fluid on speculum examination. Preterm labour was diagnosed when persistent uterine contractions 6-8 times / hour or four contractions in 20 minutes were accompanied by dilation and /or effacement of the cervix detected via speculum examination).	Not stated.
Danesh 2012	Pregnant women of low parity; 16 to 45 years of age; Between 24 and 34 weeks' gestation; Hospitalised because of high risk of preterm birth that justified preventative corticosteroid therapy; With or without intact membranes; Low Bishop score ≤5; Non smokers; Singleton pregnancy; Resident of city study taking place in; Hospitalisation planned to last at least 3 days. (Preterm rupture of membranes was diagnosed in the presence of a gush of fluid from the vagina, followed by persistent, uncontrolled leakage, or pooling of fluid on speculum examination, with positive nitrazine and Fern testing. Preterm labour was diagnosed in the presence of uterine contractions of 4 in 20 minutes, or 8 in 60 minutes, plus progressive changed in the cervix, cervical dilatation greater than 1cm and cervical effacement 80% or greater).	Evidence of fetal distress; Substantial abnormalities in neurological, psychiatric, cardiac, endocrinological, haematologic, hepatic, renal or metabolic function; Signs of infection; Positive urine culture; Vaginal bleeding due to placental praevia or abruption.
Egerman 1998	Preterm birth between 24 to 33 weeks' gestation; Preterm labour; Preterm rupture of membranes; Medical indication for delivery.	Received corticosteroids during pregnancy (except immediately before transfer); Anticonvulsant therapy; Rifampin;

	(Preterm labour was defined as contractions with either cervical change, 2 cm dilatation, 80% effacement).	Infection other than cystitis or cervicitis; Advanced cervical dilatation; Fetal pulmonary maturity.
Eliman 2007	Risk of preterm birth between 24 to 33 weeks' gestation.	Clinical chorioamnionitis; Major fetal structural abnormalities; Major fetal chromosomal abnormalities; Prior antenatal corticosteroid exposure; Use of betamethasone or dexamethasone for other medical indications; Quadruplets.
Khandelwal 2012	Steroids administered for any indication between 23 to 34 weeks' gestation.	<23 or >34 weeks' gestation; Elapsed time >12 hours since administration of the first dose of betamethasone; Known drug allergy to betamethasone; Given steroids other than betamethasone for lung maturation; Any contraindication to steroid therapy.
Magee 1997	Singleton pregnancy; At risk of preterm birth between 26 to 34 weeks' gestation; Has not received steroids in the preceding week.	Not stated.
Mulder 1997	Women with premature contractions or at risk of preterm labour; Between 26 to 33 weeks' gestation; Small for gestational age (estimated fetal size <5th centile); Premature contractions; Placenta praevia or other cause of vaginal blood loss; Preterm rupture of membranes without evidence of intrauterine infection; Pre-eclampsia; Essential hypertension; Poor obstetric history; Leiomyoma	Cervical dilatation >5 cm; Signs of intrauterine infection; Ritodrine hydrochloride treatment for <4 days at the start of the study.
Mushkat 2001	Women with preterm labour between 26 to 33 weeks' gestation.	Chronic or acute hypertension; Gestational diabetes; Vaginal bleeding due to placental praevia or placental abruption; Intrauterine growth restriction; Fetal distress.

Romejko-Wolniewicz (2013)	Women with preterm birth <35 weeks' gestation.	Not stated.
Rotmensch 1999	Women with preterm birth at 27 to 34 weeks' gestation; Preterm premature rupture of membranes with no clinical evidence of infection; Pregnancy induced hypertension syndromes; Intrauterine growth restriction; Third trimester bleeding due to placenta praevia.	Not stated.
Senat 1998	Women with preterm labour <34 weeks' gestation.	Uncertain pregnancy history; Clinical infection in women; Vaginal bleeding; Suspicion of premature rupture of membranes.
Subtil 2003	Women at high risk of preterm birth; 27 to 35 weeks' gestation; Singleton pregnancy.	Imminent birth; Multiple pregnancy; Previously participated in the protocol; Received corticosteroid therapy <10 days prior.
Urban 2005	Preterm contractions of the uterus; Preterm premature rupture of membranes; Cervical length less than 20 mm; Placenta praevia before 34 weeks'; Singleton pregnancy.	Fetal major structural malformation or abnormal karyotype.

Appendix M: Evidence summaries

M1 Benefits and harms of a single course of antenatal corticosteroids

M1 NHMRC Evidence Summary

What are the short and long term benefits and harms of a single course of antenatal corticosteroids for the mother and fetus, infant, child adult prior to preterm birth?		
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Maternal The Roberts CPG version 2015 systematic review included 26 randomised controlled trials involving 4469 women and 4853 infants (Level I). Infant The Roberts CPG version 2015 systematic review 26 randomised controlled trials involving 4469 women and 4853 infants (Level I).	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 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')*		
Maternal Results are consistent that exposure to a single course of antenatal corticosteroids does not increase the risk of maternal death, chorioamnionitis, or puerperal sepsis, pyrexia after trial entry, intrapartum fever or postnatal pyrexia. Evidence is consistent that antenatal corticosteroid administration increases maternal blood glucose concentrations. Infant Evidence is consistent that a single course of antenatal corticosteroids is associated with significant reductions in fetal and neonatal death, respiratory distress syndrome, intra-ventricular haemorrhage, necrotising enterocolitis, systemic infection, and overall need for respiratory support.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is not consistent
	NA	Not applicable (one study only)
3. Clinical impact *(indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Maternal The benefit of improved neonatal outcomes probably outweighs the impact of a transient elevation in maternal blood glucose. Infant High quality, precise evidence with large effect sizes demonstrating reduction in a number of outcomes.	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?)*		
The systematic review included one large trial from New Zealand. The majority of other studies were conducted in the United States. All studies were conducted in women at risk of preterm birth (variously defined by the authors). Some of the trials allowed repeat courses of antenatal corticosteroids if the woman remained at risk of preterm birth.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether sensible to apply
5. Applicability *(is the body of evidence relevant to the New Zealand / Australian healthcare context in terms of health services / delivery of care and cultural factors?)*		
The results are directly applicable to the New Zealand / Australian healthcare context. Betamethasone and dexamethasone are readily available and already in use in Australia and New Zealand.	A	Evidence directly applicable to New Zealand / Australian healthcare context
	B	Evidence applicable to New Zealand / Australian healthcare context with few caveats
	C	Evidence probably applicable to New Zealand / Australian healthcare context with some caveats
	D	Evidence not applicable to New Zealand / 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 *(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	A	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias
2. Consistency	A	All studies consistent
3. Clinical Impact	A	Very large
4. Generalisability	A	Evidence directly generalisable to target population
5. Applicability	A	Evidence directly applicable to New Zealand / Australian healthcare context

Evidence statement
Maternal
The evidence is from systematic reviews of randomised controlled trials and mainly addresses the risks in women with chorioamnionitis and risk of elevated blood glucose concentrations. The clinical impact is limited as the main reason for administering the antenatal corticosteroids is for fetal lung maturation. The evidence is generalizable to New Zealand and Australia.
Infant
There is clear and relevant evidence of the benefits to the fetus and neonates for the use of antenatal corticosteroids.

RECOMMENDATION *(What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible)*	**OVERALL GRADE OF RECOMMENDATION**	
In women at risk of preterm birth use a single course of antenatal corticosteroids.	**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 recommendations(s) but care should be taken in its application
	D	Body of evidence is weak and recommendation must be applied with caution
	PP	Practice Point

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

Nil

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 implementation of this recommendation?	**YES**
	NO

M1 GRADE Evidence summary

Considered Judgement - Strength of recommendation

What are the short and long term benefits and harms of a single course of antenatal corticosteroids for the mother and fetus, infant, child adult prior to preterm birth?

1. Outcome measures:	Quality of evidence				Importance of outcome in making a decision		
Maternal Outcomes	**HIGH**	**MOD**	**LOW**	**V. LOW**	**Critical**	**Important**	**Not Important**
O_1 Chorioamnionitis	✓				✓		
O_2 Puerperal sepsis		✓			✓		
O_3 Pyrexia after entry to trial		✓				✓	
O_4 Intrapartum fever requiring antibiotics		✓				✓	
O_5 Post natal pyrexia	✓					✓	
O_6 Maternal quality of life				NR	✓		
Infant Outcomes	**HIGH**	**MOD**	**LOW**	**V. LOW**	**Critical**	**Important**	**Not Important**
O_1 Combined fetal and neonatal death	✓				✓		
O_2 Neonatal death	✓				✓		
O_3 Fetal death			✓		✓		
O_4 RDS	✓				✓		
O_5 Composite of serious outcomes for the infant				NR	✓		
O_6 Neurosensory disability (composite of impairments) for infant as a child				NR	✓		
O_7 Survival free of neurosensory disability for the infant as a child				NR	✓		
O_8 Survival free of metabolic disease for the infant as a child				NR		✓	
O_9 Neurosensory disability (composite of impairments) for infant as an adult				NR	✓		
O_{10} Survival free of neurosensory disability for the infant as an adult				NR	✓		
O_{11} Survival free of metabolic disease for the infant as an adult				NR		✓	

2. Is there is insufficient evidence to make a recommendation?

Evidence statement

Maternal

The evidence for maternal infection is based on nine randomised controlled trials included in the Roberts CPG version 2015 systematic review.

Infant

There is a large volume of high quality evidence for mortality outcomes and respiratory distress syndrome. The evidence for neurosensory disability is less, but is of high quality. Evidence comes from the Roberts CPG version 2015 systematic review.

3. What benefit will the proposed intervention/action have?

Evidence statement	Quality of evidence
Maternal - There do not appear to be any direct benefits reported for maternal health. The intervention is not aimed at improving maternal health but is directed at improving fetal lung maturation. There is the evidence from other clinical questions that indicates significant benefit to the infant.	**MODERATE**
Infant - The evidence shows significant reductions in perinatal death, and neonatal death. There is also a significant reduction in the risk of respiratory distress syndrome, and duration of respiratory support. There were no statistically significant differences for death in childhood between those children exposed to a single course of antenatal corticosteroids, and those not exposed at early childhood follow up. The evidence also indicates significant reduction in developmental delay in childhood for those exposed to antenatal corticosteroids. There was no statistically significant differences in cerebral palsy in childhood or sensory impairment (visual or hearing), although there was no evidence for a composite of these impairments.	**HIGH**

Judging the benefits in context

The evidence is applicable and generalisable to the New Zealand and Australian health settings.

4. What harm might the proposed intervention/action do?

Evidence statement	Quality of evidence
Maternal - The randomised controlled trials included in the Roberts CPG version 2015 review that provided data found no increased risk of maternal infection (variously reported as puerperal sepsis, pyrexia after trial entry requiring the use of antibiotics, intrapartum fever requiring antibiotics, or postnatal fever). Amorim 1999 did find that women exposed to corticosteroids were more likely to have glucose intolerance (not clearly defined) than those women in the control arm. This trial used a regimen of weekly repeat doses in eligible women if the infant had not been born and comment was made that it was difficult to determine if this was of relevance to the outcome.	**MODERATE**
Infant - There is some evidence indicating that intrauterine exposure to synthetic glucocorticoids reduces fetal, and in some cases neonatal and infant, hypothalamic-pituitary-adrenal axis activity.	**MODERATE**

Judging the harms in context
Maternal - The evidence is from trials conducted in women at risk of preterm birth, exposed or not to antenatal corticosteroids. Some trial protocols allowed for repeat doses of antenatal corticosteroids if women were eligible. There is no indication of increased harm to the mother in terms of risk of infection. Evidence indicates that women exposed to antenatal corticosteroids may be at risk of transient elevated blood glucose concentrations (clinical significance of which is unclear).
Infant - The evidence is based on data from a single trial and relevant caution is required in extrapolation of findings.

5. What is the likely balance between good and harm?

Evidence statement	**Overall quality of evidence**
Maternal - There does not appear to be an increased risk of infection, although there is potentially increased risk of transient maternal glucose intolerance. Any effects on maternal health are probably outweighed by the significant benefits to the infant (Chapter 4).	**HIGH**
Infant - There are clear benefits to the infant in terms of survival and reduced risk of respiratory distress syndrome. The evidence for HPA axis suppression is limited in volume. There are no differences in developmental outcomes. The benefits are likely to outweigh the harms.	**HIGH**

Judging the balance of benefits and harms in context
Maternal - There do not appear to be any direct health benefits for the mother. Evidence indicates an increased risk of maternal glucose intolerance following exposure to antenatal corticosteroids the clinical significance of this in non-diabetic women in unclear and requires further research. This increased risk for the mother is outweighed by the evidence of clear and large benefits for the neonate.
Infant - Benefits clearly outweigh harms

Benefits clearly outweigh harms	**Recommend**	**STRONG**
Benefits probably outweigh harms	Consider	CONDITIONAL
Not known	Make a recommendation for research (see 8 below)	WEAK
Benefits probably don't outweigh harms	Consider against/make no recommendation	CONDITIONAL
Harms probably outweigh benefits		
Benefits clearly don't outweigh harms	Recommend against	STRONG
Harms clearly outweigh benefits		

6. Is the intervention/action implementable in the New Zealand and Australian context?

Summary statement
Antenatal corticosteroids are already widely in use in New Zealand and Australia.

Yes	**Recommend/consider**
Not known	Consider economic evaluation
No	Recommend/consider against

7. Final recommendation

	Strength of recommendation
In women at risk of preterm birth use a single course of antenatal corticosteroids.	**STRONG** **CONDITIONAL** **WEAK**

8. Recommendations for research

- There is a need to better assess the degree and health impact, if any, of changes in maternal blood glucose control from administration of a single course of antenatal corticosteroids on maternal and infant health outcomes.
- There is a need to better assess the impact, if any, of *in utero* exposure to a single course of antenatal corticosteroids on:
  - the hypothalamic-pituitary adrenal axis of the infant, child and adult.
  - the glucose-insulin axis in childhood
  - the later risk of the infant developing diabetes in adulthood.
- Future research that investigates the use of a single course of antenatal corticosteroids should include outcomes on maternal quality of life.

M2 Benefits and harms of repeat antenatal corticosteroids

M2 NHMRC Evidence Summary

For a woman at risk of preterm birth, who has received a single course of antenatal corticosteroids and remains at ongoing risk of preterm birth, what are the short and long term benefits and harms of a repeat dose(s) of antenatal corticosteroids for the mother, fetus, infant, child and adult?		
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Maternal A total of 7 randomised controlled trials (level II studies) within a systematic review (level 1 study) reported on maternal outcomes (Crowther 2011). Infant 8 randomised controlled trials (level II studies) within a systematic review (level 1 study) (Crowther 2011) and later childhood follow-up from two trials reported in Crowther CPG version 2015.	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 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')*		
Maternal Results for repeat courses are consistent. Exposure does not increase the risk of chorioamnionitis and puerperal sepsis. One trial found no statistical differences in risk of abnormal one hour glucose tolerance test. Maternal insomnia is increased with repeat antenatal corticosteroids but the duration of and the clinical significance are not discussed by the trials reporting this outcome. Infant Evidence is consistent that repeat antenatal corticosteroids are associated with a reduction in composite serious outcome, a significant reduction in respiratory distress and several other key clinical outcomes. Repeat antenatal corticosteroids have been associated with a reduction in a number of growth parameters, however the clinical significance of modest observed differences has yet to be determined.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is not consistent
	NA	Not applicable (one study only)
3. Clinical impact *(indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Maternal There are no obvious detrimental effects on the mother of repeat antenatal corticosteroids. Infant High quality, precise evidence with large effect sizes demonstrating reduction in a number of clinical health outcomes for infants exposed to a repeat antenatal corticosteroids versus a single course of antenatal corticosteroids. There is evidence of a reduced birthweight in infants who had been exposed to antenatal corticosteroids, the clinical significance of this, if any, is unknown. There was no difference between groups in birthweight at hospital discharge. The benefits for the neonate are likely to outweigh any health harms.	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?)*		
The Crowther (2011) review includes one study from Australia, and one from New Zealand, that are generalisable to this guidelines target population. The other studies were conducted in the United States/ India/ Canada and the UK. All studies were conducted in women at risk of preterm birth (variously defined by the authors). All administered betamethasone.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether sensible to apply
5. Applicability *(is the body of evidence relevant to the New Zealand / Australian healthcare context in terms of health services / delivery of care and cultural factors?)*		
The results are likely to be applicable to the New Zealand and Australian healthcare context. Betamethasone and dexamethasone and betamethasone are readily available and already in use in Australia and New Zealand.	A	Evidence directly applicable to New Zealand / Australian healthcare context
	B	Evidence applicable to New Zealand / Australian healthcare context with few caveats
	C	Evidence probably applicable to New Zealand / Australian healthcare context with some caveats
	D	Evidence not applicable to New Zealand / 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 *(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	A	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias
2. Consistency	A	All studies consistent
3. Clinical Impact	B	Substantial
4. Generalisability	A	Evidence directly generalisable to target population
5. Applicability	A	Evidence directly applicable to New Zealand / Australian healthcare context

Evidence statement
Maternal
The evidence is from systematic reviews of randomised controlled trials. The clinical impact is limited as the main reason for administering antenatal corticosteroids is for fetal lung maturation. The evidence is generalizable to New Zealand and Australia

Infant
The evidence is based on randomised controlled trials, and suggests significant respiratory benefits to the neonate. There is some evidence to suggest decrease birthweight but the clinical significance of this is unclear.

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

Use repeat antenatal corticosteroids in women at risk of early preterm, imminent birth following a single course of antenatal corticosteroids.

OVERALL GRADE OF RECOMMENDATION	
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 recommendations(s) but care should be taken in its application
D	Body of evidence is weak and recommendation must be applied with caution
PP	Practice Point

UNRESOLVED ISSUES *(If needed, keep a 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 in some practices**
	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 implementation of this recommendation?	**YES due to practitioners being uncertain about use**
	NO

M2 GRADE Evidence summary

Considered Judgement - Strength of recommendation							
For a woman at risk of preterm birth, who has received a single course of antenatal corticosteroids and remains at ongoing risk of preterm birth, what are the short and long term benefits and harms of a repeat dose(s) of antenatal corticosteroids for the mother, fetus, infant, child and adult?							
1. Outcome measures:	**Quality of evidence**				**Importance of outcome in making a decision**		
Maternal Outcomes	**HIGH**	**MOD**	**LOW**	**V. LOW**	**Critical**	**Important**	**Not Important**
O_1 Chorioamnionitis	✓				✓		
O_2 Puerperal sepsis	✓				✓		
O_3 Pyrexia after entry to trial				NR		✓	
O_4 Intrapartum fever requiring antibiotics				NR		✓	
O_5 Post natal pyrexia		✓				✓	
O_6 Maternal quality of life				NR	✓		
Infant Outcomes	**HIGH**	**MOD**	**LOW**	**V. LOW**	**Critical**	**Important**	**Not Important**
O_1 Combined fetal and neonatal death	✓				✓		
O_2 Neonatal death	✓				✓		
O_3 Fetal death		✓			✓		
O_4 RDS	✓				✓		
O_5 Composite of serious outcomes for the infant	✓				✓		
O_6 Neurosensory disability (composite of impairments) for infant as a child		✓			✓		
O_7 Survival free of neurosensory disability for the infant as a child			✓		✓		
O_8 Survival free of metabolic disease for the infant as a child				NR		✓	
O_9 Neurosensory disability (composite of impairments) for infant as an adult				NR	✓		
O_{10} Survival free of neurosensory disability for the infant as an adult				NR	✓		
O_{11} Survival free of metabolic disease for the infant as an adult				NR		✓	

2. Is there is insufficient evidence to make a recommendation?

Evidence statement

Maternal - Evidence for puerperal sepsis is based on five of the ten trials included in the Crowther 2011 Cochrane systematic review, involving over 3000 women. Evidence for postnatal pyrexia is based on one trial, included in the Crowther 2011 Cochrane systematic review, conducted on over 900 women.

Infant - There is a large volume of evidence from the Crowther 2011 Cochrane systematic review incorporating ten randomised controlled trials involving 5554 infants. Data for longer term follow-up was identified in the Crowther CPG version 2015 systematic review.

3. What benefit will the proposed intervention/action have?

Evidence statement	**Quality of evidence**
Maternal - There appear to be no direct health benefits for the mother. There is no evidence of increased risk of maternal infection. Evidence from one randomised controlled trial of 982 women indicates no increased risk of postnatal pyrexia for women exposed to repeat courses of antenatal corticosteroids. There is no increased risk of puerperal sepsis for women exposed to repeat courses of antenatal corticosteroids based on evidence from five randomised controlled trials including 3091 women.	**HIGH**
Infant - There was a 16% reduction in the risk of composite serious outcome and a 16% reduction in the risk of respiratory distress syndrome for those infants exposed to repeat courses of antenatal corticosteroids. There was no statistically significant difference in risk of fetal and neonatal mortality, or duration of respiratory support in infants exposed to repeat courses of antenatal corticosteroids compared to those exposed to placebo.	**HIGH**

Judging the benefits in context

The evidence is based on well designed and conducted randomised controlled trials with a combined sample size of over 5500. All the women and infants involved were exposed to a repeat dose(s) (or placebo), after remaining at risk of imminent preterm birth following an initial single course. The populations included women from Canada, Australia and New Zealand, the United States, India and Finland, as well as a multicentre trial involving 20 countries. There is some evidence for outcomes to early childhood, but despite follow up being ongoing, evidence is lacking for long term adult effects, as not all of the trials participants have reached adulthood as yet.

4. What harm might the proposed intervention/action do?

Evidence statement	**Quality of evidence**
Maternal - There is an increased risk of maternal insomnia in women given repeat antenatal corticosteroids compared with no repeat antenatal corticosteroids. The duration and clinical significance are not discussed by the trials reporting this outcome. One trial found no significant differences in glucose tolerance among women exposed to repeat antenatal corticosteroids.	**MODERATE**
Infant - There is no evidence of a difference between repeat and no repeat antenatal corticosteroids for fetal and neonatal mortality, or duration of respiratory support. There do not appear to be any neurodevelopmental harms	**HIGH**

into childhood associated with the exposure to repeat antenatal corticosteroids.	

Judging the harms in context
Maternal - The evidence is direct evidence from trials conducted in women at risk of preterm birth, exposed to repeat antenatal corticosteroids.
Infant - The evidence for lack of harm is direct evidence from trials in which the women and infants involved were exposed to a repeat antenatal corticosteroids (or placebo), after remaining at risk of imminent preterm birth following an initial single course.

5. What is the likely balance between good and harm?

Evidence statement	**Overall quality of evidence**
Maternal - There are no clear direct health benefits for the mother exposed to repeat antenatal corticosteroids. There is no evidence of increased risk of infection (risk of pyrexia or sepsis) when compared to women exposed to a single course of antenatal corticosteroids.	**HIGH**
Infant - The benefit of reduction in risk of composite serious outcome and respiratory distress syndrome outweigh any potential harms.	**HIGH**

Judging the balance of benefits and harms in context
Maternal - The potential health harms for the mother are clearly outweighed by the significant benefits to the infant.
Infant - The benefit of reduction in risk of composite serious outcome and respiratory distress syndrome outweigh any potential harms.

Benefits clearly outweigh harms	**Recommend**	**STRONG**
Benefits probably outweigh harms	Consider	CONDITIONAL
Not known	Make a recommendation for research (see 8 below)	WEAK
Benefits probably don't outweigh harms	Consider against/make no recommendation	CONDITIONAL
Harms probably outweigh benefits		
Benefits clearly don't outweigh harms	Recommend against	STRONG
Harms clearly outweigh benefits		

6. Is the intervention/action implementable in the New Zealand and Australian context?

Summary statement
Antenatal corticosteroids are already widely in use in New Zealand and Australia.

Yes	**Recommend/consider**
Not known	Consider economic evaluation
No	Recommend/consider against

7. Final recommendation

	Strength of recommendation
Use repeat antenatal corticosteroids in women at risk of early preterm, imminent birth following a single course of antenatal corticosteroids.	**STRONG** **CONDITIONAL** **WEAK**

8. Recommendations for research

- There is a need to better assess the impact, if any, of *in utero* exposure to repeat antenatal corticosteroids on:
  - the glucose-insulin axis in childhood,
  - hypothalamic-pituitary adrenal axis,
  - bone mass,
  - body size and body composition,
  - neurosensory impairments,
  - respiratory function,
  - cardiovascular disease,
  - metabolic disease,
  - diabetes,
  - psychological health,
  - the later risk of developing diabetes in adulthood,
  - educational attainment,
  - behaviour,
  - cognitive ability,
- Any future research to investigate the effects of treatment with repeat antenatal corticosteroids should:
  - include outcomes for maternal quality of life.
  - report on the risk factors for preterm birth of the included participants.
  - assess the degree and health impact of changes in maternal blood glucose control.

M3 Regimen of single antenatal corticosteroids for women at risk of preterm birth

M3 NHMRC Evidence Summary

Do benefits or harms in the mother, fetus, infant, child or adult vary by whether betamethasone or dexamethasone is administered as a single course of antenatal corticosteroids?		
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Maternal The Brownfoot CPG version 2015 systematic review included trials of a single course of antenatal corticosteroids and different regimens (Level I). The trials of different regimens did not report maternal outcomes. Infant Evidence from two systematic reviews that were updated in the Brownfoot CPG version 2015 and Roberts CPG version 2015 (Level I).	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 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')*		
Maternal No differential effect was seen for intrapartum pyrexia, postnatal pyrexia requiring treatment with antibiotics, and puerperal sepsis between treatment with betamethasone or dexamethasone compared with no antenatal corticosteroids. Subgroup interaction tests conducted for the purposes of these Clinical Practice Guidelines indicated that betamethasone has a protective effect against chorioamnionitis compared with no antenatal corticosteroids, and that the risk of pyrexia after trial entry is increased in women treated with dexamethasone compared with no antenatal corticosteroids. Infant Subgroup interaction tests conducted for the purposes of these Clinical Practice Guidelines indicated no differential effect between a single course of betamethasone and a single course of dexamethasone for reducing the risk of fetal death, perinatal death, and neonatal death when compared with no exposure to antenatal corticosteroids. The subgroup interaction test indicated that a single course of betamethasone was protective against respiratory distress syndrome compared with no antenatal corticosteroids, although the direction of the treatment effect was towards reduced risk for both types of antenatal corticosteroid.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is not consistent
	NA	Not applicable (one study only)
3. Clinical impact *(indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Maternal The benefit of improved infant outcomes outweighs the impact of potential increase in risk of pyrexia after trial entry, ensuring access to antibiotics, if required, is readily available. Infant The clinical impact, in terms of benefits to the neonate, is significant. There is little evidence of significant harms. Where a reduction in risk was demonstrated, the effect sizes were large, and the confidence intervals were tight.	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?)*		
The systematic review of a single course of antenatal corticosteroids included studies from a variety of countries including one study from New Zealand. All studies were conducted in women at risk of preterm labour (variously defined by the authors).	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether sensible to apply
5. Applicability *(is the body of evidence relevant to the New Zealand / Australian healthcare context in terms of health services / delivery of care and cultural factors?)*		
The results are likely to be applicable to the New Zealand / Australian healthcare context. Betamethasone and dexamethasone are readily available and already in use in Australia and New Zealand.	A	Evidence directly applicable to New Zealand / Australian healthcare context
	B	Evidence applicable to New Zealand / Australian healthcare context with few caveats
	C	Evidence probably applicable to New Zealand / Australian healthcare context with some caveats
	D	Evidence not applicable to New Zealand / 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 *(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	A	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias
2. Consistency	A	All studies consistent
3. Clinical Impact	A	Very large
4. Generalisability	A	Evidence directly generalisable to target population
5. Applicability	A	Evidence directly applicable to New Zealand / Australian healthcare context

Evidence statement

The available evidence, at present, does not suggest that one antenatal corticosteroid is clinically superior to the other, for the primary infant outcomes of these Clinical Practice Guidelines.

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

Use betamethasone or dexamethasone as a single course of antenatal corticosteroid in women at risk of preterm birth.

OVERALL GRADE OF RECOMMENDATION	
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 recommendations(s) but care should be taken in its application
D	Body of evidence is weak and recommendation must be applied with caution
PP	**Practice Point**

UNRESOLVED ISSUES *(If needed, keep a 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 implementation of this recommendation?	**YES**
	NO

M3 GRADE Evidence Summary

Considered Judgement - Strength of recommendation

Do benefits or harms in the mother, fetus, infant, child, adult vary by whether betamethasone or dexamethasone is administered as a single course of antenatal corticosteroids?

1. Outcome measures:	Quality of evidence				Importance of outcome in making a decision		
Maternal Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O_1 Chorioamnionitis	✓				✓		
O_2 Puerperal sepsis	✓				✓		
O_3 Pyrexia after entry to trial				NR		✓	
O_4 Intrapartum fever requiring antibiotics				NR		✓	
O_5 Post natal pyrexia				NR		✓	
O_6 Maternal quality of life				NR	✓		
Infant Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O_1 Combined fetal and neonatal death		✓			✓		
O_2 Neonatal death	✓				✓		
O_3 Fetal death	✓				✓		
O_4 RDS	✓				✓		
O_5 Composite of serious outcomes for the infant				NR	✓		
O_6 Neurosensory disability (composite of impairments) for infant as a child			✓		✓		
O_7 Survival free of neurosensory disability for the infant as a child				NR	✓		
O_8 Survival free of metabolic disease for the infant as a child				NR		✓	
O_9 Neurosensory disability (composite of impairments) for infant as an adult				NR	✓		
O_{10} Survival free of neurosensory disability for the infant as an adult				NR	✓		
O_{11} Survival free of metabolic disease for the infant as an adult				NR		✓	

2. Is there is insufficient evidence to make a recommendation?

Evidence statement

Maternal - The evidence for maternal outcomes following betamethasone is based on eight randomised controlled trials involving 1910 women for chorioamnionitis, and four randomised controlled trials involving 467 women for puerperal sepsis. The evidence for dexamethasone is based on four randomised controlled trials involving 575 women for chorioamnionitis, and four randomised controlled trials involving 536 women for puerperal sepsis (Roberts CPG version 2015).

Maternal outcomes were not reported in any of the trials included in the Brownfoot (2013) systematic review.

Infant - The evidence for the infant is based on up to five randomised controlled trials included in the Brownfoot (2013) systematic review involving 753 infants, which compared dexamethasone with betamethasone head to head. The Roberts CPG version 2015 systematic review included up to 18 randomised controlled trials, involving 3115 infants, which compared betamethasone with no antenatal corticosteroids and reported on infant outcomes.

3. What benefit will the proposed intervention/action have?

Evidence statement	Quality of evidence
Maternal - The evidence suggests that betamethasone does not increase the risk of puerperal sepsis or chorioamnionitis, and that dexamethasone does not increase the risk of chorioamnionitis.	**HIGH**
Infant - Both betamethasone and dexamethasone significantly reduced combined fetal and neonatal death and respiratory distress syndrome when compared to placebo or no treatment – Roberts CPG version 2015. However, no statistically significant differences in neonatal death or respiratory distress syndrome are seen between those exposed to betamethasone or dexamethasone when compared head to head (Brownfoot, 2013). A small subgroup of children followed up at 18 months of age suggested there is no difference in the rate of neurological disability between those exposed to betamethasone compared to those exposed to dexamethasone.	**HIGH**

Judging the benefits in context

Maternal - The evidence is based on well designed and conducted randomised controlled trials with a combined sample size of over 1000 women. The populations included women from Brazil, the United States, the Netherlands, South Africa, Jordan.

Infant - The evidence is based on a number of well designed and conducted randomised controlled trials with large combined sample sizes for most outcomes. The populations included women from a wide variety of countries including the United States, Canada, the United Kingdom, New Zealand, Brazil, France, The Netherlands, Jordan, Finland and Tunisia.

4. What harm might the proposed intervention/action do?

Evidence statement	Quality of evidence
Maternal - The evidence from the Roberts CPG version 2015 systematic review found that dexamethasone significantly increases the risk of puerperal sepsis. The absolute risk difference was calculated for this clinical guideline and was found to be non-significant (RD 0.06, 95% CI -0.03 to 0.16)	**MODERATE**
Infant - No evidence of harm for the infant following exposure to a single course of betamethasone or	

dexamethasone was identified. There does not appear to be any detrimental effect into early childhood, with no differences seen between those exposed to betamethasone or dexamethasone for a composite of neurosensory disability.	**HIGH**

Judging the harms in context
Maternal - The evidence of greater risk of puerperal sepsis in women treated with dexamethasone is based on an indirect comparison due to the lack of data on maternal outcomes from head to head comparison of different types of corticosteroids.
Infant - Both betamethasone and dexamethasone have demonstrated benefits on neonatal outcomes. A small subgroup followed up at 18 months of age suggests no statistically significant differences in neurosensory disability between those exposed to dexamethasone or betamethasone. There is no evidence to suggest that one is clinically superior to the other.

5. What is the likely balance between good and harm?

Evidence statement	**Overall quality of evidence**
Maternal - Both dexamethasone and betamethasone have demonstrated benefits on neonatal outcomes. While dexamethasone appears to increase the risk of puerperal sepsis, there is no evidence at present to suggest that one corticosteroid is clinically superior to the other.	**HIGH**
Infant - Both direct and indirect evidence suggest neither is clinically superior to the other. The benefits of the use of both betamethasone and dexamethasone clearly appear to outweigh any potential harms.	**HIGH**

Judging the balance of benefits and harms in context
Maternal - Exposure to a single course of betamethasone is unlikely to cause harm for the mother. The impact of harm from a possible increased risk of puerperal sepsis following exposure to dexamethasone is low within the Australian and New Zealand healthcare setting.
Infant - Exposure to a single course of betamethasone or dexamethasone is highly likely to be beneficial for the infant. The impact of the benefit for the infant is high in terms of reduced mortality, and respiratory morbidity, without long term neurodevelopmental sequelae.

Benefits clearly outweigh harms	**Recommend**	**STRONG**
Benefits probably outweigh harms	Consider	CONDITIONAL
Not known	Make a recommendation for research (see 8 below)	WEAK
Benefits probably don't outweigh harms	Consider against/make no recommendation	CONDITIONAL
Harms probably outweigh benefits		
Benefits clearly don't outweigh harms	Recommend against	STRONG
Harms clearly outweigh benefits		

6. Is the intervention/action implementable in the New Zealand and Australian context?

Summary statement
Betamethasone and dexamethasone are readily available within Australia and New Zealand, and the intervention is implementable in the Australasian context.

Yes	**Recommend/consider**
Not known	Consider economic evaluation
No	Recommend/consider against

7. Final recommendation

	Strength of recommendation
Use betamethasone or dexamethasone as a single course of antenatal corticosteroid in women at risk of preterm birth.	**STRONG** **CONDITIONAL** **WEAK**

8. Recommendations for research

- A randomised trial is needed to compare betamethasone and dexamethasone to assess the effect on the short term and long term outcomes for the infant.

M4 Regimen of repeat antenatal corticosteroids for women at risk of preterm birth

M4 NHMRC Evidence Summary

Do benefits or harms in the mother, fetus, infant, child or adult vary by whether betamethasone or dexamethasone is administered as the repeat course(s) of antenatal corticosteroids?		
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Maternal The systematic review on repeat courses only included trials that used betamethasone as no trials that used dexamethasone were identified (Crowther 2011). The systematic review on different regimens did not report maternal outcomes (Brownfoot 2013). Infant Two systematic reviews (Brownfoot 2013) (Crowther 2011) (Level I).	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 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')*		
Maternal There is no current trial evidence that directly compares betamethasone and dexamethasone as the repeat antenatal corticosteroid. The available evidence compares betamethasone as a repeat course versus a single course, and finds no differences for any of the maternal primary outcomes of the Clinical Practice Guidelines. Infant Currently, no randomised controlled trials have reported on the effects of repeat course(s) of dexamethasone. One systematic review (Brownfoot 2013) found no statistically significant differences between those exposed to betamethasone or dexamethasone for neurosensory disability in a small subgroup followed up at 18 months of age. No other childhood or adult outcomes are reported.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is not consistent
	NA	Not applicable (one study only)
3. Clinical impact *(indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Maternal The available evidence demonstrates a clear benefit for the neonate with no evidence of health harms for the mother. Infant The evidence for repeat antenatal corticosteroids is mainly found in the Crowther (2011) review which shows significant neonatal benefits when compared with a single course of antenatal corticosteroids (Chapters 7-9). There are no comparisons for betamethasone versus dexamethasone as the repeat antenatal corticosteroid.	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?)*		
All studies were conducted in women at risk of preterm labour (variously defined by the authors) from a variety of countries. The evidence is generalisable for the use of betamethasone. There is currently no evidence for the use of repeat dexamethasone on maternal or infant health outcomes.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether sensible to apply
5. Applicability *(is the body of evidence relevant to the New Zealand / Australian healthcare context in terms of health services / delivery of care and cultural factors?)*		
The results are likely to be applicable to the New Zealand / Australian healthcare context. Dexamethasone and betamethasone are readily available and already in use in Australia and New Zealand.	A	Evidence directly applicable to New Zealand / Australian healthcare context
	B	Evidence applicable to New Zealand / Australian healthcare context with few caveats
	C	Evidence probably applicable to New Zealand / Australian healthcare context with some caveats
	D	Evidence not applicable to New Zealand / 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 *(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	A	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias
2. Consistency	A	All studies consistent
3. Clinical Impact	A	Very large
4. Generalisability	A	Evidence directly generalisable to target population
5. Applicability	A	Evidence directly applicable to New Zealand / Australian healthcare context

Evidence statement
The available evidence for repeat antenatal corticosteroids has only used betamethasone. Randomised controlled trial evidence for the primary outcomes of these Clinical Practice Guidelines is limited for dexamethasone as the repeat course.
Indicate any dissenting opinions

RECOMMENDATION *(What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible)*	**OVERALL GRADE OF RECOMMENDATION**	
Use betamethasone as the repeat course antenatal corticosteroid in women at continued risk of preterm birth regardless of the corticosteroid preparation used in the first course.	**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 recommendations(s) but care should be taken in its application
	D	Body of evidence is weak and recommendation must be applied with caution
	PP	Practice Point

RECOMMENDATION *(What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible)*	**OVERALL GRADE OF RECOMMENDATION**	
If betamethasone is not available use dexamethasone.	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 recommendations(s) but care should be taken in its application
	D	Body of evidence is weak and recommendation must be applied with caution
	PP	Practice Point

UNRESOLVED ISSUES *(If needed, keep a 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 implementation of this recommendation?	**YES**
	NO

M4 GRADE Evidence Summary

Considered Judgement - Strength of recommendation

Do benefits or harms in the mother, fetus, infant, child, adult vary by whether betamethasone or dexamethasone is administered as the repeat course(s) of antenatal corticosteroids?

1. Outcome measures:	Quality of evidence (NR = not reported)				Importance of outcome in making a decision		
Maternal Outcomes	**HIGH**	**MOD**	**LOW**	**V. LOW**	**Critical**	**Important**	**Not Important**
O_1 Chorioamnionitis	✓				✓		
O_2 Puerperal sepsis	✓				✓		
O_3 Pyrexia after entry to trial				NR		✓	
O_4 Intrapartum fever requiring antibiotics				NR		✓	
O_5 Post natal pyrexia	✓					✓	
O_6 Maternal quality of life				NR	✓		
Infant Outcomes	**HIGH**	**MOD**	**LOW**	**V. LOW**	**Critical**	**Important**	**Not Important**
O_1 Combined fetal and neonatal death	✓				✓		
O_2 Neonatal death	✓				✓		
O_3 Fetal death		✓			✓		
O_4 RDS	✓				✓		
O_5 Composite of serious outcomes for the infant	✓				✓		
O_6 Neurosensory disability (composite of impairments) for infant as a child		✓			✓		
O_7 Survival free of neurosensory disability for the infant as a child			✓		✓		
O_8 Survival free of metabolic disease for the infant as a child				NR		✓	
O_9 Neurosensory disability (composite of impairments) for infant as an adult				NR	✓		
O_{10} Survival free of neurosensory disability for the infant as an adult				NR	✓		
O_{11} Survival free of metabolic disease for the infant as an adult				NR		✓	

2. Is there is insufficient evidence to make a recommendation?

Evidence statement

Maternal - None of the trials included in the Brownfoot (2013) review reported maternal outcomes. All of the trials included in the Crowther (2011) review used betamethasone.

Infant - All of the trials included in the Crowther (2011) Cochrane systematic review of repeat antenatal corticosteroids used betamethasone.

There have been no randomised controlled trials that reported the use of dexamethasone as the repeat antenatal corticosteroid.

3. What benefit will the proposed intervention/action have?

Evidence statement	Quality of evidence
Maternal - The Crowther (2011) review found no difference between women treated with repeat antenatal betamethasone compared to women who received no repeat treatment for chorioamnionitis, postnatal pyrexia and puerperal sepsis.	**HIGH**
Infant - Repeat exposure to betamethasone was found to significantly reduce the risk of respiratory distress syndrome and a composite of serious infant outcomes when compared to no repeat exposure. No differences were noted in risk of a composite of neurosensory disability, or survival free of major neurosensory disability, at early childhood follow up between children who had been exposed to repeat antenatal corticosteroids and children not exposed. None of the trials of repeat antenatal corticosteroids used dexamethasone.	**HIGH**

Judging the benefits in context

Maternal - The evidence for repeat exposure to betamethasone is based on up to 6 well conducted randomised controlled trials included in the Crowther (2011) systematic review, that involve a total of 4261 women from a range of healthcare settings. There are no randomised controlled trials on the use of dexamethasone for repeat courses.

Infant - The evidence for repeat exposure to betamethasone is based on up to 9 well conducted randomised controlled trials included in the Crowther (2011) systematic review, that involve a total of 5554 infants from a range of healthcare settings. There are no randomised controlled trials on the use of dexamethasone for repeat courses.

4. What harm might the proposed intervention/action do?

Evidence statement	Quality of evidence
Maternal - There do not appear to be any detrimental effects for the mother of repeat exposure to antenatal corticosteroids, with regard to maternal infection. The Crowther (2011) systematic review found no increased risk of chorioamnionitis, postnatal pyrexia requiring treatment or puerperal sepsis for women exposed to repeat antenatal corticosteroids (betamethasone) compared to those not exposed to repeat antenatal corticosteroids.	**HIGH**
Infant - There do not appear to be any detrimental effects for the infant of repeat exposure to antenatal corticosteroids, both in the immediate neonatal period and into early and late childhood.	**HIGH**

Judging the harms in context
Maternal - The evidence for lack of harm is direct evidence from trials conducted in women at risk of preterm birth, exposed to repeat treatment with antenatal betamethasone, or placebo, after remaining at risk of preterm birth following an initial single course.
Infant - The evidence for lack of harm is direct evidence from trials in which the infants involved were exposed to repeat exposure to betamethasone at the antenatal corticosteroid, or placebo, after remaining at risk of preterm birth following an initial single course.

5. What is the likely balance between good and harm?

Evidence statement	**Overall quality of evidence**
Maternal - There are no clear direct health benefits for the mother exposed to repeat courses of antenatal corticosteroids. There is no increased risk of infection.	**HIGH**
Infant - The benefit of a reduction in risk of respiratory distress syndrome and composite serious outcome outweigh any potential harms. There is no evidence for ongoing harm into early and late childhood.	**HIGH**

Judging the balance of benefits and harms in context
Maternal - Repeat exposure to betamethasone as the antenatal corticosteroid is unlikely to cause harm to the mother.
Infant - Repeat exposure to betamethasone as the antenatal corticosteroid is highly likely to be beneficial for the infant. The impact of the benefit is high.

Benefits clearly outweigh harms	**Recommend**	**STRONG**
Benefits probably outweigh harms	Consider	CONDITIONAL
Not known	Make a recommendation for research (see 8 below)	WEAK
Benefits probably don't outweigh harms	Consider against/make no recommendation	CONDITIONAL
Harms probably outweigh benefits		
Benefits clearly don't outweigh harms	Recommend against	STRONG
Harms clearly outweigh benefits		

6. Is the intervention/action implementable in the New Zealand and Australian context?

Summary statement
Antenatal corticosteroids are already widely in use in New Zealand and Australia.

Yes	**Recommend/consider**
Not known	Consider economic evaluation
No	Recommend/consider against

7. Final recommendation

	Strength of recommendation
Use betamethasone as the repeat course antenatal corticosteroid in women at continued risk of preterm birth regardless of the corticosteroid preparation used in the first course.	**STRONG** **CONDITIONAL** **WEAK**
If betamethasone is not available use dexamethasone.	**STRONG** **CONDITIONAL** **WEAK (Practice point)**

8. Recommendations for research

- A randomised trial of dexamethasone as the repeat corticosteroid is required.

M5 Dose and interval for a single course of antenatal corticosteroids for women at risk of preterm birth

M5 NHMRC Evidence Summary

What is the most effective dose, number of doses in a course and optimal interval between doses when using a single course of antenatal corticosteroids?		
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Two systematic reviews updated in the Roberts CPG version 2015 and Brownfoot CPG version 2015systematic review (Level I).	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 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')*		
Maternal Current evidence supports the administration of 24 mg of betamethasone completed in 24 hours. This regimen showed significantly reduced risk of chorioamnionitis and no difference in risk of puerperal sepsis in women treated with a single course compared with no antenatal corticosteroids. Evidence for chorioamnionitis and puerperal sepsis following treatment with a single course of dexamethasone is limited to one or two trials. These trials found no difference in the risk of chorioamnionitis, and a significantly increased risk of puerperal sepsis following treatment with dexamethasone compared with no treatment. Infant Current evidence supports the administration of 24 mg of betamethasone completed in 24 hours. This regimen was found to significantly reduce the risk of neonatal death and respiratory distress syndrome compared with no antenatal corticosteroids. Evidence for regimens of dexamethasone is less conclusive. Subgroup interaction tests found no differences between dexamethasone regimens, although there was a trend to a significant effect for a regimen of 24 mg of dexamethasone completed in 36 hours having a protective effect against neonatal death. No difference was seen for respiratory distress syndrome between exposure to antenatal dexamethasone and no exposure to antenatal corticosteroids, but the direction of the treatment effect was towards a reduced risk.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is not consistent
	NA	Not applicable (one study only)
3. Clinical impact *(indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Maternal There is no increased risk of maternal infection following administration of 24 mg of betamethasone completed in 24 hours compared with no antenatal corticosteroids. Regimens of dexamethasone showed no difference in risk of chorioamnionitis, but did show significantly increased risk of puerperal sepsis when compared with no antenatal corticosteroids. Infant There are significant benefits for the neonate with the use of 24 mg of betamethasone completed in 24 hours, such as reduced neonatal death and respiratory distress syndrome, compared with no antenatal corticosteroids. A regimen of 24 mg of dexamethasone completed in 36 hours appeared to have a protective effect against neonatal death, although no difference was seen for respiratory distress syndrome.	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?)*		
The systematic reviews included studies from a variety of countries. All studies were conducted in women at risk of preterm birth (variously defined by the trial authors).	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether sensible to apply
5. Applicability *(is the body of evidence relevant to the New Zealand / Australian healthcare context in terms of health services / delivery of care and cultural factors?)*		
The results are likely to be applicable to the New Zealand / Australian healthcare context.	A	Evidence directly applicable to New Zealand / Australian healthcare context

	B	Evidence applicable to New Zealand / Australian healthcare context with few caveats
	C	Evidence probably applicable to New Zealand / Australian healthcare context with some caveats
	D	Evidence not applicable to New Zealand / 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 *(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	A	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias
2. Consistency	B	Most studies consistent and inconsistency can be explained
3. Clinical Impact	A	Very large
4. Generalisability	A	Evidence directly generalisable to target population
5. Applicability	A	Evidence directly applicable to New Zealand / Australian healthcare context

Evidence statement
The current evidence supports the administration of 24 mg of betamethasone completed in 24 hours and 24 mg of dexamethasone completed in 36 hours. Evidence for other regimens is limited to a small number of trials and caution advised before generalising any observed benefits.

For women at risk of preterm birth use:

EITHER a single course of 24 mg of betamethasone in divided doses completed between 12 and 36 hours

OR a single course of 24 mg of dexamethasone in divided doses completed between 24 and 40 hours.

OVERALL GRADE OF RECOMMENDATION	
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 recommendations(s) but care should be taken in its application
D	Body of evidence is weak and recommendation must be applied with caution
PP	Practice Point

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

Administer Celestone® Chronodose®,** as two intramuscular doses of 11.4 mg, 24 hours apart.
OR
Administer dexamethasone phosphate## intramuscularly, in four doses of 6 mg, 12 hours apart.

** Celestone® Chronodose® Injection, available in New Zealand and Australia, is a sterile aqueous suspension containing betamethasone sodium phosphate and betamethasone acetate. A single dose provided in 2 mL of Celestone Chronodose Injection contains betamethasone 11.4 mg, as betamethasone sodium phosphate 7.8 mg (in solution) and betamethasone acetate 6 mg (in suspension) in an aqueous vehicle containing sodium phosphate, sodium phosphate monobasic, disodium edetate, benzalkonium chloride and water for Injections.

##Dexamethasone phosphate is available as a 4 mg/mL injection which contains 4.37 mg dexamethasone sodium phosphate, in addition propylene glycol, disodium edetate, sodium hydroxide and water for injections. The preparation in New Zealand is Dexamethasone-Hameln and in Australia is Dexamethasone Sodium Phosphate - Hospira Australia Pty Ltd Australia.

OVERALL GRADE OF RECOMMENDATION	
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 recommendations(s) but care should be taken in its application
D	Body of evidence is weak and recommendation must be applied with caution
PP	**Practice Point**

UNRESOLVED ISSUES *(If needed, keep a 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 implementation of this recommendation?	**YES**
	NO

M5 GRADE Evidence Summary

Considered Judgement - Strength of recommendation

What is the most effective dose, number of doses in a course and optimal interval between doses when using a single course of antenatal corticosteroids?

1. Outcome measures:	Quality of evidence (NR = not reported)				Importance of outcome in making a decision		
Maternal Outcomes	**HIGH**	**MOD**	**LOW**	**V. LOW**	**Critical**	**Important**	**Not Important**
O_1 Chorioamnionitis	✓				✓		
O_2 Pyrexia after entry to trial				NR		✓	
O_3 Intrapartum fever requiring antibiotics				NR		✓	
O_4 Post natal pyrexia				NR		✓	
O_5 Puerperal sepsis	✓				✓		
O_6 Maternal quality of life				NR	✓		
Infant Outcomes	**HIGH**	**MOD**	**LOW**	**V. LOW**	**Critical**	**Important**	**Not Important**
O_1 Combined fetal and neonatal death		✓			✓		
O_2 Neonatal death		✓			✓		
O_3 Fetal death			✓		✓		
O_4 RDS		✓			✓		
O_5 Composite of serious outcomes for the infant				NR	✓		
O_6 Neurosensory disability (composite of impairments) for infant as a child				NR	✓		
O_7 Survival free of neurosensory disability for the infant as a child				NR	✓		
O_8 Survival free of metabolic disease for the infant as a child				NR		✓	
O_9 Neurosensory disability (composite of impairments) for infant as an adult				NR	✓		
O_{10} Survival free of neurosensory disability for the infant as an adult				NR	✓		
O_{11} Survival free of metabolic disease for the infant as an adult				NR		✓	

2. Is there is insufficient evidence to make a recommendation?

Evidence statement

Maternal - The Roberts CPG version 2015 systematic review included 19 trials that used betamethasone, and 7 trials that used dexamethasone, both in varying dosages and intervals. As not all the trials reported maternal outcomes, meta-analyses were conducted for the Clinical Practice Guidelines.

Infant - The Roberts CPG version 2015 systematic review found included 18 trials that used betamethasone and 6 trials that used dexamethasone, both in varying dosages and intervals. Meta-analyses were conducted for these Clinical Practice Guidelines. Two trials directly compared regimens (Brownfoot CPG version 2015).

3. What benefit will the proposed intervention/action have?

Evidence statement	Quality of evidence
Maternal - Current evidence supports the administration of 24 mg of betamethasone completed in 24 hours. This regimen showed significantly reduced risk of chorioamnionitis and no difference in risk of puerperal sepsis in women treated with a single course compared with no antenatal corticosteroids. Evidence for chorioamnionitis and puerperal sepsis following treatment with a single course of dexamethasone is limited to one or two trials. These trials found no difference in the risk of chorioamnionitis, and a significantly increased risk of puerperal sepsis following treatment with dexamethasone compared with no treatment.	**HIGH**
Infant - Current evidence supports the administration of 24 mg of betamethasone completed in 24 hours. This regimen was found to significantly reduce the risk of neonatal death and respiratory distress syndrome compared with no antenatal corticosteroids. Evidence for regimens of dexamethasone is less conclusive. Subgroup interaction tests found no differences between dexamethasone regimens, although there was a trend to a significant effect for a regimen of 24 mg of dexamethasone completed in 36 hours having a protective effect against neonatal death. No difference was seen for respiratory distress syndrome between exposure to antenatal dexamethasone and no exposure to antenatal corticosteroids, but the direction of the treatment effect was towards a reduced risk.	**MOD**

Judging the benefits in context

The evidence is based randomised controlled trials that demonstrated significant reduction in risk for the primary infant outcomes of mortality and respiratory distress syndrome. There was no evidence of direct health benefits to the mother, although there was no evidence of increase in harm. The trials included in the Roberts CPG version 2015 systematic review were conducted in a variety of healthcare settings, and involved women at risk of preterm birth. The benefit of an interval of 12 hours between doses rather than 24 hours is the increased likelihood of a complete course of antenatal corticosteroids. Evidence for other dosing regimens is limited to one or two trials and caution should be taken before generalising findings.

4. What harm might the proposed intervention/action do?

Evidence statement	Quality of evidence
Maternal - Regimens of dexamethasone showed no difference in risk of chorioamnionitis, but did show significantly increased risk of puerperal sepsis when compared with no antenatal corticosteroids.	**HIGH**
Infant - There is evidence of significant benefit to the infant in terms of reduced risk of mortality and respiratory	

distress syndrome, with no evidence of increased risk of harms. There is no evidence that increasing the dose improves outcomes for the infant.	**MOD**

Judging the harms in context
Maternal - Evidence from the Roberts CPG version 2015 systematic review is based on indirect comparison of women exposed to betamethasone and those exposed to no antenatal corticosteroids, and women exposed to dexamethasone and those exposed to no antenatal corticosteroids. Evidence from the Brownfoot (2013) review is direct head to head comparison.
Infant - Evidence from the Roberts CPG version 2015 systematic review is based on indirect comparison of women exposed to betamethasone and those exposed to no antenatal corticosteroids, and women exposed to dexamethasone and those exposed to no antenatal corticosteroids. Evidence from the Brownfoot (2013) review is direct head to head comparison.

5. What is the likely balance between good and harm?

Evidence statement	**Overall quality of evidence**
Maternal - There is no increased risk of maternal infection following administration of 24 mg of betamethasone completed in 24 hours compared with no antenatal corticosteroids. Regimens of dexamethasone showed no difference in risk of chorioamnionitis, but did show significantly increased risk of puerperal sepsis when compared with no antenatal corticosteroids.	**HIGH**
Infant - There are significant benefits for the neonate with the use of 24 mg of betamethasone completed in 24 hours, such as reduced neonatal death and respiratory distress syndrome, compared with no antenatal corticosteroids. A regimen of 24 mg of dexamethasone completed in 36 hours appeared to have a protective effect against neonatal death, although no difference was seen for respiratory distress syndrome.	**MOD**

Judging the balance of benefits and harms in context
Maternal - The likelihood of harm to the mother is minimal, and the impact is low. There is no evidence of direct health benefits for the mother.

Infant - The likelihood of good for the infant is highly likely, and the impact is high. There is no evidence of harm.

Benefits clearly outweigh harms	**Recommend**	**STRONG**
Benefits probably outweigh harms	Consider	CONDITIONAL
Not known	Make a recommendation for research (see 8 below)	WEAK
Benefits probably don't outweigh harms	Consider against/make no recommendation	CONDITIONAL
Harms probably outweigh benefits		
Benefits clearly don't outweigh harms	Recommend against	STRONG
Harms clearly outweigh benefits		

6. Is the intervention/action implementable in the New Zealand and Australian context?

Summary statement
Antenatal corticosteroids are already widely in use in New Zealand and Australia.

Yes	**Recommend/consider**
Not known	Consider economic evaluation
No	Recommend/consider against

7. Final recommendation

	Strength of recommendation
For women at risk of preterm birth use: EITHER a single course of 24 mg of betamethasone in divided doses completed between 12 and 36 hours OR a single course of 24 mg of dexamethasone in divided doses completed between 24 and 40 hours.	**STRONG** **CONDITIONAL** **WEAK**
Administer Celestone® Chronodose®,** as two intramuscular doses of 11.4 mg, 24 hours apart. OR Administer dexamethasone phosphate## intramuscularly, in four doses of 6 mg , 12 hours apart.	**STRONG** **CONDITIONAL** **WEAK (Practice point)**

** Celestone® Chronodose® Injection, available in New Zealand and Australia, is a sterile aqueous suspension containing betamethasone sodium phosphate and betamethasone acetate. A single dose provided in 2 mL of Celestone Chronodose Injection contains betamethasone 11.4 mg, as betamethasone sodium phosphate 7.8 mg (in solution) and betamethasone acetate 6 mg (in suspension) in an aqueous vehicle containing sodium phosphate, sodium phosphate monobasic, disodium edetate, benzalkonium chloride and water for Injections.

##Dexamethasone phosphate is available as a 4 mg/mL injection which contains 4.37 mg dexamethasone sodium phosphate in addition propylene glycol, disodium edetate, sodium hydroxide and water for injections. The preparation in New Zealand is Dexamethasone-Hameln and in Australia is Dexamethasone Sodium Phosphate - Hospira Australia Pty Ltd Australia.

8. Recommendations for research

To maximise benefit and minimise harm to the mother and infant there is a need to establish:

- the minimally effective dose per course of both betamethasone and dexamethasone;
- the optimal timing interval per course between doses for both betamethasone and dexamethasone;
- the optimal number of doses per course for betamethasone;
- the optimal number of doses per course for dexamethasone.

M6 Dose and interval for repeat antenatal corticosteroids for women at risk of preterm birth

M6 NHRMC Evidence Summary

What is the most effective dose, number of doses in a course, and optimal interval between courses for repeat antenatal corticosteroids? **Is a single repeat dose/course (or rescue dose(s)/course) more effective than multiple repeat dose(s)/courses?**		
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One systematic review (Crowther 2011) (Level 1)	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 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')*		
Maternal All the randomised controlled trials included in the Crowther (2011) systematic review used betamethasone as the repeat antenatal corticosteroid. There are currently no randomised controlled trials of a repeat course of dexamethasone. All regimens reported in the trials were two doses of 12 mg betamethasone, 24 hours apart, and no trials reported data for more than one repeat course of antenatal corticosteroids. Infant There are currently no randomised controlled trials of a repeat course of dexamethasone. All regimens reported in the trials were two doses of 12 mg betamethasone, 24 hours apart. Treatment with one planned repeat dose was associated with a reduction in composite serious outcome (RR 0.75, 95%CI 0.60 to 0.93), with no effect seen on birthweight and small for gestational age. There were no significant differences for other primary outcomes. At early childhood follow up, no statistically significant differences were seen for infants exposed to one planned repeat dose compared with placebo. No data were reported for two or three repeat doses. Limited anthropometric data was reported in the small trial that examined four or more doses. This trial was stopped early due to safety concerns.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is not consistent
	NA	Not applicable (one study only)
3. Clinical impact *(indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Maternal No statistically significant differences were seen for chorioamnionitis or puerperal sepsis. Infant There were no differences in perinatal, neonatal or fetal death reported in the three trials included in the Crowther systematic review (Crowther, 2011) that compared one planned repeat course of antenatal betamethasone with no repeat antenatal corticosteroids. Results for respiratory distress syndrome had significant heterogeneity.	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?)*		
The systematic review included a study from Australia and New Zealand. All studies were conducted in women at risk of preterm labour (variously defined by the authors). There are currently no randomised controlled trials of a repeat course of dexamethasone.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether sensible to apply
5. Applicability *(is the body of evidence relevant to the New Zealand / Australian healthcare context in terms of health services / delivery of care and cultural factors?)*		
The results are likely to be applicable to the New Zealand / Australian healthcare context. Dexamethasone and betamethasone are readily available and already in use in Australia and New Zealand.	A	Evidence directly applicable to New Zealand / Australian healthcare context
	B	Evidence applicable to New Zealand / Australian healthcare context with few caveats
	C	Evidence probably applicable to New Zealand / Australian healthcare context with some caveats
	D	Evidence not applicable to New Zealand / 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 *(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	A	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias
2. Consistency	B	Most studies consistent and inconsistency can be explained
3. Clinical Impact	B	Substantial
4. Generalisability	A	Evidence directly generalisable to target population
5. Applicability	A	Evidence directly applicable to New Zealand / Australian healthcare context

Evidence statement
Comparative evidence on more than one repeat course of antenatal corticosteroids is limited. There was no increased risk of chorioamnionitis and puerperal sepsis for the mother, or perinatal, neonatal and fetal death, or respiratory distress syndrome among trials that compared one planned repeat course with no repeat courses of antenatal corticosteroids.
Indicate any dissenting opinions

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

EITHER
Use a single repeat dose(s) of 12 mg betamethasone following a single course of antenatal corticosteroid seven or more days prior, where the woman is still at risk of preterm birth within the next seven days.
After this dose, if the woman has not given birth seven or more days and less than 14 days from administration of the previous repeat dose and is still considered to be at risk of preterm birth within the next seven days a further repeat dose(s) of 12 mg betamethasone can be administered.
OR
Use a single repeat course of 24 mg betamethasone in divided doses completed within 24 hours following a single course of antenatal corticosteroids seven or more days prior, where the woman is still at risk of preterm birth within the next seven days
Do not give further repeat courses.

OVERALL GRADE OF RECOMMENDATION	
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 recommendations(s) but care should be taken in its application
D	Body of evidence is weak and recommendation must be applied with caution
PP	**Practice Point**

RECOMMENDATION *(What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible)*
As repeat antenatal corticosteroid use

EITHER
A single repeat dose of Celestone® Chronodose®** 11.4 mg, intramuscularly as one dose.
Use up to a maximum of three, single, repeat doses only.

OR
A single repeat course of Celestone® Chronodose®** 11.4 mg, as two intramuscular doses, 24 hours apart.
Do not give any further repeat courses.

** Celestone® Chronodose® Injection (the only currently registered product in New Zealand) is a sterile aqueous suspension containing betamethasone sodium phosphate and betamethasone acetate. A single dose provided in 2 mL of Celestone Chronodose Injection contains betamethasone 11.4 mg, as betamethasone sodium phosphate 7.8 mg (in solution) and betamethasone acetate 6 mg (in suspension) in an aqueous vehicle containing sodium phosphate, sodium phosphate monobasic, disodium edetate, benzalkonium chloride and water for injection.

OVERALL GRADE OF RECOMMENDATION	
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 recommendations(s) but care should be taken in its application
D	Body of evidence is weak and recommendation must be applied with caution
PP	**Practice Point**

UNRESOLVED ISSUES *(If needed, keep a 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 implementation of this recommendation?	**YES**
	NO

M6 GRADE Evidence Summary

Considered Judgement - Strength of recommendation

What is the most effective dose, number of doses in a course, and optimal interval between courses for repeat antenatal corticosteroids?
Is a single repeat dose/course (or rescue dose(s)/course) more effective than multiple repeat dose(s)/courses?

1. Outcome measures:	Quality of evidence (NR = not reported)				Importance of outcome in making a decision		
Maternal Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O_1 Chorioamnionitis	✓				✓		
O_2 Puerperal sepsis	✓				✓		
O_3 Pyrexia after entry to trial				NR		✓	
O_4 Intrapartum fever requiring antibiotics				NR		✓	
O_5 Post natal pyrexia				NR		✓	
O_6 Maternal quality of life				NR	✓		
Infant Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O_1 Combined fetal and neonatal death	✓				✓		
O_2 Neonatal death	✓				✓		
O_3 Fetal death	✓				✓		
O_4 RDS		✓			✓		
O_5 Composite of serious outcomes for the infant		✓			✓		
O_6 Neurosensory disability (composite of impairments) for infant as a child				NR	✓		
O_7 Survival free of neurosensory disability for the infant as a child				NR	✓		
O_8 Survival free of metabolic disease for the infant as a child				NR		✓	
O_9 Neurosensory disability (composite of impairments) for infant as an adult				NR	✓		
O_{10} Survival free of neurosensory disability for the infant as an adult				NR	✓		
O_{11} Survival free of metabolic disease for the infant as an adult				NR		✓	

2. Is there is insufficient evidence to make a recommendation?

Evidence statement
Maternal and infant - All of the randomised trials included in the Crowther (2011) systematic review used betamethasone and no trials reported on more than one repeat course of antenatal corticosteroids for primary maternal or infant outcomes for the Clinical Practice Guidelines.

3. What benefit will the proposed intervention/action have?

Evidence statement	Quality of evidence
Maternal - No difference was seen in chorioamnionitis or puerperal sepsis for women treated with one planned repeat course (2 doses of 12 mg betamethasone, 24 hours apart, 1 trial, 437 women) of antenatal corticosteroids compared with no repeat courses. Similarly, no difference was seen in puerperal sepsis for women treated with one planned repeat course (1 dose of 12 mg betamethasone, 1 trial, 249 women) of antenatal corticosteroids compared with no repeat courses.	**HIGH**
Infant - A reduction in composite serious outcome was seen in one trial included in the Crowther (2011) systematic review, following treatment with one planned repeat course of antenatal corticosteroids compared with placebo. No difference was seen in perinatal, fetal or neonatal death, or respiratory distress syndrome, birthweight, or small for gestational age in the trials that compared one planned repeat course of antenatal corticosteroids compared with no repeat antenatal corticosteroid. At early childhood follow-up, no statistically significant differences in survival free of major disability and major disability at childhood follow-up were seen for infants exposed to one planned repeat dose compared with placebo.	**HIGH**

Judging the benefits in context
The evidence is based on a systematic review of well conducted randomised controlled trials that found no differences in perinatal, neonatal or fetal death, respiratory distress syndrome, or major disability at childhood follow up between those exposed to one planned repeat course of antenatal corticosteroids and those not exposed to repeat antenatal corticosteroids. There was significant heterogeneity for respiratory distress syndrome. One planned repeat course of antenatal corticosteroids was associated with a reduction in composite serious outcome. The trials included in the Crowther (2011) review were conducted in a variety of countries and healthcare settings, and included women who were at continued risk of preterm birth following an initial course of antenatal corticosteroids.

4. What harm might the proposed intervention/action do?

Evidence statement	Quality of evidence
Maternal - There was no evidence of harm to the mother of one planned repeat course of antenatal corticosteroids. The risk of chorioamnionitis or puerperal sepsis was not increased.	**HIGH**
Infant - There is no evidence of increased risk of mortality, respiratory distress syndrome, or disability at early childhood follow-up, following one planned repeat of antenatal corticosteroids. There was limited evidence from one trial (Wapner, 2006) that infants exposed to four or more repeat courses of antenatal corticosteroids had a	

significant decrease in birthweight, and significantly more infants exposed to four or more courses of antenatal corticosteroids born below the 5th percentile for birthweight.	**MODERATE**

Judging the harms in context
Maternal - There was no evidence of harm to the mother of one planned repeat course of antenatal corticosteroids.
Infant - There was no evidence of increase in risk of mortality, respiratory distress syndrome or disability at early childhood follow-up following one planned repeat course of antenatal corticosteroids. The evidence of reduction in birthweight following exposure to four or more repeat courses is based on one trial that was stopped early due to concerns about the reduced birthweight outcomes. The clinical significance of the reduced birthweight is unclear and there is evidence of imprecision reflected it the wide confidence intervals for these outcomes.

5. What is the likely balance between good and harm?

Evidence statement	**Overall quality of evidence**
Maternal - Exposure to one planned repeat course of antenatal corticosteroids does not increase the risk of chorioamnionitis or puerperal sepsis compared with no repeat antenatal corticosteroids.	**HIGH**
Infant - Exposure to one planned repeat course of antenatal corticosteroids was associated with a reduction in a composite of serious neonatal outcomes, with no difference in mortality, respiratory distress syndrome, birthweight, small for gestational age, or major disability at early childhood follow-up compared to no repeat antenatal corticosteroids.	**HIGH**

Judging the balance of benefits and harms in context
Maternal - The likelihood of harm to the mother is minimal, and the impact is low. There is no evidence of direct health benefits for the mother.

Infant - The likelihood of benefit for the infant is high, and the impact is high. There is no evidence of harm for one planned repeat course of antenatal corticosteroids.

Benefits clearly outweigh harms	**Recommend**	**STRONG**
Benefits probably outweigh harms	Consider	CONDITIONAL
Not known	Make a recommendation for research (see 8 below)	WEAK
Benefits probably don't outweigh harms Harms probably outweigh benefits	Consider against/make no recommendation	CONDITIONAL
Benefits clearly don't outweigh harms Harms clearly outweigh benefits	Recommend against	STRONG

6. Is the intervention/action implementable in the New Zealand and Australian context?

Summary statement
Antenatal corticosteroids are already widely in use in New Zealand and Australia.

Yes	**Recommend/consider**
Not known	Consider economic evaluation
No	Recommend/consider against

7. Final recommendation

EITHER **Use a single repeat dose(s)** of 12 mg betamethasone following a single course of antenatal corticosteroid seven or more days prior, where the woman is still at risk of preterm birth within the next seven days. After this dose, if the woman has not given birth seven or more days and less than 14 days from administration of the previous repeat dose and is still considered to be at risk of preterm birth within the next seven days a further repeat dose(s) of 12 mg betamethasone can be administered. **OR** **Use a single repeat course** of 24 mg betamethasone in divided doses completed within 24 hours following a single course of antenatal corticosteroids seven or more days prior, where the woman is still at risk of preterm birth within the next seven days Do not give further repeat courses.	**Strength of recommendation** **STRONG** **CONDITIONAL** **WEAK**
As repeat antenatal corticosteroid use **EITHER** **A single repeat dose** of Celestone® Chronodose®** 11.4 mg, intramuscularly as one dose. Use up to a maximum of three, single, repeat doses only. **OR** **A single repeat course** of Celestone® Chronodose®** 11.4 mg, as two intramuscular doses, 24 hours apart. Do not give any further repeat courses. ** Celestone® Chronodose® Injection (the only currently registered product in New Zealand) is a sterile aqueous suspension containing betamethasone sodium phosphate and betamethasone acetate. A single dose provided in 2 mL of Celestone Chronodose Injection contains betamethasone 11.4 mg, as betamethasone sodium phosphate 7.8 mg (in solution) and betamethasone acetate 6 mg (in suspension) in an aqueous vehicle containing sodium phosphate, sodium phosphate monobasic, disodium edetate, benzalkonium chloride and water for injection.	**Strength of recommendation** **STRONG** **CONDITIONAL** **WEAK**

8. Recommendations for research

Further research is required to explore betamethasone and dexamethasone as the repeat antenatal corticosteroid for:

- the optimal dose;
- the optimal number of dose(s) in a course;
- the optimal interval between courses;
- the effect of multiple, repeat doses/courses.

M7 Optimal time prior to preterm birth to administer a single course of antenatal corticosteroids

M7 NHMRC Evidence summary

What is the optimal time prior to preterm birth to administer a single course of antenatal corticosteroids?		
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Maternal Roberts CPG version 2015 systematic review for a single course of antenatal corticosteroids (Level 1) included two randomised controlled trials that reported on chorioamnionitis and puerperal sepsis in relation to time interval from administration of first dose to birth. Infant Roberts CPG version 2015 systematic review for a single course of antenatal corticosteroids included nine randomised controlled trials (Level 1), that reported on mortality and respiratory distress syndrome in relation to the time interval from administration of first dose to birth.	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 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')*		
Maternal The evidence is consistent that there is no increased risk of chorioamnionitis for those who received antenatal corticosteroids compared with those who did not receive antenatal corticosteroids at any of the time points reported in the Roberts CPG version 2015 systematic review (<24 hours before birth, <48 hours before birth, between one to seven days before birth, ≥7 days before birth). A single trial reported no difference in puerperal sepsis for women giving birth <24 hours from receiving the first dose, no data were reported for other time points for this outcome. Infant The evidence shows a significant reduction in risk of mortality when exposure to antenatal corticosteroids occurs <48 hours before birth compared with no exposure. No further benefit for mortality outcomes are observed after this time point. The risk of respiratory distress syndrome is reduced where the infant had been exposed to antenatal corticosteroids between 1 and up to 7 days prior to birth compared with no exposure. No further benefit of a single course of antenatal corticosteroids was seen for respiratory distress syndrome after 7 days.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is not consistent
	NA	Not applicable (one study only)
3. Clinical impact *(indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Maternal No maternal benefits or harms were associated with the timing of administration. Infant Evidence shows large effect sizes and precise confidence intervals for infant outcomes. The optimal timing of a single course of antenatal corticosteroids appears to be within 7 days of anticipated birth, with significant reductions in mortality and RDS seen at this time.	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?)*		
Evidence is generalizable. All studies included in the Roberts CPG version 2015 systematic review were conducted in women at risk of preterm birth (variously defined by the trial authors), in a variety of countries and healthcare settings.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether sensible to apply
5. Applicability *(is the body of evidence relevant to the New Zealand / Australian healthcare context in terms of health services / delivery of care and cultural factors?)*		
Evidence is applicable to the New Zealand and Australian health care setting	A	Evidence directly applicable to New Zealand / Australian healthcare context
	B	Evidence applicable to New Zealand / Australian healthcare context with few caveats
	C	Evidence probably applicable to New Zealand / Australian healthcare context with some caveats
	D	Evidence not applicable to New Zealand / 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 *(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	A	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias
2. Consistency	A	All studies consistent
3. Clinical Impact	A	Very large
4. Generalisability	A	Evidence directly generalisable to target population
5. Applicability	A	Evidence directly applicable to New Zealand / Australian healthcare context

Evidence statement
The evidence indicates that the optimal time prior to birth to administer a single course of antenatal corticosteroids is when preterm birth is anticipated to occur within 7 days from the first dose.

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

Use a single course of antenatal corticosteroids in women at risk of preterm birth when birth is planned or expected within the next seven days even if birth is likely within 24 hours.

OVERALL GRADE OF RECOMMENDATION	
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 recommendations(s) but care should be taken in its application
D	Body of evidence is weak and recommendation must be applied with caution
PP	Practice Point

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

Where appropriate, estimate the risk of preterm birth by considering the use of adjunct prediction tests including fetal fibronectin and assessment of cervical length.

The optimal time to administer antenatal corticosteroids is when preterm birth is planned or expected within the next 48 hours.

OVERALL GRADE OF RECOMMENDATION	
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 recommendations(s) but care should be taken in its application
D	Body of evidence is weak and recommendation must be applied with caution
PP	**Practice Points**

UNRESOLVED ISSUES *(If needed, keep a 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 implementation of this recommendation?	**YES**
	NO

M7 GRADE Evidence summary

Considered Judgement - Strength of recommendation							
What is the optimal time prior to birth to administer a single course of antenatal corticosteroids?							
1. Outcome measures:	**Quality of evidence**				**Importance of outcome in making a decision**		
Maternal Outcomes	**HIGH**	**MOD**	**LOW**	**V. LOW**	**Critical**	**Important**	**Not Important**
O_1 Chorioamnionitis	✓				✓		
O_2 Puerperal sepsis	✓				✓		
O_3 Pyrexia after entry to trial				NR		✓	
O_4 Intrapartum fever requiring antibiotics				NR		✓	
O_5 Post natal pyrexia				NR		✓	
O_6 Maternal quality of life				NR	✓		
Infant Outcomes	**HIGH**	**MOD**	**LOW**	**V. LOW**	**Critical**	**Important**	**Not Important**
O_1 Combined fetal and neonatal death	✓				✓		
O_2 Neonatal death	✓				✓		
O_3 Fetal death	✓				✓		
O_4 RDS	✓				✓		
O_5 Composite of serious outcomes for the infant				NR	✓		
O_6 Neurosensory disability (composite of impairments) for infant as a child				NR	✓		
O_7 Survival free of neurosensory disability for the infant as a child				NR	✓		
O_8 Survival free of metabolic disease for the infant as a child				NR		✓	
O_9 Neurosensory disability (composite of impairments) for infant as an adult				NR	✓		
O_{10} Survival free of neurosensory disability for the infant as an adult				NR	✓		
O_{11} Survival free of metabolic disease for the infant as an adult				NR		✓	

2. Is there is insufficient evidence to make a recommendation?

Evidence statement

Maternal - Evidence for maternal outcomes is based on two trials included in the Roberts CPG version 2015 systematic review for a single course of antenatal corticosteroids that report on chorioamnionitis and puerperal sepsis in relation to time interval from administration of first dose to birth.

Infant - Evidence for infant outcomes is based on up to 9 trials included in the Roberts CPG version 2015 systematic review for a single course of antenatal corticosteroids, which reported on mortality and respiratory distress syndrome in relation to the time interval from administration of first dose to birth.

3. What benefit will the proposed intervention/action have?

Evidence statement	**Quality of evidence**
Maternal - There was no increased risk of maternal infection for those who received antenatal corticosteroids compared with those who did not received antenatal corticosteroids at any of the time points reported (<24 hours before birth, <48 hours before birth, between one to seven days before birth, ≥7 days before birth).	**HIGH**
Infant - The risk of perinatal or neonatal death was significantly reduced if exposure to antenatal corticosteroids occurred <48 hours before birth compared with no exposure. No further benefit was observed after this time point. The risk of respiratory distress syndrome was reduced when the infant had been exposed to antenatal corticosteroids between 1 and 7 days before birth compared with no exposure. There was no additional benefit from exposure to a single course of antenatal corticosteroids after 7 days. There was no difference in birthweight between those infants exposed to antenatal corticosteroids between one and 7 days before birth and those not exposed to antenatal corticosteroids.	**HIGH**

Judging the benefits in context

Maternal - The evidence is based on well designed and conducted randomised controlled trials. The populations included participants from South Africa and New Zealand.

Infant - Evidence for infant outcomes is based on up to 9 trials included in the Roberts CPG version 2015 systematic review, which reported on mortality and respiratory distress syndrome in relation to the time interval from administration of first dose to birth. These trials were conducted in a variety of countries and health care settings, and include up to 1110 infants.

4. What harm might the proposed intervention/action do?

Evidence statement	**Quality of evidence**
Maternal - There was no increased risk of maternal infection for those who received antenatal corticosteroids compared with those who did not received antenatal corticosteroids at any of the time points reported (<24 hours	**HIGH**

before birth, <48 hours before birth, between one to seven days before birth, ≥7 days before birth). *Infant* - When the interval from first dose to birth was 7 days or more, there was significantly reduced birthweight among those infants exposed compared to infants not exposed.	**HIGH**

Judging the harms in context
Maternal - There was no evidence of harm for the mother in terms of increased risk of infection at following exposure to antenatal corticosteroids at any of the time points reported (<24 hours before birth, <48 hours before birth, between 1 and seven days before birth, ≥7 days before birth).
Infant - The evidence is direct evidence from trials that reported outcomes in relation to time interval of administration of first dose to birth. The clinical significance of reduced birthweight has not been explored and is not reported adjusted for gestational age.

5. What is the likely balance between good and harm?

Evidence statement	**Overall quality of evidence**
Maternal - There are no direct health benefits to the mother of exposure to antenatal corticosteroids. There are significant benefits to the infant.	**HIGH**
Infant - The significant benefits of significant reductions in mortality following exposure to antenatal corticosteroids <48 hours before birth, and reduced risk of respiratory distress syndrome following exposure to antenatal corticosteroids between 1 and 7 days before birth, outweigh any potential harms.	**HIGH**

Judging the balance of benefits and harms in context
Maternal - The likelihood of harm to the mother is minimal, and the impact is low. While there is no evidence of direct health benefits for the mother, there is also no evidence of harms.
Infant - The likelihood of benefit for the infant is high, and the impact is high. There is no evidence of harm for the infant.

Benefits clearly outweigh harms	**Recommend**	**STRONG**
Benefits probably outweigh harms	Consider	CONDITIONAL
Not known	Make a recommendation for research (see 8 below)	WEAK
Benefits probably don't outweigh harms	Consider against/make no recommendation	CONDITIONAL
Harms probably outweigh benefits		
Benefits clearly don't outweigh harms	Recommend against	STRONG
Harms clearly outweigh benefits		

6. Is the intervention/action implementable in the New Zealand and Australian context?

Summary statement
Antenatal corticosteroids are already widely in use in New Zealand and Australia.

Yes	**Recommend/consider**
Not known	Consider economic evaluation
No	Recommend/consider against

7. Final recommendation

Use a single course of antenatal corticosteroids in women at risk of preterm birth when birth is planned or expected within the next seven days even if birth is likely within 24 hours.	**Strength of recommendation** **STRONG** **CONDITIONAL** **WEAK**
Where appropriate, estimate the risk of preterm birth by considering the use of adjunct prediction tests including fetal fibronectin and assessment of cervical length. The optimal time to administer antenatal corticosteroids is when preterm birth is planned or expected within the next 48 hours.	**Strength of recommendation** **STRONG** **CONDITIONAL** **WEAK (Practice Points)**

8. Recommendations for research

- Evidence from randomised trials is required to investigate the optimal timing for antenatal corticosteroids where preterm birth is planned (e.g. maternal medical indications or fetal compromise) and women can be randomised to administration of antenatal corticosteroids at different time intervals prior to birth.
- An individual patient data meta-analysis may provide further information on optimal timing from administration of first dose to birth.

M8 Optimal time prior to preterm birth to administer repeat antenatal corticosteroids.

M8 NHMRC Evidence summary

What is the optimal time prior to preterm birth to administer a repeat dose(s)of antenatal corticosteroids?		
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Maternal None of the randomised controlled trials in the Crowther (2011) systematic review reported post-randomisation subgroup analysis of optimal timing to administer repeat dose(s) antenatal corticosteroids on maternal outcomes. Infant None of the randomised controlled trials identified in the Crowther (2011) systematic review reported post-randomisation subgroup analysis of optimal timing to administer repeat dose(s) of antenatal corticosteroids for infant mortality, respiratory distress syndrome or composite of serious infant outcomes. The evidence is equivalent to the overall effect of repeat antenatal corticosteroids summarised in Chapter 8	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 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')*		
See Chapter 8	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is not consistent
	NA	Not applicable (one study only)
3. Clinical impact *(indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
See Chapter 8	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?)*		
See Chapter 8	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether sensible to apply
5. Applicability *(is the body of evidence relevant to the New Zealand / Australian healthcare context in terms of health services / delivery of care and cultural factors?)*		
See Chapter 8	A	Evidence directly applicable to New Zealand / Australian healthcare context
	B	Evidence applicable to New Zealand / Australian healthcare context with few caveats
	C	Evidence probably applicable to New Zealand / Australian healthcare context with some caveats
	D	Evidence not applicable to New Zealand / 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 *(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	A	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias
2. Consistency	A	All studies consistent
3. Clinical Impact	B	Substantial
4. Generalisability	A	Evidence directly generalisable to target population
5. Applicability	A	Evidence directly applicable to New Zealand / Australian healthcare context
Evidence statement		

RECOMMENDATION *(What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible)* Use repeat antenatal corticosteroids in women at continued risk of preterm birth where the antenatal corticosteroids were given seven or more days prior, when birth is planned or expected within the next seven days, even if birth is likely within 24 hours	**OVERALL GRADE OF RECOMMENDATION**	
	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 recommendations(s) but care should be taken in its application
	D	Body of evidence is weak and recommendation must be applied with caution
	PP	Practice Point
RECOMMENDATION *(What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible)* Where appropriate, estimate the risk of preterm birth by considering the use of adjunct prediction tests including fetal fibronectin and assessment of cervical length. If betamethasone is not available use dexamethasone.	**OVERALL GRADE OF RECOMMENDATION**	
	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 recommendations(s) but care should be taken in its application
	D	Body of evidence is weak and recommendation must be applied with caution
	PP	**Practice Point**

UNRESOLVED ISSUES *(If needed, keep a 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 implementation of this recommendation?	**YES**
	NO

M8 GRADE Evidence summary

Considered Judgement - Strength of recommendation							
What is the optimal time prior to birth to administer a repeat dose(s) of antenatal corticosteroids?							
1. Outcome measures:	**Quality of evidence**				**Importance of outcome in making a decision**		
Maternal Outcomes	**HIGH**	**MOD**	**LOW**	**V. LOW**	**Critical**	**Important**	**Not Important**
O_1 Chorioamnionitis				NR	✓		
O_2 Puerperal sepsis				NR	✓		
O_3 Pyrexia after entry to trial				NR		✓	
O_4 Intrapartum fever requiring antibiotics				NR		✓	
O_5 Post natal pyrexia				NR		✓	
O_6 Maternal quality of life				NR	✓		
Infant Outcomes	**HIGH**	**MOD**	**LOW**	**V. LOW**	**Critical**	**Important**	**Not Important**
O_1 Combined fetal and neonatal death				NR	✓		
O_2 Neonatal death				NR	✓		
O_3 Fetal death				NR	✓		
O_4 RDS				NR	✓		
O_5 Composite of serious outcomes for the infant				NR	✓		
O_6 Neurosensory disability (composite of impairments) for infant as a child				NR	✓		
O_7 Survival free of neurosensory disability for the infant as a child				NR	✓		
O_8 Survival free of metabolic disease for the infant as a child				NR		✓	
O_9 Neurosensory disability (composite of impairments) for infant as an adult				NR	✓		
O_{10} Survival free of neurosensory disability for the infant as an adult				NR	✓		
O_{11} Survival free of metabolic disease for the infant as an adult				NR		✓	

2. Is there is insufficient evidence to make a recommendation?

Evidence statement
Maternal - None of the randomised controlled trials in the Crowther (2011) systematic review reported post-randomisation subgroup analysis of optimal timing to administer repeat dose(s) of antenatal corticosteroids on maternal outcomes.
Infant - None of the randomised controlled trials identified in the Crowther (2011) systematic review reported post-randomisation subgroup analysis of optimal timing to administer repeat dose(s) of antenatal corticosteroids for infant mortality, respiratory distress syndrome or composite of serious infant outcomes.

3. What benefit will the proposed intervention/action have?

Evidence statement	**Quality of evidence**
Maternal - Evidence is based on overall summary of repeat antenatal corticosteroids summarised in Chapter 8 *Infant* - Evidence is based on overall summary of repeat antenatal corticosteroids summarised in Chapter 8	**HIGH**

Judging the benefits in context
Evidence is based on overall summary of repeat antenatal corticosteroids summarised in Chapter 8

4. What harm might the proposed intervention/action do?

Evidence statement	**Quality of evidence**
Maternal - Evidence is based on overall summary of repeat antenatal corticosteroids summarised in Chapter 8 *Infant* - Evidence is based on overall summary of repeat antenatal corticosteroids summarised in Chapter 8	**HIGH**

Judging the harms in context
-

5. What is the likely balance between good and harm?

Evidence statement	**Overall quality of evidence**
Maternal - Evidence is based on overall summary of repeat antenatal corticosteroids summarised in Chapter 8 *Infant* - Evidence is based on overall summary of repeat antenatal corticosteroids summarised in Chapter 8	**HIGH**

Judging the balance of benefits and harms in context
Maternal - Evidence is based on overall summary of repeat antenatal corticosteroids summarised in Chapter 8
Infant - Evidence is based on overall summary of repeat antenatal corticosteroids summarised in Chapter 8

Benefits clearly outweigh harms	**Recommend**	**STRONG**
Benefits probably outweigh harms	Consider	CONDITIONAL
Not known	Make a recommendation for research (see 8 below)	WEAK

Benefits probably don't outweigh harms	Consider against/make no recommendation	CONDITIONAL
Harms probably outweigh benefits		
Benefits clearly don't outweigh harms	Recommend against	STRONG
Harms clearly outweigh benefits		

6. Is the intervention/action implementable in the New Zealand and Australian context?

Summary statement
Antenatal corticosteroids are already widely in use in New Zealand and Australia.

Yes	**Recommend/consider**
Not known	Consider economic evaluation
No	Recommend/consider against

7. Final recommendation

	Strength of recommendation
Use repeat antenatal corticosteroids in women at continued risk of preterm birth where the antenatal corticosteroids were given seven or more days prior, when birth is planned or expected within the next seven days, even if birth is likely within 24 hours.	**STRONG** **CONDITIONAL** **WEAK**
Where appropriate, estimate the risk of preterm birth by considering the use of adjunct prediction tests including fetal fibronectin and assessment of cervical length. If betamethasone is not available use dexamethasone..	**STRONG** **CONDITIONAL** **WEAK (Practice points)**

8. Recommendations for research

- An individual patient data meta-analysis may provide further information on optimal timing prior to preterm birth to administer a repeat course of antenatal corticosteroids.
- Randomised trials should be conducted that compare the use of different timing of administration of repeat antenatal corticosteroids prior to preterm birth where preterm birth is definitely expected or planned.

M9 Optimal time between a first course and initiating repeat antenatal corticosteroids prior to preterm birth

M9 NHMRC Evidence summary

What is the optimal timing between a first course of antenatal corticosteroids and initiating a repeat dose(s)?		
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Maternal The evidence for maternal outcomes following exposure to repeat antenatal corticosteroids from 7 to 14 days between single and repeat dose (s) is based on four randomised controlled trials included in the Crowther (2011) systematic review involving up to 1971 women. Evidence for maternal outcomes following exposure to repeat antenatal corticosteroids more than 14 days between single and repeat dose(s) is based on two randomised controlled trials included in the Crowther (2011) review involving up to 2290 women Infant The evidence for infant outcomes following exposure to repeat antenatal corticosteroids from 7 to 14 days between single and repeat dose(s) is based on six randomised controlled trials included in the Crowther (2011) systematic review involving up to 2871 infants. Evidence for infant outcomes following exposure to repeat antenatal corticosteroids more than 14 days between single and repeat dose(s) is based on three randomised controlled trials included in the Crowther (2011) review involving up to 2993 infants.	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 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')*		
Maternal The evidence is consistent for no increased risk of chorioamnionitis or puerperal sepsis for women treated with repeat antenatal corticosteroids between 7 and 14 days, or more than 14 days from the single course compared with those with no repeat treatment. Infant No differences were seen in measures of infant mortality among infants exposed to repeat antenatal corticosteroids between 7 and 14 days, or more than 14 days, from the single course compared with no repeat exposure. Respiratory distress syndrome was significantly reduced among infants exposed to antenatal corticosteroids at both intervals of between 7 and 14 days, and more than 14 days from the single course compared with no repeat exposure. An interval of between 7 and 14 days from the single course was associated with a significant reduction in a composite of serious infant outcomes when compared with no repeat exposure. An interval of more than 14 days or more from a single course had no effect on the incidence of a composite of serious infant outcomes when compared with no repeat exposure, but subgroup interaction test was not significant indicating no differential effect between the timing intervals. There was no evidence of increased risk of neurosensory disability at early childhood follow up when the interval was between 7 and 14 days or greater than 14 days from the single course.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is not consistent
	NA	Not applicable (one study only)
3. Clinical impact *(indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Maternal There are no direct health benefits for the mother, and there do not appear to be any detrimental effects. Infant Significant reductions in risk of respiratory distress syndrome, with precise confidence intervals were seen for administration intervals of between 7 to 14 days, and 14 days or more following first dose(s). Birthweight was significantly reduced when the interval between single and repeat antenatal corticosteroids was more than 14 days after the single course, with no significant difference in birthweight z scores. The clinical impact of this, if any, is unclear. Although the data is very limited, when gestational age is taken into account as a variable, there is no evidence of a fundamental reduction in birthweight following repeat antenatal corticosteroids compared with no repeat exposure.	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?)*		
Evidence is generalisable. All studies included in the Crowther (2011) systematic review were conducted in women who remained at risk of preterm birth (variously defined by the trial authors) following an initial course of antenatal corticosteroids, in a variety of countries and healthcare settings.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether sensible to apply

5. Applicability *(is the body of evidence relevant to the New Zealand / Australian healthcare context in terms of health services / delivery of care and cultural factors?)*		
Evidence is applicable to the New Zealand and Australian health care settings	A	Evidence directly applicable to New Zealand / Australian healthcare context
	B	Evidence applicable to New Zealand / Australian healthcare context with few caveats
	C	Evidence probably applicable to New Zealand / Australian healthcare context with some caveats
	D	Evidence not applicable to New Zealand / 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 *(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	A	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias
2. Consistency	A	All studies consistent
3. Clinical Impact	B	Substantial
4. Generalisability	A	Evidence directly generalisable to target population
5. Applicability	A	Evidence directly applicable to New Zealand / Australian healthcare context

Evidence statement: More benefits are observed when the interval between the single course of antenatal corticosteroids and the repeat course is between 7 and up to 14 days.

RECOMMENDATION *(What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible)*	**OVERALL GRADE OF RECOMMENDATION**	
EITHER Use a **single repeat dose** of repeat antenatal corticosteroids if preterm has not occurred seven or more days and less than fourteen days following a single course and preterm birth is still expected within the next seven days. If the woman has not given birth after a repeat dose(s) and is still considered to be at risk of preterm birth within the next seven days, a further repeat dose of 12 mg betamethasone can be administered. **OR** Use a **single repeat course** of repeat antenatal corticosteroids if preterm birth has not occurred seven or more days and less than fourteen days following a single course and preterm birth is still expected within the next seven days. Do not give further repeat courses.	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 recommendations(s) but care should be taken in its application
	D	Body of evidence is weak and recommendation must be applied with caution
	PP	Practice Point

RECOMMENDATION *(What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible)*	**OVERALL GRADE OF RECOMMENDATION**	
Use up to a maximum of three single repeat doses. If using a single repeat dose, use of a further repeat dose, up to a maximum of three single repeat doses, should be re-evaluated after seven or more days and less than 14 days from administration of a previous repeat course. The clinical decision to use a repeat dose should be based on an	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 recommendations(s) but care should be taken in its application
	D	Body of evidence is weak and recommendation must be applied with caution
	PP	Practice Points

assessment of ongoing risk for preterm birth. Where appropriate, estimate the risk of preterm birth by considering the use of adjunct prediction tests including fetal fibronectin and assessment of cervical length.		

UNRESOLVED ISSUES *(If needed, keep a 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 implementation of this recommendation?	**YES** **NO**

M9 GRADE Evidence summary

Considered Judgement - Strength of recommendation

What is the optimal timing between a first course of antenatal corticosteroids and initiating a repeat dose(s)?

1. Outcome measures:	Quality of evidence				Importance of outcome in making a decision		
Maternal Outcomes	**HIGH**	**MOD**	**LOW**	**V. LOW**	**Critical**	**Important**	**Not Important**
O_1 Chorioamnionitis	✓				✓		
O_2 Puerperal sepsis	✓				✓		
O_3 Pyrexia after entry to trial				NR		✓	
O_4 Intrapartum fever requiring antibiotics				NR		✓	
O_5 Post natal pyrexia				NR		✓	
O_6 Maternal quality of life				NR	✓		
Infant Outcomes	**HIGH**	**MOD**	**LOW**	**V. LOW**	**Critical**	**Important**	**Not Important**
O_1 Combined fetal and neonatal death		✓			✓		
O_2 Neonatal death		✓			✓		
O_3 Fetal death			✓		✓		
O_4 RDS	✓				✓		
O_5 Composite of serious outcomes for the infant	✓				✓		
O_6 Neurosensory disability (composite of impairments) for infant as a child		✓			✓		
O_7 Survival free of neurosensory disability for the infant as a child		✓			✓		
O_8 Survival free of metabolic disease for the infant as a child				NR		✓	
O_9 Neurosensory disability (composite of impairments) for infant as an adult				NR	✓		
O_{10} Survival free of neurosensory disability for the infant as an adult				NR	✓		
O_{11} Survival free of metabolic disease for the infant as an adult				NR		✓	

2. Is there is insufficient evidence to make a recommendation?

Evidence statement

Maternal - The evidence for maternal outcomes following exposure to repeat antenatal corticosteroids from 7 to 14 days between single and repeat antenatal corticosteoids is based on four randomised trials included in the Crowther (2011) systematic review involving up to 1971 women. Evidence for maternal outcomes following exposure to repeat antenatal corticosteroids more than 14 days between single and repeat doses(s) is based on two randomised trials included in the Crowther (2011) review involving 2290 women.

Infant - The evidence for infant outcomes following exposure to repeat antenatal corticosteroids from 7 to 14 days between single and repeat dose(s) is based on six randomised trials included in the Crowther (2011) systematic review involving up to 2871 infants. Evidence for infant outcomes following exposure to repeat antenatal corticosteroids more than 14 days between single and repeat dose(s) is based on three randomised trials included in the Crowther (2011) review involving 2993 infants.

3. What benefit will the proposed intervention/action have?

Evidence statement	**Quality of evidence**
Maternal - No differences were seen in risk of chorioamnionitis or puerperal sepsis for women treated with repeat antenatal corticosteroids between 7 and 14 days, or more than 14 days from the single course compared with those with no repeat treatment.	**HIGH**
Infant - No differences in measures of infant mortality among infants exposed to repeat antenatal corticosteroids between 7 and 14 days, or more than 14 days, from the single course compared with no repeat exposure. Respiratory distress syndrome was significantly reduced among infants exposed to antenatal corticosteroids at both intervals of between 7 and 14 days, and more than 14 days from the single course compared with no repeat exposure. An interval of between 7 and 14 days from the single course was associated with a significant reduction in a composite of serious infant outcomes when compared with no repeat exposure. An interval of more than 14 days or more from a single course had no effect on the incidence of a composite of serious infant outcomes when compared with no repeat exposure, however subgroup interaction test was not significant indicating no differential effect between timing intervals. There was no evidence of increased risk of neurosensory disability at early childhood follow up when the interval was between 7 and 14 days or greater than 14 days from the single course.	**HIGH**

Judging the benefits in context

The evidence is based on a number of well conducted randomised controlled trials, undertaken in a variety of countries and healthcare settings, involving a large number of women who remained at risk of preterm birth following an initial course of antenatal corticosteroids.

4. What harm might the proposed intervention/action do?

Evidence statement	**Quality of evidence**
Maternal - There is no evidence of increased risk of infection for the mother.	
Infant - Birthweight z scores were decreased following exposure to repeat antenatal corticosteroids at an interval of between 7 and 14 days from single course. No difference was seen in birthweight. Birthweight was significantly	**HIGH**

reduced when the interval between single and repeat antenatal corticosteroid was more than 14 days after the single course, with no significant difference in birthweight z scores. The clinical impact of this, if any, is unclear.	**HIGH**

Judging the harms in context
Maternal - There is no evidence of harm to the mother. There do not appear to be any direct health benefits for the mother.
Infant - The clinical significance, if any, of reduced birthweight is unclear. There was no increase in risk of mortality. More benefit is observed when the interval between the single course of antenatal corticosteroids and the repeat dose(s) is between 7 and up to 14 days.

5. What is the likely balance between good and harm?

Evidence statement	**Overall quality of evidence**
Maternal - There is no evidence of harm to the mother. There do not appear to be any direct health benefits for the mother.	
Infant - The significant reductions in respiratory distress seen for infants exposed to a repeat dose(s) of antenatal corticosteroids, at intervals of between 7 and 14 days, and more than 14 days, and the reduction in a composite of serious outcomes seen at an interval of between 7 and 14 days, outweighs the potential harm of reduced birthweight, and birthweight z scores.	**HIGH** **HIGH**

Judging the balance of benefits and harms in context
Maternal - The likelihood of causing harm to the mother is minimal, and the impact is low. There do not appear to be any detrimental effects for the mother.
Infant - The likelihood of doing good for the infant is high, and the impact is high for those infants remaining at risk of preterm birth following an initial single course.

Benefits clearly outweigh harms	**Recommend**	**STRONG**
Benefits probably outweigh harms	Consider	CONDITIONAL
Not known	Make a recommendation for research (see 8 below)	WEAK
Benefits probably don't outweigh harms	Consider against/make no recommendation	CONDITIONAL
Harms probably outweigh benefits		
Benefits clearly don't outweigh harms	Recommend against	STRONG
Harms clearly outweigh benefits		

6. Is the intervention/action implementable in the New Zealand and Australian context?

Summary statement
Antenatal corticosteroids are already widely in use in New Zealand and Australia.

Yes	**Recommend/consider**
Not known	Consider economic evaluation
No	Recommend/consider against

7. Final recommendation

	Strength of recommendation
EITHER Use a **single repeat dose** of repeat antenatal corticosteroids if preterm has not occurred seven or more days and less than fourteen days following a single course and preterm birth is still expected within the next seven days. If the woman has not given birth after a repeat dose(s) and is still considered to be at risk of preterm birth within the next seven days, a further repeat dose of 12 mg betamethasone can be administered.	**STRONG** **CONDITIONAL** **WEAK**
OR Use a **single repeat course** of repeat antenatal corticosteroids if preterm birth has not occurred seven or more days and less than fourteen days following a single course and preterm birth is still expected within the next seven days. Do not give further repeat courses.	
Use up to a maximum of three single repeat doses. If using a single repeat dose, use of a further repeat dose, up to a maximum of three single repeat doses, should be re-evaluated after seven or more days and less than 14 days from administration of a previous repeat course. The clinical decision to use a repeat dose should be based on an assessment of ongoing risk for preterm birth. Where appropriate, estimate the risk of preterm birth by considering the use of adjunct prediction tests including fetal fibronectin and assessment of cervical length.	**STRONG** **CONDITIONAL** **WEAK (Practice points)**

8. Recommendations for research

M10 Gestational age for administration of a single course of antenatal corticosteroids

M10 NHMRC Evidence summary

At what gestational age is a single course of antenatal corticosteroids effective?		
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Maternal No trials included in the Roberts CPG version 2015 systematic review for a single course of antenatal corticosteroids that recruited and randomised women with a gestational age at trial entry >34 weeks' reported on maternal infection outcomes. When gestational age at trial entry was ≤34 weeks' and 6 days, ten trials reported on chorioamnionitis, six trials reported on puerperal sepsis, two trials reported on pyrexia after trial entry, one trial reported on intrapartum pyrexia, and three trials reported on postnatal pyrexia requiring treatment. Infant When gestational age at trial entry was ≤34 weeks' and 6 days, seven of the 26 trials included in the Roberts CPG version 2015 systematic review for a single course of antenatal corticosteroids reported on perinatal death, thirteen trials reported on neonatal death, and seven trials reported on fetal death. One trial reported data for neonatal death in infants who had a gestational age >34 weeks' at time of trial entry. No trials that recruited and randomised women with a gestation at trial entry of >34 weeks' reported on perinatal or fetal death. For respiratory distress syndrome, gestational age at trial entry of ≤34 weeks' and 6 days was reported in sixteen trials and 2 trials reported gestational age at trial entry of >34 weeks'.	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 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')*		
Maternal Evidence is consistent that there is no increased risk of maternal infection when gestation at trial entry (time of first dose) was ≤34 weeks' and 6 days. The treatment effects for chorioamnionitis, puerperal sepsis, pyrexia after trial entry, and intrapartum pyrexia tended toward increased risk when compared to the overall treatment effect, but were not significant. Infant Evidence is consistent that the risk of perinatal death, neonatal death and respiratory distress syndrome were significantly reduced following exposure to a single course of antenatal corticosteroids compared with no exposure when gestational age at trial entry was ≤34 weeks' and 6 days. There was no difference in risk of fetal death. There was no difference in risk of neonatal death or respiratory distress syndrome when gestational age at trial entry was >34 weeks'.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is not consistent
	NA	Not applicable (one study only)
3. Clinical impact *(indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Maternal The risk of maternal infection is not increased when a single course of antenatal corticosteroids is administered at ≤34 weeks' and 6 days gestation. The significant benefits to the infant outweigh any risk of maternal infection. Infant The evidence for reductions in risk of perinatal death, neonatal death and respiratory distress syndrome when gestational age at trial entry was ≤34 weeks' and 6 days is precise with large effect sizes. The evidence for gestational age at trial entry of >34 weeks' is less precise with wide confidence intervals.	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?)*		
Evidence from a variety of healthcare settings. Studies conducted in USA, France, Australia, and The Netherlands.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether sensible to apply
5. Applicability *(is the body of evidence relevant to the New Zealand / Australian healthcare context in terms of health services / delivery of care and cultural factors?)*		

Corticosteroids are readily available in Australia and New Zealand and their use is feasible.	A	Evidence directly applicable to New Zealand / Australian healthcare context
	B	Evidence applicable to New Zealand / Australian healthcare context with few caveats
	C	Evidence probably applicable to New Zealand / Australian healthcare context with some caveats
	D	Evidence not applicable to New Zealand / 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)*

The evidence is based on a subset of data from the trials, true subgroups cannot be explored as the groups selected are not mutally exclusive. Clinical recommendations cannot be made.

EVIDENCE STATEMENT MATRIX *(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	NA	Not applicable
2. Consistency	NA	Not applicable
3. Clinical Impact	NA	Not applicable
4. Generalisability	NA	Not applicable
5. Applicability	NA	Not applicable

Evidence statement

There was no increased risk of maternal infection following treatment with a single course of antenatal corticosteroids, compared with no antenatal corticosteroids, when gestation at trial entry was ≤34 weeks' and 6 days. No trials reported data for maternal infection when gestation at trial entry was >34 weeks'. The risk of perinatal and neonatal death and respiratory distress syndrome were significantly reduced following exposure to a single course of antenatal corticosteroids, compared with no exposure, when gestational age at trial entry was >34 weeks'. No data was identified on the use of antenatal corticosteroids <24 weeks' gestation.

RECOMMENDATION *(What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible)*	**OVERALL GRADE OF RECOMMENDATION**	
Use a single course of antenatal corticosteroids in women of 34 weeks' and 6 days or less gestation if birth is expected within the next seven days.	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 recommendations(s) but care should be taken in its application
	D	Body of evidence is weak and recommendation must be applied with caution
	PP	**Practice Point**

RECOMMENDATION *(What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible)*	**OVERALL GRADE OF RECOMMENDATION**	
If considering use of antenatal corticosteroids prior to 24 weeks' gestation, there should be careful consideration of benefit and risks with parental consultation.	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 recommendations(s) but care should be taken in its application
	D	Body of evidence is weak and recommendation must be applied with caution
	PP	**Practice Point**

UNRESOLVED ISSUES *(If needed, keep a 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 May be some change in practice**
	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 implementation of this recommendation?	**YES Educational requirement to change practice if required**
	NO

M10 GRADE Evidence summary

Considered Judgement - Strength of recommendation							
At what gestational age is a single course of antenatal corticosteroids effective?							
1. Outcome measures:	**Quality of evidence**				**Importance of outcome in making a decision**		
Maternal Outcomes	**HIGH**	**MOD**	**LOW**	**V. LOW**	**Critical**	**Important**	**Not Important**
O_1 Chorioamnionitis	✓				✓		
O_2 Puerperal sepsis		✓			✓		
O_3 Pyrexia after entry to trial		✓				✓	
O_4 Intrapartum fever requiring antibiotics		✓				✓	
O_5 Post natal pyrexia	✓					✓	
O_6 Maternal quality of life				NR	✓		
Infant Outcomes	**HIGH**	**MOD**	**LOW**	**V. LOW**	**Critical**	**Important**	**Not Important**
O_1 Combined fetal and neonatal death		✓			✓		
O_2 Neonatal death		✓			✓		
O_3 Fetal death			✓		✓		
O_4 RDS		✓			✓		
O_5 Composite of serious outcomes for the infant				NR	✓		
O_6 Neurosensory disability (composite of impairments) for infant as a child				NR	✓		
O_7 Survival free of neurosensory disability for the infant as a child				NR	✓		
O_8 Survival free of metabolic disease for the infant as a child				NR		✓	
O_9 Neurosensory disability (composite of impairments) for infant as an adult				NR	✓		
O_{10} Survival free of neurosensory disability for the infant as an adult				NR	✓		
O_{11} Survival free of metabolic disease for the infant as an adult				NR		✓	

2. Is there is insufficient evidence to make a recommendation?

Evidence statement - The evidence is based on a subset of data from the trials, true subgroups cannot be explored as the groups selected are not mutually exclusive. Clinical recommendations cannot be made.

Maternal - No trials included in the Roberts CPG version 2015 systematic review for a single course of antenatal corticosteroids that recruited and randomised women with a gestational age at trial entry >34 weeks' reported on maternal infection outcomes. When gestational age at trial entry was ≤34 weeks' and 6 days, ten trials reported on chorioamnionitis, six trials reported on puerperal sepsis, two trials reported on pyrexia after trial entry, one trial reported on intrapartum pyrexia, and three trials reported on postnatal pyrexia requiring treatment.
Infant - When gestational age at trial entry was ≤34 weeks' and 6 days, seven of the 26 trials included in the Roberts CPG version 2015 systematic review for a single course of antenatal corticosteroids reported on perinatal death, thirteen trials reported on neonatal death, and seven trials reported on fetal death. One trial reported data for neonatal death in infants who had a gestational age >34 weeks' at time of trial entry. No trials that recruited and randomised women with a gestation at trial entry of >34 weeks' reported on perinatal or fetal death.
For respiratory distress syndrome, gestational age at trial entry of ≤34 weeks' and 6 days was reported in sixteen trials, and 2 trials reported gestational age at trial entry of >34 weeks'.

3. What benefit will the proposed intervention/action have?

Evidence statement	**Quality of evidence**
Maternal - There is no increased risk of maternal infection when gestation at trial entry (time of first dose) was ≤34 weeks' and 6 days. The treatment effects for chorioamnionitis, puerperal sepsis, pyrexia after trial entry, and intrapartum pyrexia tended toward increased risk when compared to the overall treatment effect, but were not significant. *Infant* - The risk of perinatal death, neonatal death and respiratory distress syndrome were significantly reduced following exposure to a single course of antenatal corticosteroids compared with no exposure when gestational age at trial entry was ≤34 weeks' and 6 days. There was no difference in risk of fetal death. There was no difference in risk of neonatal death or respiratory distress syndrome when gestational age at trial entry was >34 weeks'.	**Not applicable**

Judging the benefits in context
The evidence is based overall on well designed and conducted randomised controlled trials investigating the use of antenatal corticosteroids in women at risk of preterm birth. The populations were drawn from a range of healthcare settings around the world.

4. What harm might the proposed intervention/action do?

Evidence statement	**Quality of evidence**
Maternal - The risk of maternal infection is not increased when a single course of antenatal corticosteroids is administered at ≤34 weeks' and 6 days gestation. The significant benefits to the infant outweigh any risk of maternal infection. *Infant* - There is no evidence of harm to the infant. There is evidence for reductions in a number of important	**Not applicable**

clinical outcomes such as perinatal death, neonatal death and respiratory distress syndrome following exposure to a single course of antenatal corticosteroids compared with no antenatal corticosteroids when gestation at trial entry was ≤34 weeks' and 6 days.	

Judging the harms in context
Maternal - The evidence is direct evidence from trials that recruited and randomised women at risk of preterm birth.
Infant - The evidence for reductions in risk of perinatal death, neonatal death and respiratory distress syndrome when gestational age at trial entry was ≤34 weeks' and 6 days is precise with large effect sizes. The evidence for gestational age at trial entry of >34 weeks' is less precise with wide confidence intervals.

5. What is the likely balance between good and harm?

Evidence statement *Maternal* - Evidence suggests no increased risk of maternal infection for women treated with a single course of antenatal corticosteroids compared with no antenatal corticosteroids at gestations ≤34 weeks' and 6 days. No trials reported data for maternal infection when gestation at trial entry was >34 weeks'. *Infant* - The evidence suggests clear benefits for the infant of reduced risk of a number of important clinical outcomes, with no increased risk of harm following exposure to antenatal corticosteroids at gestational ages less than 34 weeks'.	**Overall quality of evidence** **Not applicable**

Judging the balance of benefits and harms in context
Maternal - The benefits to the infant are significant with no obvious health harms to the infant.
Infant - The benefits to the infant are significant with no evidence of health harms.

Benefits clearly outweigh harms	Recommend	STRONG
Benefits probably outweigh harms	Consider	CONDITIONAL
Not known	**Make a recommendation for research (see 8 below)**	**WEAK**
Benefits probably don't outweigh harms Harms probably outweigh benefits	Consider against/make no recommendation	CONDITIONAL
Benefits clearly don't outweigh harms Harms clearly outweigh benefits	Recommend against	STRONG

6. Is the intervention/action implementable in the New Zealand context?

Summary statement
Antenatal corticosteroids are already widely in use in New Zealand and Australia.

Yes	**Recommend/consider**
Not known	Consider economic evaluation
No	Recommend/consider against

7. Final recommendation

Use a single course of antenatal corticosteroids in women of 34 weeks' and 6 days or less gestation if birth is expected within the next seven days. If considering use of antenatal corticosteroids prior to 24 weeks' gestation, there should be careful consideration of benefit and risks with parental consultation.	**Strength of recommendation** **STRONG** **CONDITIONAL** **WEAK (Practice points)**

8. Recommendations for research

Randomised trials are needed to:

- investigate the neonatal benefits of antenatal corticosteroids administered to women at less than 24 weeks' gestation.
- investigate if smaller doses are needed at lower gestational ages.
- investigate the neonatal benefits of antenatal corticosteroids administered late preterm (34 weeks' and 6 days to <37 weeks' gestation).

M11 Gestational age for administration of repeat antenatal corticosteroids

M11 NHMRC Evidence summary

At what gestational age is a repeat dose(s) of antenatal corticosteroids effective?		
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Maternal Three trials included in the Crowther (2011) Cochrane systematic review randomised women up to a gestational age at trial entry of ≤31 weeks' and 6 days. Three trials randomised women up to ≤32 weeks' and 6 days gestation at trial entry, and one trial randomised women up to ≤33 weeks' and 6 days at trial entry. Infant Three trials included in the Crowther (2011) Cochrane systematic review reported outcomes in infants exposed to repeat doses(s) of antenatal corticosteroids at ≤31 weeks' and 6 days gestation at trial entry, four trials reported outcomes in infants exposed to repeat doses(s) of antenatal corticosteroids at ≤32 weeks' and 6 days gestation at trial entry, two trials reported outcomes in infants exposed to repeat doses(s) of antenatal corticosteroids at ≤33 weeks' and 6 days gestation at trial entry.	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 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')*		
Maternal There is no difference in risk of chorioamnionitis between women treated with repeat antenatal corticosteroids and those with no repeat corticosteroids when the gestational age at trial entry was ≤31 weeks' and 6 days or ≤32 weeks' and 6 days. No data were reported for ≤33 weeks' and 6 days. There is no difference in risk of puerperal sepsis between women treated with repeat antenatal corticosteroids and those with no repeat corticosteroids when the gestational age at trial entry was ≤31 weeks' and 6 days, ≤32 weeks' and 6 days or ≤33 weeks' and 6 days. There was no data on pyrexia after trial entry or intrapartum pyrexia requiring treatment. Infant There was no difference in perinatal, neonatal or fetal death between exposure to repeat antenatal corticosteroids and no repeat exposure at the three gestational age categories examined for these Clinical Practice Guidelines. The risk of respiratory distress syndrome was significantly reduced following repeat exposure to antenatal corticosteroids compared with no repeat exposure when gestational age at trial entry was ≤31 weeks' and 6 day, ≤32 weeks' and 6 days There was no difference in risk when gestational age at trial entry was ≤33 weeks' and 6 days. A composite of serious infant outcomes was significantly reduced following exposure to repeat antenatal corticosteroids compared with no repeat exposure when the gestational age at trial entry was ≤31 weeks' and 6 days. No difference was seen when gestational age at trial entry was ≤32 weeks' and 6 days weeks' and no data were reported for ≤33 weeks' and 6 days.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is not consistent
	NA	Not applicable (one study only)
3. Clinical impact *(indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Maternal There does not appear to be an increased risk of maternal infection following repeat antenatal corticosteroids compared with no repeat exposure when the gestational age at trial entry was ≤31 weeks' and 6 days, ≤32 weeks' and 6 days, or ≤33 weeks' and 6 days. Infant Data for perinatal death following exposure to repeat antenatal corticosteroids at ≤33 weeks' and 6 days is imprecise with wide confidence intervals. This is also the case with the data for fetal death, indicating some statistical imprecision. However other treatment effects for outcomes by gestational age categories are similar to the overall treatment effect, in the direction toward reduced risk. Birthweight was reduced in all three gestational age categories, the clinical significance of which is unclear. Only two trials adjusted for gestational age using z scores, and there is evidence of statistical imprecision with wide confidence intervals. An individual patient data meta-analysis may be of use in interpreting this information.	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?)*		
Evidence from a variety of healthcare settings. Studies conducted in USA, France, Australia, and The Netherlands.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether sensible to apply
5. Applicability *(is the body of evidence relevant to the New Zealand / Australian healthcare context in terms of health services / delivery of care and cultural factors?)*		
Corticosteroids are readily available in Australia and New Zealand and their use is feasible.	A	Evidence directly applicable to New Zealand / Australian healthcare context
	B	Evidence applicable to New Zealand / Australian healthcare context with few caveats
	C	Evidence probably applicable to New Zealand / Australian healthcare context with some caveats
	D	Evidence not applicable to New Zealand / 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)*

The evidence is based on a subset of data from the trials, true subgroups cannot be explored as the groups selected are not mutually exclusive. Clinical recommendations cannot be made.

EVIDENCE STATEMENT MATRIX *(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	NA	Not applicable
2. Consistency	NA	Not applicable
3. Clinical Impact	NA	Not applicable
4. Generalisability	NA	Not applicable
5. Applicability	NA	Not applicable

Evidence statement
Repeat exposure to antenatal corticosteroids does not appear to increase the risk of infection for the mother, while affording significant benefits for the infant in terms of reduced risk of mortality and respiratory distress syndrome.

RECOMMENDATION *(What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible)* Use repeat antenatal corticosteroids in women at risk of preterm birth (<32 weeks' and 6 days gestation). Refer to Chapter 10 of these Clinical Practice Guidelines.	**OVERALL GRADE OF RECOMMENDATION**	
	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 recommendations(s) but care should be taken in its application
	D	Body of evidence is weak and recommendation must be applied with caution
	PP	**Practice Point**

UNRESOLVED ISSUES *(If needed, keep a 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 Potentially will change current practice**
	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 implementation of this recommendation?	**YES Education may be required to facilitate change if required**
	NO

M11 GRADE Evidence summary

Considered Judgement - Strength of recommendation

At what gestational age is a repeat dose(s) of antenatal corticosteroids effective?

1. Outcome measures:	Quality of evidence				Importance of outcome in making a decision		
Maternal Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O_1 Chorioamnionitis	✓				✓		
O_2 Puerperal sepsis	✓				✓		
O_3 Pyrexia after entry to trial				NR		✓	
O_4 Intrapartum fever requiring antibiotics				NR		✓	
O_5 Post natal pyrexia		✓				✓	
O_6 Maternal quality of life				NR	✓		
Infant Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O_1 Combined fetal and neonatal death	✓				✓		
O_2 Neonatal death	✓				✓		
O_3 Fetal death		✓			✓		
O_4 RDS	✓				✓		
O_5 Composite of serious outcomes for the infant	✓				✓		
O_6 Neurosensory disability (composite of impairments) for infant as a child				NR	✓		
O_7 Survival free of neurosensory disability for the infant as a child				NR	✓		
O_8 Survival free of metabolic disease for the infant as a child				NR		✓	
O_9 Neurosensory disability (composite of impairments) for infant as an adult				NR	✓		
O_{10} Survival free of neurosensory disability for the infant as an adult				NR	✓		
O_{11} Survival free of metabolic disease for the infant as an adult				NR		✓	

2. Is there is insufficient evidence to make a recommendation?

Evidence statement: The evidence is based on a subset of data from the trials, true subgroups cannot be explored as the groups selected are not mutually exclusive. Clinical recommendations cannot be made.

Maternal - The evidence is based on trials included in the Crowther (2011) systematic review. The evidence for chorioamnionitis in women treated with repeat antenatal corticosteroids when gestational age at trial entry was ≤31 weeks' and 6 days is based on 3 trials involving 1486 women, and gestational age at trial entry of ≤32 weeks' and 6 days is based on 3 trials involving 2775 women. No data on chorioamnionitis were reported when gestational age at trial entry was ≤33 weeks' and 6 days. The evidence for puerperal sepsis in women treated with repeat antenatal corticosteroids when gestational age at trial entry was ≤31 weeks' and 6 days is based on 2 trials involving 504 women, gestational age at trial entry of ≤32 weeks' and 6 days is based on 2 trials involving 2338 women, and gestational age at trial entry of ≤33 weeks' and 6 days is based on one trial involving 249 women. One trial that randomised 972 women at ≤31 weeks' and 6 days gestation reported on postnatal pyrexia. There was no data on pyrexia after trial entry or intrapartum pyrexia.
Infant - Evidence is based on the Crowther (2011) systematic review. Evidence for outcomes at gestational age ≤31 weeks' and 6 days at trial entry is based on 3 trials, involving 1657 infants, that reported on perinatal death, 2 trials, involving 1160 infants, that reported on neonatal death, 2 trials, involving 1162 infants, that reported on fetal death. Three trials involving 1655 infants reported on respiratory distress syndrome and composite serious infant outcome at ≤31 weeks' and 6 days gestation at trial entry. Evidence for outcomes at ≤32 weeks' and 6 days gestation at trial entry is based on 4 trials, involving 3459 infants, that reported on perinatal death, 3 trials involving 1115 infants that reported on neonatal death, and three trials, involving 1155 infants, that reported on fetal death. Three trials, involving 1113 infants reported on respiratory distress syndrome, and four trials, involving 3439 infants, reported on composite serious infant outcome at ≤32 weeks' and 6 days gestational age at trial entry. Evidence for outcomes at ≤33 weeks' and 6 days gestational age at trial entry is based on two trials, involving 438 infants that reported on perinatal death, neonatal death, fetal death and respiratory distress syndrome. No data were available for composite serious infant outcome at ≤33 weeks' and 6 days gestation at trial entry.

3. What benefit will the proposed intervention/action have?

Evidence statement	Quality of evidence
Maternal - There was no increased risk of measures of maternal infection (chorioamnionitis, puerperal sepsis and postnatal pyrexia requiring treatment with antibiotics) following repeat antenatal corticosteroids compared with no repeat antenatal corticosteroids with the gestational age at trial entry was ≤31 weeks' and 6 days, ≤32 weeks' and 6 days or ≤33 weeks' and 6 days. *Infant* - There was no difference in the risk of infant mortality (perinatal, neonatal or fetal) between those exposed to repeat antenatal corticosteroids and those not exposed to repeat antenatal corticosteroids at ≤31 weeks' and 6 days, ≤32 weeks' and 6 days and ≤33 weeks' and 6 days gestation at trial entry. Respiratory distress syndrome was significantly reduced following repeat antenatal corticosteroids compared with no repeat exposure at ≤31 weeks' and 6 days and ≤32 weeks' and 6 days gestation at trial entry. There was no significant difference in respiratory distress syndrome between those exposed to repeat antenatal corticosteroids and those not exposed when the	**Not applicable**

gestational age at trial entry was ≤33 weeks' and 6 days. A composite of serious infant outcomes was significantly reduced following exposure to repeat antenatal corticosteroids compared with no repeat exposure when the gestational age at trial entry was ≤31 weeks' and 6 days. There was no significant difference between those exposed to repeat antenatal corticosteroids and those not exposed when the gestational age at trial entry was ≤32 weeks' and 6 days for a composite of serious infant outcomes.	

Judging the benefits in context
The evidence is based on well designed and conducted randomised controlled trials conducted in women who remained at risk of preterm birth following an initial course of antenatal corticosteroids and exposed to repeat antenatal corticosteroids or placebo. The populations were drawn from a variety of healthcare settings worldwide.

4. What harm might the proposed intervention/action do?

Evidence statement	**Quality of evidence**
Maternal - There is no evidence of health harms for the mother in terms of increased risk of maternal infection. *Infant* - There was evidence of reduced birthweight in all three gestational age at trial entry categories following repeat antenatal corticosteroids compared with no repeat exposure.	**Not applicable**

Judging the harms in context
Maternal - There was no evidence of harm to the mother.
Infant - The clinical significance of reduced birthweight following exposure to repeat antenatal corticosteroids is unclear. Only two trials adjusted birthweight for gestational age using z scores, and there was evidence of statistical imprecision with wide confidence intervals.

5. What is the likely balance between good and harm?

Evidence statement	**Overall quality of evidence**
Maternal - The evidence suggests no increased risk of harm to the mother. *Infant* - The evidence for significant reductions in risk of mortality, respiratory distress syndrome and a composite of serious infant outcomes for infants exposed to repeat antenatal corticosteroids suggests clear benefit to the infant. This outweighs the potential for reduced birthweight, the clinical significant of which is not yet clear.	**Not applicable**

Judging the balance of benefits and harms in context
Maternal - There do not appear to be increased risk of harm at any of the gestational age at trial entry categories selected for analysis for these Clinical Practice Guidelines. **Although the evidence is ranked HIGH it is indirect and a STRONG recommendation cannot be made.**
Infant - The benefits to the infant are significant, and outweigh the possibility of having reduced birthweight. **Although the evidence is ranked HIGH it is indirect and a STRONG recommendation cannot be made.**

Benefits clearly outweigh harms	Recommend	STRONG
Benefits probably outweigh harms	Consider	CONDITIONAL
Not known	**Make a recommendation for research (see 8 below)**	**WEAK**
Benefits probably don't outweigh harms Harms probably outweigh benefits	Consider against/make no recommendation	CONDITIONAL
Benefits clearly don't outweigh harms Harms clearly outweigh benefits	Recommend against	STRONG

6. Is the intervention/action implementable in the New Zealand context?

Summary statement
Antenatal corticosteroids are already widely in use in New Zealand and Australia.

Yes	**Recommend/consider**
Not known	Consider economic evaluation
No	Recommend/consider against

7. Final recommendation

Use repeat antenatal corticosteroids in women at risk of preterm birth (<32 weeks' and 6 days gestation). Refer to Chapter 10 of these Clinical Practice Guidelines.	Strength of recommendation **STRONG** **CONDITIONAL** **WEAK (Practice point)**

8. Recommendations for research

- Randomised trials are needed to investigate the effects of repeat antenatal corticosteroids in women ≥32 weeks' and 6 days gestation.

M12 Use of antenatal corticosteroids for women planning an elective caesarean section at term

M12 NHMRC Evidence summary

What are the benefits and harms for the mother, fetus, infant, child and adult of administering antenatal corticosteroids for fetal lung maturation to women planning an elective caesarean section at term?		
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Maternal No data on maternal outcomes was reported in the Sotiriadis (2009) Cochrane systematic review or Ahmed (2014). Infant The Sotiriadis CPG version 2015 systematic review included one systematic review including one randomised controlled trial involving 943 women and 942 infants, a follow-up report of that trial and one trial including 452 infants Risk of bias in both trials was unclear and there was no blinding of participants	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 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')*		
Maternal No data on maternal outcomes was reported in the Sotiriadis CPG version 2015 Infant There were no cases of perinatal death in either group reported in the single trial included in the Sotiriadis (2009) systematic review. The Ahmed (2014) trial did not report on fetal death, and there were no cases of neonatal death. There was a significant decrease in respiratory distress syndrome and respiratory distress in those exposed to antenatal corticosteroids. There was no evidence of adverse behavioural, cognitive or developmental effects at long term follow up (median age 12.2 years) for those born following exposure to a single course of betamethasone at term compared to controls who did not receive betamethasone. However there was evidence that the children were low academic achievers reported in only one trial	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is not consistent
	NA	Not applicable (one study only)
3. Clinical impact *(indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Maternal No data on maternal outcomes were reported in the Sotiriadis CPG version 2015. Infant Event rates for respiratory distress were very low, and the trial included in the Cochrane systematic review was underpowered to detect differences in this outcome. Unclear if there are long term harms.	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?)*		
Evidence from a single trial, conducted in the United Kingdom, included in a Cochrane systematic review.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether sensible to apply
5. Applicability *(is the body of evidence relevant to the New Zealand / Australian healthcare context in terms of health services / delivery of care and cultural factors?)*		
Corticosteroids are readily available in Australia and New Zealand and their use is feasible. Variations in practice across Australian and New Zealand for use of corticosteroids at term before elective caesarean section	A	Evidence directly applicable to New Zealand / Australian healthcare context
	B	Evidence applicable to New Zealand / Australian healthcare context with few caveats
	C	Evidence probably applicable to New Zealand / Australian healthcare context with some caveats
	D	Evidence not applicable to New Zealand / 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 is limited in volume and quality. Event rates are low and respiratory distress was not the primary outcome of one of the trials. Only one trial has reported on longer term childhood follow-up and there is concern about lower academic achievement in children exposed to antenatal corticosteroids. A clinical recommendation cannot be made with the current lack of certainty		

EVIDENCE STATEMENT MATRIX *(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	D	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias
2. Consistency	B	All studies consistent
3. Clinical Impact	C	Moderate
4. Generalisability	D	Evidence directly generalisable to target population with some caveats
5. Applicability	C	Evidence applicable to New Zealand / Australian healthcare context with few caveats

Evidence statement

The evidence for the use of antenatal corticosteroids at term and with elective caesarean section remains unclear with the evidence currently limited to a single trial. There were no cases of perinatal death reported, and no difference in respiratory distress syndrome between infants exposed to antenatal corticosteroids and those with no exposure. There were low event rates and the trial was underpowered to detect differences in this outcome. No maternal data were reported.

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

For elective caesarean section at term, where possible, plan at ≥39 weeks' gestation.

Use antenatal corticosteroids 48 hours prior to caesarean birth planned beyond 34 weeks' and 6 days gestation if there is known fetal lung immaturity.

OVERALL GRADE OF RECOMMENDATION	
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 recommendations(s) but care should be taken in its application
D	Body of evidence is weak and recommendation must be applied with caution
PP	**Practice Points**

UNRESOLVED ISSUES *(If needed, keep a 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 Likely to be a change in practice for not giving steroids and changing timing of elective caesarean section**
	NO
Are there any resource implications associated with implementing this recommendation?	**YES More women may go into spontaneous labour and reduce resource implications associated with caesarean section**
	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 implementation of this recommendation?	**YES Giving steroids prior to caesarean section is used around New Zealand and Australia**
	NO

M12 GRADE Evidence summary

Considered Judgement - Strength of recommendation

What are the benefits and harms for the mother, fetus, infant, child and adult of administering antenatal corticosteroids for fetal lung maturation to women planning an elective caesarean section at term?

1. Outcome measures:	Quality of evidence				Importance of outcome in making a decision		
Maternal Outcomes	**HIGH**	**MOD**	**LOW**	**V. LOW**	**Critical**	**Important**	**Not Important**
O_1 Chorioamnionitis				NR	✓		
O_2 Puerperal sepsis				NR	✓		
O_3 Pyrexia after entry to trial				NR		✓	
O_4 Intrapartum fever requiring antibiotics				NR		✓	
O_5 Post natal pyrexia				NR		✓	
O_6 Maternal quality of life				NR	✓		
Infant Outcomes	**HIGH**	**MOD**	**LOW**	**V. LOW**	**Critical**	**Important**	**Not Important**
O_1 Combined fetal and neonatal death				NR	✓		
O_2 Neonatal death				NR	✓		
O_3 Fetal death				NR	✓		
O_4 RDS		✓				✓	
O_5 Composite of serious outcomes for the infant				NR	✓		
O_6 Neurosensory disability (composite of impairments) for infant as a child				NR	✓		
O_7 Survival free of neurosensory disability for the infant as a child				NR	✓		
O_8 Survival free of metabolic disease for the infant as a child				NR		✓	
O_9 Neurosensory disability (composite of impairments) for infant as an adult				NR	✓		
O_{10} Survival free of neurosensory disability for the infant as an adult				NR	✓		
O_{11} Survival free of metabolic disease for the infant as an adult				NR		✓	

2. Is there is insufficient evidence to make a recommendation?

Evidence statement - Evidence is limited in volume and quality. Event rates are low and respiratory distress was not the primary outcome of one of the trials. Only one trial has reported on longer term childhood follow-up and there is concern about lower academic achievement in children exposed to antenatal corticosteroids. A clinical recommendation cannot be made with the current lack of certainty

Maternal - The one trial (Stutchfield, 2005) included in the Sotiriadis (2009) systematic review did not report maternal outcomes. The Ahmed (2014) trial did not report maternal outcomes.
Infant - Infant mortality outcomes were not reported in either the Ahmed (2014) trial, or the Sotiriadis (2009) systematic review. Respiratory distress syndrome was reported in Ahmed (2014) and Stutchfield (2005) but event rates are very low

3. What benefit will the proposed intervention/action have?

Evidence statement	**Quality of evidence**
Maternal - No data were reported in the Sotiriadis (2009) systematic review on the maternal primary outcomes for these Clinical Practice Guidelines. The Ahmed (2014) trial did not pre-specify or report on any maternal outcomes. *Infant* - There were no cases of perinatal death in either group reported in the single included trial (Stutchfield 2005) in the Sotiriadis (2009) systematic review. Fetal death was not reported in either the Stutchfield (2005) or the Ahmed (2014) trials. There were no cases of neonatal death in either group reported in the Ahmed (2014) trial. The Stutchfield (2005) trial did not report on neonatal death. Overall there was a significant reduction in respiratory distress syndrome for infants exposed to antenatal corticosteroids compared with no exposure (RR 0.27, 95%CI 0.09 to 0.81; 2 trials, n=1390). No data were reported on a composite of serious infant outcomes in the Stutchfield (2005) or Ahmed (2014) trials. There was a significant reduction in transient tachypnoea of the newborn, admissions to neonatal intensive care and length of stay in neonatal intensive care for infants exposed to antenatal corticosteroids compared with no exposure following elective caesarean section at term. There were no adverse effects on behavioural, cognitive or developmental outcome for those born following exposure to a single course of betamethasone (2 x 12 mg, 24 hours apart) at term compared to controls who did not receive betamethasone. No follow-up has as yet been reported for the Ahmed (2014) trial.	**Not applicable**

Judging the benefits in context There are benefits for the infant in terms of reduced respiratory distress syndrome and respiratory distress and reduced length of stay in neonatal intensive care. Likely to be reduced costs	
4. What harm might the proposed intervention/action do?	
Evidence statement *Maternal* - No data were reported in the Sotiriadis (2009) systematic review on the maternal primary outcomes for these Clinical Practice Guidelines. The Ahmed (2014) trials did not pre-specify or report on any maternal outcomes. *Infant* - School performance data was available from 352 children (37% of original study) followed-up from the Stutchfield (2005) trial. Children who had been exposed to antenatal corticosteroids *in utero* were more likely to be in the lowest achievement group at school compared with children who had not been exposed to antenatal corticosteroids (RR 2.1, 95%CI 1.1 to 3.7). There was no formalised testing of academic ability reported (Stutchfield 2013).	**Quality of evidence** **Not applicable**
Judging the harms in context *Maternal* - Unable to judge due to lack of data *Infant* - Evidence of benefit for the infant especially for reduced transient tachypnoea of the newborn and for admission to neonatal intensive care	
5. What is the likely balance between good and harm?	
Evidence statement *Maternal* - Unable to judge due to lack of data *Infant* - Likely to be benefit with no evidence of harms although long term data is not available	**Overall quality of evidence** **Not applicable**
Judging the balance of benefits and harms in context *Maternal* - No evidence reported *Infant* - There is evidence of benefit for the infant but the long term outcomes for neurodevelopment are unclear. There may be a risk of long term harm	

Benefits clearly outweigh harms	Recommend	STRONG
Benefits probably outweigh harms	Consider	CONDITIONAL
Not known	**Make a recommendation for research (see 8 below)**	**WEAK**
Benefits probably don't outweigh harms	Consider against/make no recommendation	CONDITIONAL
Harms probably outweigh benefits		
Benefits clearly don't outweigh harms	Recommend against	STRONG
Harms clearly outweigh benefits		

6. Is the intervention/action implementable in the New Zealand and Australian context?	
Summary statement Antenatal corticosteroids are already widely in use in New Zealand and Australia.	
Yes	**Recommend/consider**
Not known	Consider economic evaluation
No	Recommend/consider against

7. Final recommendation	
For elective caesarean section at term, where possible, plan at ≥39 weeks' gestation. Use antenatal corticosteroids 48 hours prior to caesarean birth planned beyond 34 weeks' and 6 days gestation if there is known fetal lung immaturity.	**Strength of recommendation** **STRONG** **CONDITIONAL** **WEAK (Practice Points)**

8. Recommendations for research

- Randomised trials are needed to investigate the neonatal effects and childhood disability rates when antenatal corticosteroids are administered to women prior to planned caesarean section at term gestation (≥37 weeks') where their infants are at increased risk of neonatal respiratory disease.

M13 Women with a previous history of preterm birth – Single course of antenatal corticosteroids

M13 NHMRC Evidence summary

What is the safety for the mother and fetus, infant, child, adult of administering a single course of antenatal corticosteroids to women with history of previous preterm birth?		
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Maternal No randomised controlled trial evidence was found for the use of prophylactic antenatal corticosteroids for women whose only risk factor for preterm birth in the current pregnancy is a history of previous preterm birth. However, as two trials in the Roberts CPG version 2015 systematic review for a single course of antenatal corticosteroids included a proportion of women who had a previous history of preterm birth and were at risk of preterm birth in the current pregnancy, overall treatment effects were compared with this subgroup of trials. Infant No randomised controlled trial evidence was found for the use of prophylactic antenatal corticosteroids for women whose only risk factor for preterm birth in the current pregnancy is a history of previous preterm birth. However, as three trials in the Roberts CPG version 2015 systematic review for a single course of antenatal corticosteroids included a proportion of women who had a previous history of preterm birth and were at risk of preterm birth in the current pregnancy, overall treatment effects were compared with this subgroup of trials.	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 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')*		
Maternal Within the subgroup of trials that included a proportion of women who had had a previous preterm birth, there was no increased risk of chorioamnionitis or puerperal sepsis. Infant The overall beneficial effect of reduced neonatal mortality and respiratory distress syndrome was absent from the subgroup of trials that reported the proportion of women with a history of preterm birth.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is not consistent
	N A	Not applicable (one study only)
3. Clinical impact *(indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Maternal There was some imprecision in the confidence intervals for puerperal sepsis in the subgroup of trials that reported the proportion of women with previous history of preterm birth. Infant Among those trials that reported the proportion of women with the history of preterm birth, the beneficial effect of reduced mortality and respiratory distress syndrome was absent. The risk of these outcomes was not increased.	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?)*		
For women whose only risk factor in the current pregnancy is previous history of preterm birth, evidence from the overall treatment effect is not generalizable, however the evidence can sensibly be applied to women at current risk.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether sensible to apply
5. Applicability *(is the body of evidence relevant to the New Zealand / Australian healthcare context in terms of health services / delivery of care and cultural factors?)*		
The use of antenatal corticosteroids is applicable to this subgroup of women in New Zealand and Australia	A	Evidence directly applicable to New Zealand / Australian healthcare context
	B	Evidence applicable to New Zealand / Australian healthcare context with few caveats
	C	Evidence probably applicable to New Zealand / Australian healthcare context with some caveats
	D	Evidence not applicable to New Zealand / 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 is based on a subset of data from trials that reported they included a proportion of women with a previous history of preterm birth. This level of evidence cannot be used to form a clinical recommendation

EVIDENCE STATEMENT MATRIX *(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	NA	Not applicable
2. Consistency	NA	Not applicable
3. Clinical Impact	NA	Not applicable
4. Generalisability	NA	Not applicable
5. Applicability	NA	Not applicable

Evidence statement
There was no evidence to contraindicate the use of antenatal corticosteroids in women with a previous history of preterm birth who are at current risk of preterm birth. For women whose only risk factor is previous history of preterm birth, there is no evidence of benefit.

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

Use a single course of antenatal corticosteroids in women with a history of a previous preterm birth and with an additional risk factor(s) for preterm birth.

Where appropriate, estimate the risk of preterm birth by considering the use of adjunct prediction tests including fetal fibronectin and assessment of cervical length.

OVERALL GRADE OF RECOMMENDATION	
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 recommendations(s) but care should be taken in its application
D	Body of evidence is weak and recommendation must be applied with caution
PP	**Practice Points**

UNRESOLVED ISSUES *(If needed, keep a 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 implementation of this recommendation?	**YES**
	NO

M13 GRADE Evidence summary

Considered Judgement - Strength of recommendation

What is the safety for the mother and fetus, infant, child, adult of administering a single course of antenatal corticosteroids to women with previous history of preterm birth?

1. Outcome measures:	Quality of evidence				Importance of outcome in making a decision		
Maternal Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O_1 Chorioamnionitis		✓			✓		
O_2 Puerperal sepsis			✓		✓		
O_3 Pyrexia after entry to trial				NR		✓	
O_4 Intrapartum fever requiring antibiotics				NR		✓	
O_5 Post natal pyrexia				NR		✓	
O_6 Maternal quality of life				NR	✓		
Infant Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O_1 Combined fetal and neonatal death				NR	✓		
O_2 Neonatal death	✓				✓		
O_3 Fetal death				NR	✓		
O_4 RDS	✓				✓		
O_5 Composite of serious outcomes for the infant				NR	✓		
O_6 Neurosensory disability (composite of impairments) for infant as a child				NR	✓		
O_7 Survival free of neurosensory disability for the infant as a child				NR	✓		
O_8 Survival free of metabolic disease for the infant as a child				NR		✓	
O_9 Neurosensory disability (composite of impairments) for infant as an adult				NR	✓		
O_{10} Survival free of neurosensory disability for the infant as an adult				NR	✓		
O_{11} Survival free of metabolic disease for the infant as an adult				NR		✓	

2. Is there is insufficient evidence to make a recommendation?

Evidence statement - Evidence is based on a subset of data from trials that reported they included a proportion of women with a previous history of preterm birth. This level of evidence cannot be used to form a clinical recommendation

Maternal - No randomised controlled trial evidence was identified for the prophylactic use of antenatal corticosteroids in women with a previous history of preterm labour being the only risk factor for preterm birth in the current pregnancy. The Roberts CPG version 2015 systematic review for a single course of antenatal corticosteroids included two trials that detailed the proportion of women with a previous history of preterm birth and reported on maternal outcomes. Overall treatment effects for a single course were compared with this subgroup of trials.

Infant - The Roberts CPG version 2015 systematic review for a single course of antenatal corticosteroids included three trials reporting infant outcomes that reported the proportion of women with a previous history of preterm birth. Overall treatment effects for a single course were compared with this subgroup of trials.

3. What benefit will the proposed intervention/action have?

Evidence statement	Quality of evidence
Maternal - As with the overall treatment effect, there was no increased risk of chorioamnionitis or puerperal sepsis for the mother exposed to a single course of antenatal corticosteroids from trials that included a proportion of women with a previous preterm birth. *Infant* - The beneficial effect of significant reductions in neonatal death and respiratory distress syndrome observed in the overall treatment effect, was not evident in the three trials that reported a proportion of women with a previous preterm birth.	**Not applicable**

Judging the benefits in context

Maternal - The evidence for maternal outcomes is based on two trials within the RobertsCPG version 2015 systematic review for a single course of antenatal corticosteroids that reported including a proportion of women with a previous preterm birth. There was some imprecision in the confidence intervals for puerperal sepsis.

Infant - The evidence for infant outcomes is based on three trials within the Roberts CPG version 2015 systematic review for a single course of antenatal corticosteroids that involved 493 infants.

4. What harm might the proposed intervention/action do?

Evidence statement	Quality of evidence
Maternal - There is no evidence of increased risk of chorioamnionitis or puerperal sepsis for the women with a previous preterm birth following exposure to a single course of antenatal corticosteroids. *Infant* - Although the beneficial effect for the infant of reduced neonatal mortality and respiratory distress syndrome, seen in the overall treatment effect is not present in the subgroup of trials that reported including proportion of women with a history of preterm birth, there is no increased risk of harm in this population.	**Not applicable**

Judging the harms in context

Maternal - The evidence for maternal outcomes is based on two trials that reported including a proportion of women with a previous preterm

birth. There was some imprecision in the confidence intervals for puerperal sepsis.
Infant - The evidence for infant outcomes is based on three trials that involved up to 493 infants.

5. What is the likely balance between good and harm?

Evidence statement	**Overall quality of evidence**
Maternal - There is a lack of evidence for the use of a prophylactic single course of antenatal corticosteroids in women whose only risk factor in the current pregnancy is a previous history of preterm birth. There are no clear health benefits for the mother, however there is no increased risk of chorioamnionitis or puerperal sepsis following a single course of antenatal corticosteroids in women with a history of preterm birth who are at risk of preterm birth in the current pregnancy. *Infant* - There is no increased risk of harm for infants of women with a history of preterm birth who were administered a single course of antenatal corticosteroids for risk of preterm birth in the current pregnancy.	**Not applicable**

Judging the balance of benefits and harms in context
There was no evidence to contraindicate the use of antenatal corticosteroids in women with a previous history of preterm birth who are at current risk of preterm birth. For women whose only risk factor is previous history of preterm birth, there is no evidence of benefit.

Benefits clearly outweigh harms	Recommend	STRONG
Benefits probably outweigh harms	Consider	CONDITIONAL
Not known	Make a recommendation for research (see 8 below)	**WEAK**
Benefits probably don't outweigh harms Harms probably outweigh benefits	Consider against/make no recommendation	CONDITIONAL
Benefits clearly don't outweigh harms Harms clearly outweigh benefits	Recommend against	STRONG

6. Is the intervention/action implementable in the New Zealand and Australian context?

Summary statement
Antenatal corticosteroids are already widely in use in New Zealand and Australia.

Yes	**Recommend/consider**
Not known	Consider economic evaluation
No	Recommend/consider against

7. Final recommendation

	Strength of recommendation
Use a single course of antenatal corticosteroids in women with a history of a previous preterm birth and with an additional risk factor(s) for preterm birth. Where appropriate, estimate the risk of preterm birth by considering the use of adjunct prediction tests including fetal fibronectin and assessment of cervical length..	**STRONG** **CONDITIONAL** **WEAK (Practice Point)**

8. Recommendations for research

- Any future randomised trials of a single course of antenatal corticosteroids should report on the risk factors for preterm birth of the included participants.

M14 Women with a previous history of preterm birth – Repeat antenatal corticosteroids

M14 NHMRC Evidence summary

What is the safety for the mother and fetus, infant, child, adult of administering a repeat course(s) of antenatal corticosteroids to women with a history of previous preterm birth?		
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Maternal No randomised controlled trial evidence was found for the use of prophylactic antenatal corticosteroids for women whose only risk factor for preterm birth in the current pregnancy is a history of previous preterm birth. However, as four trials in the Crowther (2011) Cochrane systematic review included a proportion of women who had a previous history of preterm birth, overall treatment effects were compared with this subgroup of trials. Infant No randomised controlled trial evidence was found for the use of prophylactic antenatal corticosteroids for women whose only risk factor for preterm birth in the current pregnancy is a history of previous preterm birth. However, as four trials in the Crowther (2011) Cochrane systematic review included a proportion of women who had a history of previous preterm birth, overall treatment effects were compared with this subgroup of trials.	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 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')*		
Maternal There was no evidence of increased risk of chorioamnionitis, post-natal pyrexia requiring treatment, or puerperal sepsis from the trials that reported the proportion of women in their trial with a previous history of preterm birth. Infant As per the overall treatment effect, there was no difference in neonatal death between exposure to repeat antenatal corticosteroids and no exposure in the trials that detailed the proportion of women with a previous history of preterm birth. There was a significant reduction in respiratory distress syndrome following exposure to repeat antenatal corticosteroids compared with no repeat exposure in the trials that reported including a proportion of women with a previous history of preterm birth.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is not consistent
	NA	Not applicable (one study only)
3. Clinical impact *(indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Maternal There is no difference in the risk of infection among the trials that reported including a proportion of women with a previous history of preterm birth. Infant There is a large amount of imprecision in the confidence intervals for fetal death among the subgroup of trials that are known to have included a proportion of women with a previous history of preterm birth. Although there was reduced risk of respiratory distress, there was no difference in composite serious outcome as observed in the overall treatment effect.	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?)*		
For women whose only risk factor in the current pregnancy is previous history of preterm birth, evidence from the overall treatment effect is not generalizable, however the evidence can sensibly be applied to women at current risk.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether sensible to apply
5. Applicability *(is the body of evidence relevant to the New Zealand / Australian healthcare context in terms of health services / delivery of care and cultural factors?)*		
The use of antenatal corticosteroids is applicable to this subgroup of women in New Zealand and Australia	A	Evidence directly applicable to New Zealand / Australian healthcare context
	B	Evidence applicable to New Zealand / Australian healthcare context with few caveats
	C	Evidence probably applicable to New Zealand / Australian healthcare context with some caveats
	D	Evidence not applicable to New Zealand / 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 is based on a subset of data from trials that reported they included a proportion of women with a previous history of preterm birth. This level of evidence cannot be used to form a clinical recommendation

EVIDENCE STATEMENT MATRIX *(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	NA	Not applicable
2. Consistency	NA	Not applicable
3. Clinical Impact	NA	Not applicable
4. Generalisability	NA	Not applicable
5. Applicability	NA	Not applicable

Evidence statement
There was no evidence to contraindicate the use of antenatal corticosteroids in women with a previous history of preterm birth who are at current risk of preterm birth. For women whose only risk factor is previous history of preterm birth, there is no evidence of benefit.

RECOMMENDATION *(What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible)*	**OVERALL GRADE OF RECOMMENDATION**	
Repeat antenatal corticosteroids for a woman with a history of preterm birth and with an additional risk factor(s) for preterm birth.	**A**	Body of evidence can be trusted to guide practice
	B	Body of evidence can be trusted to guide practice in most situations
Where appropriate, estimate the risk of preterm birth by considering the use of adjunct prediction tests including fetal fibronectin and assessment of cervical length.	**C**	Body of evidence provides some support for recommendations(s) but care should be taken in its application
	D	Body of evidence is weak and recommendation must be applied with caution
	PP	**Practice Points**

UNRESOLVED ISSUES *(If needed, keep a 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 implementation of this recommendation?	**YES**
	NO

M14 GRADE Evidence summary

Considered Judgement - Strength of recommendation

What is the safety for the mother and fetus, infant, child, adult of administering a repeat course(s) of antenatal corticosteroids to women with a history of previous preterm birth?

1. Outcome measures:	Quality of evidence				Importance of outcome in making a decision		
Maternal Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O_1 Chorioamnionitis	✓				✓		
O_2 Puerperal sepsis	✓				✓		
O_3 Pyrexia after entry to trial				NR		✓	
O_4 Intrapartum fever requiring antibiotics				NR		✓	
O_5 Post natal pyrexia		✓				✓	
O_6 Maternal quality of life				NR	✓		
Infant Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O_1 Combined fetal and neonatal death	✓				✓		
O_2 Neonatal death	✓				✓		
O_3 Fetal death			✓		✓		
O_4 RDS	✓				✓		
O_5 Composite of serious outcomes for the infant	✓				✓		
O_6 Neurosensory disability (composite of impairments) for infant as a child				NR	✓		
O_7 Survival free of neurosensory disability for the infant as a child				NR	✓		
O_8 Survival free of metabolic disease for the infant as a child				NR		✓	
O_9 Neurosensory disability (composite of impairments) for infant as an adult				NR	✓		
O_{10} Survival free of neurosensory disability for the infant as an adult				NR	✓		
O_{11} Survival free of metabolic disease for the infant as an adult				NR		✓	

2. Is there is insufficient evidence to make a recommendation?

Evidence statement - Evidence is based on a subset of data from trials that reported they included a proportion of women with a previous history of preterm birth. This level of evidence cannot be used to form a clinical recommendation

Maternal - No randomised controlled trial evidence was identified for the prophylactic use of antenatal corticosteroids in women with a previous history of preterm labour being the only risk factor for preterm birth in the current pregnancy. The Crowther (2011) Cochrane systematic review included four trials that detailed the proportion of women with a previous history of preterm birth and reported on maternal outcomes. Overall treatment effects for a repeat course were compared with this subgroup of trials.
Infant - The Crowther (2011) Cochrane systematic review included four trials reporting infant outcomes that reported the proportion of women with a previous history of preterm birth. Overall treatment effects for a repeat course were compared with this subgroup of trials.

3. What benefit will the proposed intervention/action have?

Evidence statement	Quality of evidence
Maternal - There was no increased risk of chorioamnionitis, postnatal pyrexia requiring treatment or puerperal sepsis in the mother from the trials that reported that a proportion of women in their trial had a previous preterm birth. *Infant* - In line with the overall treatment effect for a repeat course of antenatal corticosteroids, there was no difference for neonatal death between those exposed to a repeat course and those not exposed to a repeat course in the trials that detailed that a proportion of the women in their trial had a previous preterm birth. As observed for the overall treatment effect, there was a significant reduction in respiratory distress syndrome following exposure to a repeat course compared to no repeat course in the subgroup of trials that reported a proportion of women in their trial with a previous preterm birth.	**Not applicable**

Judging the benefits in context
Maternal - The evidence for maternal outcomes is based on four trials, involving up to 3339 women, included in the Crowther (2011) Cochrane systematic review that detailed the proportion of women with a previous preterm birth in their trial. The women had already received a single course of antenatal corticosteroids between 7 and 21 days prior and were at continued risk of preterm birth.
Infant - The evidence for infant outcomes is based on four trials, involving up to 3961 infants, included in the Crowther (2011) Cochrane systematic review that detailed the proportion of women with a previous preterm birth in their trial. The women had already received a single course of antenatal corticosteroids between 7 and 21 days prior and were at continued risk of preterm birth.

4. What harm might the proposed intervention/action do?

Evidence statement	Quality of evidence
Maternal - There is no evidence of increased risk of chorioamnionitis, postnatal pyrexia requiring treatment or puerperal sepsis in the mother from the trials that detailed the proportion of women in their trial with a previous preterm birth.	**Not applicable**

Infant - The beneficial effect of reduced composite serious outcome seen in the overall treatment effect does not exist in the subgroup of trials that reported a proportion of women with a previous preterm birth. However, there is no increase in harms.	

Judging the harms in context
Maternal - The evidence for maternal outcomes is based on four trials, involving up to 3339 women, included in the Crowther (2011) Cochrane systematic review that detailed the proportion of women with a previous preterm birth in their trial. The women had already received a single course of antenatal corticosteroids between 7 and 21 days prior and were at continued risk of preterm birth.
Infant - The evidence for infant outcomes is based on four trials, involving up to 3961 infants, included in the Crowther (2011) Cochrane systematic review that detailed the proportion of women with a previous preterm birth in their trial. The women had already received a single course of antenatal corticosteroids between 7 and 21 days prior and were at continued risk of preterm birth.

5. What is the likely balance between good and harm?

Evidence statement	**Overall quality of evidence**
Maternal - There is a lack of evidence for the use of a prophylactic repeat course of antenatal corticosteroids in women whose only risk factor in the current pregnancy is a previous history of preterm birth. There are no clear health benefits for the mother, however there is no increased risk of chorioamnionitis, postnatal pyrexia requiring treatment or puerperal sepsis following a repeat course of antenatal corticosteroids in women with a history of preterm birth who are at risk of preterm birth in the current pregnancy. *Infant* - There is a significant reduction in respiratory distress syndrome, and no increased risk of harm for infants of women with a history of preterm birth who were administered a single course of antenatal corticosteroids for risk of preterm birth in the current pregnancy.	**Not applicable**

Judging the balance of benefits and harms in context
There was no evidence to contraindicate the use of antenatal corticosteroids in women with a previous history of preterm birth who are at current risk of preterm birth. For women whose only risk factor is previous history of preterm birth, there is no evidence of benefit.

Benefits clearly outweigh harms	Recommend	STRONG
Benefits probably outweigh harms	Consider	CONDITIONAL
Not known	Make a recommendation for research (see 8 below)	**WEAK**
Benefits probably don't outweigh harms Harms probably outweigh benefits	Consider against/make no recommendation	CONDITIONAL
Benefits clearly don't outweigh harms Harms clearly outweigh benefits	Recommend against	STRONG

6. Is the intervention/action implementable in the New Zealand and Australian context?

Summary statement
Antenatal corticosteroids are already widely in use in New Zealand and Australia.

Yes	**Recommend/consider**
Not known	Consider economic evaluation
No	Recommend/consider against

7. Final recommendation

Repeat antenatal corticosteroids for a woman with a history of preterm birth and with an additional risk factor(s) for preterm birth. Where appropriate, estimate the risk of preterm birth by considering the use of adjunct prediction tests including fetal fibronectin and assessment of cervical length.	**Strength of recommendation** **STRONG** **CONDITIONAL** **WEAK (Practice Points)**

8. Recommendations for research

- Any future randomised trials of repeat antenatal corticosteroids should report on the risk factors for preterm birth of the included participants.

M15 Women in preterm labour – Single course of antenatal corticosteroids

M15 NHMRC Evidence summary

What is the safety for the mother and the fetus, infant, child, adult of administering a single course of antenatal steroids to women in preterm labour?		
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Seven trials reporting on maternal outcomes, and fifteen trials reporting on infant outcomes included in the Roberts CPG version 2015 systematic review for a single course of antenatal corticosteroids detailed the proportion of women who were in preterm labour with 74% of women being in spontaneous labour, where reported.	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 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')*		
All studies indicated that even an incomplete course could have potential benefit to the neonate.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is not consistent
	NA	Not applicable (one study only)
3. Clinical impact *(indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Maternal For the mother in spontaneous labour, an increased risk of puerperal sepsis following a single course of antenatal corticosteroids is suggested, although there is no evidence of an increased risk of chorioamnionitis, or pyrexia at trial entry, intrapartum pyrexia or postnatal pyrexia requiring treatment. Infant As with the overall treatment effects for exposure to a single course of antenatal corticosteroids compared with no antenatal corticosteroids, there were significant reductions in perinatal and neonatal death. Respiratory distress syndrome was reduced following a single course of antenatal corticosteroids compared with no antenatal corticosteroids.	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?)*		
Evidence is probably generalizable to the New Zealand and Australasian health setting.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether sensible to apply
5. Applicability *(is the body of evidence relevant to the New Zealand / Australian healthcare context in terms of health services / delivery of care and cultural factors?)*		
The evidence is relevant and applicable to the health care setting.	A	Evidence directly applicable to New Zealand / Australian healthcare context
	B	Evidence applicable to New Zealand / Australian healthcare context with few caveats
	C	Evidence probably applicable to New Zealand / Australian healthcare context with some caveats
	D	Evidence not applicable to New Zealand / 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 is based on a subset of data from trials that reported they included a proportion of women in preterm labour. This level of evidence cannot be used to form a clinical recommendation		
EVIDENCE STATEMENT MATRIX *(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	NA	Not applicable

2. Consistency	NA	Not applicable
3. Clinical Impact	NA	Not applicable
4. Generalisability	NA	Not applicable
5. Applicability	NA	Not applicable

Evidence statement

The evidence suggests that even an incomplete course of antenatal corticosteroids may have benefits to the neonate when the mother is in preterm labour.

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

Use a single course of antenatal corticosteroids in women in preterm labour.

Where appropriate, estimate the risk of preterm birth by considering the use of adjunct prediction tests including fetal fibronectin and assessment of cervical length.

Where appropriate, monitor women in preterm labour for signs of puerperal sepsis when antenatal corticosteroids have been given.

OVERALL GRADE OF RECOMMENDATION	
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 recommendations(s) but care should be taken in its application
D	Body of evidence is weak and recommendation must be applied with caution
PP	**Practice Points**

UNRESOLVED ISSUES *(If needed, keep a 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 implementation of this recommendation?	**YES**
	NO

M15 GRADE Evidence summary

Considered Judgement - Strength of recommendation

What is the safety for the mother and fetus, infant, child, adult of administering a single course of antenatal corticosteroids to women in preterm labour?

1. Outcome measures:	Quality of evidence				Importance of outcome in making a decision		
Maternal Outcomes	**HIGH**	**MOD**	**LOW**	**V. LOW**	**Critical**	**Important**	**Not Important**
O_1 Chorioamnionitis	✓				✓		
O_2 Puerperal sepsis		✓			✓		
O_3 Pyrexia after entry to trial		✓				✓	
O_4 Intrapartum fever requiring antibiotics		✓				✓	
O_5 Post natal pyrexia		✓				✓	
O_6 Maternal quality of life				NR	✓		
Infant Outcomes	**HIGH**	**MOD**	**LOW**	**V. LOW**	**Critical**	**Important**	**Not Important**
O_1 Combined fetal and neonatal death	✓				✓		
O_2 Neonatal death	✓				✓		
O_3 Fetal death		✓			✓		
O_4 RDS	✓				✓		
O_5 Composite of serious outcomes for the infant				NR	✓		
O_6 Neurosensory disability (composite of impairments) for infant as a child				NR	✓		
O_7 Survival free of neurosensory disability for the infant as a child				NR	✓		
O_8 Survival free of metabolic disease for the infant as a child				NR		✓	
O_9 Neurosensory disability (composite of impairments) for infant as an adult				NR	✓		
O_{10} Survival free of neurosensory disability for the infant as an adult				NR	✓		
O_{11} Survival free of metabolic disease for the infant as an adult				NR		✓	

2. Is there is insufficient evidence to make a recommendation?

Evidence statement - Evidence is based on a subset of data from trials that reported they included a proportion of women in preterm labour. This level of evidence cannot be used to form a clinical recommendation

Maternal – The Roberts CPG version 2015 systematic review for a single course of antenatal corticosteroids included thirteen trials that detailed the proportion of women in preterm labour, up to seven of which reported maternal outcomes and involved 1797 women. An average of 74% of women included in these trials were in spontaneous preterm labour. Overall treatment effects for a single course of antenatal corticosteroids were compared with this subgroup of trials that detailed the proportion of women included in their trial who were in spontaneous preterm labour.
Infant - The Roberts CPG version 2015 systematic review for a single course of antenatal corticosteroids included fifteen trials that detailed the proportion of women in preterm labour and reported on infant outcomes. These trials involved up to 3683 infants. Overall treatment effects for a single course of antenatal corticosteroids were compared with this subgroup of trials that detailed the proportion of women included in their trial who were in spontaneous preterm labour.

3. What benefit will the proposed intervention/action have?

Evidence statement	**Quality of evidence**
Maternal - There was no increased risk of chorioamnionitis, pyrexia after trial entry requiring treatment, intrapartum pyrexia requiring treatment or postnatal pyrexia requiring treatment in trials that detailed the included proportion of women in spontaneous preterm labour. This was in line with the overall treatment effect for a single course of antenatal corticosteroids. Our subgroup analysis did find an increased risk of puerperal sepsis among those women treated with antenatal corticosteroids when compared to no antenatal corticosteroids. *Infant* - Among women treated with a single course of antenatal corticosteroids in the trials that detailed the proportion of women in spontaneous preterm labour, there was no difference in fetal death, but significant reductions in perinatal and neonatal death, and respiratory distress syndrome for those exposed to a single course of antenatal corticosteroids compared to no exposure. This was in line with the overall treatment effect.	**Not applicable**

Judging the benefits in context
Maternal - The evidence is based on seven trials involving 1797 women who were in spontaneous preterm labour and received a single course of antenatal corticosteroids (or placebo).
Infant - The evidence is based on 15 trials involving 3683 infants who were exposed to a single course of antenatal corticosteroids and whose mothers were in spontaneous preterm labour.

4. What harm might the proposed intervention/action do?

Evidence statement	**Quality of evidence**
Maternal - There was an increased risk of puerperal sepsis among women treated with antenatal corticosteroids in trials that included a proportion of women in spontaneous preterm labour. *Infant* - There was no evidence of harms for the infant following exposure to a single course of antenatal	**Not applicable**

corticosteroids in the trials that reported including a proportion of women in spontaneous preterm labour.	

Judging the harms in context
Maternal - The evidence is based on seven trials involving 1797 women who were in spontaneous preterm labour and received a single course of antenatal corticosteroids (or placebo).
Infant - The evidence is based on 15 trials involving 3683 infants who were exposed to a single course of antenatal corticosteroids and whose mothers were in spontaneous preterm labour.

5. What is the likely balance between good and harm?

Evidence statement	**Overall quality of evidence**
Maternal - For the mother in spontaneous labour there is an increased risk in puerperal sepsis following a single course of antenatal corticosteroids although there is no evidence of an increased risk of chorioamnionitis, or pyrexia at trial entry, intrapartum pyrexia or postnatal pyrexia requiring treatment. *Infant* - As with the overall treatment effects for exposure to a single course of antenatal corticosteroids compared with no antenatal corticosteroids, there were significant reductions in perinatal and neonatal death. Respiratory distress syndrome was reduced in infants of women in preterm labour for a single course of antenatal corticosteroids compared with no antenatal corticosteroids.	**Not applicable**

Judging the balance of benefits and harms in context
Maternal - The evidence is based on seven trials involving 1797 women who were in spontaneous preterm labour and received a single course of antenatal corticosteroids (or placebo).
Infant - The evidence is based on 15 trials involving 3683 infants who were exposed to a single course of antenatal corticosteroids and whose mothers were in spontaneous preterm labour.

Benefits clearly outweigh harms	Recommend	STRONG
Benefits probably outweigh harms	Consider	CONDITIONAL
Not known	**Make a recommendation for research (see 8 below)**	**WEAK**
Benefits probably don't outweigh harms	Consider against/make no recommendation	CONDITIONAL
Harms probably outweigh benefits		
Benefits clearly don't outweigh harms	Recommend against	STRONG
Harms clearly outweigh benefits		

6. Is the intervention/action implementable in the New Zealand and Australian context?

Summary statement
Antenatal corticosteroids are already widely in use in New Zealand and Australia.

Yes	**Recommend/consider**
Not known	Consider economic evaluation
No	Recommend/consider against

7. Final recommendation

	Strength of recommendation
Use a single course of antenatal corticosteroids in women in preterm labour. Where appropriate, estimate the risk of preterm birth by considering the use of adjunct prediction tests including fetal fibronectin and assessment of cervical length. Where appropriate, monitor women in preterm labour for signs of puerperal sepsis when antenatal corticosteroids have been given.	**STRONG** **CONDITIONAL** **WEAK (Practice Points)**

8. Recommendations for research

M16 Women in preterm labour – Repeat course of antenatal corticosteroids

M16 NHMRC Evidence summary

What is the safety for the mother and the fetus, infant, child, adult of administering repeat dose(s) of antenatal steroids to women in preterm labour?		
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Six trials included in the Crowther (2011) Cochrane systematic review reported on maternal outcomes and detailed a proportion of women who were in preterm labour with 49% of women being in spontaneous labour, where reported. Eight trials included in the Crowther (2011) Cochrane systematic review reported on infant outcomes and detailed a proportion of women who were in preterm labour with 49% of women being in spontaneous labour, where reported	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 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')*		
All studies indicated that even an incomplete course could have potential benefit to the neonate.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is not consistent
	NA	Not applicable (one study only)
3. Clinical impact *(indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Maternal Following a repeat dose(s) of antenatal corticosteroids there is no evidence of an increased risk for any maternal infection (chorioamnionitis, pyrexia at trial entry, intrapartum pyrexia or postnatal pyrexia requiring treatment, puerperal sepsis). Infant There were no differences between repeat and no repeat antenatal corticosteroids for infant mortality in trials that reported a proportion of women in preterm labour. Respiratory distress syndrome was reduced following a repeat dose(s) of antenatal corticosteroids compared with no repeat exposure. There was a significant reduction in a composite of serious infant outcomes following a repeat dose(s) of antenatal corticosteroids compared with no repeat exposure.	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?)*		
Evidence is probably generalizable to the New Zealand and Australasian health setting	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether sensible to apply
5. Applicability *(is the body of evidence relevant to the New Zealand / Australian healthcare context in terms of health services / delivery of care and cultural factors?)*		
The evidence is relevant and applicable to the health care setting.	A	Evidence directly applicable to New Zealand / Australian healthcare context
	B	Evidence applicable to New Zealand / Australian healthcare context with few caveats
	C	Evidence probably applicable to New Zealand / Australian healthcare context with some caveats
	D	Evidence not applicable to New Zealand / 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 is based on a subset of data from trials that reported they included a proportion of women in preterm labour. This level of evidence cannot be used to form a clinical recommendation		
EVIDENCE STATEMENT MATRIX *(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	NA	Not applicable
2. Consistency	NA	Not applicable
3. Clinical Impact	NA	Not applicable
4. Generalisability	NA	Not applicable
5. Applicability	NA	Not applicable

Evidence statement The evidence suggests that even an incomplete course of antenatal corticosteroids may have benefits to the neonate when the mother is in preterm labour.		
RECOMMENDATION *(What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible)*	**OVERALL GRADE OF RECOMMENDATION**	
Repeat antenatal corticosteroids for a woman in preterm labour. Where appropriate, estimate the risk of preterm birth by considering the use of adjunct prediction tests including fetal fibronectin and assessment of cervical length.	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 recommendations(s) but care should be taken in its application
	D	Body of evidence is weak and recommendation must be applied with caution
	PP	**Practice Points**
UNRESOLVED ISSUES *(If needed, keep a 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 implementation of this recommendation?	**YES**	
	NO	

M16 GRADE Evidence summary

Considered Judgement - Strength of recommendation

What is the safety for the mother and fetus, infant, child, adult of administering repeat dose(s) of antenatal corticosteroids to women in preterm labour?

1. Outcome measures:	Quality of evidence				Importance of outcome in making a decision		
Maternal Outcomes	**HIGH**	**MOD**	**LOW**	**V. LOW**	**Critical**	**Important**	**Not Important**
O_1 Chorioamnionitis	✓				✓		
O_2 Puerperal sepsis	✓				✓		
O_3 Pyrexia after entry to trial				NR		✓	
O_4 Intrapartum fever requiring antibiotics				NR		✓	
O_5 Post natal pyrexia	✓					✓	
O_6 Maternal quality of life				NR	✓		
Infant Outcomes	**HIGH**	**MOD**	**LOW**	**V. LOW**	**Critical**	**Important**	**Not Important**
O_1 Combined fetal and neonatal death	✓				✓		
O_2 Neonatal death	✓				✓		
O_3 Fetal death		✓			✓		
O_4 RDS	✓				✓		
O_5 Composite of serious outcomes for the infant	✓				✓		
O_6 Neurosensory disability (composite of impairments) for infant as a child				NR	✓		
O_7 Survival free of neurosensory disability for the infant as a child				NR	✓		
O_8 Survival free of metabolic disease for the infant as a child				NR		✓	
O_9 Neurosensory disability (composite of impairments) for infant as an adult				NR	✓		
O_{10} Survival free of neurosensory disability for the infant as an adult				NR	✓		
O_{11} Survival free of metabolic disease for the infant as an adult				NR		✓	

2. Is there is insufficient evidence to make a recommendation?

Evidence statement - Evidence is based on a subset of data from trials that reported they included a proportion of women in preterm labour. This level of evidence cannot be used to form a clinical recommendation

Maternal - Six trials included in the Crowther (2011) Cochrane systematic review reported on maternal outcomes and included a proportion of women who were in preterm labour with 49% of women being in spontaneous labour, where reported.
Infant - Eight trials included in the Crowther (2011) Cochrane systematic review included a proportion of women who were in preterm labour with 49% of women being in spontaneous labour, and reported on maternal outcomes.

3. What benefit will the proposed intervention/action have?

Evidence statement	**Quality of evidence**
Maternal. -Following a repeat dose(s) of antenatal corticosteroids there is no evidence of an increased risk for any maternal infection (chorioamnionitis, pyrexia at trial entry, intrapartum pyrexia or postnatal pyrexia requiring treatment, puerperal sepsis). *Infant* - There were no differences between repeat and no repeat antenatal corticosteroids for infant mortality in trials that reported a proportion of women in preterm labour. Respiratory distress syndrome was reduced following a repeat dose(s) of antenatal corticosteroids compared with no repeat exposure. There was a significant reduction in a composite of serious infant outcomes following a repeat dose(s) of antenatal corticosteroids compared with no repeat exposure.	**Not applicable**

Judging the benefits in context
Maternal - Evidence is based on six well conducted trials involving up to 4261 women, and is generalizable to the target population and applicable to the New Zealand and Australian health care setting.
Infant - Evidence is based on eight well conducted trials involving up to 5228 infants, generalizable to the target population and applicable to the New Zealand and Australian health care setting.

4. What harm might the proposed intervention/action do?

Evidence statement	**Quality of evidence**
Maternal - There is no evidence of any increased risk of maternal infection (chorioamnionitis, pyrexia at trial entry, intrapartum pyrexia or postnatal pyrexia requiring treatment, puerperal sepsis) following exposure to a repeat dose(s) of antenatal corticosteroids. *Infant* - The evidence demonstrated significant reductions in risk of a number of important clinical outcomes. No evidence of harm was identified.	**Not applicable**

Judging the harms in context
Maternal - Evidence is based on six well conducted trials involving up to 4261 women, and is generalizable to the target population and applicable to the New Zealand and Australian health care setting.

Infant - Evidence is based on eight well conducted trials involving up to 5228 infants, generalizable to the target population and applicable to the New Zealand and Australian health care setting.
5. What is the likely balance between good and harm?

Evidence statement	**Overall quality of evidence**
Maternal - Following a repeat dose(s) of antenatal corticosteroids there is no evidence of an increased risk for any maternal infection (chorioamnionitis, pyrexia at trial entry, intrapartum pyrexia or postnatal pyrexia requiring treatment, puerperal sepsis). *Infant* - There were no differences between repeat and no repeat antenatal corticosteroids for infant mortality in trials that reported a proportion of women in preterm labour. Respiratory distress syndrome was reduced in women in preterm labour for a repeat dose(s) of antenatal corticosteroids compared with no repeat exposure. There was a significant reduction in a composite of serious infant outcomes following a repeat dose(s) of antenatal corticosteroids compared with no repeat exposure in women in preterm labour.	**Not applicable**

Judging the balance of benefits and harms in context
Maternal - No evidence of harm or benefit to the mother.
Infant - No evidence of harm for the infant and clear evidence of benefit.

Benefits clearly outweigh harms	Recommend	STRONG
Benefits probably outweigh harms	Consider	CONDITIONAL
Not known	**Make a recommendation for research (see 8 below)**	**WEAK**
Benefits probably don't outweigh harms	Consider against/make no recommendation	CONDITIONAL
Harms probably outweigh benefits		
Benefits clearly don't outweigh harms	Recommend against	STRONG
Harms clearly outweigh benefits		

6. Is the intervention/action implementable in the New Zealand and Australian context?

Summary statement
Antenatal corticosteroids are already widely in use in New Zealand and Australia.

Yes	**Recommend/consider**
Not known	Consider economic evaluation
No	Recommend/consider against

7. Final recommendation

	Strength of recommendation
Repeat antenatal corticosteroids for a woman in preterm labour. Where appropriate, estimate the risk of preterm birth by considering the use of adjunct prediction tests including fetal fibronectin and assessment of cervical length.	**STRONG** **CONDITIONAL** **WEAK (Practice points)**

8. Recommendations for research

M17 Women with preterm prelabour rupture of membranes – Single course of antenatal corticosteroids

M17 NHMRC Evidence summary

What is the safety for the mother and fetus, infant, child, adult of administering a single course of antenatal corticosteroids to women with preterm prelabour rupture of membranes (at trial entry) at risk of preterm birth?		
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Maternal The evidence for maternal infection is based the Roberts CPG version 2015 systematic review for a single course of antenatal corticosteroids that included sixteen trials that reported including a proportion of women with preterm prelabour rupture of membranes at trial entry, and seven trials that only included women with preterm prelabour rupture of membranes at trial entry. Infant The evidence for infant outcomes is based on the Roberts CPG version 2015 systematic review for a single course of antenatal corticosteroids that included sixteen trials that reported including a proportion of women with preterm prelabour rupture of membranes at trial entry, and seven trials that only included women with preterm prelabour rupture of membranes at trial entry.	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 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')*		
Maternal There was no difference seen for chorioamnionitis, intrapartum pyrexia, postnatal pyrexia and puerperal sepsis with treatment effects similar to the overall treatment effect, among trials that reported including a proportion of women with preterm prelabour rupture of membranes. Infant Among trials that reported including a proportion of women with preterm prelabour rupture of membranes, treatment effects for perinatal death, neonatal death, respiratory distress syndrome and moderate/severe respiratory distress syndrome were similar to the overall effect and the difference was statistically significant for infants exposed to a single course of antenatal corticosteroids compared with no exposure.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is not consistent
	NA	Not applicable (one study only)
3. Clinical impact *(indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Maternal The benefit of improved infant outcomes probably outweighs any potential risk of maternal infection. Infant High quality evidence with large effect sizes that demonstrate significant reductions in measures of mortality, and respiratory distress syndrome from trials that reported including a proportion of women with preterm prelabour rupture of membranes. There was a lack of statistical effect for those trials that only included women with preterm prelabour rupture of membranes, and this is probably due to the small number of babies.	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?)*		
Evidence from a variety of healthcare settings. Studies conducted in USA, France, Australia, New Zealand.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether sensible to apply
5. Applicability *(is the body of evidence relevant to the New Zealand / Australian healthcare context in terms of health services / delivery of care and cultural factors?)*		
Corticosteroids are readily available in Australia and New Zealand and their use is feasible.	A	Evidence directly applicable to New Zealand / Australian healthcare context
	B	Evidence applicable to New Zealand / Australian healthcare context with few caveats
	C	Evidence probably applicable to New Zealand / Australian healthcare context with some caveats
	D	Evidence not applicable to New Zealand / 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 *(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	NA	Not applicable
2. Consistency	NA	Not applicable
3. Clinical Impact	NA	Not applicable
4. Generalisability	NA	Not applicable
5. Applicability	NA	Not applicable

Evidence statement

Evidence is based on a subset of data from trials that reported they included a proportion of women with preterm prelabour rupture of membranes. This level of evidence cannot be used to form a clinical recommendation

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

Use a single course of antenatal corticosteroids for women with preterm prelabour rupture of membranes.

OVERALL GRADE OF RECOMMENDATION	
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 recommendations(s) but care should be taken in its application
D	Body of evidence is weak and recommendation must be applied with caution
PP	**Practice Point**

UNRESOLVED ISSUES *(If needed, keep a 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 implementation of this recommendation?	**YES**
	NO

M17 GRADE Evidence summary

Considered Judgement - Strength of recommendation

What is the safety for the mother and fetus, infant, child, adult of administering a single course of antenatal corticosteroids to women with preterm prelabour rupture of membranes (at trial entry) at risk of preterm birth?

1. Outcome measures:	Quality of evidence				Importance of outcome in making a decision		
Maternal Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O_1 Chorioamnionitis				NR	✓		
O_2 Puerperal sepsis		✓			✓		
O_3 Pyrexia after entry to trial		✓				✓	
O_4 Intrapartum fever requiring antibiotics				NR		✓	
O_5 Post natal pyrexia		✓				✓	
O_6 Maternal quality of life				NR	✓		
Infant Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O_1 Combined fetal and neonatal death	✓				✓		
O_2 Neonatal death	✓				✓		
O_3 Fetal death	✓				✓		
O_4 RDS		✓			✓		
O_5 Composite of serious outcomes for the infant				NR	✓		
O_6 Neurosensory disability (composite of impairments) for infant as a child				NR	✓		
O_7 Survival free of neurosensory disability for the infant as a child				NR	✓		
O_8 Survival free of metabolic disease for the infant as a child				NR		✓	
O_9 Neurosensory disability (composite of impairments) for infant as an adult				NR	✓		
O_{10} Survival free of neurosensory disability for the infant as an adult				NR	✓		
O_{11} Survival free of metabolic disease for the infant as an adult				NR		✓	

2. Is there is insufficient evidence to make a recommendation?

Evidence statement - Evidence is based on a subset of data from trials that reported they included a proportion of women with preterm prelabour rupture of membranes. This level of evidence cannot be used to form a clinical recommendation

Maternal - The evidence for maternal infection is based on the Roberts CPG version 2015 systematic review for a single course of antenatal corticosteroids that included sixteen trials that reported including a proportion of women with preterm prelabour rupture of membranes at trial entry. Five trials involving 596 women reported on puerperal sepsis, of which one trial of 204 women specified preterm prelabour rupture of membranes as entry criteria. Three trials involving 987 women reported on postnatal pyrexia, of which one trial of 204 women specified preterm prelabour rupture of membranes as entry criteria, and two trials of 145 women reported on fever after trial entry requiring antibiotics, one of which specified preterm prelabour rupture of membranes as entry criteria. It should be noted that where the demographics of the populations were described up to 70% of women recruited in the single course of antenatal corticosteroid trials had preterm prelabour rupture of membranes.
Infant - The evidence for infant outcomes is based on the Roberts CPG version 2015 systematic review for a single course of antenatal corticosteroids that included sixteen trials that reported including a proportion of women with preterm prelabour rupture of membranes at trial entry. Eight trials involving 2748 infants reported on perinatal mortality, of which two trials of 253 infants specified preterm prelabour rupture of membranes as entry criteria. Eight trials involving 2748 infants reported on fetal death, of which two trials of 253 infants specified preterm prelabour rupture of membranes as entry criteria. Fourteen trials involving 3348 infants reported on neonatal death, of which five trials involving 501 infants specified preterm prelabour rupture of membranes as entry criteria, and sixteen trials of 3348 infants reported on respiratory distress syndrome, seven of which specified preterm prelabour rupture of membranes as entry criteria.

3. What benefit will the proposed intervention/action have?

Evidence statement	Quality of evidence
Maternal - The evidence does not indicate direct benefits to the mother. There is no evidence of an increased risk of maternal infection requiring treatment as a result of exposure to antenatal corticosteroids. *Infant* - There is evidence of a significant reduction (38%) in combined fetal, neonatal and later death, and a significant reduction (39%) in neonatal death following exposure to antenatal corticosteroids in the presence of ruptured membranes > 24 hours.	**Not applicable**

Judging the benefits in context

The evidence is based overall on well designed and conducted randomised controlled trials. All the women included in the subgroup "Preterm prelabour rupture of membranes at trial entry" had rupture of membranes confirmed by sterile speculum examination. The populations included women from South Africa, United States, New Zealand and Jordan.

4. What harm might the proposed intervention/action do?	
Evidence statement *Maternal* - There was no evidence of harm to the mother in terms of increased risk of maternal infection outcomes where reported *Infant* - There was no evidence of harm to the infant. Exposure to antenatal corticosteroids was associated with a reduction in risk of a number of important clinical outcomes such as fetal, neonatal or later death, and respiratory distress syndrome.	**Quality of evidence** **Not applicable**
Judging the harms in context *Maternal* - The evidence is direct evidence from trials that involved women with confirmed rupture of membranes. There was no indication of significant harms to the mother *Infant* - The evidence is direct evidence from trials that involved women with confirmed rupture of membranes. There was no indication of significant harms to the infant.	

5. What is the likely balance between good and harm?	
Evidence statement *Maternal* - The evidence suggests no increased risk of harms for the mother when treated with antenatal corticosteroids in the presence of ruptured membranes. *Infant* - The evidence suggests clear benefits for the infant of reduced risk of fetal, neonatal and later death, and respiratory distress syndrome, with no increased risk of harms when exposed to antenatal corticosteroids in the presence of ruptured membranes.	**Overall quality of evidence** **Not applicable**
Judging the balance of benefits and harms in context *Maternal* - The benefits to the infant are significant with no obvious health harms to the mother *Infant* - The benefits to the infant are significant with no evidence of health harms.	

Benefits clearly outweigh harms	Recommend	STRONG
Benefits probably outweigh harms	Consider	CONDITIONAL
Not known	**Make a recommendation for research (see 8 below)**	**WEAK**
Benefits probably don't outweigh harms	Consider against/make no recommendation	CONDITIONAL
Harms probably outweigh benefits		
Benefits clearly don't outweigh harms	Recommend against	STRONG
Harms clearly outweigh benefits		

6. Is the intervention/action implementable in the New Zealand and Australian context?	
Summary statement Antenatal corticosteroids are already widely in use in New Zealand and Australia.	
Yes	**Recommend/consider**
Not known	Consider economic evaluation
No	Recommend/consider against

7. Final recommendation	
Use a single course of antenatal corticosteroids for women with preterm prelabour rupture of membranes.	**Strength of recommendation** **STRONG** **CONDITIONAL** **WEAK (Practice Point)**

8. Recommendations for research

M18 Women with preterm prelabour rupture of membranes – Repeat antenatal corticosteroids

M18 NHMRC Evidence summary

What is the safety for the mother and fetus, infant, child, adult of administering repeat antenatal corticosteroids to women with preterm prelabour rupture of membranes (at trial entry) at risk of preterm birth?		
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Maternal The evidence for maternal infection is based on a systematic review (Crowther, 2011) that included six trials that reported including a proportion of women with preterm prelabour rupture of membranes at trial entry. Infant The evidence for infant outcomes is based on a systematic review (Crowther, 2011) that included six trials that reported including a proportion of women with preterm prelabour rupture of membranes at trial entry.	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 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')*		
Maternal There was no difference seen for chorioamnionitis, postnatal pyrexia and puerperal sepsis with treatment effects similar to the overall treatment effect and no difference between groups, among trials that reported including a proportion of women with preterm prelabour rupture of membranes. Infant Among trials that reported including a proportion of women with preterm prelabour rupture of membranes, treatment effects for perinatal, fetal and neonatal death and a composite of serious infant outcomes were similar to the overall effect with no significant differences between groups. For respiratory distress syndrome, the treatment effect was similar to the overall effect and there was a significant reduction in risk for infants exposed to repeat antenatal corticosteroids compared with no exposure.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is not consistent
	NA	Not applicable (one study only)
3. Clinical impact *(indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Maternal The benefit of improved infant outcomes probably outweighs any potential risk of maternal infection. Infant High quality evidence with large effect sizes that demonstrates a significant reduction in risk of respiratory distress syndrome from trials that reported including a proportion of women with preterm prelabour rupture of membranes.	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?)*		
Evidence from a variety of healthcare settings. Studies conducted in USA, France, Australia, New Zealand.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether sensible to apply
5. Applicability *(is the body of evidence relevant to the New Zealand / Australian healthcare context in terms of health services / delivery of care and cultural factors?)*		
Corticosteroids are readily available in Australia and New Zealand and their use is feasible.	A	Evidence directly applicable to New Zealand / Australian healthcare context
	B	Evidence applicable to New Zealand / Australian healthcare context with few caveats
	C	Evidence probably applicable to New Zealand / Australian healthcare context with some caveats
	D	Evidence not applicable to New Zealand / 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 *(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	NA	Not applicable
2. Consistency	NA	Not applicable
3. Clinical Impact	NA	Not applicable
4. Generalisability	NA	Not applicable
5. Applicability	NA	Not applicable

Evidence statement

Evidence is based on a subset of data from trials that reported they included a proportion of women with preterm prelabour rupture of membranes. This level of evidence cannot be used to form a clinical recommendation

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

Repeat antenatal corticosteroids for a woman with preterm prelabour rupture of membranes.

OVERALL GRADE OF RECOMMENDATION	
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 recommendations(s) but care should be taken in its application
D	Body of evidence is weak and recommendation must be applied with caution
PP	**Practice Point**

UNRESOLVED ISSUES *(If needed, keep a 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 implementation of this recommendation?	**YES**
	NO

M18 GRADE Evidence summary

Considered Judgement - Strength of recommendation

What is the safety for the mother and fetus, infant, child, adult of administering a repeat course(s) of antenatal corticosteroids to women with preterm prelabour rupture of membranes (at trial entry) at risk of preterm birth?

1. Outcome measures:	Quality of evidence				Importance of outcome in making a decision		
Maternal Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O_1 Chorioamnionitis	✓				✓		
O_2 Puerperal sepsis	✓				✓		
O_3 Pyrexia after entry to trial				NR		✓	
O_4 Intrapartum fever requiring antibiotics				NR		✓	
O_5 Post natal pyrexia	✓					✓	
O_6 Maternal quality of life				NR	✓		
Infant Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O_1 Combined fetal and neonatal death	✓				✓		
O_2 Neonatal death	✓				✓		
O_3 Fetal death		✓			✓		
O_4 RDS	✓				✓		
O_5 Composite of serious outcomes for the infant	✓				✓		
O_6 Neurosensory disability (composite of impairments) for infant as a child				NR	✓		
O_7 Survival free of neurosensory disability for the infant as a child				NR	✓		
O_8 Survival free of metabolic disease for the infant as a child				NR		✓	
O_9 Neurosensory disability (composite of impairments) for infant as an adult				NR	✓		
O_{10} Survival free of neurosensory disability for the infant as an adult				NR	✓		
O_{11} Survival free of metabolic disease for the infant as an adult				NR		✓	

2. Is there is insufficient evidence to make a recommendation?

Evidence statement - Evidence is based on a subset of data from trials that reported they included a proportion of women with preterm prelabour rupture of membranes. This level of evidence cannot be used to form a clinical recommendation

Maternal - The evidence for chorioamnionitis is based on four trials involving 3332 women included in the Crowther (2011) Cochrane Systematic Review that reported the proportion of the women recruited with preterm prelabour rupture of membranes. Similarly, the evidence for postnatal pyrexia requiring treatment and puerperal sepsis is based on one trial involving 982 women, and four trials involving 2599 women respectively, included in the Crowther (2011) Cochrane systematic review that reported a proportion of women recruited with preterm prelabour rupture of membranes. There was no evidence for the other outcomes of pyrexia after trial entry, intrapartum fever requiring antibiotics, and maternal quality of life.
Infant - The evidence for infant outcomes is based on up to 6 trials involving 4406 infants included in the Crowther (2011) Cochrane systematic review that reported the proportion of women recruited with preterm prelabour rupture of membranes.

3. What benefit will the proposed intervention/action have?

Evidence statement	Quality of evidence
Maternal - There is no evidence of increased risk of chorioamnionitis, postnatal pyrexia requiring treatment or puerperal sepsis following exposure to a repeat course of antenatal corticosteroid in trials where a proportion of the women recruited had preterm prelabour rupture of membranes. *Infant* - There is evidence of a significant reduction in respiratory distress syndrome in infants exposed to a repeat course of antenatal corticosteroids compared with no repeat exposure in trials where a proportion of the women had preterm prelabour rupture of membranes at trial entry.	**Not applicable**

Judging the benefits in context
The evidence is based on well conducted randomised controlled trials that recruited women at continued risk of preterm birth following an initial course of antenatal corticosteroids, and reported the proportion of women with preterm, prelabour rupture of membranes at trial entry. The populations included women from Canada, Australia and New Zealand, The United States and Finland.

4. What harm might the proposed intervention/action do?

Evidence statement	Quality of evidence
Maternal - There was no evidence of harm to the mother in terms of increased risk of maternal infection outcomes, where reported. *Infant* - There was no evidence of harm to the infant. There was no difference in risk of mortality, or composite serious outcome among those infants with repeat exposure to antenatal corticosteroids compared with no repeat exposure in trials were a proportion of women recruited had preterm prelabour rupture of membranes.	**Not applicable**

Judging the harms in context The evidence is direct evidence from randomised controlled trials that reported the proportion of women with preterm prelabour rupture of membranes. There was no evidence of increased risk of maternal infection, or increased risk of mortality for the infant.	
5. What is the likely balance between good and harm?	
Evidence statement *Maternal* - The evidence suggests no increased risk of harm for the mother when treated with repeat antenatal corticosteroids in the presence of preterm prelabour rupture of membranes. *Infant* - There is clear benefit for the infant of significantly reduced risk of respiratory distress syndrome, with no increased risk of mortality, when exposed to repeat antenatal corticosteroids in the presence of preterm prelabour rupture of membranes.	**Overall quality of evidence** **Not applicable**

Judging the balance of benefits and harms in context *Maternal* - Repeat antenatal corticosteroids in the presence of preterm prelabour rupture of membranes are unlikely to cause harm to the mother. *Infant* - Repeat antenatal corticosteroids in the presence of preterm prelabour rupture of membranes are unlikely to cause harm to the infant. The impact of the benefit of reduced risk of respiratory distress syndrome is high.		
Benefits clearly outweigh harms	Recommend	STRONG
Benefits probably outweigh harms	Consider	CONDITIONAL
Not known	**Make a recommendation for research (see 8 below)**	**WEAK**
Benefits probably don't outweigh harms	Consider against/make no recommendation	CONDITIONAL
Harms probably outweigh benefits		
Benefits clearly don't outweigh harms	Recommend against	STRONG
Harms clearly outweigh benefits		

6. Is the intervention/action implementable in the New Zealand context?	
Summary statement Antenatal corticosteroids are already widely in use in New Zealand and Australia.	
Yes	**Recommend/consider**
Not known	Consider economic evaluation
No	Recommend/consider against

7. Final recommendation	
Repeat antenatal corticosteroids for a woman with preterm prelabour rupture of membranes.	**Strength of recommendation** **STRONG** **CONDITIONAL** **WEAK (Practice Points)**
8. Recommendations for research	

M19 Women with chorioamnionitis at risk of preterm birth – Single course of antenatal corticosteroids

M19 NHMRC Evidence summary

What is the safety for the mother and fetus, infant, child, adult of administering a single course of antenatal corticosteroids to women with chorioamnionitis at risk of preterm birth?		
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Four trials included in the Roberts CPG version 2015 systematic review for a single course of antenatal corticosteroids recruited a proportion of women with chorioamnionitis in their trial (at trial entry), and three of the trials reported on the proportion of women subsequently diagnosed with chorioamnionitis. Women with chorioamnionitis were not eligible for 14 of the 26 trials included in the CPG 2015 version, and no details were provided for the remaining eight trials.	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 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')*		
Maternal Results for trials that recruited and reported on a proportion of women with chorioamnionitis are consistent with the overall treatment effect of a single course of antenatal corticosteroids, however the treatment effect tended toward increased risk. Two trials reported on puerperal sepsis and found a significantly increased risk. Both these trials used dexamethasone as the antenatal corticosteroid. There was no difference in risk of postnatal pyrexia. Infant Results were consistent that infants of women with chorioamnionitis at trial entry exposed to a single course of antenatal corticosteroids had significantly reduced risk of perinatal and neonatal death. There was no difference in the risk of fetal death. There was also a significant reduction in respiratory distress syndrome among infants of women with chorioamnionitis who were exposed to antenatal corticosteroids, similar to the overall treatment effect.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is not consistent
	NA	Not applicable (one study only)
3. Clinical impact *(indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Maternal The benefit of reductions in risk of perinatal and neonatal death, and respiratory distress syndrome probably outweigh the increased risk of maternal infection. Infant Significant reductions in absolute risk of perinatal death and neonatal death, and significant reduction in absolute risk of respiratory distress syndrome, were seen in favour of a single course of antenatal corticosteroids compared with no antenatal corticosteroids in.	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?)*		
Evidence from a variety of healthcare settings. Studies conducted in USA, France, Australia, and The Netherlands.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether sensible to apply
5. Applicability *(is the body of evidence relevant to the New Zealand / Australian healthcare context in terms of health services / delivery of care and cultural factors?)*		
Corticosteroids are readily available in Australia and New Zealand and their use is feasible.	A	Evidence directly applicable to New Zealand / Australian healthcare context
	B	Evidence applicable to New Zealand / Australian healthcare context with few caveats
	C	Evidence probably applicable to New Zealand / Australian healthcare context with some caveats
	D	Evidence not applicable to New Zealand / 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 *(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	NA	Not applicable
2. Consistency	NA	Not applicable
3. Clinical Impact	NA	Not applicable
4. Generalisability	NA	Not applicable
5. Applicability	NA	Not applicable
Evidence statement **Evidence is based on a subset of data from trials that reported they included a proportion of women with chorioamnionitis. This level of evidence cannot be used to form a clinical recommendation**		

RECOMMENDATION *(What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible)*	**OVERALL GRADE OF RECOMMENDATION**	
Use a single course of antenatal corticosteroids for women with chorioamnionitis at risk of preterm birth. Do not delay birth in women with chorioamnionitis to administer a single course of antenatal corticosteroids. Where appropriate, monitor women with chorioamnionitis for signs of puerperal sepsis when antenatal corticosteroids have been given.	**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 recommendations(s) but care should be taken in its application
	D	Body of evidence is weak and recommendation must be applied with caution
	PP	**Practice Points**

UNRESOLVED ISSUES *(If needed, keep a 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 implementation of this recommendation?	**YES**
	NO

M19 GRADE Evidence summary

Considered Judgement - Strength of recommendation							
What is the safety for the mother and fetus, infant, child, adult of administering a single course of antenatal corticosteroids to women with chorioamnionitis at risk of preterm birth?							
1. Outcome measures:	**Quality of evidence**				**Importance of outcome in making a decision**		
Maternal Outcomes	**HIGH**	**MOD**	**LOW**	**V. LOW**	**Critical**	**Important**	**Not Important**
O_1 Chorioamnionitis	✓				✓		
O_2 Puerperal sepsis		✓			✓		
O_3 Pyrexia after entry to trial				NR		✓	
O_4 Intrapartum fever requiring antibiotics				NR		✓	
O_5 Post natal pyrexia		✓				✓	
O_6 Maternal quality of life				NR	✓		
Infant Outcomes	**HIGH**	**MOD**	**LOW**	**V. LOW**	**Critical**	**Important**	**Not Important**
O_1 Combined fetal and neonatal death		✓			✓		
O_2 Neonatal death		✓			✓		
O_3 Fetal death			✓		✓		
O_4 RDS		✓			✓		
O_5 Composite of serious outcomes for the infant				NR	✓		
O_6 Neurosensory disability (composite of impairments) for infant as a child				NR	✓		
O_7 Survival free of neurosensory disability for the infant as a child				NR	✓		
O_8 Survival free of metabolic disease for the infant as a child				NR		✓	
O_9 Neurosensory disability (composite of impairments) for infant as an adult				NR	✓		
O_{10} Survival free of neurosensory disability for the infant as an adult				NR	✓		
O_{11} Survival free of metabolic disease for the infant as an adult				NR		✓	

2. Is there is insufficient evidence to make a recommendation?

Evidence statement - Evidence is based on a subset of data from trials that reported they included a proportion of women with chorioamnionitis. This level of evidence cannot be used to form a clinical recommendation.

Maternal - The evidence for chorioamnionitis as an outcome is based on four trials, involving 356 women, included in the Roberts CPG version 2015 systematic review for a single course of antenatal corticosteroids, which reported recruiting a proportion of women with chorioamnionitis at trial entry. The evidence for puerperal sepsis is based on two trials involving 214 women, and the evidence for postnatal pyrexia is based on one trial involving 118 women, included in the Roberts CPG version 2015 systematic review for a single course of antenatal corticosteroids. No data are reported for other maternal infectious morbidity outcomes or maternal quality of life.
Infant - The evidence for infant mortality is based on trials included in the Roberts CPG version 2015 systematic review for a single course of antenatal corticosteroids that recruited and reported a proportion of women with chorioamnionitis at trial entry. One trial involving 139 infants reported on fetal death and perinatal death, three trials involving 362 infants reported on neonatal death, and three trials involving 386 infants reported on respiratory distress syndrome following exposure to a single course of antenatal corticosteroids.

3. What benefit will the proposed intervention/action have?

Evidence statement	**Quality of evidence**
Maternal - The evidence suggests no difference in chorioamnionitis or postnatal pyrexia requiring treatment for women who received a single course of antenatal corticosteroids compared with no antenatal corticosteroids at trial entry. *Infant* - Significant reductions in the risk of perinatal and neonatal death following exposure to a single course of antenatal corticosteroids, compared with no exposure, were seen in trials that reported the inclusion of a proportion of women with chorioamnionitis at trial entry. There was no difference in the risk of fetal death between exposure to a single course of antenatal corticosteroids and no exposure in trials that reported a proportion of women with chorioamnionitis at trial entry.	**Not applicable**

Judging the benefits in context
The evidence is based on up to four randomised controlled trials, included in the Roberts CPG version 2015 systematic review for a single course of antenatal corticosteroids, from a variety of healthcare settings such as the United States, Tunisia and Jordan.

4. What harm might the proposed intervention/action do?

Evidence statement	**Quality of evidence**
Maternal - There was a significant increase of more than two and a half times the risk of puerperal sepsis following treatment with antenatal corticosteroids compared with no antenatal corticosteroids in trials that recruited and reported a proportion of women with chorioamnionitis at trial entry. Of note is that both these trials used dexamethasone as the antenatal corticosteroid. *Infant* - There is no evidence of harms to the infant.	**Not applicable**

Judging the harms in context
Maternal - The evidence is from two trials included that recruited and reported on women with chorioamnionitis at trial entry.
Infant - There is no evidence of harm to the infant, and evidence of significant benefit in terms of reduced mortality and respiratory distress syndrome.

5. What is the likely balance between good and harm?

Evidence statement	**Overall quality of evidence**
Maternal - While there was no difference in risk of chorioamnionitis or postnatal pyrexia requiring treatment following a single course of antenatal corticosteroids in women with chorioamnionitis at trial entry, the evidence suggests a significantly increased risk of puerperal sepsis in this population of women. *Infant* - The evidence suggests substantial benefit for the infant in terms of significant reductions in risk of perinatal and neonatal death, and respiratory distress syndrome.	**Not applicable**

Judging the balance of benefits and harms in context
Maternal - There is evidence of increased risk of puerperal sepsis in the mother following exposure to a single course of antenatal corticosteroids in trials that recruited and reported on women with chorioamnionitis at trial entry. However, in a clinical healthcare setting where there are facilities for monitoring and treating infection, the impact of this harm is low, particularly in view of the substantial health benefits for the infant. There is no evidence for harm to the mother from increased risk of other infection outcomes.
Infant - There are significant health benefits for the infant in terms of reduced risk of perinatal and neonatal death and respiratory distress syndrome.

Benefits clearly outweigh harms	Recommend	STRONG
Benefits probably outweigh harms	Consider	CONDITIONAL
Not known	**Make a recommendation for research (see 8 below)**	**WEAK**
Benefits probably don't outweigh harms	Consider against/make no recommendation	CONDITIONAL
Harms probably outweigh benefits		
Benefits clearly don't outweigh harms	Recommend against	STRONG
Harms clearly outweigh benefits		

6. Is the intervention/action implementable in the New Zealand context?

Summary statement
Antenatal corticosteroids are already widely in use in New Zealand and Australia.

Yes	**Recommend/consider**
Not known	Consider economic evaluation
No	Recommend/consider against

7. Final recommendation

	Strength of recommendation
Use a single course of antenatal corticosteroids for women with chorioamnionitis at risk of preterm birth. Do not delay birth in women with chorioamnionitis to administer a single course of antenatal corticosteroids. Where appropriate, monitor women with chorioamnionitis for signs of puerperal sepsis when antenatal corticosteroids have been given.	**STRONG** **CONDITIONAL** **WEAK (Practice Points)**

8. Recommendations for research

M20 Women with chorioamnionitis at risk of preterm birth – Repeat antenatal corticosteroids

M20 NHMRC Evidence summary

What is the safety for the mother and fetus, infant, child, adult of administering a repeat course(s) of antenatal corticosteroids to women with chorioamnionitis at risk of preterm birth?

1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*

Eight of the ten trials included in the Crowther (2011) Cochrane systematic review excluded women with chorioamnionitis at time of trial entry. The remaining two trials did not provide information on whether women with chorioamnionitis were included in their trials. Therefore no randomised controlled trial data was available.	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 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')*

N/A	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is not consistent
	NA	Not applicable (one study only)

3. Clinical impact *(indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*

N/A	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?)*

N/A	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether sensible to apply

5. Applicability *(is the body of evidence relevant to the New Zealand / Australian healthcare context in terms of health services / delivery of care and cultural factors?)*

Corticosteroids are readily available in Australia and New Zealand and their use is feasible.	A	Evidence directly applicable to New Zealand / Australian healthcare context
	B	Evidence applicable to New Zealand / Australian healthcare context with few caveats
	C	Evidence probably applicable to New Zealand / Australian healthcare context with some caveats
	D	Evidence not applicable to New Zealand / 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 *(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	NA	Not applicable
2. Consistency	NA	Not applicable
3. Clinical Impact	NA	Not applicable
4. Generalisability	NA	Not applicable
5. Applicability	NA	Not applicable

Evidence statement
No randomised controlled trial data was available for the use of repeat antenatal corticosteroids in women with chorioamnionitis.

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

Repeat antenatal corticosteroids for a woman with chorioamnionitis at risk of preterm birth.

Do not delay birth in women with chorioamnionitis to administer repeat antenatal corticosteroids.

Use repeat antenatal corticosteroids in women with chorioamnionitis at the discretion of the attending physician.

OVERALL GRADE OF RECOMMENDATION	
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 recommendations(s) but care should be taken in its application
D	Body of evidence is weak and recommendation must be applied with caution

Where appropriate, monitor women with chorioamnionitis for signs of puerperal sepsis when antenatal corticosteroids have been given..	**PP**	**Practice Points**
UNRESOLVED ISSUES *(If needed, keep a 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 implementation of this recommendation?	**YES**	
	NO	

M20 GRADE Evidence summary

Considered Judgement - Strength of recommendation							
What is the safety for the mother and fetus, infant, child, adult of administering a repeat course(s) of antenatal corticosteroids to women with chorioamnionitis at risk of preterm birth?							
1. Outcome measures:	**Quality of evidence**				**Importance of outcome in making a decision**		
Maternal Outcomes	**HIGH**	**MOD**	**LOW**	**V. LOW**	**Critical**	**Important**	**Not Important**
O_1 Chorioamnionitis				NR	✓		
O_2 Puerperal sepsis				NR	✓		
O_3 Pyrexia after entry to trial				NR		✓	
O_4 Intrapartum fever requiring antibiotics				NR		✓	
O_5 Post natal pyrexia				NR		✓	
O_6 Maternal quality of life				NR	✓		
Infant Outcomes	**HIGH**	**MOD**	**LOW**	**V. LOW**	**Critical**	**Important**	**Not Important**
O_1 Combined fetal and neonatal death				NR	✓		
O_2 Neonatal death				NR	✓		
O_3 Fetal death				NR	✓		
O_4 RDS				NR	✓		
O_5 Composite of serious outcomes for the infant				NR	✓		
O_6 Neurosensory disability (composite of impairments) for infant as a child				NR	✓		
O_7 Survival free of neurosensory disability for the infant as a child				NR	✓		
O_8 Survival free of metabolic disease for the infant as a child				NR		✓	
O_9 Neurosensory disability (composite of impairments) for infant as an adult				NR	✓		
O_{10} Survival free of neurosensory disability for the infant as an adult				NR	✓		
O_{11} Survival free of metabolic disease for the infant as an adult				NR		✓	
2. Is there is insufficient evidence to make a recommendation?							
Evidence statement - Evidence is based on a subset of data from trials that reported they included a proportion of women with chorioamnionitis. This level of evidence cannot be used to form a clinical recommendation. *Maternal* - No maternal infectious morbidity data were reported in the randomised controlled trials of repeat courses of antenatal corticosteroids where women with chorioamnionitis were recruited. Women with chorioamnionitis at the time of trial entry were excluded from eight of the ten trials in the Crowther (2011) Cochrane systematic review. *Infant* - No infant primary outcome data were reported in the randomised controlled trials of repeat courses of antenatal corticosteroids where women with chorioamnionitis were recruited. Women with chorioamnionitis at the time of trial entry were excluded from eight of the ten trials in the Crowther (2011) Cochrane systematic review.							
3. What benefit will the proposed intervention/action have?							
Evidence statement *Maternal* - No relevant data for maternal primary outcomes were reported in the two randomised controlled trials included in the Crowther (2011) Cochrane systematic review that recruited women with chorioamnionitis at trial entry. Women with chorioamnionitis at the time of trial entry were excluded from the remaining eight trials in the Crowther (2011) Cochrane systematic review. *Infant* - No relevant data for infant primary outcomes were reported in the two randomised controlled trials included in the Crowther (2011) Cochrane systematic review that recruited women with chorioamnionitis at trial entry. Women with chorioamnionitis at the time of trial entry were excluded from the remaining eight trials in the Crowther (2011) Cochrane systematic review.					**Quality of evidence** **Not applicable**		
Judging the benefits in context N/A							
4. What harm might the proposed intervention/action do?							
Evidence statement *Maternal* - No relevant data for maternal primary outcomes were reported in the two randomised controlled trials included in the Crowther (2011) Cochrane systematic review that recruited women with chorioamnionitis at trial entry. Women with chorioamnionitis at the time of trial entry were excluded from the remaining eight trials in the Crowther (2011) Cochrane systematic review. *Infant* - No relevant data for infant primary outcomes were reported in the two randomised controlled trials included in the Crowther (2011) Cochrane systematic review that recruited women with chorioamnionitis at trial entry. Women with chorioamnionitis at the time of trial entry were excluded from the remaining eight trials in the Crowther (2011) Cochrane systematic review.					**Quality of evidence** **Not applicable**		

Judging the harms in context N/A	
5. What is the likely balance between good and harm?	
Evidence statement *Maternal* - No relevant data for maternal primary outcomes were reported in the two randomised controlled trials included in the Crowther (2011) Cochrane systematic review that recruited women with chorioamnionitis at trial entry. Women with chorioamnionitis at the time of trial entry were excluded from the remaining eight trials in the Crowther (2011) Cochrane systematic review. *Infant* - No relevant data for infant primary outcomes were reported in the two randomised controlled trials included in the Crowther (2011) Cochrane systematic review that recruited women with chorioamnionitis at trial entry. Women with chorioamnionitis at the time of trial entry were excluded from the remaining eight trials in the Crowther (2011) Cochrane systematic review.	**Quality of evidence** **Not applicable**

Judging the balance of benefits and harms in context N/A		
Benefits clearly outweigh harms	Recommend	**STRONG**
Benefits probably outweigh harms	Consider	**CONDITIONAL**
Not known	Make a recommendation for research (see 8 below)	**WEAK**
Benefits probably don't outweigh harms Harms probably outweigh benefits	Consider against/make no recommendation	**CONDITIONAL**
Benefits clearly don't outweigh harms Harms clearly outweigh benefits	Recommend against	**STRONG**

6. Is the intervention/action implementable in the New Zealand context?	
Summary statement Antenatal corticosteroids are already widely in use in New Zealand and Australia.	
Yes	**Recommend/consider**
Not known	Consider economic evaluation
No	Recommend/consider against

7. Final recommendation	
Repeat antenatal corticosteroids for a woman with chorioamnionitis at risk of preterm birth. Do not delay birth in women with chorioamnionitis to administer repeat antenatal corticosteroids. Use repeat antenatal corticosteroids in women with chorioamnionitis at the discretion of the attending physician. Where appropriate, monitor women with chorioamnionitis for signs of puerperal sepsis when antenatal corticosteroids have been given..	**Strength of recommendation** *Please select level* **STRONG** **CONDITIONAL** **WEAK (Practice Points)**

8. Recommendations for research
• Randomised trials are needed to investigate if antenatal corticosteroids should be repeated in women at risk of preterm birth who had antenatal corticosteroids 7 days previously and then present with chorioamnionitis.

M21 Women with antepartum haemorrhage at risk of preterm birth – Single course of antenatal corticosteroids

M21 NHMRC Evidence summary

What is the safety for the mother, fetus, infant, child, adult of administering a single course of antenatal corticosteroids to women with antepartum haemorrhage at risk of preterm birth?		
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Six of the 26 trials included in the Roberts CPG version 2015 systematic review for a single course of antenatal corticosteroids reported including a small proportion of women with an antepartum haemorrhage in their trials.	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 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')*		
Maternal The evidence for chorioamnionitis appears consistent with the overall treatment effect with no difference seen in the risk. Infant Evidence for perinatal death, fetal death, neonatal death, and respiratory distress syndrome appears to be consistent with the overall treatment effect with no difference seen in the risk.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is not consistent
	NA	Not applicable (one study only)
3. Clinical impact *(indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The proportion of women and infants in trials that reported including women with an antepartum haemorrhage are too small to make inferences about benefits and harms, and the data should be interpreted with caution.	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?)*		
Evidence from a variety of healthcare settings. Studies conducted in USA, France, Australia, and The Netherlands.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether sensible to apply
5. Applicability *(is the body of evidence relevant to the New Zealand / Australian healthcare context in terms of health services / delivery of care and cultural factors?)*		
Corticosteroids are readily available in Australia and New Zealand and their use is feasible.	A	Evidence directly applicable to New Zealand / Australian healthcare context
	B	Evidence applicable to New Zealand / Australian healthcare context with few caveats
	C	Evidence probably applicable to New Zealand / Australian healthcare context with some caveats
	D	Evidence not applicable to New Zealand / 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 is based on a subset of data from trials that reported they included a proportion of women with an antepartum haemorrhage. This level of evidence cannot be used to form a clinical recommendation		
EVIDENCE STATEMENT MATRIX *(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	NA	Not applicable
2. Consistency	NA	Not applicable
3. Clinical Impact	NA	Not applicable

4. Generalisability	NA	Not applicable
5. Applicability	NA	Not applicable

Evidence statement -

RECOMMENDATION *(What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible)*	**OVERALL GRADE OF RECOMMENDATION**	
Use a single course of antenatal corticosteroids for women with an ante-partum haemorrhage at risk of preterm birth. Where appropriate, monitor for signs of puerperal sepsis in women with an antepartum haemorrhage when antenatal corticosteroids have been given.	**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 recommendations(s) but care should be taken in its application
	D	Body of evidence is weak and recommendation must be applied with caution
	PP	**Practice Points**

UNRESOLVED ISSUES *(If needed, keep a 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 implementation of this recommendation?	**YES**
	NO

M21 GRADE Evidence summary

Considered Judgement - Strength of recommendation

What is the safety for the mother and fetus, infant, child, adult of administering a single course of antenatal corticosteroids to women with antepartum haemorrhage at risk of preterm birth?

1. Outcome measures:	Quality of evidence				Importance of outcome in making a decision		
Maternal Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O_1 Chorioamnionitis	✓				✓		
O_2 Puerperal sepsis		✓			✓		
O_3 Pyrexia after entry to trial		✓				✓	
O_4 Intrapartum fever requiring antibiotics				NR		✓	
O_5 Post natal pyrexia				NR		✓	
O_6 Maternal quality of life				NR	✓		
Infant Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O_1 Combined fetal and neonatal death		✓			✓		
O_2 Neonatal death		✓			✓		
O_3 Fetal death			✓		✓		
O_4 RDS		✓			✓		
O_5 Composite of serious outcomes for the infant				NR	✓		
O_6 Neurosensory disability (composite of impairments) for infant as a child				NR	✓		
O_7 Survival free of neurosensory disability for the infant as a child				NR	✓		
O_8 Survival free of metabolic disease for the infant as a child				NR		✓	
O_9 Neurosensory disability (composite of impairments) for infant as an adult				NR	✓		
O_{10} Survival free of neurosensory disability for the infant as an adult				NR	✓		
O_{11} Survival free of metabolic disease for the infant as an adult				NR		✓	

2. Is there is insufficient evidence to make a recommendation?

Evidence statement - Evidence is based on a subset of data from trials that reported they included a proportion of women with an antepartum haemorrhage. This level of evidence cannot be used to form a clinical recommendation

Maternal - Evidence for maternal outcomes is based on six randomised controlled trials included in the Roberts CPG version 2015 systematic review for a single course of antenatal corticosteroids that recruited and reported on the proportion of women with antepartum haemorrhage in their trials. Four trials involving 442 women reported on chorioamnionitis, evidence for puerperal sepsis is based on four trials involving 403 women, and the evidence for pyrexia after trial entry requiring treatment is based on one trial involving 118 women. No data were reported for other measures of maternal infection or maternal quality of life.
Infant - Evidence for infant outcomes is based on randomised controlled trials included in the Roberts CPG version 2015 systematic review for a single course of antenatal corticosteroids that recruited and reported on the proportion of women with antepartum haemorrhage in their trials. Fetal death and perinatal death is based on five trials involving 800 infants, and neonatal death is based on 6 trials involving 868 infants. Six trials involving 870 infants reported data on respiratory distress syndrome.

3. What benefit will the proposed intervention/action have?

Evidence statement	Quality of evidence
Maternal - There was no difference in risk for chorioamnionitis in trials that recruited and reported a proportion of women with an antepartum haemorrhage at trial entry for a single course of antenatal corticosteroids compared with no antenatal corticosteroids. *Infant* - In line with the overall treatment effect, there was a significant reduction in risk of perinatal and neonatal death, and respiratory distress syndrome among those infants exposed to a single course of antenatal corticosteroids compared with no exposure in trials that recruited and reported on the proportion of women with an antepartum haemorrhage. There was no difference in risk of fetal death.	**Not applicable**

Judging the benefits in context
The evidence is based on overall well conducted randomised controlled trials, with sample sizes up to 442 women and up to 870 infants, that reported a proportion of women with antepartum haemorrhage at risk of preterm birth in their sample. The studies include populations from a variety of healthcare settings including the United Kingdom, the United States, Finland and Jordan.

4. What harm might the proposed intervention/action do?

Evidence statement	Quality of evidence
Maternal - There was an increased risk of pyrexia after trial entry requiring treatment in the one trial reporting on this outcome. This trial used dexamethasone as the antenatal corticosteroid. There was also an increased risk of puerperal sepsis for women treated with a single course of antenatal corticosteroids in the four trials reporting this outcome and that included a proportion of women with an antepartum haemorrhage. Three of these trials also used dexamethasone.	**Not applicable**

Infant - There was no evidence of any harm to the infant.	

Judging the harms in context
Maternal - The evidence for increased risk of pyrexia after trial entry requiring treatment and puerperal sepsis following exposure to a single course of antenatal corticosteroids is based on direct evidence from trials that recruited and reported on a proportion of women with antepartum haemorrhage at trial entry. The confidence intervals are wide indicating some imprecision in the result.
Infant - There is no evidence of harm to the infant.

5. What is the likely balance between good and harm?

Evidence statement	**Overall quality of evidence**
Maternal - The evidence from trials that recruited and reported on a proportion of women with antepartum haemorrhage at trial entry suggests an increased risk of pyrexia and puerperal sepsis among women treated with a single course of antenatal corticosteroids compared to no antenatal corticosteroids. *Infant* - There are significant health benefits for the infant in terms of substantial reductions in risk of fetal and perinatal death and risk of respiratory distress syndrome.	**Not applicable**

Judging the balance of benefits and harms in context
The evidence for an increased risk of infection in the mother suggests a likelihood of harm in the mother, the impact of which is low in healthcare settings that are able to provide monitoring and antibiotics. The evidence for significant benefits to the infant, in terms of reduced risk of perinatal and neonatal death, and reduced risk of respiratory distress syndrome, suggests a high likelihood of doing good, the impact of which would be high for the infant.

Benefits clearly outweigh harms	Recommend	STRONG
Benefits probably outweigh harms	Consider	CONDITIONAL
Not known	**Make a recommendation for research (see 8 below)**	**WEAK**
Benefits probably don't outweigh harms	Consider against/make no recommendation	CONDITIONAL
Harms probably outweigh benefits		
Benefits clearly don't outweigh harms	Recommend against	STRONG
Harms clearly outweigh benefits		

6. Is the intervention/action implementable in the New Zealand context?

Summary statement
Antenatal corticosteroids are already widely in use in New Zealand and Australia.

Yes	**Recommend/consider**
Not known	Consider economic evaluation
No	Recommend/consider against

7. Final recommendation

Use a single course of antenatal corticosteroids for women with an ante-partum haemorrhage at risk of preterm birth. Where appropriate, monitor for signs of puerperal sepsis in women with an antepartum haemorrhage when antenatal corticosteroids have been given.	**Strength of recommendation** **STRONG** **CONDITIONAL** **WEAK (Practice point)**

8. Recommendations for research

M22 Women with antepartum haemorrhage at risk of preterm birth – Repeat antenatal corticosteroids

M22 NHMRC Evidence summary

What is the safety for the mother, fetus, infant, child, adult of administering repeat antenatal corticosteroids to women with antepartum haemorrhage at risk of preterm birth?		
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Seven of the ten trials included in the Crowther, 2011 review reported including a small proportion of women with an antepartum haemorrhage in their trials.	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 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')*		
Maternal The evidence for chorioamnionitis, postnatal pyrexia and puerperal sepsis appears to be consistent with the overall treatment effect with no difference seen in the risk between those women treated with repeat antenatal corticosteroids and those not treated. Infant Evidence for perinatal death, fetal death, neonatal death, respiratory distress syndrome, severe respiratory distress syndrome, composite of serious infant outcomes appears consistent with the overall treatment effect observed for exposure to repeat antenatal corticosteroids compared with no repeat exposure.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is not consistent
	NA	Not applicable (one study only)
3. Clinical impact *(indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The proportion of women and infants in trials that reported including women with an antepartum haemorrhage are too small to make inferences about benefits and harms, and the data should be interpreted with caution.	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?)*		
Evidence from a variety of healthcare settings. Studies conducted in Canada, Australia and New Zealand, the United States, and a multicentre trial involving 20 countries.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether sensible to apply
5. Applicability *(is the body of evidence relevant to the New Zealand / Australian healthcare context in terms of health services / delivery of care and cultural factors?)*		
Corticosteroids are readily available in Australia and New Zealand and their use is feasible.	A	Evidence directly applicable to New Zealand / Australian healthcare context
	B	Evidence applicable to New Zealand / Australian healthcare context with few caveats
	C	Evidence probably applicable to New Zealand / Australian healthcare context with some caveats
	D	Evidence not applicable to New Zealand / 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 is based on a subset of data from trials that reported they included a proportion of women with an antepartum haemorrhage. This level of evidence cannot be used to form a clinical recommendation		
EVIDENCE STATEMENT MATRIX *(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	NA	Not applicable

2. Consistency	NA	Not applicable
3. Clinical Impact	NA	Not applicable
4. Generalisability	NA	Not applicable
5. Applicability	NA	Not applicable

Evidence statement

RECOMMENDATION *(What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible)*	**OVERALL GRADE OF RECOMMENDATION**	
Repeat antenatal corticosteroids for a woman with an antepartum haemorrhage at risk of preterm birth. Where appropriate, monitor for signs of puerperal sepsis in women with an antepartum haemorrhage when antenatal corticosteroids have been given.	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 recommendations(s) but care should be taken in its application
	D	Body of evidence is weak and recommendation must be applied with caution
	PP	**Practice Points**

UNRESOLVED ISSUES *(If needed, keep a 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 implementation of this recommendation?	**YES**
	NO

M22 GRADE Evidence summary

Considered Judgement - Strength of recommendation

What is the safety for the mother, fetus, infant, child, adult of administering a repeat course(s) of antenatal corticosteroids to women with antepartum haemorrhage at risk of preterm birth?

1. Outcome measures:	Quality of evidence				Importance of outcome in making a decision		
Maternal Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O_1 Chorioamnionitis	✓				✓		
O_2 Puerperal sepsis	✓				✓		
O_3 Pyrexia after entry to trial				NR		✓	
O_4 Intrapartum fever requiring antibiotics				NR		✓	
O_5 Post natal pyrexia		✓				✓	
O_6 Maternal quality of life				NR	✓		
Infant Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O_1 Combined fetal and neonatal death		✓			✓		
O_2 Neonatal death		✓			✓		
O_3 Fetal death			✓		✓		
O_4 RDS		✓			✓		
O_5 Composite of serious outcomes for the infant		✓			✓		
O_6 Neurosensory disability (composite of impairments) for infant as a child				NR	✓		
O_7 Survival free of neurosensory disability for the infant as a child				NR	✓		
O_8 Survival free of metabolic disease for the infant as a child				NR		✓	
O_9 Neurosensory disability (composite of impairments) for infant as an adult				NR	✓		
O_{10} Survival free of neurosensory disability for the infant as an adult				NR	✓		
O_{11} Survival free of metabolic disease for the infant as an adult				NR		✓	

2. Is there is insufficient evidence to make a recommendation?

Evidence statement - Evidence is based on a subset of data from trials that reported they included a proportion of women with an antepartum haemorrhage. This level of evidence cannot be used to form a clinical recommendation

Maternal - The evidence for maternal outcomes is based on the trials included in the Crowther (2011) Cochrane systematic review that recruited and reported a proportion of women who had an antepartum haemorrhage, and compared those who had received a repeat course of antenatal corticosteroids with those who did not. Five trials involving 3776 women reported on chorioamnionitis, one trial involving 982 women reported on postnatal pyrexia requiring treatment, and three trials involving 2357 women reported on puerperal sepsis. No data was reported for other measures of maternal infection or maternal quality of life.
Infant - The evidence for infant outcomes is based on the trials included in the Crowther (2011) Cochrane systematic review that recruited and reported a proportion of women who had an antepartum haemorrhage, and compared those who had received a repeat course of antenatal corticosteroids with those who did not. Six trials involving 4650 infants reported on perinatal death. Four trials involving 1828 infants reported on neonatal death, and four trials involving 1851 infants reported on fetal death. Five trials involving 2323 reported on respiratory distress syndrome, and five trails involving 4517 infants reported on a composite of serious infant outcomes. No data was reported for longer term outcomes.

3. What benefit will the proposed intervention/action have?

Evidence statement	Quality of evidence
Maternal - There was no difference in risk of chorioamnionitis, postnatal pyrexia or puerperal sepsis in women exposed to repeat antenatal corticosteroids compared with no repeat exposure in trials that recruited and reported a proportion of women with an antepartum haemorrhage. *Infant* - There was no difference is risk of perinatal, neonatal or fetal death for infants exposed to repeat antenatal corticosteroids comparted with no repeat exposure in trials that recruited and reported a proportion of women with antepartum haemorrhage. There were significant reductions in the risk of respiratory distress syndrome and a composite of serious outcomes for infants exposed to repeat antenatal corticosteroids compared with no repeat exposure in trials that recruited and reported a proportion of women with antepartum haemorrhage.	**Not applicable**

Judging the benefits in context
The evidence is based on trials included in the Crowther (2011) Cochrane systematic review that recruited and reported a proportion of women with antepartum haemorrhage. They are conducted trials involving women exposed to repeat antenatal corticosteroids (or placebo) after remaining at risk of imminent preterm birth following an initial single course of antenatal corticosteroids. The populations were drawn from a variety of healthcare settings including Canada, Australia and New Zealand, the United States, as well as a multicentre trial involving 20 countries.

4. What harm might the proposed intervention/action do?

Evidence statement	Quality of evidence
Maternal - There was no evidence of health harms for the mother following exposure to repeat antenatal	

corticosteroids in trials that recruited and reported a proportion of women with antenatal corticosteroids. *Infant* - There was no evidence of health harms for the infant following exposure to repeat antenatal corticosteroids in trials that recruited and reported a proportion of women with antenatal corticosteroids.	**Not applicable**
Judging the harms in context Direct evidence from trials conducted in women exposed to repeat antenatal corticosteroids after remaining at imminent risk of preterm birth following an initial single course suggests no health harms for the mother or the infant.	
5. What is the likely balance between good and harm?	
Evidence statement *Maternal* - There are no clear direct health benefits for the woman with an antepartum haemorrhage following exposure to repeat antenatal corticosteroids. There does not appear to be any increased risk of infection. *Infant* - There is evidence for substantial benefit for the infant in terms of significant reductions in risk of respiratory distress syndrome and composite serious outcome, with no increased risk of mortality.	**Overall quality of evidence** **Not applicable**
Judging the balance of benefits and harms in context *Maternal* - It is unlikely that women with antepartum haemorrhage would suffer harm following exposure to repeat courses of antenatal corticosteroids. The impact of any potential harm would be low in healthcare settings with facilities for monitoring signs and timely treatment of infection. *Infant* - It is likely that exposure to repeat antenatal corticosteroids for infants of mothers with an antepartum haemorrhage is highly beneficial. The impact of reduced risk of respiratory distress syndrome and composite of serious outcomes with no increased risk of mortality is high for preterm infants.	

Benefits clearly outweigh harms	Recommend	STRONG
Benefits probably outweigh harms	Consider	CONDITIONAL
Not known	**Make a recommendation for research (see 8 below)**	**WEAK**
Benefits probably don't outweigh harms Harms probably outweigh benefits	Consider against/make no recommendation	CONDITIONAL
Benefits clearly don't outweigh harms Harms clearly outweigh benefits	Recommend against	STRONG

6. Is the intervention/action implementable in the New Zealand context?	
Summary statement *Consider evidence of cost effectiveness, financial (cost and value for money), human and other resource implications.* Antenatal corticosteroids are already widely in use in New Zealand and Australia.	
Yes	**Recommend/consider**
Not known	Consider economic evaluation
No	Recommend/consider against

7. Final recommendation	
Repeat antenatal corticosteroids for a woman with an antepartum haemorrhage at risk of preterm birth. Where appropriate, monitor for signs of puerperal sepsis in women with an antepartum haemorrhage when antenatal corticosteroids have been given.	**Strength of recommendation** *Please select level* **STRONG** **CONDITIONAL** **WEAK (Practice points)**
8. Recommendations for research	

M23 Women with a multiple pregnancy at risk of preterm birth – Single course of antenatal corticosteroids

M23 NHMRC Evidence summary

What is the safety for the mother and fetus, infant, child, adult of administering a single course of antenatal corticosteroids to women with a multiple pregnancy (twins and higher order) with an additional risk factor(s) for preterm birth?		
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Twelve of the 26 trials in the Roberts CPG version 2015 systematic review for a single course of antenatal corticosteroids reported including a small proportion of women with a multiple pregnancy with an additional risk of imminent preterm birth.	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 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')*		
Maternal The evidence for chorioamnionitis, pyrexia after trial entry, intrapartum or postnatal pyrexia requiring treatment was consistent with the overall treatment effect with no difference seen in the risk between those treated with antenatal corticosteroids and those with no treatment. Infant The evidence for perinatal death, fetal death, neonatal death, respiratory distress syndrome, moderate/severe respiratory distress syndrome were consistent with the overall treatment effect with no difference seen in the risk between those exposed to antenatal corticosteroids and those with no exposure.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is not consistent
	NA	Not applicable (one study only)
3. Clinical impact *(indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The proportion of women and infants in trials that reported including women with an antepartum haemorrhage are too small to make inferences about benefits and harms. The data should be interpreted with caution.	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?)*		
Evidence from a variety of healthcare settings. Studies conducted in USA, South Africa, Canada, Tunisia, UK, Finland, New Zealand and The Netherlands	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether sensible to apply
5. Applicability *(is the body of evidence relevant to the New Zealand / Australian healthcare context in terms of health services / delivery of care and cultural factors?)*		
Corticosteroids are readily available in Australia and New Zealand and their use is feasible.	A	Evidence directly applicable to New Zealand / Australian healthcare context
	B	Evidence applicable to New Zealand / Australian healthcare context with few caveats
	C	Evidence probably applicable to New Zealand / Australian healthcare context with some caveats
	D	Evidence not applicable to New Zealand / 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 is based on a subset of data from trials that reported they included a proportion of women with a multiple pregnancy at risk of preterm birth. This level of evidence cannot be used to form a clinical recommendation		
EVIDENCE STATEMENT MATRIX *(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	NA	Not applicable

2. Consistency	NA	Not applicable
3. Clinical Impact	NA	Not applicable
4. Generalisability	NA	Not applicable
5. Applicability	NA	Not applicable

Evidence statement

RECOMMENDATION *(What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible)*	**OVERALL GRADE OF RECOMMENDATION**	
Use a single course of antenatal corticosteroids for women with a multiple pregnancy with an additional risk factor(s) for preterm birth. Where appropriate, estimate the risk of preterm birth by considering the use of adjunct prediction tests including fetal fibronectin and assessment of cervical length. Where appropriate, monitor women with a multiple pregnancy at risk of preterm birth for signs of puerperal sepsis when antenatal corticosteroids have been given.	**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 recommendations(s) but care should be taken in its application
	D	Body of evidence is weak and recommendation must be applied with caution
	PP	**Practice Points**

UNRESOLVED ISSUES *(If needed, keep a 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 implementation of this recommendation?	**YES**
	NO

M23 GRADE Evidence summary

Considered Judgement - Strength of recommendation

What is the safety for the mother and fetus, infant, child, adult of administering a single course of antenatal corticosteroids to women with a multiple pregnancy (twins and higher order) with an additional risk factor(s) for preterm birth?

1. Outcome measures:	Quality of evidence				Importance of outcome in making a decision		
Maternal Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O_1 Chorioamnionitis	✓				✓		
O_2 Puerperal sepsis		✓			✓		
O_3 Pyrexia after entry to trial		✓				✓	
O_4 Intrapartum fever requiring antibiotics		✓				✓	
O_5 Post natal pyrexia	✓					✓	
O_6 Maternal quality of life				NR	✓		
Infant Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O_1 Combined fetal and neonatal death		✓			✓		
O_2 Neonatal death		✓			✓		
O_3 Fetal death			✓		✓		
O_4 RDS		✓			✓		
O_5 Composite of serious outcomes for the infant				NR	✓		
O_6 Neurosensory disability (composite of impairments) for infant as a child				NR	✓		
O_7 Survival free of neurosensory disability for the infant as a child				NR	✓		
O_8 Survival free of metabolic disease for the infant as a child				NR		✓	
O_9 Neurosensory disability (composite of impairments) for infant as an adult				NR	✓		
O_{10} Survival free of neurosensory disability for the infant as an adult				NR	✓		
O_{11} Survival free of metabolic disease for the infant as an adult				NR		✓	

2. Is there is insufficient evidence to make a recommendation?

Evidence statement - Evidence is based on a subset of data from trials that reported they included a proportion of women with a multiple pregnancy with an additional risk factor(s) for preterm birth. This level of evidence cannot be used to form a clinical recommendation

Maternal - The evidence is based on twelve trials included in the Roberts CPG version 2015 systematic review for a single course of antenatal corticosteroids that recruited and reported a proportion of women with a multiple pregnancy, nine of which reported maternal outcomes for these Clinical Practice guidelines. Seven trials, involving 1862 women, reported on chorioamnionitis. Two trials involving 219 women reported on pyrexia after trial entry requiring antibiotics, one trial involving 101 women reported on intrapartum pyrexia requiring treatment. Four trials involving 1105 women reported on postnatal pyrexia requiring treatment, and five trials involving 569 women reported on puerperal sepsis. No data were reported for maternal quality of life.
Infant - The evidence is based on twelve trials included in the Roberts CPG version 2015 systematic review for a single course of antenatal corticosteroids that recruited and reported a proportion of women with a multiple pregnancy. Ten trials involving 3225 infants reported on perinatal death, twelve trials involving 3290 infants reported on neonatal death, and ten trials involving 3225 trials reported on fetal death. Twelve trials involving 3250 infants reported on respiratory distress syndrome. No data were reported for a composite of serious infant outcomes.

3. What benefit will the proposed intervention/action have?

Evidence statement	Quality of evidence
Maternal - There was no increase in risk of chorioamnionitis, pyrexia after trial entry, intrapartum or postnatal pyrexia requiring treatment between women exposed to a single course of antenatal corticosteroids and those not exposed in trials that recruited and reported a proportion of women with a multiple pregnancy. *Infant* - There was a significant reduction in the risk of perinatal and neonatal death, and no difference in the risk of fetal death in trials that recruited and reported a proportion of women with a multiple pregnancy. There was also a significant reduction in respiratory distress syndrome, and severe respiratory distress syndrome. No data were reported for a composite of serious infant outcomes.	**Not applicable**

Judging the benefits in context
The evidence is direct evidence from trials comparing outcomes in women and infants exposed to a single course of antenatal corticosteroids with those exposed to placebo or not exposed to antenatal corticosteroids. The trials were conducted in a variety of countries and healthcare settings, including Canada, the United Kingdom, South Africa, Tunisia, the United States, Finland, New Zealand and The Netherlands. Effect sizes for infant mortality outcomes, where applicable, are substantial and demonstrate significant reductions in risk.

4. What harm might the proposed intervention/action do?

Evidence statement	Quality of evidence
Maternal - There was an increased risk of puerperal sepsis among women exposed to a single course of antenatal corticosteroids in trials that included a proportion of women with a multiple pregnancy.	**Not applicable**

Infant - There was no evidence of any harm to the infant.	

Judging the harms in context
The evidence is from trials that recruited and reported a proportion of women with a multiple pregnancy.

5. What is the likely balance between good and harm?

Evidence statement	**Overall quality of evidence**
Maternal - There is no increased risk of chorioamnionitis and intrapartum or postnatal pyrexia, although the evidence suggests an increased risk of puerperal sepsis. *Infant* - Significant reductions in mortality and respiratory distress syndrome for infants.	**Not applicable**

Judging the balance of benefits and harms in context
Exposure to a single course of antenatal corticosteroids is unlikely to cause harm to the mother in settings with adequate facilities for monitoring and treating signs of possible puerperal sepsis. The significant health benefits for the infant, in terms of reduced risk of mortality and respiratory morbidity outweigh potential low impact harm for the mother.

Benefits clearly outweigh harms	Recommend	STRONG
Benefits probably outweigh harms	Consider	CONDITIONAL
Not known	**Make a recommendation for research (see 8 below)**	**WEAK**
Benefits probably don't outweigh harms	Consider against/make no recommendation	CONDITIONAL
Harms probably outweigh benefits		
Benefits clearly don't outweigh harms	Recommend against	STRONG
Harms clearly outweigh benefits		

6. Is the intervention/action implementable in the New Zealand context?

Summary statement
Antenatal corticosteroids are already widely in use in New Zealand and Australia.

Yes	**Recommend/consider**
Not known	Consider economic evaluation
No	Recommend/consider against

7. Final recommendation

	Strength of recommendation
Use a single course of antenatal corticosteroids for women with a multiple pregnancy with an additional risk factor(s) for preterm birth. Where appropriate, estimate the risk of preterm birth by considering the use of adjunct prediction tests including fetal fibronectin and assessment of cervical length. Where appropriate, monitor women with a multiple pregnancy at risk of preterm birth for signs of puerperal sepsis when antenatal corticosteroids have been given.	**STRONG** **CONDITIONAL** **WEAK (Practice points)**

8. Recommendations for research

M24 Women with a multiple pregnancy at risk of preterm birth – Repeat antenatal corticosteroids

M24 NHMRC Evidence summary

What is the safety for the mother and fetus, infant, child, adult of administering repeat antenatal corticosteroids to women with a multiple pregnancy (twins and higher order) with an additional risk factor(s) for preterm birth?		
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Nine of the ten trials in the Crowther, 2011 systematic review reporting maternal and infant primary outcomes for these Clinical Practice Guidelines included a proportion of women in their trials who had a multiple pregnancy with an additional risk of preterm birth.	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 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')*		
Maternal Evidence for chorioamnionitis, postnatal pyrexia requiring treatment and puerperal sepsis is consistent with the overall treatment effect. There was no difference between those treated with repeat antenatal corticosteroids and those not treated. Infant Evidence for perinatal death, fetal death, neonatal death and severe respiratory distress syndrome the size of the treatment effect was similar to the overall effect and there were no differences between groups. The treatment effects for respiratory distress syndrome and a composite of serious infant outcomes were consistent with the overall treatment effect, and there was a significant reduction in risk for infants exposed to repeat antenatal corticosteroids compared with those not exposed.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is not consistent
	NA	Not applicable (one study only)
3. Clinical impact *(indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Maternal There does not appear to be an increase in risk of infection for women with multiple pregnancy and an additional risk of preterm birth following exposure to repeat antenatal corticosteroids. Infant Significant benefits for the infants in terms of reduction in risk of respiratory distress syndrome and a composite of serious infant outcomes. There is no evidence of harm for infants born of multiple pregnancies exposed to repeat antenatal corticosteroids.	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?)*		
Evidence from a variety of healthcare settings. Studies conducted in USA, France and Australia.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether sensible to apply
5. Applicability *(is the body of evidence relevant to the New Zealand / Australian healthcare context in terms of health services / delivery of care and cultural factors?)*		
Corticosteroids are readily available in Australia and New Zealand and their use is feasible.	A	Evidence directly generalisable to target population
	B	Evidence applicable to New Zealand / Australian healthcare context with few caveats
	C	Evidence probably applicable to New Zealand / Australian healthcare context with some caveats
	D	Evidence not applicable to New Zealand / 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 is based on a subset of data from trials that reported they included a proportion of women with a multiple pregnancy at risk of preterm birth. This level of evidence cannot be used to form a clinical recommendation		
EVIDENCE STATEMENT MATRIX *(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	NA	Not applicable
2. Consistency	NA	Not applicable
3. Clinical Impact	NA	Not applicable
4. Generalisability	NA	Not applicable
5. Applicability	NA	Not applicable

Evidence statement

RECOMMENDATION *(What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible)*	**OVERALL GRADE OF RECOMMENDATION**	
Repeat antenatal corticosteroids for a woman with a multiple pregnancy with an additional risk factor(s) for preterm birth Where appropriate, estimate the risk of preterm birth by considering the use of adjunct prediction tests including fetal fibronectin and assessment of cervical length. Where appropriate, monitor women with a multiple pregnancy at risk of preterm birth for signs of puerperal sepsis when antenatal corticosteroids have been given.	**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 recommendations(s) but care should be taken in its application
	D	Body of evidence is weak and recommendation must be applied with caution
	PP	**Practice Point**

UNRESOLVED ISSUES *(If needed, keep a 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 implementation of this recommendation?	**YES**
	NO

M24 GRADE Evidence summary

Considered Judgement - Strength of recommendation							
What is the safety for the mother and fetus, infant, child, adult of administering a repeat course(s) of antenatal corticosteroids to women with a multiple pregnancy (twins and higher order) with an additional risk factor(s) for preterm birth?							
1. Outcome measures:	**Quality of evidence**				**Importance of outcome in making a decision**		
Maternal Outcomes	**HIGH**	**MOD**	**LOW**	**V. LOW**	**Critical**	**Important**	**Not Important**
O_1 Chorioamnionitis	✓				✓		
O_2 Puerperal sepsis	✓				✓		
O_3 Pyrexia after entry to trial				NR		✓	
O_4 Intrapartum fever requiring antibiotics				NR		✓	
O_5 Post natal pyrexia		✓				✓	
O_6 Maternal quality of life				NR	✓		
Infant Outcomes	**HIGH**	**MOD**	**LOW**	**V. LOW**	**Critical**	**Important**	**Not Important**
O_1 Combined fetal and neonatal death	✓				✓		
O_2 Neonatal death	✓				✓		
O_3 Fetal death		✓			✓		
O_4 RDS	✓				✓		
O_5 Composite of serious outcomes for the infant	✓				✓		
O_6 Neurosensory disability (composite of impairments) for infant as a child		✓			✓		
O_7 Survival free of neurosensory disability for the infant as a child				NR	✓		
O_8 Survival free of metabolic disease for the infant as a child				NR		✓	
O_9 Neurosensory disability (composite of impairments) for infant as an adult				NR	✓		
O_{10} Survival free of neurosensory disability for the infant as an adult				NR	✓		
O_{11} Survival free of metabolic disease for the infant as an adult				NR		✓	

2. Is there is insufficient evidence to make a recommendation?

Evidence statement - Evidence is based on a subset of data from trials that reported they included a proportion of women with a multiple pregnancy with an additional risk factor(s) for preterm birth. This level of evidence cannot be used to form a clinical recommendation

Maternal - Evidence for maternal outcomes is based on six trials included in the Crowther (2011) Cochrane systematic review that recruited and reported a proportion of women with a multiple pregnancy and an additional risk of preterm birth, that were exposed to repeat antenatal corticosteroids or placebo following an initial single course. All six trials, involving 4261 women reported on chorioamnionitis, five trials involving 3091 women reported on puerperal sepsis, and one trial involving 982 women reported on postnatal pyrexia requiring treatment. No data were reported for pyrexia after trial entry or intrapartum pyrexia.
Infant - Evidence for infant outcomes is based on nine trials included in the Crowther (2011) Cochrane systematic review that recruited and reported a proportion of women with a multiple pregnancy and an additional risk of preterm birth, that were exposed to repeat antenatal corticosteroids or placebo following an initial single course. All nine of these trials, involving 5554 infants, reported on perinatal death. Seven trials involving 2713 infants reported on neonatal death and seven trials involving 2755 infants reported on fetal death. Eight trials involving 3206 infants reported on respiratory distress syndrome, and seven trials involving 3959 infants reported on a composite of serious infant outcomes.

3. What benefit will the proposed intervention/action have?

Evidence statement	**Quality of evidence**
Maternal - In trials that recruited and reported a proportion of women with a multiple pregnancy and an additional risk of imminent preterm birth, there was no difference in measures of maternal infection between women who received repeat antenatal corticosteroids and those with no repeat antenatal corticosteroids. *Infant* - In trials that recruited and reported a proportion of women with a multiple pregnancy and an additional risk of imminent preterm birth, the risk of respiratory distress syndrome and a composite of serious infant outcomes were significantly reduced in favour of repeat antenatal corticosteroids. There was no difference in risk of perinatal, fetal or neonatal death in trials that recruited and reported a proportion of women with a multiple pregnancy and an additional risk of imminent preterm birth.	**Not applicable**

Judging the benefits in context
The evidence is direct evidence from trials conducted in women at risk of preterm birth following an initial single course. The trials were conducted in a variety of healthcare settings, including Canada, Australia and New Zealand, the United States, India and Finland, as well as a multicentre study encompassing 80 centres in 20 countries. Effect sizes for respiratory distress syndrome and a composite of serious infant outcomes are substantial and demonstrate significant reductions in risk.

4. What harm might the proposed intervention/action do?

Evidence statement	**Quality of evidence**
Maternal - There was no evidence of harm for the mother in terms of maternal infection. There was no increased	

risk of chorioamnionitis, postnatal pyrexia requiring treatment or puerperal sepsis in trials that recruited and reported a proportion of women with a multiple pregnancy and an additional risk of imminent preterm birth. *Infant* - There was no evidence of harm to the infant. There was reduced risk of respiratory distress syndrome or composite of serious infant outcomes. There is an absence of short and long term neonatal and childhood follow up data reported for exposure to repeat antenatal corticosteroids in infants whose mothers had a multiple pregnancy with an additional risk of imminent preterm birth.	**Not applicable**

Judging the harms in context
The evidence is direct evidence taken from trials that recruited and reported a proportion of women with a multiple pregnancy and imminent risk of preterm birth following an initial single course of antenatal corticosteroids.

5. What is the likely balance between good and harm?

Evidence statement	**Overall quality of evidence**
Maternal - There are no clear health benefits of the mother. There does not appear to be any increased risk of maternal infection in terms of chorioamnionitis, postnatal pyrexia requiring treatment or puerperal sepsis. *Infant* - There are significant benefits for the infant in terms of substantial reductions in risk of respiratory distress syndrome, and a composite of serious infant outcomes.	**Not applicable**

Judging the balance of benefits and harms in context
Whilst there are no direct health benefits for the mother, exposure to repeat antenatal corticosteroids is unlikely to cause harm. There are significant health benefits for the infant in terms of reduced risk of respiratory distress syndrome and composite serious outcome. These are high impact benefits, outweighing potential lower impact harms.

Benefits clearly outweigh harms	Recommend	STRONG
Benefits probably outweigh harms	Consider	CONDITIONAL
Not known	**Make a recommendation for research (see 8 below)**	**WEAK**
Benefits probably don't outweigh harms	Consider against/make no recommendation	CONDITIONAL
Harms probably outweigh benefits		
Benefits clearly don't outweigh harms	Recommend against	STRONG
Harms clearly outweigh benefits		

6. Is the intervention/action implementable in the New Zealand context?

Summary statement
Antenatal corticosteroids are already widely in use in New Zealand and Australia.

Yes	**Recommend/consider**
Not known	Consider economic evaluation
No	Recommend/consider against

7. Final recommendation

	Strength of recommendation *Please select level*
Repeat antenatal corticosteroids for a woman with a multiple pregnancy with an additional risk factor(s) for preterm birth Where appropriate, estimate the risk of preterm birth by considering the use of adjunct prediction tests including fetal fibronectin and assessment of cervical length. Where appropriate, monitor women with a multiple pregnancy at risk of preterm birth for signs of puerperal sepsis when antenatal corticosteroids have been given.	**STRONG** **CONDITIONAL** **WEAK (Practice points)**

8. Recommendations for research

M25 Women with a multiple pregnancy with no risk of preterm birth – Single course of antenatal corticosteroids

M25 NHMRC Evidence summary

Clinical questions: **What is the safety for the mother and fetus, infant, child, adult of administering a single course of antenatal corticosteroids to women with a multiple pregnancy (twins and higher order) prophylactically (not at additional risk for preterm birth)?**		
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
There was no randomised controlled trial evidence for the prophylactic use of antenatal corticosteroids in women with multiple pregnancy with no additional risk of preterm birth.	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 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')*		
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 not consistent
	NA	Not applicable (one study only)
3. Clinical impact *(indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Not applicable	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?)*		
Not applicable	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether sensible to apply
5. Applicability *(is the body of evidence relevant to the New Zealand / Australian healthcare context in terms of health services / delivery of care and cultural factors?)*		
Corticosteroids are readily available in Australia and New Zealand and their use is feasible.	A	Evidence directly applicable to New Zealand / Australian healthcare context
	B	Evidence applicable to New Zealand / Australian healthcare context with few caveats
	C	Evidence probably applicable to New Zealand / Australian healthcare context with some caveats
	D	Evidence not applicable to New Zealand / 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)*		
No randomised controlled trial evidence identified		
EVIDENCE STATEMENT MATRIX *(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	NA	Not applicable

2. Consistency	NA	Not applicable
3. Clinical Impact	NA	Not applicable
4. Generalisability	NA	Not applicable
5. Applicability	NA	Not applicable

Evidence statement

No randomised controlled trial evidence for the prophylactic use of antenatal corticosteroids in women with multiple pregnancy and no additional risk of preterm birth.

RECOMMENDATION *(What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible)*	**OVERALL GRADE OF RECOMMENDATION**	
Do not use a single course of antenatal corticosteroids in women with a multiple pregnancy where there is no other identified risk of preterm birth.	**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 recommendations(s) but care should be taken in its application
	D	Body of evidence is weak and recommendation must be applied with caution
	PP	**Practice Point**

UNRESOLVED ISSUES *(If needed, keep a 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 implementation of this recommendation?	**YES**
	NO

M25 GRADE Evidence summary

Considered Judgement - Strength of recommendation							
What is the safety for the mother and fetus, infant, child, adult of administering a single course of antenatal corticosteroids to women with a multiple pregnancy (twins and higher order) prophylactically (not at additional risk for preterm birth)?							
1. Outcome measures:	**Quality of evidence**				**Importance of outcome in making a decision**		
Maternal Outcomes	**HIGH**	**MOD**	**LOW**	**V. LOW**	**Critical**	**Important**	**Not Important**
O_1 Chorioamnionitis				NR	✓		
O_2 Puerperal sepsis				NR	✓		
O_3 Pyrexia after entry to trial				NR		✓	
O_4 Intrapartum fever requiring antibiotics				NR		✓	
O_5 Post natal pyrexia				NR		✓	
O_6 Maternal quality of life				NR	✓		
Infant Outcomes	**HIGH**	**MOD**	**LOW**	**V. LOW**	**Critical**	**Important**	**Not Important**
O_1 Combined fetal and neonatal death				NR	✓		
O_2 Neonatal death				NR	✓		
O_3 Fetal death				NR	✓		
O_4 RDS				NR	✓		
O_5 Composite of serious outcomes for the infant				NR	✓		
O_6 Neurosensory disability (composite of impairments) for infant as a child				NR	✓		
O_7 Survival free of neurosensory disability for the infant as a child				NR	✓		
O_8 Survival free of metabolic disease for the infant as a child				NR		✓	
O_9 Neurosensory disability (composite of impairments) for infant as an adult				NR	✓		
O_{10} Survival free of neurosensory disability for the infant as an adult				NR	✓		
O_{11} Survival free of metabolic disease for the infant as an adult				NR		✓	
2. Is there is insufficient evidence to make a recommendation?							
Evidence statement *Maternal* - No evidence was identified for maternal primary outcomes of these Clinical Practice Guidelines for the use of a single course of prophylactic antenatal corticosteroids where there is no additional risk of imminent preterm birth in women with a multiple pregnancy. *Infant* - No evidence was available from randomised controlled trials.							
3. What benefit will the proposed intervention/action have?							
Evidence statement *Maternal* - No evidence was available on maternal outcomes. *Infant* - No randomised controlled trial evidence.						**Quality of evidence** **NOT REPORTED**	
Judging the benefits in context Not applicable							
4. What harm might the proposed intervention/action do?							
Evidence statement *Maternal* - No evidence was available on maternal outcomes. *Infant* - No randomised controlled trial evidence.						**Quality of evidence** **NOT REPORTED**	
Judging the harms in context Not applicable							
5. What is the likely balance between good and harm?							
Evidence statement *Maternal* - No evidence was available on maternal outcomes. *Infant* - No randomised controlled trial evidence.						**Overall quality of evidence** **NOT REPORTED**	
Judging the balance of benefits and harms in context Not applicable							
Benefits clearly outweigh harms	Recommend					STRONG	
Benefits probably outweigh harms	Consider					CONDITIONAL	
Not known	**Make a recommendation for research (see 8 below)**					**WEAK**	
Benefits probably don't outweigh harms	Consider against/make no recommendation					CONDITIONAL	
Harms probably outweigh benefits							

Benefits clearly don't outweigh harms Harms clearly outweigh benefits	Recommend against	STRONG

6. Is the intervention/action implementable in the New Zealand context?

Summary statement
Antenatal corticosteroids are already widely in use in New Zealand and Australia.

Yes	**Recommend/consider**
Not known	Consider economic evaluation
No	Recommend/consider against

7. Final recommendation

	Strength of recommendation
Do not use a single course of antenatal corticosteroids in women with a multiple pregnancy where there is no other identified risk of preterm birth.	**STRONG** **CONDITIONAL** **WEAK (Practice Point)**

8. Recommendations for research

- In settings where prophylactic antenatal corticosteroids are being used in women with a multiple pregnancy, with no other identified risk of preterm birth, there is a need for a randomised trial.

M26 Women with a multiple pregnancy with no risk of risk of preterm birth – Repeat antenatal corticosteroids

M26 NHMRC Evidence summary

What is the safety for the mother and fetus, infant, child, adult of administering repeat course(s) of antenatal corticosteroids to women with multiple pregnancy (twins and higher order) prophylactically (not at additional risk for preterm birth)?		
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
There is no randomised controlled trial evidence for the use of prophylactic antenatal corticosteroids in women with multiple pregnancy with no additional risk of preterm birth.	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 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')*		
N/A	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is not consistent
	NA	Not applicable (one study only)
3. Clinical impact *(indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
N/A	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?)*		
N/A	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether sensible to apply
5. Applicability *(is the body of evidence relevant to the New Zealand / Australian healthcare context in terms of health services / delivery of care and cultural factors?)*		
N/A	A	Evidence directly applicable to New Zealand / Australian healthcare context
	B	Evidence applicable to New Zealand / Australian healthcare context with few caveats
	C	Evidence probably applicable to New Zealand / Australian healthcare context with some caveats
	D	Evidence not applicable to New Zealand / 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)*		
No randomised controlled trial data were available		
EVIDENCE STATEMENT MATRIX *(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	N/A	
2. Consistency	N/A	
3. Clinical Impact	N/A	

4. Generalisability	N/A	
5. Applicability	N/A	

Evidence statement

RECOMMENDATION *(What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible)*	**OVERALL GRADE OF RECOMMENDATION**	
Do not use repeat antenatal corticosteroids in women with a multiple pregnancy where there is no other identified risk of preterm birth.	**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 recommendations(s) but care should be taken in its application
	D	Body of evidence is weak and recommendation must be applied with caution
	PP	**Practice Point**

UNRESOLVED ISSUES *(If needed, keep a 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 implementation of this recommendation?	**YES**
	NO

M26 GRADE Evidence summary

Considered Judgement - Strength of recommendation							
What is the safety for the mother and fetus, infant, child, adult of administering a repeat course(s) of antenatal corticosteroids to women with a multiple pregnancy (twins and higher order) prophylactically (not at additional risk for preterm birth)?							
1. Outcome measures:	**Quality of evidence**				**Importance of outcome in making a decision**		
Maternal Outcomes	**HIGH**	**MOD**	**LOW**	**V. LOW**	**Critical**	**Important**	**Not Important**
O_1 Chorioamnionitis				NR	✓		
O_2 Puerperal sepsis				NR	✓		
O_3 Pyrexia after entry to trial				NR		✓	
O_4 Intrapartum fever requiring antibiotics				NR		✓	
O_5 Post natal pyrexia				NR		✓	
O_6 Maternal quality of life				NR	✓		
Infant Outcomes	**HIGH**	**MOD**	**LOW**	**V. LOW**	**Critical**	**Important**	**Not Important**
O_1 Combined fetal and neonatal death				NR	✓		
O_2 Neonatal death				NR	✓		
O_3 Fetal death				NR	✓		
O_4 RDS				NR	✓		
O_5 Composite of serious outcomes for the infant				NR	✓		
O_6 Neurosensory disability (composite of impairments) for infant as a child				NR	✓		
O_7 Survival free of neurosensory disability for the infant as a child				NR	✓		
O_8 Survival free of metabolic disease for the infant as a child				NR		✓	
O_9 Neurosensory disability (composite of impairments) for infant as an adult				NR	✓		
O_{10} Survival free of neurosensory disability for the infant as an adult				NR	✓		
O_{11} Survival free of metabolic disease for the infant as an adult				NR		✓	
2. Is there is insufficient evidence to make a recommendation?							
Evidence statement *Maternal* No evidence was identified for maternal primary outcomes of these Clinical Practice Guidelines for the use of a single course of prophylactic antenatal corticosteroids where there is no additional risk of imminent preterm birth in women with a multiple pregnancy. *Infant* No evidence was available from randomised controlled trials.							
3. What benefit will the proposed intervention/action have?							
Evidence statement *Maternal* - No evidence was available on maternal outcomes. *Infant* - No randomised controlled trial evidence.						**Quality of evidence** **NOT REPORTED**	
Judging the benefits in context Not applicable.							
4. What harm might the proposed intervention/action do?							
Evidence statement *Maternal* - No evidence was available on maternal outcomes. *Infant* - No randomised controlled trial evidence. .						**Quality of evidence** **NOT REPORTED**	
Judging the harms in context Not applicable.							
5. What is the likely balance between good and harm?							
Evidence statement *Maternal* - No evidence was available on maternal outcomes. *Infant* - No randomised controlled trial evidence.						**Overall quality of evidence** **NOT REPORTED**	
Judging the balance of benefits and harms in context Not applicable.							
Benefits clearly outweigh harms	Recommend					**STRONG**	
Benefits probably outweigh harms	Consider					**CONDITIONAL**	

Not known	**Make a recommendation for research (see 8 below)**	**WEAK**
Benefits probably don't outweigh harms	Consider against/make no recommendation	**CONDITIONAL**
Harms probably outweigh benefits		
Benefits clearly don't outweigh harms	Recommend against	**STRONG**
Harms clearly outweigh benefits		

6. Is the intervention/action implementable in the New Zealand context?

Summary statement
Antenatal corticosteroids are already widely in use in New Zealand and Australia.

Yes	**Recommend/consider**
Not known	Consider economic evaluation
No	Recommend/consider against

7. Final recommendation

	Strength of recommendation
Do not use repeat antenatal corticosteroids in women with a multiple pregnancy where there is no other identified risk of preterm birth.	**STRONG** **CONDITIONAL** **WEAK (Practice Point)**

8. Recommendations for research

- In settings where prophylactic antenatal corticosteroids are being used in women with a multiple pregnancy, with no other identified risk of preterm birth, there is a need for a randomised trial.

M27 Women with diabetes mellitus or gestational diabetes at risk of preterm birth – Single course of antenatal corticosteroids

M27 NHMRC Evidence summary

What is the safety for the mother and fetus, infant, child, adult of administering a single course of antenatal corticosteroids to women with diabetes mellitus or gestational diabetes at risk of preterm birth?		
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Maternal Five trials included in the Roberts CPG version 2015 systematic review for a single course of antenatal corticosteroids reported the inclusion of a very small proportion of women with diabetes in pregnancy. Two of these trials reported on maternal outcomes. Infant Four of the five trials included in the Roberts CPG version 2015 systematic review for a single course of antenatal corticosteroids that reported the inclusion of a very small proportion of women with diabetes in pregnancy contributed data on infant outcomes.	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 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')*		
Maternal The treatment effects for chorioamnionitis and intrapartum pyrexia were in the opposite direction of the overall treatment effect, but there were no significant differences between treatment groups. The confidence intervals are extremely wide for these outcomes indicating imprecision. Treatment effects for pyrexia after trial entry, postnatal pyrexia and puerperal sepsis were similar to the overall treatment effect, and there were no significant differences between groups. A single trial conducted in women with severe pre-eclampsia reported a significant increase in maternal blood glucose ≥72 hours following administration of antenatal corticosteroids. Infant There were statistically significant reductions in risk of perinatal death, neonatal death, respiratory distress syndrome and moderate/severe respiratory distress syndrome with treatment effects similar to the overall treatment effect. The treatment effect for fetal death was similar to the overall treatment effect and was not statistically significant.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is not consistent
	NA	Not applicable (one study only)
3. Clinical impact *(indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Maternal No increased risk of maternal infection. Some evidence of increased maternal blood glucose in women with severe pre-eclampsia following a single course of antenatal corticosteroids. Infant Significant reductions in mortality and respiratory distress syndrome.	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?)*		
Evidence from a variety of healthcare settings. Studies conducted Brazil, Canada, and USA.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether sensible to apply
5. Applicability *(is the body of evidence relevant to the New Zealand / Australian healthcare context in terms of health services / delivery of care and cultural factors?)*		
Corticosteroids are readily available in Australia and New Zealand and their use is feasible.	A	Evidence directly applicable to New Zealand / Australian healthcare context
	B	Evidence applicable to New Zealand / Australian healthcare context with few caveats
	C	Evidence probably applicable to New Zealand / Australian healthcare context with some caveats
	D	Evidence not applicable to New Zealand / 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 is based on a subset of data from trials that reported they included a proportion of women with diabetes in pregnancy. This level of evidence cannot be used to form a clinical recommendation

EVIDENCE STATEMENT MATRIX *(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	NA	Not applicable
2. Consistency	NA	Not applicable
3. Clinical Impact	NA	Not applicable
4. Generalisability	NA	Not applicable
5. Applicability	NA	Not applicable

Evidence statement

The presence of maternal diabetes in pregnancy is not a reason to withhold antenatal corticosteroids where there is a risk of preterm birth. These women will require blood glucose monitoring and management of hyperglycaemia as per local protocols.

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

Use a single course of antenatal corticosteroids for women with diabetes in pregnancy or gestational diabetes at risk of preterm birth.

Where appropriate, monitor women with diabetes in pregnancy or gestational diabetes at risk of preterm birth for signs of puerperal sepsis when antenatal corticosteroids have been given.

OVERALL GRADE OF RECOMMENDATION	
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 recommendations(s) but care should be taken in its application
D	Body of evidence is weak and recommendation must be applied with caution
PP	**Practice Points**

UNRESOLVED ISSUES *(If needed, keep a 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 implementation of this recommendation?	**YES**
	NO

M27 GRADE Evidence summary

Considered Judgement - Strength of recommendation

What is the safety for the mother and fetus, infant, child, adult of administering a single course of antenatal corticosteroids to women with diabetes mellitus or gestational diabetes at risk of preterm birth?

1. Outcome measures:	Quality of evidence				Importance of outcome in making a decision		
Maternal Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O_1 Chorioamnionitis	✓				✓		
O_2 Puerperal sepsis		✓			✓		
O_3 Pyrexia after entry to trial		✓				✓	
O_4 Intrapartum fever requiring antibiotics		✓				✓	
O_5 Post natal pyrexia	✓					✓	
O_6 Maternal quality of life				NR	✓		
Infant Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O_1 Combined fetal and neonatal death		✓			✓		
O_2 Neonatal death		✓			✓		
O_3 Fetal death			✓		✓		
O_4 RDS		✓			✓		
O_5 Composite of serious outcomes for the infant				NR	✓		
O_6 Neurosensory disability (composite of impairments) for infant as a child				NR	✓		
O_7 Survival free of neurosensory disability for the infant as a child				NR	✓		
O_8 Survival free of metabolic disease for the infant as a child				NR		✓	
O_9 Neurosensory disability (composite of impairments) for infant as an adult				NR	✓		
O_{10} Survival free of neurosensory disability for the infant as an adult				NR	✓		
O_{11} Survival free of metabolic disease for the infant as an adult				NR		✓	

2. Is there is insufficient evidence to make a recommendation?

Evidence statement - Evidence is based on a subset of data from trials that reported they included a proportion of women with diabetes in pregnancy. This level of evidence cannot be used to form a clinical recommendation

Maternal - Evidence for maternal primary outcomes is based on trials included in the Roberts CPG version 2015 systematic review for a single course of antenatal corticosteroids that recruited and reported on a proportion of women with diabetes mellitus or gestational diabetes. Evidence for pyrexia after trial entry and puerperal sepsis is based on two trials, involving 336 women, and evidence for chorioamnionitis, intrapartum pyrexia requiring treatment, and postnatal pyrexia requiring treatment is based on one trial involving 218 women. No data were reported for maternal quality of life.
Infant - The evidence for infant primary outcomes is based on trials included in the Roberts CPG version 2015 systematic review for a single course of antenatal corticosteroids that recruited and reported on a proportion of women with diabetes mellitus or gestational diabetes. Three trials, involving 489 infants reported on perinatal and fetal death, and four trials involving 783 infants reported on neonatal death. Four trials involving 783 infants reported on respiratory distress syndrome. No data were reported for composite serious outcome.

3. What benefit will the proposed intervention/action have?

Evidence statement	Quality of evidence
Maternal - One trial reporting maternal outcomes in women with diabetes mellitus or gestational diabetes following exposure to single course of antenatal corticosteroids found no difference in risk of chorioamnionitis, intrapartum pyrexia or postnatal pyrexia requiring treatment, or pyrexia after trial entry between those exposed to a single course of antenatal corticosteroids and those not exposed. *Infant* - There were significant reductions in perinatal and neonatal death, and respiratory distress syndrome following exposure to a single course of antenatal corticosteroids in trials that recruited and reported a proportion of women with diabetes in pregnancy. There was no difference in risk of fetal death.	**Not applicable**

Judging the benefits in context
The evidence is direct evidence from trials that recruited and reported a proportion of women with diabetes in pregnancy and that compared outcomes in women and infants exposed to a single course of antenatal corticosteroid with those exposed to placebo or no treatment. The trials were conducted in Brazil and the United States. Effect sizes for respiratory distress syndrome, and measures of mortality (where applicable) are substantial and demonstrate significant reductions in risk.

4. What harm might the proposed intervention/action do?

Evidence statement	Quality of evidence
Maternal - One trial recruited and reported that 18% of participants had gestational diabetes and reported a significant increase in maternal blood glucose. There was no other evidence of health harm for the mother. *Infant* - There was no evidence of harm to the infant.	**Not applicable**

Judging the harms in context Evidence for increased maternal blood glucose following a single course of antenatal corticosteroid is based on a single trial involving a small number of women with a major co-morbidity (severe pre-eclampsia) limiting its generalizability. The wide confidence interval suggests imprecision and this analysis should be interpreted with caution.	
5. What is the likely balance between good and harm?	
Evidence statement *Maternal* - There does not appear to be an increased risk of maternal infection although there is a possibility of increased risk of maternal blood glucose following exposure to a single course of antenatal corticosteroids. *Infant* - Significant reductions in mortality and respiratory distress syndrome for the infants.	**Overall quality of evidence** **Not applicable**

Judging the balance of benefits and harms in context Exposure to a single course of antenatal corticosteroid is unlikely to cause harm to the mother in settings with adequate facilities for monitoring and treating increased blood glucose levels. The significant health benefits for the infant, in terms of reduced risk of mortality and respiratory morbidity outweigh the potential harm to the mother of transient elevations in blood glucose levels.		
Benefits clearly outweigh harms	Recommend	STRONG
Benefits probably outweigh harms	Consider	CONDITIONAL
Not known	**Make a recommendation for research (see 8 below)**	**WEAK**
Benefits probably don't outweigh harms	Consider against/make no recommendation	CONDITIONAL
Harms probably outweigh benefits		
Benefits clearly don't outweigh harms	Recommend against	STRONG
Harms clearly outweigh benefits		

6. Is the intervention/action implementable in the New Zealand context?	
Summary statement Antenatal corticosteroids are already widely in use in New Zealand and Australia.	
Yes	**Recommend/consider**
Not known	Consider economic evaluation
No	Recommend/consider against

7. Final recommendation	
Use a single course of antenatal corticosteroids for women with diabetes in pregnancy or gestational diabetes at risk of preterm birth. Where appropriate, monitor women with diabetes in pregnancy or gestational diabetes at risk of preterm birth for signs of puerperal sepsis when antenatal corticosteroids have been given.	**Strength of recommendation** *Please select level* **STRONG** **CONDITIONAL** **WEAK (Practice points)**

8. Recommendations for research
• Future randomised trials of antenatal corticosteroids should review the effect on maternal glucose tolerance.

M28 Women with diabetes mellitus or gestational diabetes at risk of preterm birth – Repeat antenatal corticosteroids

M28 NHMRC Evidence summary

What is the safety for the mother and fetus, infant, child, adult of administering repeat antenatal corticosteroids to women with diabetes mellitus or gestational diabetes at risk of preterm birth?		
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Maternal Four of the ten trials included in the Crowther (2011) systematic review reported including a small proportion of women with diabetes in pregnancy and report on maternal outcomes. Infant Four trials included in the Crowther (2011) systematic review reported including a small proportion of women with diabetes in pregnancy and report on infant outcomes.	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 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')*		
Maternal The treatment effects for chorioamnionitis and puerperal sepsis were similar to the overall treatment effect and no significant difference was seen between the treatment groups. Infant For perinatal, fetal and neonatal death, respiratory distress syndrome, severe respiratory distress syndrome and a composite of serious infant outcomes the treatment effect was similar to the overall treatment effect with no statistically significant differences seen between those exposed to repeat antenatal corticosteroids and those not exposed.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is not consistent
	NA	Not applicable (one study only)
3. Clinical impact *(indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Maternal No evidence of increased risk of infection following treatment with repeat antenatal corticosteroids. Infant No increased risk of mortality. Although the treatment effect for respiratory distress syndrome and a composite of serious infant outcomes was similar to the overall treatment effect, there were no statistically significant differences between groups from trials that reported including a proportion of women with diabetes in pregnancy.	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?)*		
Evidence from a variety of healthcare settings. Studies conducted in USA, Finland and a multicentre trial including 80 centres in 20 countries.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether sensible to apply
5. Applicability *(is the body of evidence relevant to the New Zealand / Australian healthcare context in terms of health services / delivery of care and cultural factors?)*		
Corticosteroids are readily available in Australia and New Zealand and their use is feasible.	A	Evidence directly applicable to New Zealand / Australian healthcare context
	B	Evidence applicable to New Zealand / Australian healthcare context with few caveats
	C	Evidence probably applicable to New Zealand / Australian healthcare context with some caveats
	D	Evidence not applicable to New Zealand / 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 is based on a subset of data from trials that reported they included a proportion of women with diabetes in pregnancy. This level of evidence cannot be used to form a clinical recommendation		

EVIDENCE STATEMENT MATRIX *(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	NA	Not applicable
2. Consistency	NA	Not applicable
3. Clinical Impact	NA	Not applicable
4. Generalisability	NA	Not applicable
5. Applicability	NA	Not applicable

Evidence statement

The presence of maternal diabetes in pregnancy is not a reason to withhold antenatal corticosteroids where there is a risk of preterm birth. These women will require blood glucose monitoring and management of hyperglycaemia as per local protocols.

RECOMMENDATION *(What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible)*	**OVERALL GRADE OF RECOMMENDATION**	
Repeat antenatal corticosteroids for a woman with diabetes in pregnancy or gestational diabetes at risk of preterm birth. Women with diabetes in pregnancy or gestational diabetes at risk of preterm birth and receiving antenatal corticosteroids will require blood glucose monitoring and management of any hyperglycaemia. Where appropriate, monitor women with diabetes in pregnancy or gestational diabetes for signs of puerperal sepsis when antenatal corticosteroids have been given. Where appropriate, estimate the risk of preterm birth by considering the use of adjunct prediction tests including fetal fibronectin and assessment of cervical length.	**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 recommendations(s) but care should be taken in its application
	D	Body of evidence is weak and recommendation must be applied with caution
	PP	**Practice Point**

UNRESOLVED ISSUES *(If needed, keep a 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 There may be changes in practice to give antenatal corticosteroids to this group and monitor blood glucose concentrations**
	NO
Are there any resource implications associated with implementing this recommendation?	**YES Additional monitoring**
	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 implementation of this recommendation?	**YES in terms of educational requirements to effectively change practice if required**
	NO

M28 GRADE Evidence summary

Considered Judgement - Strength of recommendation

What is the safety for the mother and fetus, infant, child, adult of administering a repeat course(s) of antenatal corticosteroids to women with diabetes mellitus or gestational diabetes at risk of preterm birth?

1. Outcome measures:	Quality of evidence				Importance of outcome in making a decision		
Maternal Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O_1 Chorioamnionitis	✓				✓		
O_2 Puerperal sepsis	✓				✓		
O_3 Pyrexia after entry to trial				NR		✓	
O_4 Intrapartum fever requiring antibiotics				NR		✓	
O_5 Post natal pyrexia				NR		✓	
O_6 Maternal quality of life				NR	✓		
Infant Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O_1 Combined fetal and neonatal death	✓				✓		
O_2 Neonatal death	✓				✓		
O_3 Fetal death		✓			✓		
O_4 RDS	✓				✓		
O_5 Composite of serious outcomes for the infant	✓				✓		
O_6 Neurosensory disability (composite of impairments) for infant as a child				NR	✓		
O_7 Survival free of neurosensory disability for the infant as a child				NR	✓		
O_8 Survival free of metabolic disease for the infant as a child				NR		✓	
O_9 Neurosensory disability (composite of impairments) for infant as an adult				NR	✓		
O_{10} Survival free of neurosensory disability for the infant as an adult				NR	✓		
O_{11} Survival free of metabolic disease for the infant as an adult				NR		✓	

2. Is there is insufficient evidence to make a recommendation?

Evidence statement - Evidence is based on a subset of data from trials that reported they included a proportion of women with diabetes in pregnancy. This level of evidence cannot be used to form a clinical recommendation

Maternal - Evidence for maternal primary outcomes is based on trials included in the Crowther (2011) Cochrane systematic review that recruited and reported a proportion of women with diabetes in pregnancy. One trial involving 1853 women reported on chorioamnionitis, and two trials involving 2102 women reported on puerperal sepsis. No data were reported for the other primary outcomes.
Infant - Evidence for infant primary outcomes is based on trials included in the Crowther (2011) Cochrane systematic review that recruited and reported a proportion of women with diabetes in pregnancy. Three trials involving 2742 infants reported on perinatal death, two trials involving 438 infants reported on neonatal death and fetal death. Two trials involving 438 infants reported on respiratory distress syndrome and one trial involving 2304 infants reported on a composite of serious infant outcomes.

3. What benefit will the proposed intervention/action have?

Evidence statement	Quality of evidence
Maternal - There is no difference in the risk of chorioamnionitis or puerperal sepsis between women who received repeat antenatal corticosteroids and no repeat treatment in trials that recruited and reported a proportion of women with diabetes in pregnancy. *Infant* - There were no differences between exposure to repeat antenatal corticosteroids and no repeat exposure for perinatal death, neonatal death or fetal death in trials that recruited and reported a proportion of women with diabetes in pregnancy. In trials that recruited and reported a proportion of women with diabetes in pregnancy, no difference was seen in respiratory distress syndrome between repeat antenatal corticosteroids and no repeat antenatal corticosteroids.	**Not applicable**

Judging the benefits in context
The evidence is direct evidence from trials conducted in women exposed to repeat antenatal corticosteroids (or placebo) after remaining at imminent risk of preterm birth following an initial single course of antenatal corticosteroids that were included in the Crowther (2011) Cochrane systematic review. Evidence for outcomes of these Clinical Practice Guidelines is based on the trials included in the review that recruited and reported on the proportion of women with diabetes in pregnancy. The populations are from a variety of healthcare settings including the United States and Finland, and a multicentre trial involving 80 centres in 20 countries.

4. What harm might the proposed intervention/action do?

Evidence statement	Quality of evidence
Maternal -There do not appear to be health harms for the mother in terms of increased risk of infection. *Infant* - There do not appear to be health harms for the infant.	**Not applicable**

Judging the harms in context
The proportion of women with diabetes in trials of repeat antenatal corticosteroids is relatively small and independent effects of gestational

diabetes or type 2 diabetes were unable to be determined, if any.

5. What is the likely balance between good and harm?

Evidence statement	**Overall quality of evidence**
Maternal - There does not appear to be an increased risk of maternal infection. Overall evidence indicates an increased risk of elevated maternal blood glucose levels following antenatal corticosteroids in non-diabetic women. *Infant* - There do not appear to be any health harms for the infant. Overall evidence indicates significant benefits for the infant.	**Not applicable**

Judging the balance of benefits and harms in context
In view of the significant benefits to the infant in terms of reduced mortality and respiratory morbidity, the presence of maternal diabetes in pregnancy is not a reason to withhold antenatal corticosteroids where there is a risk of preterm birth and facilities exist to monitor and manage maternal hyperglycaemia.

Benefits clearly outweigh harms	Recommend	STRONG
Benefits probably outweigh harms	Consider	CONDITIONAL
Not known	**Make a recommendation for research (see 8 below)**	**WEAK**
Benefits probably don't outweigh harms	Consider against/make no recommendation	CONDITIONAL
Harms probably outweigh benefits		
Benefits clearly don't outweigh harms	Recommend against	STRONG
Harms clearly outweigh benefits		

6. Is the intervention/action implementable in the New Zealand context?

Summary statement
Antenatal corticosteroids are already widely in use in New Zealand and Australia.

Yes	**Recommend/consider**
Not known	Consider economic evaluation
No	Recommend/consider against

7. Final recommendation

	Strength of recommendation *Please select level*
Repeat antenatal corticosteroids for a woman with diabetes in pregnancy or gestational diabetes at risk of preterm birth. Women with diabetes in pregnancy or gestational diabetes at risk of preterm birth and receiving antenatal corticosteroids will require blood glucose monitoring and management of any hyperglycaemia. Where appropriate, monitor women with diabetes in pregnancy or gestational diabetes for signs of puerperal sepsis when antenatal corticosteroids have been given. Where appropriate, estimate the risk of preterm birth by considering the use of adjunct prediction tests including fetal fibronectin and assessment of cervical length.	**STRONG** **CONDITIONAL** **WEAK (Practice points)**

8. Recommendations for research

- Any future randomised trials of repeat antenatal corticosteroids should report their effect on maternal glucose tolerance.
- Identify the best management of women with diabetes in pregnancy given repeat antenatal corticosteroids.

M29 Women with systemic infection at trial entry at risk of preterm birth – Single course of antenatal corticosteroids

M29 NHMRC Evidence summary

What is the safety for the mother and fetus, infant, child, adult of administering a single course of antenatal corticosteroids to women with systemic infection at trial entry at risk of preterm birth?		
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Eight of the 26 trials included in the Roberts CPG version 2015 systematic review for a single course of antenatal corticosteroids excluded women with systemic infection at trial entry and the remaining 18 did not state if a proportion of women included in their trials had systemic infection at trial entry. Consequently there is no evidence available for maternal or infant outcomes.	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 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')*		
N/A	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is not consistent
	NA	Not applicable (one study only)
3. Clinical impact *(indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
N/A	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?)*		
N/A	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether sensible to apply
5. Applicability *(is the body of evidence relevant to the New Zealand / Australian healthcare context in terms of health services / delivery of care and cultural factors?)*		
N/A	A	Evidence directly applicable to New Zealand / Australian healthcare context
	B	Evidence applicable to New Zealand / Australian healthcare context with few caveats
	C	Evidence probably applicable to New Zealand / Australian healthcare context with some caveats
	D	Evidence not applicable to New Zealand / 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)*		
There was no RCT evidence identified		

EVIDENCE STATEMENT MATRIX *(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	NA	Not applicable
2. Consistency	NA	Not applicable
3. Clinical Impact	NA	Not applicable

4. Generalisability	NA	Not applicable
5. Applicability	NA	Not applicable

Evidence statement

No randomised controlled trial evidence was available for the use of a single course of antenatal corticosteroids in women with systemic infection at trial entry.

RECOMMENDATION *(What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible)*	**OVERALL GRADE OF RECOMMENDATION**	
Use a single course of antenatal corticosteroids for women with a systemic infection at risk of preterm birth. Do not delay birth in women with a systemic infection to administer a single course antenatal corticosteroids if at risk of preterm birth.	**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 recommendations(s) but care should be taken in its application
	D	Body of evidence is weak and recommendation must be applied with caution
	PP	**Practice Points**

UNRESOLVED ISSUES *(If needed, keep a 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 implementation of this recommendation?	**YES**
	NO

M29 GRADE Evidence summary

Considered Judgement - Strength of recommendation							
What is the safety for the mother and fetus, infant, child, adult of administering a single course of antenatal corticosteroids to women with systemic infection at trial entry at risk of preterm birth?							
1. Outcome measures:	**Quality of evidence**				**Importance of outcome in making a decision**		
Maternal Outcomes	**HIGH**	**MOD**	**LOW**	**V. LOW**	**Critical**	**Important**	**Not Important**
O_1 Chorioamnionitis				NR	✓		
O_2 Puerperal sepsis				NR	✓		
O_3 Pyrexia after entry to trial				NR		✓	
O_4 Intrapartum fever requiring antibiotics				NR		✓	
O_5 Post natal pyrexia				NR		✓	
O_6 Maternal quality of life				NR	✓		
Infant Outcomes	**HIGH**	**MOD**	**LOW**	**V. LOW**	**Critical**	**Important**	**Not Important**
O_1 Combined fetal and neonatal death				NR	✓		
O_2 Neonatal death				NR	✓		
O_3 Fetal death				NR	✓		
O_4 RDS				NR	✓		
O_5 Composite of serious outcomes for the infant				NR	✓		
O_6 Neurosensory disability (composite of impairments) for infant as a child				NR	✓		
O_7 Survival free of neurosensory disability for the infant as a child				NR	✓		
O_8 Survival free of metabolic disease for the infant as a child				NR		✓	
O_9 Neurosensory disability (composite of impairments) for infant as an adult				NR	✓		
O_{10} Survival free of neurosensory disability for the infant as an adult				NR	✓		
O_{11} Survival free of metabolic disease for the infant as an adult				NR		✓	
2. Is there is insufficient evidence to make a recommendation?							
Evidence statement *(For example, low volume or inconsistent evidence, low patient numbers.)* *Maternal* - The Roberts CPG version 2015 systematic review for a single course of antenatal corticosteroids did not report data for women with a known infection at trial entry. There is no randomised controlled trial evidence currently reported for the maternal primary outcomes for theses Clinical Practice Guidelines for the use of a single course of antenatal corticosteroids in women with a known systemic infection at trial entry and who were at risk of preterm birth. *Infant* - No randomised controlled trial evidence is currently reported for the infant primary outcomes for these Clinical Practice Guidelines following exposure to a single course of antenatal corticosteroids where the mother was known to have a systemic infection at trial entry and who were at risk of preterm birth.							
3. What benefit will the proposed intervention/action have?							
Evidence statement *Maternal* - Not applicable. *Infant* - Not applicable.						**Quality of evidence** **NOT REPORTED**	
Judging the benefits in context Not applicable.							
4. What harm might the proposed intervention/action do?							
Evidence statement *Maternal* - Not applicable. *Infant* - Not applicable.						**Quality of evidence** **NOT REPORTED**	
Judging the harms in context *Maternal* - Not applicable. *Infant* - Not applicable.							
5. What is the likely balance between good and harm?							
Evidence statement *Maternal* - Not applicable. *Infant* - Not applicable.						**Overall quality of evidence** **NOT REPORTED**	
Judging the balance of benefits and harms in context Not applicable.							
Benefits clearly outweigh harms	Recommend					STRONG	
Benefits probably outweigh harms	Consider					**CONDITIONAL**	

Not known	**Make a recommendation for research (see 8 below)**	**WEAK**
Benefits probably don't outweigh harms	Consider against/make no recommendation	**CONDITIONAL**
Harms probably outweigh benefits		
Benefits clearly don't outweigh harms	Recommend against	**STRONG**
Harms clearly outweigh benefits		

6. Is the intervention/action implementable in the New Zealand context?

Summary statement
Antenatal corticosteroids are already widely in use in New Zealand and Australia.

Yes	**Recommend/consider**
Not known	Consider economic evaluation
No	Recommend/consider against

7. Final recommendation

	Strength of recommendation *Please select level* **STRONG** **CONDITIONAL** **WEAK (Practice Points)**
Use a single course of antenatal corticosteroids for women with a systemic infection at risk of preterm birth. Do not delay birth in women with a systemic infection to administer a single course antenatal corticosteroids if at risk of preterm birth.	

8. Recommendations for research

- In future randomised trials of antenatal corticosteroids there is a need to assess the impact, if any, of a single course of antenatal corticosteroids in women with systemic infection at risk of preterm birth.

M30 Women with systemic infection at trial entry at risk of preterm birth – Repeat antenatal corticosteroids

M30 NHMRC Evidence summary

What is the safety for the mother and fetus, infant, child, adult of administering repeat antenatal corticosteroids to women with systemic infection at trial entry at risk of preterm birth?		
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Women with active tuberculosis or human immunodeficiency virus were not eligible for two trials in the Crowther (2011) systematic review. There was insufficient detail in the remaining trials to ascertain if women with a known systemic infection were included. As such, no data was available on maternal or infant outcomes.	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 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')*		
N/A	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is not consistent
	NA	Not applicable (one study only)
3. Clinical impact *(indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
N/A	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?)*		
N/A	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether sensible to apply
5. Applicability *(is the body of evidence relevant to the New Zealand / Australian healthcare context in terms of health services / delivery of care and cultural factors?)*		
N/A	A	Evidence directly applicable to New Zealand / Australian healthcare context
	B	Evidence applicable to New Zealand / Australian healthcare context with few caveats
	C	Evidence probably applicable to New Zealand / Australian healthcare context with some caveats
	D	Evidence not applicable to New Zealand / 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)*		
No randomised controlled trial evidence identified		
EVIDENCE STATEMENT MATRIX *(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	NA	Not applicable
2. Consistency	NA	Not applicable
3. Clinical Impact	NA	Not applicable
4. Generalisability	NA	Not applicable
5. Applicability	NA	Not applicable

Evidence statement No randomised controlled trial evidence was available on maternal and infant outcomes.		
RECOMMENDATION *(What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible)* Repeat antenatal corticosteroids for women with a systemic infection at risk of preterm birth. Do not delay birth in women with a systemic infection to administer repeat antenatal corticosteroids if at risk of preterm birth. Where appropriate, monitor women with systemic infection at risk of preterm birth for signs of puerperal sepsis when antenatal corticosteroids have been given	**OVERALL GRADE OF RECOMMENDATION**	
	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 recommendations(s) but care should be taken in its application
	D	Body of evidence is weak and recommendation must be applied with caution
	PP	**Practice Points**
UNRESOLVED ISSUES *(If needed, keep a 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 implementation of this recommendation?	**YES**	
	NO	

M30 GRADE Evidence summary

Considered Judgement - Strength of recommendation							
What is the safety for the mother and fetus, infant, child, adult of administering a repeat course(s) of antenatal corticosteroids to women with systemic infection at trial entry at risk of preterm birth?							
1. Outcome measures:	**Quality of evidence**				**Importance of outcome in making a decision**		
Maternal Outcomes	**HIGH**	**MOD**	**LOW**	**V. LOW**	**Critical**	**Important**	**Not Important**
O_1 Chorioamnionitis				NR	✓		
O_2 Puerperal sepsis				NR	✓		
O_3 Pyrexia after entry to trial				NR		✓	
O_4 Intrapartum fever requiring antibiotics				NR		✓	
O_5 Post natal pyrexia				NR		✓	
O_6 Maternal quality of life				NR	✓		
Infant Outcomes	**HIGH**	**MOD**	**LOW**	**V. LOW**	**Critical**	**Important**	**Not Important**
O_1 Combined fetal and neonatal death				NR	✓		
O_2 Neonatal death				NR	✓		
O_3 Fetal death				NR	✓		
O_4 RDS				NR	✓		
O_5 Composite of serious outcomes for the infant				NR	✓		
O_6 Neurosensory disability (composite of impairments) for infant as a child				NR	✓		
O_7 Survival free of neurosensory disability for the infant as a child				NR	✓		
O_8 Survival free of metabolic disease for the infant as a child				NR		✓	
O_9 Neurosensory disability (composite of impairments) for infant as an adult				NR	✓		
O_{10} Survival free of neurosensory disability for the infant as an adult				NR	✓		
O_{11} Survival free of metabolic disease for the infant as an adult				NR		✓	
2. Is there is insufficient evidence to make a recommendation?							
Evidence statement *Maternal* - The Crowther (2011) systematic review did not report data for women with a known infection at trial entry. There is no randomised controlled trial evidence currently reported for the maternal primary outcomes for theses Clinical Practice Guidelines for the use of a repeat course of antenatal corticosteroids in women with a known systemic infection at trial entry and who were at risk of preterm birth. *Infant* - No randomised controlled trial evidence is currently reported for the infant primary outcomes for these Clinical Practice Guidelines following exposure to a repeat course of antenatal corticosteroids where the mother was known to have a systemic infection at trial entry and who were at risk of preterm birth.							
3. What benefit will the proposed intervention/action have?							
Evidence statement *Maternal* - Not applicable. *Infant* - Not applicable.						**Quality of evidence** **NOT REPORTED**	
Judging the benefits in context Not applicable.							
4. What harm might the proposed intervention/action do?							
Evidence statement *Maternal* - Not applicable. *Infant* - Not applicable						**Quality of evidence** **NOT REPORTED**	
Judging the harms in context *Maternal* - Not applicable. *Infant* - Not applicable							
5. What is the likely balance between good and harm?							
Evidence statement *Maternal* - Not applicable. *Infant* - Not applicable						**Overall quality of evidence** **NOT REPORTED**	
Judging the balance of benefits and harms in context Not applicable.							
Benefits clearly outweigh harms	Recommend					**STRONG**	
Benefits probably outweigh harms	Consider					**CONDITIONAL**	

Not known	**Make a recommendation for research (see 8 below)**	**WEAK**
Benefits probably don't outweigh harms	Consider against/make no recommendation	**CONDITIONAL**
Harms probably outweigh benefits		
Benefits clearly don't outweigh harms	Recommend against	**STRONG**
Harms clearly outweigh benefits		

6. Is the intervention/action implementable in the New Zealand context?

Summary statement
Antenatal corticosteroids are already widely in use in New Zealand and Australia.

Yes	**Recommend/consider**
Not known	Consider economic evaluation
No	Recommend/consider against

7. Final recommendation

Repeat antenatal corticosteroids for women with a systemic infection at risk of preterm birth. Do not delay birth in women with a systemic infection to administer repeat antenatal corticosteroids if at risk of preterm birth. Where appropriate, monitor women with systemic infection at risk of preterm birth for signs of puerperal sepsis when antenatal corticosteroids have been given	**Strength of recommendation** *Please select level* **STRONG** **CONDITIONAL** **WEAK (Practice Point)**

8. Recommendations for research

- In future randomised trials of repeat antenatal corticosteroids there is a need to assess the impact, if any, on women with systemic infection at risk of preterm birth.

M31 Women with pregnancy associated hypertension/pre-eclampsia at risk of preterm birth – Single course of antenatal corticosteroids

M31 NHMRC Evidence summary

What is the safety for the mother and fetus, infant, child, adult of administering a single course of antenatal corticosteroids to women with pregnancy associated hypertension / pre-eclampsia at risk of preterm birth?		
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Maternal Women with pregnancy associated hypertension were included in a small proportion of women in ten of the trials included in the Roberts CPG version 2015 systematic review for a single course of antenatal corticosteroids. Infant Ten trials included in the Roberts CPG version 2015 systematic review for a single course of antenatal corticosteroids reported including a small proportion of women with pregnancy associated hypertension.	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 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')*		
Maternal Treatment effects for chorioamnionitis, postnatal pyrexia and puerperal sepsis were similar to the overall treatment effect and there was no difference between groups. Intrapartum pyrexia and pyrexia after trial entry had treatment effects opposite to the overall effect, with no difference between groups. Infant There was a significant reduction in risk of neonatal death, respiratory distress syndrome and moderate/severe respiratory distress syndrome. There was no difference in risk of fetal and perinatal death.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is not consistent
	NA	Not applicable (one study only)
3. Clinical impact *(indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Maternal No evidence of increased risk of maternal infection. Infant Significant reductions in the infant outcomes neonatal death and respiratory distress syndrome.	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?)*		
Evidence from a variety of healthcare settings. Studies conducted in Brazil, USA, Tunisia, UK, Finland, and New Zealand.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether sensible to apply
5. Applicability *(is the body of evidence relevant to the New Zealand / Australian healthcare context in terms of health services / delivery of care and cultural factors?)*		
Corticosteroids are readily available in Australia and New Zealand and their use is feasible.	A	Evidence directly applicable to New Zealand / Australian healthcare context
	B	Evidence applicable to New Zealand / Australian healthcare context with few caveats
	C	Evidence probably applicable to New Zealand / Australian healthcare context with some caveats
	D	Evidence not applicable to New Zealand / 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 is based on a subset of data from trials that reported they included a proportion of women with pregnancy associated hypertension. This level of evidence cannot be used to form a clinical recommendation		
EVIDENCE STATEMENT MATRIX *(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	NA	Not applicable
2. Consistency	NA	Not applicable
3. Clinical Impact	NA	Not applicable
4. Generalisability	NA	Not applicable
5. Applicability	NA	Not applicable
Evidence statement		

RECOMMENDATION *(What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible)*	**OVERALL GRADE OF RECOMMENDATION**	
Use a single course of antenatal corticosteroids for women with pregnancy associated hypertension at risk of preterm birth.	**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 recommendations(s) but care should be taken in its application
	D	Body of evidence is weak and recommendation must be applied with caution
	PP	**Practice Points**

UNRESOLVED ISSUES *(If needed, keep a 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 implementation of this recommendation?	**YES**
	NO

M31 GRADE Evidence summary

Considered Judgement - Strength of recommendation

What is the safety for the mother and fetus, infant, child, adult of administering a single course of antenatal corticosteroid to women with pregnancy associated hypertension / pre-eclampsia at risk of preterm birth?

1. Outcome measures:	Quality of evidence				Importance of outcome in making a decision		
Maternal Outcomes	**HIGH**	**MOD**	**LOW**	**V. LOW**	**Critical**	**Important**	**Not Important**
O_1 Chorioamnionitis	✓				✓		
O_2 Puerperal sepsis		✓			✓		
O_3 Pyrexia after entry to trial		✓				✓	
O_4 Intrapartum fever requiring antibiotics		✓				✓	
O_5 Post natal pyrexia	✓					✓	
O_6 Maternal quality of life				NR	✓		
Infant Outcomes	**HIGH**	**MOD**	**LOW**	**V. LOW**	**Critical**	**Important**	**Not Important**
O_1 Combined fetal and neonatal death		✓			✓		
O_2 Neonatal death		✓			✓		
O_3 Fetal death			✓		✓		
O_4 RDS		✓			✓		
O_5 Composite of serious outcomes for the infant				NR	✓		
O_6 Neurosensory disability (composite of impairments) for infant as a child				NR	✓		
O_7 Survival free of neurosensory disability for the infant as a child				NR	✓		
O_8 Survival free of metabolic disease for the infant as a child				NR		✓	
O_9 Neurosensory disability (composite of impairments) for infant as an adult				NR	✓		
O_{10} Survival free of neurosensory disability for the infant as an adult				NR	✓		
O_{11} Survival free of metabolic disease for the infant as an adult				NR		✓	

2. Is there is insufficient evidence to make a recommendation?

Evidence statement - Evidence is based on a subset of data from trials that reported they included a proportion of women with pregnancy associated hypertension. This level of evidence cannot be used to form a clinical recommendation

Maternal - The Roberts CPG version 2015 systematic review for a single course of antenatal corticosteroids reported data from two trials for women with pregnancy associated hypertension at risk of preterm birth. These Clinical Practice Guidelines analysed ten trials included in Roberts (2006) that recruited and reported a proportion of women in their trial with pregnancy associated hypertension. Women with pre-eclampsia were not eligible for five trials, and the remaining twelve trials did not specify if women with pregnancy associated hypertension were eligible for recruitment.
Infant - The Roberts CPG version 2015 systematic review for a single course of antenatal corticosteroids reported data from two trials for infants of women with pregnancy induced hypertension at risk of preterm birth. These Clinical Practice Guidelines analysed data from ten trials included in the Roberts (2006) review that recruited and reported a proportion of women in their trial with pregnancy associated hypertension.

3. What benefit will the proposed intervention/action have?

Evidence statement	**Quality of evidence**
Maternal - There does not appear to be an increase in risk of maternal infection in women with pregnancy associated hypertension exposed to a single course of antenatal corticosteroids. *Infant* - There was a significant reduction in relative risk of neonatal mortality by 50% following exposure to antenatal corticosteroids compared with no exposure in mothers with pregnancy associated hypertension. There was no difference in the risk of fetal or perinatal death. There was also a significant reduction in the risk of respiratory distress syndrome in favour of those infants exposed to antenatal corticosteroids.	**Not applicable**

Judging the benefits in context
The evidence is direct evidence from trials that recruited and reported on a proportion of women with pregnancy induced hypertension, and compared outcomes in women and infants exposed to antenatal corticosteroids with those unexposed. The trials were conducted in a variety of healthcare settings, including Brazil, United Kingdom, United States, Finland and New Zealand. Effect sizes for neonatal mortality are substantial and demonstrate significant reductions in risk.

4. What harm might the proposed intervention/action do?

Evidence statement	**Quality of evidence**
Maternal - There was no evidence of harm to the mother. *Infant* - There was no evidence of harm to the infant.	**Not applicable**

Judging the harms in context
The evidence is from trials that recruited and reported a proportion of women with pregnancy induced hypertension.

5. What is the likely balance between good and harm?		
Evidence statement *Maternal* - There does not appear to be an increased risk to the mother. *Infant* - There are significant benefits for the infant in terms of reduced risk of neonatal mortality and respiratory distress syndrome.		**Overall quality of evidence** **Not applicable**
Judging the balance of benefits and harms in context Exposure to a single course of antenatal corticosteroids in the presence of pregnancy induced hypertension is unlikely to harm to the mother. The significant health benefits for the infant, in terms of reduced risk of mortality and respiratory distress syndrome outweigh potential low impact harm for the mother.		
Benefits clearly outweigh harms	Recommend	STRONG
Benefits probably outweigh harms	Consider	CONDITIONAL
Not known	**Make a recommendation for research (see 8 below)**	**WEAK**
Benefits probably don't outweigh harms Harms probably outweigh benefits	Consider against/make no recommendation	CONDITIONAL
Benefits clearly don't outweigh harms Harms clearly outweigh benefits	Recommend against	STRONG

6. Is the intervention/action implementable in the New Zealand context?	
Summary statement Antenatal corticosteroids are already widely in use in New Zealand and Australia.	
Yes	**Recommend/consider**
Not known	Consider economic evaluation
No	Recommend/consider against

7. Final recommendation	
Use a single course of antenatal corticosteroids for women with pregnancy associated hypertension at risk of preterm birth.	**Strength of recommendation** *Please select level* **STRONG** **CONDITIONAL** **WEAK (Practice points)**

8. Recommendations for research

M32 Women with pregnancy associated hypertension/pre-eclampsia at risk of preterm birth – Repeat antenatal corticosteroids

M32 NHMRC Evidence summary

What is the safety for the mother and fetus, infant, child, adult of administering repeat antenatal corticosteroids to women with pregnancy associated hypertension / pre-eclampsia at risk of preterm birth?		
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Maternal Seven of the ten trials included in the Crowther (2011) systematic review reported including a small proportion of women in their trial with pregnancy associated hypertension. Four of these reported on chorioamnionitis, one provided data on postnatal pyrexia, and three provided data on puerperal sepsis. Infant Seven trials included in the Crowther (2011) systematic review reported including a proportion of women with pregnancy associated hypertension. Six trials provided data on perinatal death, five provided data for fetal death, five for neonatal death and respiratory distress syndrome and four for composite of serious infant outcomes.	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 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')*		
Maternal Treatment effects for chorioamnionitis, postnatal pyrexia and puerperal sepsis were similar to the overall treatment effect. There was no difference in risk of maternal infection between those exposed to repeat antenatal corticosteroids and those not exposed from trials that reported including a proportion of women with pregnancy associated hypertension. Infant Treatment effect sizes for respiratory distress syndrome and a composite of serious infant outcomes were similar to the overall treatment effects, with a significant reduction in risk for those exposed to repeat antenatal corticosteroids comparted with no repeat exposure. There was no statistically significant difference in risk of perinatal, fetal and neonatal death between groups.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is not consistent
	NA	Not applicable (one study only)
3. Clinical impact *(indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Maternal No evidence of increased risk of infection for the mother. Infant Significant reductions in risk of respiratory distress syndrome and a composite of serious infant outcomes. No increased risk of mortality.	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?)*		
Evidence from a variety of healthcare settings. Studies conducted in Australia and New Zealand, USA, Finland and a multicentre trial incorporating 80 centres in 20 countries.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether sensible to apply
5. Applicability *(is the body of evidence relevant to the New Zealand / Australian healthcare context in terms of health services / delivery of care and cultural factors?)*		
Corticosteroids are readily available in Australia and New Zealand and their use is feasible.	A	Evidence directly applicable to New Zealand / Australian healthcare context
	B	Evidence applicable to New Zealand / Australian healthcare context with few caveats
	C	Evidence probably applicable to New Zealand / Australian healthcare context with some caveats
	D	Evidence not applicable to New Zealand / 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 is based on a subset of data from trials that reported they included a proportion of women with pregnancy associated hypertension. This level of evidence cannot be used to form a clinical recommendation		

EVIDENCE STATEMENT MATRIX *(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	NA	Not applicable
2. Consistency	NA	Not applicable
3. Clinical Impact	NA	Not applicable
4. Generalisability	NA	Not applicable
5. Applicability	NA	Not applicable
Evidence statement		

RECOMMENDATION *(What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible)* Repeat antenatal corticosteroids for a woman with pregnancy associated hypertension at risk of preterm birth.	**OVERALL GRADE OF RECOMMENDATION**	
	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 recommendations(s) but care should be taken in its application
	D	Body of evidence is weak and recommendation must be applied with caution
	PP	**Practice Points**

UNRESOLVED ISSUES *(If needed, keep a 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 implementation of this recommendation?	**YES**
	NO

M32 GRADE Evidence summary

Considered Judgement - Strength of recommendation

What is the safety for the mother and fetus, infant, child, adult of administering a repeat course(s) of antenatal corticosteroid to women with pregnancy associated hypertension / pre-eclampsia at risk of preterm birth?

1. Outcome measures:	Quality of evidence				Importance of outcome in making a decision		
Maternal Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O_1 Chorioamnionitis	✓				✓		
O_2 Puerperal sepsis	✓				✓		
O_3 Pyrexia after entry to trial				NR		✓	
O_4 Intrapartum fever requiring antibiotics				NR		✓	
O_5 Post natal pyrexia		✓				✓	
O_6 Maternal quality of life				NR	✓		
Infant Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O_1 Combined fetal and neonatal death	✓				✓		
O_2 Neonatal death	✓				✓		
O_3 Fetal death		✓			✓		
O_4 RDS	✓				✓		
O_5 Composite of serious outcomes for the infant	✓				✓		
O_6 Neurosensory disability (composite of impairments) for infant as a child				NR	✓		
O_7 Survival free of neurosensory disability for the infant as a child				NR	✓		
O_8 Survival free of metabolic disease for the infant as a child				NR		✓	
O_9 Neurosensory disability (composite of impairments) for infant as an adult				NR	✓		
O_{10} Survival free of neurosensory disability for the infant as an adult				NR	✓		
O_{11} Survival free of metabolic disease for the infant as an adult				NR		✓	

2. Is there is insufficient evidence to make a recommendation?

Evidence statement - Evidence is based on a subset of data from trials that reported they included a proportion of women with pregnancy associated hypertension. This level of evidence cannot be used to form a clinical recommendation

Maternal - The Crowther (2011) systematic review did not report specific data for women with pregnancy associated hypertension at risk of preterm birth. These Clinical Practice Guidelines analysed trials that recruited and reported the inclusion of a proportion of women with pregnancy induced hypertension at risk of preterm birth.
Infant - These Clinical Practice Guidelines analysed trials that recruited and reported the inclusion of women with pregnancy induced hypertension at risk of preterm birth.

3. What benefit will the proposed intervention/action have?

Evidence statement	Quality of evidence
Maternal - There was no evidence for increased risk of maternal infection (chorioamnionitis, postnatal pyrexia requiring treatment, or puerperal sepsis) following exposure to a repeat course of antenatal corticosteroids. There was no data on quality of life. *Infant* - There was no evidence of an increase in risk of fetal, perinatal or neonatal mortality. There was a significant reduction in respiratory distress syndrome and a significant reduction in a composite of serious infant outcomes.	**Not applicable**

Judging the benefits in context
The evidence is from randomised controlled trials conducted in women at continued risk of preterm birth following a single course of antenatal corticosteroids, and which reported including a proportion of women with pregnancy associated hypertension. Effect sizes are similar to overall treatment effect.

4. What harm might the proposed intervention/action do?

Evidence statement	Quality of evidence
Maternal - There was no difference in risk between repeat exposure to antenatal corticosteroids and no repeat exposure for chorioamnionitis, postnatal pyrexia requiring treatment or puerperal sepsis in trials that recruited and reported a proportion of women with pregnancy associated hypertension at risk of preterm birth *Infant* - There was no difference in risk between repeat exposure to antenatal corticosteroids and no repeat exposure for perinatal, neonatal or fetal death among infants born to mothers with pregnancy associated hypertension from trials that recruited and reported a proportion of women with pregnancy associated hypertension at risk of preterm birth. There was a significant reduction in the risk of respiratory distress syndrome and a composite of serious infant outcomes in infants born to mothers with pregnancy associated hypertension following exposure to repeat antenatal corticosteroids.	**Not applicable**

Judging the harms in context
From analysis conducted for these Clinical Practice Guidelines, there does not appear to be an increased risk of harm from exposure to repeat

antenatal corticosteroids for the women with pregnancy associated hypertension, or their infants.

5. What is the likely balance between good and harm?

Evidence statement	**Overall quality of evidence**
Maternal - There are no direct health benefits for the mother of repeat antenatal corticosteroids. There does not appear to be any increased risk of harm for women with pregnancy associated hypertension exposed to repeat antenatal corticosteroids. *Infant* - There does not appear to be an increased risk of mortality for infants born to mothers with pregnancy associated hypertension, following exposure to repeat antenatal corticosteroids. There were significant reductions in the risk of respiratory distress syndrome and a composite of serious infant outcomes following exposure to repeat antenatal corticosteroids for infants born to mothers with pregnancy associated hypertension, in trials that recruited and reported a proportion of women with this condition.	**Not applicable**

Judging the balance of benefits and harms in context

Maternal - The use of repeat antenatal corticosteroids in women with pregnancy associated hypertension is unlikely to cause harm or benefit.
Infant - The use of repeat antenatal corticosteroids in infants of women with pregnancy associated hypertension is likely to be highly beneficial in terms of reduced risk of respiratory distress syndrome and composite.

Benefits clearly outweigh harms	Recommend	STRONG
Benefits probably outweigh harms	Consider	CONDITIONAL
Not known	**Make a recommendation for research (see 8 below)**	**WEAK**
Benefits probably don't outweigh harms	Consider against/make no recommendation	CONDITIONAL
Harms probably outweigh benefits		
Benefits clearly don't outweigh harms	Recommend against	STRONG
Harms clearly outweigh benefits		

6. Is the intervention/action implementable in the New Zealand context?

Summary statement
Antenatal corticosteroids are already widely in use in New Zealand and Australia.

Yes	**Recommend/consider**
Not known	Consider economic evaluation
No	Recommend/consider against

7. Final recommendation

	Strength of recommendation *Please select level*
Repeat antenatal corticosteroids for a woman with pregnancy associated hypertension at risk of preterm birth.	**STRONG** **CONDITIONAL** **WEAK (Practice points)**

8. Recommendations for research

M33 Women with a fetus with intrauterine growth restriction at risk of preterm birth – Single course of antenatal corticosteroids

M33 NHMRC Evidence summary

What is the safety for the mother and fetus, infant, child, adult of administering a single course of antenatal corticosteroids to women with a fetus with intrauterine growth restriction at risk of preterm birth?		
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Maternal Three of the 26 trials in the Roberts CPG version 2015 systematic review for a single course of antenatal corticosteroids reported including a very small proportion of women in their trial with a fetus with intrauterine growth restriction. Two of these trials report on chorioamnionitis and puerperal sepsis. Infant Three trials in the Roberts CPG version 2015 systematic review for a single course of antenatal corticosteroids reported including a very small proportion of women with a fetus with intrauterine growth restriction. One trial reported on perinatal death, one trial reported on fetal death, three trials reported on neonatal death and respiratory distress syndrome	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 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')*		
Maternal There was no evidence of increased risk of chorioamnionitis. The treatment effect for puerperal sepsis was in the same direction as the overall treatment effect, but reached statistical significance. However the confidence intervals were wide and overlapped the overall treatment effect that was not significant. Infant Perinatal and fetal death had treatment effects in the opposite direction of the overall treatment effect, but there were no statistically significant differences between the groups. There was also no difference between groups for risk of neonatal death or respiratory distress syndrome.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is not consistent
	NA	Not applicable (one study only)
3. Clinical impact *(indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Maternal No evidence of increased risk of maternal infection. Infant No evidence of increased risk of mortality.	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?)*		
Evidence from a variety of healthcare settings. Studies conducted in USA, and Brazil.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether sensible to apply
5. Applicability *(is the body of evidence relevant to the New Zealand / Australian healthcare context in terms of health services / delivery of care and cultural factors?)*		
Corticosteroids are readily available in Australia and New Zealand and their use is feasible.	A	Evidence directly applicable to New Zealand / Australian healthcare context
	B	Evidence applicable to New Zealand / Australian healthcare context with few caveats
	C	Evidence probably applicable to New Zealand / Australian healthcare context with some caveats
	D	Evidence not applicable to New Zealand / 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 is based on a subset of data from trials that reported they included a proportion of women with a fetus with intrauterine growth restriction. This level of evidence cannot be used to form a clinical recommendation		

EVIDENCE STATEMENT MATRIX *(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	NA	Not applicable
2. Consistency	NA	Not applicable
3. Clinical Impact	NA	Not applicable
4. Generalisability	NA	Not applicable
5. Applicability	NA	Not applicable

Evidence statement

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

Use a single course of antenatal corticosteroids for women with a fetus with intrauterine growth restriction at risk of preterm birth.

Where appropriate, monitor women with intrauterine fetal growth restriction for signs of puerperal sepsis when antenatal corticosteroids have been given.

OVERALL GRADE OF RECOMMENDATION	
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 recommendations(s) but care should be taken in its application
D	Body of evidence is weak and recommendation must be applied with caution
PP	**Practice Points**

UNRESOLVED ISSUES *(If needed, keep a 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 implementation of this recommendation?	**YES**
	NO

M33 GRADE Evidence summary

Considered Judgement - Strength of recommendation

Clinical question:
What is the safety for the mother and fetus, infant, child, adult of administering a single course of antenatal corticosteroids to women with a fetus with intrauterine growth restriction at risk of preterm birth?

1. Outcome measures:	Quality of evidence				Importance of outcome in making a decision		
Maternal Outcomes	**HIGH**	**MOD**	**LOW**	**V. LOW**	**Critical**	**Important**	**Not Important**
O_1 Chorioamnionitis	✓				✓		
O_2 Puerperal sepsis		✓			✓		
O_3 Pyrexia after entry to trial				NR		✓	
O_4 Intrapartum fever requiring antibiotics				NR		✓	
O_5 Post natal pyrexia				NR		✓	
O_6 Maternal quality of life				NR	✓		
Infant Outcomes	**HIGH**	**MOD**	**LOW**	**V. LOW**	**Critical**	**Important**	**Not Important**
O_1 Combined fetal and neonatal death		✓			✓		
O_2 Neonatal death		✓			✓		
O_3 Fetal death			✓		✓		
O_4 RDS		✓			✓		
O_5 Composite of serious outcomes for the infant				NR	✓		
O_6 Neurosensory disability (composite of impairments) for infant as a child				NR	✓		
O_7 Survival free of neurosensory disability for the infant as a child				NR	✓		
O_8 Survival free of metabolic disease for the infant as a child				NR		✓	
O_9 Neurosensory disability (composite of impairments) for infant as an adult				NR	✓		
O_{10} Survival free of neurosensory disability for the infant as an adult				NR	✓		
O_{11} Survival free of metabolic disease for the infant as an adult				NR		✓	

2. Is there is insufficient evidence to make a recommendation?

Evidence statement - Evidence is based on a subset of data from trials that reported they included a proportion of women with a fetus with intrauterine growth restriction. This level of evidence cannot be used to form a clinical recommendation

Maternal - The Roberts CPG version 2015 systematic review for a single course of antenatal corticosteroids did not report data for women with a fetus with intrauterine growth restriction at preterm birth. Two of the included studies were known to have recruited a proportion of women with intrauterine growth restriction. These two trials found no differences for chorioamnionitis and puerperal sepsis between women who had no antenatal corticosteroids and those who received a single course of antenatal corticosteroids. No data was reported for pyrexia after trials entry, intrapartum pyrexia or postpartum pyrexia requiring treatment.
Infant - A single trial in the Roberts CPG version 2015 systematic review for a single course of antenatal corticosteroids that recruited and reported on the proportion of women with a growth restricted fetus reported on mortality. There were no differences between infants exposed to a single course of antenatal corticosteroids and those with no exposure for perinatal or fetal death. Similarly, there was no difference between infants exposed to a single course of antenatal corticosteroids and those with no exposure for neonatal death or respiratory distress in the three trials that recruited and reported including a proportion of women with a fetus with intrauterine growth restriction.

3. What benefit will the proposed intervention/action have?

Evidence statement	**Quality of evidence**
Maternal - There do not appear do by any direct health benefits for the mother. *Infant* - There does not appear to be increased risk of mortality or respiratory distress syndrome among infants exposed to a single course of antenatal corticosteroids compared with those not exposed in trials that recruited and reported a proportion of women with a fetus with intrauterine growth restriction.	**Not applicable**

Judging the benefits in context
The evidence is direct evidence from trials that compared exposure to a single course of antenatal corticosteroid with no exposure, and that recruited and reported a proportion of women with a fetus with intrauterine growth restriction. Study populations were from the United States (two trials) and Brazil.

4. What harm might the proposed intervention/action do?

Evidence statement	**Quality of evidence**
Maternal - There is no evidence of harm to the mother. *Infant* - There is no evidence of harm to the infant.	**Not applicable**

Judging the harms in context
Maternal - The evidence is from trials that recruited and reported a proportion of women with a fetus with intrauterine growth restriction and compared exposure to a single course of antenatal corticosteroids with no exposure.
Infant - One trial included in the Roberts CPG version 2015 systematic review recruited and reported including a proportion of women with a

fetus with intrauterine growth restriction reported on perinatal and fetal death. This trial was small and there was evidence of imprecision with wide confidence intervals.

5. What is the likely balance between good and harm?

Evidence statement *Maternal* - There does not appear to be increased risk to the mother. *Infant* - The overall treatment effect indicates significant benefit to the infant in terms of reduced risk of mortality, and respiratory distress syndrome. In trials that recruited and reported on a proportion of women with a fetus with intrauterine growth restriction there was no evidence of increased risk of mortality or morbidity for these infants.	**Overall quality of evidence** **Not applicable**

Judging the balance of benefits and harms in context

Exposure to a single course of antenatal corticosteroids in the presence of intrauterine growth restriction is unlikely to cause harm to the mother. The significant health benefits for the infant, in terms of reduced mortality and respiratory distress syndrome outweigh potential low impact harm for the mother.

Benefits clearly outweigh harms	Recommend	STRONG
Benefits probably outweigh harms	Consider	CONDITIONAL
Not known	**Make a recommendation for research (see 8 below)**	**WEAK**
Benefits probably don't outweigh harms Harms probably outweigh benefits	Consider against/make no recommendation	CONDITIONAL
Benefits clearly don't outweigh harms Harms clearly outweigh benefits	Recommend against	STRONG

6. Is the intervention/action implementable in the New Zealand context?

Summary statement

Antenatal corticosteroids are already widely in use in New Zealand and Australia.

Yes	**Recommend/consider**
Not known	Consider economic evaluation
No	Recommend/consider against

7. Final recommendation

Use a single course of antenatal corticosteroids for women with a fetus with intrauterine growth restriction at risk of preterm birth. Where appropriate, monitor women with intrauterine fetal growth restriction for signs of puerperal sepsis when antenatal corticosteroids have been given.	**Strength of recommendation** *Please select level* **STRONG** **CONDITIONAL** **WEAK (Practice points)**

8. Recommendations for research

- What are the haemodynamic effects of antenatal corticosteroids on the growth restricted fetus?
- What is the optimal timing of birth following administration of antenatal corticosteroids for women with a fetus with intrauterine growth restriction?

M34 Women with a fetus with intrauterine growth restriction at risk of preterm birth – Repeat course of antenatal corticosteroids

M34 NHMRC Evidence summary

What is the safety for the mother and fetus, infant, child, adult of administering repeat antenatal corticosteroids to women with a fetus with intrauterine growth restriction/fetal compromise at risk of preterm birth?		
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Maternal Six of the trials included in the Crowther (2011) systematic review reported including a very small proportion of women with a fetus with intrauterine growth restriction. Five of these trials reported on chorioamnionitis and puerperal sepsis, and one trial reported on postnatal pyrexia. Infant Six of the trials included in the Crowther (2011) systematic review reported including a very small proportion of women with a fetus with intrauterine growth restriction. Five trials reported on perinatal death, composite of serious infant outcomes and birthweight. Four trials reported on fetal death, neonatal death and respiratory distress syndrome.	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 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')*		
Maternal The evidence was consistent that there was no difference in risk of maternal infection for women with a fetus with intrauterine growth restriction treated with antenatal corticosteroids compared to those not treated. Infant The evidence was consistent for significant reduction in risk of respiratory distress syndrome and composite of serious infant outcomes for infants with intrauterine growth restriction exposed to repeat antenatal corticosteroids compared with no repeat exposure. There was no difference in risk of mortality. Similar to the overall treatment effect, there was a significant reduction in birthweight for infants with intrauterine growth restriction exposed to antenatal corticosteroids compared with no exposure.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is not consistent
	NA	Not applicable (one study only)
3. Clinical impact *(indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Maternal There is no evidence of increased risk of infection for the mother with a fetus with intrauterine growth restriction. Infant There are significant benefits for the infant in terms of reduced risk of respiratory distress and a composite of serious infant outcomes. The clinical significance of reduced birthweight is unclear.	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?)*		
Evidence from a variety of healthcare settings. Studies conducted in Canada, Australia and New Zealand, USA, and a multicentre trial incorporating 80 centres in 20 countries.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether sensible to apply
5. Applicability *(is the body of evidence relevant to the New Zealand / Australian healthcare context in terms of health services / delivery of care and cultural factors?)*		
Corticosteroids are readily available in Australia and New Zealand and their use is feasible.	A	Evidence directly applicable to New Zealand / Australian healthcare context
	B	Evidence applicable to New Zealand / Australian healthcare context with few caveats
	C	Evidence probably applicable to New Zealand / Australian healthcare context with some caveats
	D	Evidence not applicable to New Zealand / 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 is based on a subset of data from trials that reported they included a proportion of women with a fetus with intrauterine growth restriction. This level of evidence cannot be used to form a clinical recommendation		

EVIDENCE STATEMENT MATRIX *(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	NA	Not applicable
2. Consistency	NA	Not applicable
3. Clinical Impact	NA	Not applicable
4. Generalisability	NA	Not applicable
5. Applicability	NA	Not applicable
Evidence statement		

RECOMMENDATION *(What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible)*	**OVERALL GRADE OF RECOMMENDATION**	
Repeat antenatal corticosteroids for a woman with a fetus with intrauterine growth restriction at risk of preterm birth.	**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 recommendations(s) but care should be taken in its application
	D	Body of evidence is weak and recommendation must be applied with caution
	PP	**Practice Points**

UNRESOLVED ISSUES *(If needed, keep a 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 implementation of this recommendation?	**YES**
	NO

M34 GRADE Evidence summary

Considered Judgement - Strength of recommendation							
What is the safety for the mother and fetus, infant, child, adult of administering a repeat course(s) of antenatal corticosteroids to women with a fetus with intrauterine growth restriction at risk of preterm birth?							
1. Outcome measures:	**Quality of evidence**				**Importance of outcome in making a decision**		
Maternal Outcomes	**HIGH**	**MOD**	**LOW**	**V. LOW**	**Critical**	**Important**	**Not Important**
O_1 Chorioamnionitis	✓				✓		
O_2 Puerperal sepsis	✓				✓		
O_3 Pyrexia after entry to trial				NR		✓	
O_4 Intrapartum fever requiring antibiotics				NR		✓	
O_5 Post natal pyrexia	✓					✓	
O_6 Maternal quality of life				NR	✓		
Infant Outcomes	**HIGH**	**MOD**	**LOW**	**V. LOW**	**Critical**	**Important**	**Not Important**
O_1 Combined fetal and neonatal death		✓			✓		
O_2 Neonatal death		✓			✓		
O_3 Fetal death			✓		✓		
O_4 RDS		✓			✓		
O_5 Composite of serious outcomes for the infant		✓			✓		
O_6 Neurosensory disability (composite of impairments) for infant as a child				NR	✓		
O_7 Survival free of neurosensory disability for the infant as a child				NR	✓		
O_8 Survival free of metabolic disease for the infant as a child				NR		✓	
O_9 Neurosensory disability (composite of impairments) for infant as an adult				NR	✓		
O_{10} Survival free of neurosensory disability for the infant as an adult				NR	✓		
O_{11} Survival free of metabolic disease for the infant as an adult				NR		✓	

2. Is there is insufficient evidence to make a recommendation?

Evidence statement - Evidence is based on a subset of data from trials that reported they included a proportion of women with a fetus with intrauterine growth restriction. This level of evidence cannot be used to form a clinical recommendation

Maternal - The Crowther (2011) systematic review did not present data for women with a fetus with intrauterine growth restriction at risk of preterm birth. Analyses was conducted for the purpose of these Clinical Practice Guidelines on the five trials included in the Crowther (2011) systematic review that recruited and reported including a proportion of women with a fetus with intrauterine growth restriction.

Infant - The Crowther (2011) systematic review did not present data for infants with intrauterine growth restriction. Analyses was conducted for the purpose of these Clinical Practice Guidelines on the five trials included in the Crowther (2011) systematic review that recruited and reported including a proportion of women with a fetus with intrauterine growth restriction.

3. What benefit will the proposed intervention/action have?

Evidence statement	**Quality of evidence**
Maternal - There do not appear to be any direct health benefits for the mother. In line with the overall treatment effect, no differences between repeat antenatal corticosteroids and no repeat antenatal corticosteroids were found for chorioamnionitis, postnatal pyrexia requiring treatment or puerperal sepsis. *Infant* - In line with the overall treatment effect, no difference were seen for perinatal, neonatal or fetal mortality between infants exposed to repeat antenatal corticosteroids and those not exposed to repeat antenatal corticosteroids in trials that recruited and reported a proportion of women with a fetus with intrauterine growth restriction. Significant reductions were seen for respiratory distress syndrome and a composite of serious infant outcomes for infants exposed to repeat antenatal corticosteroids compared with no exposure in trials that recruited and reported a proportion of women with a fetus with intrauterine growth restriction.	**Not applicable**

Judging the benefits in context
The evidence is direct evidence from trials conducted in women who remained at risk of preterm birth following an initial single course of antenatal corticosteroid, and that recruited and reported the proportion of women with a fetus with intrauterine growth restriction. Study populations were drawn from health care settings in Canada, Australia and New Zealand, the United States, and a multicentre trial involving 80 centres in 20 countries.

4. What harm might the proposed intervention/action do?

Evidence statement	**Quality of evidence**
Maternal - There is no evidence of increased risk of harm for the mother. *Infant* - There is no evidence of increased risk of harm for the infant.	**Not applicable**

Judging the harms in context
The evidence is direct evidence from trials conducted in women who remained at risk of preterm birth following an initial single course of

antenatal corticosteroids, and that recruited and reported the proportion of women with a fetus with intrauterine growth restriction.

5. What is the likely balance between good and harm?

Evidence statement	**Overall quality of evidence**
Maternal - There does not appear to be increased risk to the mother. *Infant* - The evidence indicates considerable benefit to the infant in terms of significantly reduced risk of respiratory distress syndrome and composite serious infant outcome following exposure to repeat antenatal corticosteroids.	**Not applicable**

Judging the balance of benefits and harms in context
Exposure to a repeat course of antenatal corticosteroid in the presence of intrauterine growth restriction is unlikely to cause harm to the mother. The significant health benefits for the infant, in terms of reduced respiratory distress and composite serious outcome, outweigh any potential low impact harm for the mother.

Benefits clearly outweigh harms	Recommend	STRONG
Benefits probably outweigh harms	Consider	CONDITIONAL
Not known	**Make a recommendation for research (see 8 below)**	**WEAK**
Benefits probably don't outweigh harms	Consider against/make no recommendation	CONDITIONAL
Harms probably outweigh benefits		
Benefits clearly don't outweigh harms	Recommend against	STRONG
Harms clearly outweigh benefits		

6. Is the intervention/action implementable in the New Zealand context?

Summary statement
Antenatal corticosteroids are already widely in use in New Zealand and Australia.

Yes	**Recommend/consider**
Not known	Consider economic evaluation
No	Recommend/consider against

7. Final recommendation

	Strength of recommendation *Please select level*
Repeat antenatal corticosteroids for a woman with a fetus with intrauterine growth restriction at risk of preterm birth.	**STRONG** **CONDITIONAL** **WEAK (Practice point)**

8. Recommendations for research

M35 Women with ultrasound evidence of cervical shortening /funnelling – Single course or repeat antenatal corticosteroids

M35 NHMRC Evidence summary

What is the safety for the mother and fetus, infant, child, adult of administering a single course or repeat antenatal corticosteroids to women with ultrasound evidence of cervical shortening/funnelling at risk of preterm birth?		
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
There was no randomised controlled trial data for the use of a single course of antenatal corticosteroids in women with ultrasound evidence of a short cervix at risk of preterm birth.	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 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')*		
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 not consistent
	NA	Not applicable (one study only)
3. Clinical impact *(indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Not applicable	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?)*		
Not applicable	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether sensible to apply
5. Applicability *(is the body of evidence relevant to the New Zealand / Australian healthcare context in terms of health services / delivery of care and cultural factors?)*		
Corticosteroids are readily available in Australia and New Zealand and their use is feasible.	A	Evidence directly applicable to New Zealand / Australian healthcare context
	B	Evidence applicable to New Zealand / Australian healthcare context with few caveats
	C	Evidence probably applicable to New Zealand / Australian healthcare context with some caveats
	D	Evidence not applicable to New Zealand / 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)*		
No randomised trial evidence identified		
EVIDENCE STATEMENT MATRIX *(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	NA	Not applicable
2. Consistency	NA	Not applicable
3. Clinical Impact	NA	Not applicable
4. Generalisability	NA	Not applicable
5. Applicability	NA	Not applicable

Evidence statement

No randomised controlled trial data for the use of a single course of antenatal corticosteroids in women with ultrasound evidence of a short

cervix at risk of preterm birth.		
RECOMMENDATION *(What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible)* Use a single course of antenatal corticosteroids for a woman presenting with symptoms of preterm labour and with ultrasound evidence of cervical shortening (<15mm) and at risk of preterm birth. Repeat antenatal corticosteroids for a woman presenting with symptoms of preterm labour with ultrasound evidence of cervical shortening (<15mm) at risk of preterm birth.	**OVERALL GRADE OF RECOMMENDATION**	
	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 recommendations(s) but care should be taken in its application
	D	Body of evidence is weak and recommendation must be applied with caution
	PP	**Practice Point**
UNRESOLVED ISSUES *(If needed, keep a 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 implementation of this recommendation?	**YES**	
	NO	

M35 GRADE Evidence summary

Considered Judgement - Strength of recommendation							
What is the safety for the mother and fetus, infant, child, adult of administering a single course or repeat antenatal corticosteroids to women with ultrasound evidence of cervical shortening /funnelling at risk of preterm birth?							
1. Outcome measures:	**Quality of evidence**				**Importance of outcome in making a decision**		
Maternal Outcomes	**HIGH**	**MOD**	**LOW**	**V. LOW**	**Critical**	**Important**	**Not Important**
O_1 Chorioamnionitis				NR	✓		
O_2 Puerperal sepsis				NR	✓		
O_3 Pyrexia after entry to trial				NR		✓	
O_4 Intrapartum fever requiring antibiotics				NR		✓	
O_5 Post natal pyrexia				NR		✓	
O_6 Maternal quality of life				NR	✓		
Infant Outcomes	**HIGH**	**MOD**	**LOW**	**V. LOW**	**Critical**	**Important**	**Not Important**
O_1 Combined fetal and neonatal death				NR	✓		
O_2 Neonatal death				NR	✓		
O_3 Fetal death				NR	✓		
O_4 RDS				NR	✓		
O_5 Composite of serious outcomes for the infant				NR	✓		
O_6 Neurosensory disability (composite of impairments) for infant as a child				NR	✓		
O_7 Survival free of neurosensory disability for the infant as a child				NR	✓		
O_8 Survival free of metabolic disease for the infant as a child				NR		✓	
O_9 Neurosensory disability (composite of impairments) for infant as an adult				NR	✓		
O_{10} Survival free of neurosensory disability for the infant as an adult				NR	✓		
O_{11} Survival free of metabolic disease for the infant as an adult				NR		✓	
2. Is there is insufficient evidence to make a recommendation?							
Evidence statement *Maternal* - There was no randomised controlled trial data for women with a short cervix at risk of preterm birth reported for a single course or repeat antenatal corticosteroids. *Infant* - There was no randomised controlled trial data for infants born to mothers with a shortened cervix at risk of preterm birth for a single course or repeat antenatal corticosteroids.							
3. What benefit will the proposed intervention/action have?							
Evidence statement Based on the evidence of the overall treatment effect of a single course or repeat antenatal corticosteroids reported in Chapters 4 to 8, there is unlikely to be health benefits to the mother and there is likely to be significant benefits to the infant.					**Quality of evidence** **Not reported**		
Judging the benefits in context Not applicable.							
4. What harm might the proposed intervention/action do?							
Evidence statement Based on overall treatment effects of a single course or repeat antenatal corticosteroids detailed in Chapters 4 to 8, there is no evidence of harm to the mother or infant and significant benefits to the infant.					**Quality of evidence** **Not reported**		
Judging the harms in context Not applicable.							
5. What is the likely balance between good and harm?							
Evidence statement Based on overall treatment effects of a single course or repeat antenatal corticosteroids detailed in Chapters 4 to 8, there is no evidence of harm to the mother or infant and significant benefits to the infant.					**Overall quality of evidence** **Not reported**		
Judging the balance of benefits and harms in context Not applicable.							
Benefits clearly outweigh harms	Recommend				STRONG		
Benefits probably outweigh harms	Consider				CONDITIONAL		

Not known	**Make a recommendation for research (see 8 below)**	**WEAK**
Benefits probably don't outweigh harms	Consider against/make no recommendation	CONDITIONAL
Harms probably outweigh benefits		
Benefits clearly don't outweigh harms	Recommend against	STRONG
Harms clearly outweigh benefits		

6. Is the intervention/action implementable in the New Zealand context?

Summary statement
Antenatal corticosteroids are already widely in use in New Zealand and Australia.

Yes	**Recommend/consider**
Not known	Consider economic evaluation
No	Recommend/consider against

7. Final recommendation

	Strength of recommendation
Use a single course of antenatal corticosteroids for a woman presenting with symptoms of preterm labour and with ultrasound evidence of cervical shortening (<15mm) and at risk of preterm birth. Repeat antenatal corticosteroids for a woman presenting with symptoms of preterm labour with ultrasound evidence of cervical shortening (<15mm) at risk of preterm birth.	**STRONG** **CONDITIONAL** **WEAK (Practice Point)**

8. Recommendations for research

M36 Fetal fibronectin test and the use of antenatal corticosteroids in women at risk of preterm birth – Single course or repeat antenatal corticosteroids

M36 NHMRC Evidence summary

What is the safety for the mother and fetus, infant, child, adult of administering a single course or repeat antenatal corticosteroids to women having undergone fetal fibronectin testing?		
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
There was no randomised controlled trial evidence that addressed the use of antenatal corticosteroids in the presence of a positive or negative fetal fibronectin test.	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 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')*		
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 not consistent
	NA	Not applicable (one study only)
3. Clinical impact *(indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Not applicable	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?)*		
Not applicable	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether sensible to apply
5. Applicability *(is the body of evidence relevant to the New Zealand / Australian healthcare context in terms of health services / delivery of care and cultural factors?)*		
Corticosteroids are readily available in Australia and New Zealand and their use is feasible.	A	Evidence directly applicable to New Zealand / Australian healthcare context
	B	Evidence applicable to New Zealand / Australian healthcare context with few caveats
	C	Evidence probably applicable to New Zealand / Australian healthcare context with some caveats
	D	Evidence not applicable to New Zealand / 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 *(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	NA	Not applicable
2. Consistency	NA	Not applicable
3. Clinical Impact	NA	Not applicable
4. Generalisability	NA	Not applicable
5. Applicability	NA	Not applicable

Evidence statement

There was no randomised controlled trial evidence that addressed the use of antenatal corticosteroids in the presence of a positive or negative fetal fibronectin test.

RECOMMENDATION *(What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible)*	**OVERALL GRADE OF RECOMMENDATION**	
Use a single course of antenatal corticosteroids for a woman presenting with symptoms of preterm labour with a positive fetal fibronectin test and at risk of preterm birth. Repeat antenatal corticosteroids for a woman presenting with symptoms of preterm labour with a positive fetal fibronectin test at risk of preterm birth. Do not use antenatal corticosteroids in a woman where a fetal fibronectin test is negative due to the high negative predictive value of the test.	**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 recommendations(s) but care should be taken in its application
	D	Body of evidence is weak and recommendation must be applied with caution
	PP	**Practice Points**

UNRESOLVED ISSUES *(If needed, keep a 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 implementation of this recommendation?	**YES**
	NO

M36 GRADE Evidence summary

Considered Judgement - Strength of recommendation							
What is the safety for the mother and fetus, infant, child, adult of administering a single course or repeat antenatal corticosteroids to women having undergone fetal fibronectin testing?							
1. Outcome measures:	**Quality of evidence**				**Importance of outcome in making a decision**		
Maternal Outcomes	**HIGH**	**MOD**	**LOW**	**V. LOW**	**Critical**	**Important**	**Not Important**
O_1 Chorioamnionitis				NR	✓		
O_2 Puerperal sepsis				NR	✓		
O_3 Pyrexia after entry to trial				NR		✓	
O_4 Intrapartum fever requiring antibiotics				NR		✓	
O_5 Post natal pyrexia				NR		✓	
O_6 Maternal quality of life				NR	✓		
Infant Outcomes	**HIGH**	**MOD**	**LOW**	**V. LOW**	**Critical**	**Important**	**Not Important**
O_1 Combined fetal and neonatal death				NR	✓		
O_2 Neonatal death				NR	✓		
O_3 Fetal death				NR	✓		
O_4 RDS				NR	✓		
O_5 Composite of serious outcomes for the infant				NR	✓		
O_6 Neurosensory disability (composite of impairments) for infant as a child				NR	✓		
O_7 Survival free of neurosensory disability for the infant as a child				NR	✓		
O_8 Survival free of metabolic disease for the infant as a child				NR		✓	
O_9 Neurosensory disability (composite of impairments) for infant as an adult				NR	✓		
O_{10} Survival free of neurosensory disability for the infant as an adult				NR	✓		
O_{11} Survival free of metabolic disease for the infant as an adult				NR		✓	
2. Is there is insufficient evidence to make a recommendation?							
Evidence statement *Maternal* - There was no randomised controlled trial evidence that addressed the use of repeat antenatal corticosteroids in the presence of a positive or negative fetal fibronectin test. *Infant* - There was no randomised controlled trial evidence that addressed the use of repeat antenatal corticosteroids in the presence of a positive or negative fetal fibronectin test.							
3. What benefit will the proposed intervention/action have?							
Evidence statement Not applicable						**Quality of evidence** **Not reported**	
Judging the benefits in context Not applicable							
4. What harm might the proposed intervention/action do?							
Evidence statement Not applicable						**Quality of evidence** **Not reported**	
Judging the harms in context Not applicable							
5. What is the likely balance between good and harm?							
Evidence statement Not applicable						**Overall quality of evidence** **Not reported**	
Judging the balance of benefits and harms in context Not applicable							
Benefits clearly outweigh harms	Recommend					STRONG	
Benefits probably outweigh harms	Consider					CONDITIONAL	
Not known	**Make a recommendation for research (see 8 below)**					**WEAK**	
Benefits probably don't outweigh harms	Consider against/make no recommendation					CONDITIONAL	

Harms probably outweigh benefits		
Benefits clearly don't outweigh harms	Recommend against	STRONG
Harms clearly outweigh benefits		

6. Is the intervention/action implementable in the New Zealand context?

Summary statement
Antenatal corticosteroids are already widely in use in New Zealand and Australia.

Yes	**Recommend/consider**
Not known	Consider economic evaluation
No	Recommend/consider against

7. Final recommendation

	Strength of recommendation *Please select level* **STRONG** **CONDITIONAL** **WEAK (Practice Points)**
Use a single course of antenatal corticosteroids for a woman presenting with symptoms of preterm labour with a positive fetal fibronectin test and at risk of preterm birth. Repeat antenatal corticosteroids for a woman presenting with symptoms of preterm labour with a positive fetal fibronectin test at risk of preterm birth. Do not use antenatal corticosteroids in a woman where a fetal fibronectin test is negative due to the high negative predictive value of the test.	

8. Recommendations for research

M37 Women for whom preterm birth is medically indicated for other reasons – Single course of antenatal corticosteroids

M37 NHMRC Evidence summary

What is the safety for the mother and fetus, infant, child, adult of administering a single course of antenatal corticosteroids to women for whom preterm birth is medically indicated?		
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
No randomised controlled trial evidence was reported for the use of a single course of antenatal corticosteroids for a variety of maternal conditions where preterm birth may be medically indicated.	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 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')*		
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 not consistent
	NA	Not applicable (one study only)
3. Clinical impact *(indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Not applicable	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?)*		
Not applicable	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether sensible to apply
5. Applicability *(is the body of evidence relevant to the New Zealand / Australian healthcare context in terms of health services / delivery of care and cultural factors?)*		
Corticosteroids are readily available in Australia and New Zealand and their use is feasible.	A	Evidence directly applicable to New Zealand / Australian healthcare context
	B	Evidence applicable to New Zealand / Australian healthcare context with few caveats
	C	Evidence probably applicable to New Zealand / Australian healthcare context with some caveats
	D	Evidence not applicable to New Zealand / 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)*		
No randomised trial evidence identified		
EVIDENCE STATEMENT MATRIX *(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	NA	Not applicable
2. Consistency	NA	Not applicable

3. Clinical Impact	NA	Not applicable
4. Generalisability	NA	Not applicable
5. Applicability	NA	Not applicable

Evidence statement

No randomised controlled trial evidence was reported for the use of a single course of antenatal corticosteroids for a variety of maternal conditions where preterm birth may be medically indicated.

RECOMMENDATION *(What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible)*	**OVERALL GRADE OF RECOMMENDATION**	
Use a single course of antenatal corticosteroids for women with other medical indications for preterm birth. Do not delay birth to administer antenatal corticosteroids if preterm birth is medically indicated.	**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 recommendations(s) but care should be taken in its application
	D	Body of evidence is weak and recommendation must be applied with caution
	PP	**Practice Points**

UNRESOLVED ISSUES *(If needed, keep a 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 implementation of this recommendation?	**YES**
	NO

M37 GRADE Evidence summary

Considered Judgement - Strength of recommendation							
What is the safety for the mother and fetus, infant, child, adult of administering a single course of antenatal corticosteroids to women for whom preterm birth is medically indicated?							
1. Outcome measures:	**Quality of evidence**				**Importance of outcome in making a decision**		
Maternal Outcomes	**HIGH**	**MOD**	**LOW**	**V. LOW**	**Critical**	**Important**	**Not Important**
O_1 Chorioamnionitis				NR	✓		
O_2 Puerperal sepsis				NR	✓		
O_3 Pyrexia after entry to trial				NR		✓	
O_4 Intrapartum fever requiring antibiotics				NR		✓	
O_5 Post natal pyrexia				NR		✓	
O_6 Maternal quality of life				NR	✓		
Infant Outcomes	**HIGH**	**MOD**	**LOW**	**V. LOW**	**Critical**	**Important**	**Not Important**
O_1 Combined fetal and neonatal death				NR	✓		
O_2 Neonatal death				NR	✓		
O_3 Fetal death				NR	✓		
O_4 RDS				NR	✓		
O_5 Composite of serious outcomes for the infant				NR	✓		
O_6 Neurosensory disability (composite of impairments) for infant as a child				NR	✓		
O_7 Survival free of neurosensory disability for the infant as a child				NR	✓		
O_8 Survival free of metabolic disease for the infant as a child				NR		✓	
O_9 Neurosensory disability (composite of impairments) for infant as an adult				NR	✓		
O_{10} Survival free of neurosensory disability for the infant as an adult				NR	✓		
O_{11} Survival free of metabolic disease for the infant as an adult				NR		✓	
2. Is there is insufficient evidence to make a recommendation?							
Evidence statement No randomised controlled trial evidence was reported the use of antenatal corticosteroids for a variety of maternal conditions where preterm birth may be medically indicated such as maternal cardiac disease, chronic asthma, renal disease, cancer or cholestasis.							
3. What benefit will the proposed intervention/action have?							
Evidence statement Based on the overall treatment effect, it is likely there would be benefit to the infant of exposure to antenatal corticosteroids, with no health harms for the mother. However, the benefits and harms of antenatal corticosteroids in cases where preterm birth is medically indicated have not been fully explored in randomised controlled trials and further research is required.						**Quality of evidence** **Not reported**	
Judging the benefits in context Not applicable							
4. What harm might the proposed intervention/action do?							
Evidence statement Not applicable						**Quality of evidence** **Not reported**	
Judging the harms in context Not applicable							
5. What is the likely balance between good and harm?							
Evidence statement Not applicable						**Overall quality of evidence** **Not reported**	
Judging the balance of benefits and harms in context Not applicable							
Benefits clearly outweigh harms	Recommend					STRONG	
Benefits probably outweigh harms	Consider					CONDITIONAL	
Not known	**Make a recommendation for research (see 8 below)**					**WEAK**	
Benefits probably don't outweigh harms	Consider against/make no recommendation					CONDITIONAL	

Harms probably outweigh benefits		
Benefits clearly don't outweigh harms	Recommend against	STRONG
Harms clearly outweigh benefits		

6. Is the intervention/action implementable in the New Zealand context?

Summary statement
Antenatal corticosteroids are already widely in use in New Zealand and Australia.

Yes	**Recommend/consider**
Not known	Consider economic evaluation
No	Recommend/consider against

7. Final recommendation

	Strength of recommendation
Use a single course of antenatal corticosteroids for women with other medical indications for preterm birth. Do not delay birth to administer antenatal corticosteroids if preterm birth is medically indicated.	**STRONG** **CONDITIONAL** **WEAK (Practice Point)**

8. Recommendations for research

M38 Women for whom preterm birth is medically indicated for other reasons – Repeat antenatal corticosteroids

M38 NHMRC Evidence summary

What is the safety for the mother and fetus, infant, child, adult of administering repeat antenatal corticosteroids to women for whom preterm birth is medically indicated?		
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
No randomised controlled trial evidence was reported for the use of repeat antenatal corticosteroids for a variety of maternal conditions where preterm birth may be medically indicated.	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 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')*		
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 not consistent
	NA	Not applicable (one study only)
3. Clinical impact *(indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Not applicable	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?)*		
Not applicable	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether sensible to apply
5. Applicability *(is the body of evidence relevant to the New Zealand / Australian healthcare context in terms of health services / delivery of care and cultural factors?)*		
Corticosteroids are readily available in Australia and New Zealand and their use is feasible.	A	Evidence directly applicable to New Zealand / Australian healthcare context
	B	Evidence applicable to New Zealand / Australian healthcare context with few caveats
	C	Evidence probably applicable to New Zealand / Australian healthcare context with some caveats
	D	Evidence not applicable to New Zealand / 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)*		
Not randomised evidence identified		

EVIDENCE STATEMENT MATRIX *(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	NA	Not applicable
2. Consistency	NA	Not applicable
3. Clinical Impact	NA	Not applicable
4. Generalisability	NA	Not applicable
5. Applicability	NA	Not applicable

Evidence statement No randomised controlled trial evidence was reported for the use of repeat antenatal corticosteroids for a variety of maternal conditions where preterm birth may be medically indicated.		
RECOMMENDATION *(What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible)* Repeat antenatal corticosteroids for a woman with other medical indications for preterm birth.	**OVERALL GRADE OF RECOMMENDATION**	
	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 recommendations(s) but care should be taken in its application
	D	Body of evidence is weak and recommendation must be applied with caution
	PP	**Practice Point**
UNRESOLVED ISSUES *(If needed, keep a 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 implementation of this recommendation?	**YES**	
	NO	

M38 GRADE Evidence summary

Considered Judgement - Strength of recommendation							
What is the safety for the mother and fetus, infant, child, adult of administering a repeat course(s) of antenatal corticosteroids to women for whom preterm birth is medically indicated?							
1. Outcome measures:	**Quality of evidence**				**Importance of outcome in making a decision**		
Maternal Outcomes	**HIGH**	**MOD**	**LOW**	**V. LOW**	**Critical**	**Important**	**Not Important**
O_1 Chorioamnionitis				NR	✓		
O_2 Puerperal sepsis				NR	✓		
O_3 Pyrexia after entry to trial				NR		✓	
O_4 Intrapartum fever requiring antibiotics				NR		✓	
O_5 Post natal pyrexia				NR		✓	
O_6 Maternal quality of life				NR	✓		
Infant Outcomes	**HIGH**	**MOD**	**LOW**	**V. LOW**	**Critical**	**Important**	**Not Important**
O_1 Combined fetal and neonatal death				NR	✓		
O_2 Neonatal death				NR	✓		
O_3 Fetal death				NR	✓		
O_4 RDS				NR	✓		
O_5 Composite of serious outcomes for the infant				NR	✓		
O_6 Neurosensory disability (composite of impairments) for infant as a child				NR	✓		
O_7 Survival free of neurosensory disability for the infant as a child				NR	✓		
O_8 Survival free of metabolic disease for the infant as a child				NR		✓	
O_9 Neurosensory disability (composite of impairments) for infant as an adult				NR	✓		
O_{10} Survival free of neurosensory disability for the infant as an adult				NR	✓		
O_{11} Survival free of metabolic disease for the infant as an adult				NR		✓	
2. Is there is insufficient evidence to make a recommendation?							
Evidence statement (No randomised controlled trial evidence was reported the use of repeat antenatal corticosteroids for a variety of maternal conditions where preterm birth may be medically indicated such as maternal cardiac disease, chronic asthma, renal disease, cancer or cholestasis.							
3. What benefit will the proposed intervention/action have?							
Evidence statement Based on the overall treatment effect, it is likely there would be benefit to the infant of exposure to antenatal corticosteroids, with no health harms for the mother. However, the benefits and harms of antenatal corticosteroids in cases where preterm birth is medically indicated have not been fully explored in randomised controlled trials and further research is required.						**Quality of evidence** **Not reported**	
Judging the benefits in context Not applicable							
4. What harm might the proposed intervention/action do?							
Evidence statement Not applicable						**Quality of evidence** **Not reported**	
Judging the harms in context Not applicable							
5. What is the likely balance between good and harm?							
Evidence statement Not applicable						**Overall quality of evidence** **Not reported**	
Judging the balance of benefits and harms in context Not applicable							
Benefits clearly outweigh harms	Recommend					STRONG	
Benefits probably outweigh harms	Consider					CONDITIONAL	
Not known	**Make a recommendation for research (see 8 below)**					**WEAK**	
Benefits probably don't outweigh harms	Consider against/make no recommendation					CONDITIONAL	

Harms probably outweigh benefits		
Benefits clearly don't outweigh harms	Recommend against	STRONG
Harms clearly outweigh benefits		

6. Is the intervention/action implementable in the New Zealand context?	
Summary statement Antenatal corticosteroids are already widely in use in New Zealand and Australia.	
Yes	**Recommend/consider**
Not known	Consider economic evaluation
No	Recommend/consider against

7. Final recommendation	
Repeat antenatal corticosteroids for a woman with other medical indications for preterm birth.	**Strength of recommendation** *Please select level* **STRONG** **CONDITIONAL** **WEAK (Practice Point)**

8. Recommendations for research

M39 Use of antenatal corticosteroids for women with diabetes in pregnancy at term – Single course and repeat antenatal corticosteroids

M39 NHMRC evidence summary

What are the benefits and harms for the mother and fetus, infant, child and adult of administering a single course or repeat antenatal corticosteroids for fetal lung maturation to women with diabetes mellitus or gestational diabetes at term?		
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
There were no data from randomised trials identified for maternal or neonatal outcomes associated with the use of a single course of antenatal corticosteroids in women with diabetes or gestational diabetes at term.	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 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')*		
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 not consistent
	NA	Not applicable (one study only)
3. Clinical impact *(indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Not applicable	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?)*		
Not applicable	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether sensible to apply
5. Applicability *(is the body of evidence relevant to the New Zealand / Australian healthcare context in terms of health services / delivery of care and cultural factors?)*		
Corticosteroids are readily available in Australia and New Zealand and their use is feasible.	A	Evidence directly applicable to New Zealand / Australian healthcare context
	B	Evidence applicable to New Zealand / Australian healthcare context with few caveats
	C	Evidence probably applicable to New Zealand / Australian healthcare context with some caveats
	D	Evidence not applicable to New Zealand / 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 *(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	N/A	
2. Consistency	N/A	
3. Clinical Impact	N/A	
4. Generalisability	N/A	
5. Applicability	N/A	

Evidence statement

There were no data from randomised trials identified for maternal or neonatal outcomes associated with the use of a single course or repeat antenatal corticosteroids in women with diabetes or gestational diabetes at term.

RECOMMENDATION *(What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible)*	**OVERALL GRADE OF RECOMMENDATION**	
There is insufficient evidence currently to make a recommendation for antenatal corticosteroids at term (≥37 weeks' gestation) for women with diabetes in pregnancy. Use antenatal corticosteroids 48 hours prior to caesarean birth planned beyond 34 weeks' and 6 days gestation if there is known fetal lung immaturity. Monitor maternal blood glucose concentrations and treat if elevated.	**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 recommendations(s) but care should be taken in its application
	D	Body of evidence is weak and recommendation must be applied with caution
	PP	**Practice Points**

UNRESOLVED ISSUES *(If needed, keep a 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 implementation of this recommendation?	**YES**
	NO

M39 GRADE Evidence summary

Considered Judgement - Strength of recommendation							
What are the maternal and fetus, infant, child, adult benefits and harms of administering a single course or repeat antenatal corticosteroids for fetal lung maturation to women with diabetes mellitus or gestational diabetes at term?							
1. Outcome measures:	**Quality of evidence**				**Importance of outcome in making a decision**		
Maternal Outcomes	**HIGH**	**MOD**	**LOW**	**V. LOW**	**Critical**	**Important**	**Not Important**
O_1 Chorioamnionitis				NR	✓		
O_2 Puerperal sepsis				NR	✓		
O_3 Pyrexia after entry to trial				NR		✓	
O_4 Intrapartum fever requiring antibiotics				NR		✓	
O_5 Post natal pyrexia				NR		✓	
O_6 Maternal quality of life				NR	✓		
Infant Outcomes	**HIGH**	**MOD**	**LOW**	**V. LOW**	**Critical**	**Important**	**Not Important**
O_1 Combined fetal and neonatal death				NR	✓		
O_2 Neonatal death				NR	✓		
O_3 Fetal death				NR	✓		
O_4 RDS				NR	✓		
O_5 Composite of serious outcomes for the infant				NR	✓		
O_6 Neurosensory disability (composite of impairments) for infant as a child				NR	✓		
O_7 Survival free of neurosensory disability for the infant as a child				NR	✓		
O_8 Survival free of metabolic disease for the infant as a child				NR		✓	
O_9 Neurosensory disability (composite of impairments) for infant as an adult				NR	✓		
O_{10} Survival free of neurosensory disability for the infant as an adult				NR	✓		
O_{11} Survival free of metabolic disease for the infant as an adult				NR		✓	
2. Is there is insufficient evidence to make a recommendation?							
Evidence statement *(For example, low volume or inconsistent evidence, low patient numbers.)* No evidence was identified for maternal or neonatal outcomes associated with the use of antenatal corticosteroids in women with diabetes or gestational diabetes at term.							
3. What benefit will the proposed intervention/action have?							
Evidence statement There is no evidence for the use of antenatal corticosteroids for women with diabetes or gestational diabetes at term. Based on the evidence from Chapter 12 of these Clinical Practice Guidelines on the optimal gestational age to administer antenatal corticosteroids, there is no current evidence to support the use beyond 34 weeks' gestation.						**Quality of evidence** **Not reported**	
Judging the benefits in context Not applicable.							
4. What harm might the proposed intervention/action do?							
Evidence statement Not applicable.						**Quality of evidence** **Not reported**	
Judging the harms in context Not applicable.							
5. What is the likely balance between good and harm?							
Evidence statement Not applicable.						**Overall quality of evidence** **Not reported**	
Judging the balance of benefits and harms in context Not applicable.							
Benefits clearly outweigh harms	Recommend					STRONG	
Benefits probably outweigh harms	Consider					CONDITIONAL	
Not known	**Make a recommendation for research (see 8 below)**					**WEAK**	
Benefits probably don't outweigh harms	Consider against/make no recommendation					CONDITIONAL	

Harms probably outweigh benefits		
Benefits clearly don't outweigh harms	Recommend against	STRONG
Harms clearly outweigh benefits		

6. Is the intervention/action implementable in the New Zealand context?

Summary statement
Antenatal corticosteroids are already widely in use in New Zealand and Australia.

Yes	**Recommend/consider**
Not known	Consider economic evaluation
No	Recommend/consider against

7. Final recommendation

	Strength of recommendation
There is insufficient evidence currently to make a recommendation for antenatal corticosteroids at term (≥37 weeks' gestation) for women with diabetes in pregnancy. Use antenatal corticosteroids 48 hours prior to caesarean birth planned beyond 34 weeks' and 6 days gestation if there is known fetal lung immaturity. Monitor maternal blood glucose concentrations and treat if elevated.	**STRONG** **CONDITIONAL** **WEAK (Practice points)**

8. Recommendations for research

- Randomised trials are needed to investigate the effects, if any, of using antenatal corticosteroids at term gestation in women with diabetes in pregnancy.

Appendix N: Forest plots for meta-analyses

Figure 1: Single course of antenatal corticosteroids - respiratory distress syndrome

Study or Subgroup	Antenatal corticosteroids Events	Total	No corticosteroids Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
5.1.1 Moderate/severe RDS						
Amorim 1999	9	50	23	50	9.7%	0.39 [0.20, 0.76]
Fekih 2002	1	31	15	34	2.7%	0.07 [0.01, 0.52]
Liggins 1972	41	271	73	275	12.8%	0.57 [0.40, 0.80]
Nelson 1985	6	11	6	11	8.7%	1.00 [0.47, 2.14]
Silver 1996	18	27	14	21	12.3%	1.00 [0.67, 1.50]
Taeusch 1979	6	27	14	34	8.3%	0.54 [0.24, 1.22]
Subtotal (95% CI)		**417**		**425**	**54.5%**	**0.60 [0.38, 0.95]**
Total events	81		145			
Heterogeneity: Tau² = 0.19; Chi² = 15.69, df = 5 (P = 0.008); I² = 68%						
Test for overall effect: Z = 2.20 (P = 0.03)						
5.1.2 Mild RDS						
Amorim 1999	14	50	20	50	10.7%	0.70 [0.40, 1.22]
Fekih 2002	2	32	4	34	3.6%	0.53 [0.10, 2.70]
Liggins 1972	12	271	16	275	9.0%	0.76 [0.37, 1.58]
Nelson 1985	4	11	5	11	6.7%	0.80 [0.29, 2.21]
Silver 1996	25	27	20	21	14.3%	0.97 [0.84, 1.12]
Taeusch 1979	1	27	0	35	1.2%	3.86 [0.16, 91.12]
Subtotal (95% CI)		**418**		**426**	**45.5%**	**0.86 [0.64, 1.17]**
Total events	58		65			
Heterogeneity: Tau² = 0.04; Chi² = 6.76, df = 5 (P = 0.24); I² = 26%						
Test for overall effect: Z = 0.97 (P = 0.33)						
Total (95% CI)		**835**		**851**	**100.0%**	**0.69 [0.48, 0.98]**
Total events	139		210			
Heterogeneity: Tau² = 0.23; Chi² = 47.85, df = 11 (P < 0.00001); I² = 77%						
Test for overall effect: Z = 2.06 (P = 0.04)						
Test for subgroup differences: Chi² = 1.68, df = 1 (P = 0.19), I² = 40.6%						

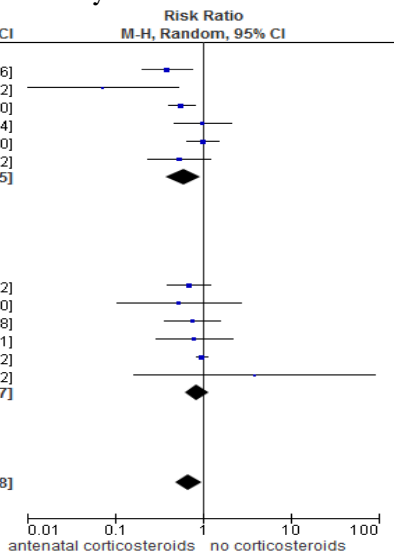

Figure 2: Repeat antenatal corticosteroids – respiratory distress syndrome

Study or Subgroup	Repeat corticosteroids Events	Total	No repeat corticosteroids Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
7.1.1 Severe respiratory distress						
Crowther 2006	65	284	114	289	15.2%	0.58 [0.45, 0.75]
Guinn 2002	38	124	57	118	14.2%	0.63 [0.46, 0.88]
Mazumder 2008	1	19	3	19	1.6%	0.33 [0.04, 2.93]
Peltoniemi 2007	70	80	60	84	16.4%	1.23 [1.05, 1.44]
Wapner 2006	6	126	10	122	5.9%	0.58 [0.22, 1.55]
Subtotal (95% CI)		**633**		**632**	**53.3%**	**0.71 [0.41, 1.23]**
Total events	180		244			
Heterogeneity: Tau² = 0.28; Chi² = 43.06, df = 4 (P < 0.00001); I² = 91%						
Test for overall effect: Z = 1.23 (P = 0.22)						
7.1.2 Moderate/Mild respiratory distress						
Crowther 2006	121	283	125	288	16.1%	0.99 [0.82, 1.19]
Guinn 2002	31	124	12	117	9.8%	2.44 [1.32, 4.52]
Mazumder 2008	1	18	1	18	1.1%	1.00 [0.07, 14.79]
Peltoniemi 2007	12	79	20	83	9.4%	0.63 [0.33, 1.20]
Wapner 2006	18	126	22	121	10.4%	0.79 [0.44, 1.39]
Subtotal (95% CI)		**630**		**627**	**46.7%**	**1.04 [0.68, 1.58]**
Total events	183		180			
Heterogeneity: Tau² = 0.13; Chi² = 10.74, df = 4 (P = 0.03); I² = 63%						
Test for overall effect: Z = 0.16 (P = 0.87)						
Total (95% CI)		**1263**		**1259**	**100.0%**	**0.86 [0.64, 1.16]**
Total events	363		424			
Heterogeneity: Tau² = 0.13; Chi² = 46.58, df = 9 (P < 0.00001); I² = 81%						
Test for overall effect: Z = 0.99 (P = 0.32)						
Test for subgroup differences: Chi² = 1.14, df = 1 (P = 0.28), I² = 12.6%						

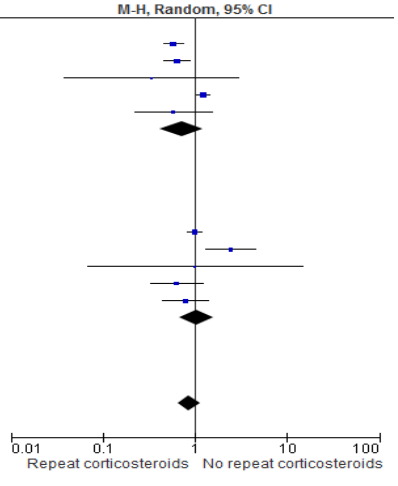

Figure 3: Subgroup analysis: Chorioamnionitis by of type of antenatal corticosteroid administered

Study or Subgroup	Antenatal corticosteroid Events	Total	No corticosteroid Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 Betamethasone						
Amorim 1999	2	110	1	108	1.0%	1.96 [0.18, 21.34]
Carlan 1991	0	11	3	13	3.2%	0.17 [0.01, 2.91]
Fekih 2002	1	59	0	59	0.5%	3.00 [0.12, 72.18]
Garite 1992	1	33	2	38	1.8%	0.58 [0.05, 6.07]
Lewis 1996	6	38	6	39	5.8%	1.03 [0.36, 2.90]
Liggins 1972	28	556	37	580	35.3%	0.79 [0.49, 1.27]
Lopez 1989	0	20	1	20	1.5%	0.33 [0.01, 7.72]
Morales 1989	9	87	16	78	16.5%	0.50 [0.24, 1.08]
Schutte 1980	1	50	4	51	3.9%	0.26 [0.03, 2.20]
Subtotal (95% CI)		**964**		**986**	**69.3%**	**0.70 [0.49, 0.99]**
Total events	48		70			
Heterogeneity: Chi² = 5.06, df = 8 (P = 0.75); I² = 0%						
Test for overall effect: Z = 2.01 (P = 0.04)						
1.2.2 Dexamethasone						
Dexiprom 1999	11	102	8	102	7.8%	1.38 [0.58, 3.28]
Kari 1994	13	77	8	80	7.7%	1.69 [0.74, 3.85]
Qublan 2001	6	72	3	67	3.0%	1.86 [0.48, 7.15]
Silver 1996	13	39	12	36	12.2%	1.00 [0.53, 1.90]
Subtotal (95% CI)		**290**		**285**	**30.7%**	**1.35 [0.89, 2.05]**
Total events	43		31			
Heterogeneity: Chi² = 1.35, df = 3 (P = 0.72); I² = 0%						
Test for overall effect: Z = 1.42 (P = 0.16)						
Total (95% CI)		**1254**		**1271**	**100.0%**	**0.90 [0.69, 1.17]**
Total events	91		101			
Heterogeneity: Chi² = 11.11, df = 12 (P = 0.52); I² = 0%						
Test for overall effect: Z = 0.78 (P = 0.44)						
Test for subgroup differences: Chi² = 5.63, df = 1 (P = 0.02), I² = 82.2%						

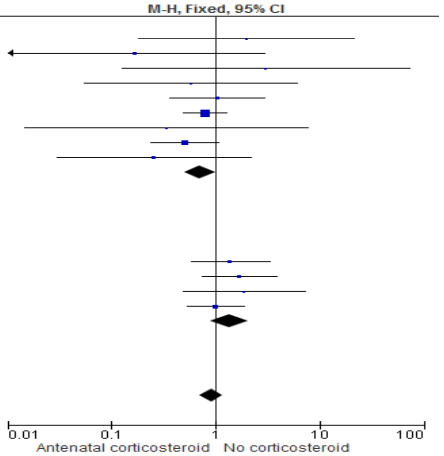

Figure 4: Subgroup analysis: Puerperal sepsis by type of antenatal corticosteroid administered

Study or Subgroup	Antenatal corticosteroids Events	Total	No corticosteroids Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 Betamethasone						
Amorim 1999	9	110	13	108	19.0%	0.68 [0.30, 1.52]
Garite 1992	10	33	5	38	15.8%	2.30 [0.88, 6.06]
Lewis 1996	2	38	4	39	7.7%	0.51 [0.10, 2.64]
Schutte 1980	1	50	1	51	3.2%	1.02 [0.07, 15.86]
Subtotal (95% CI)		**231**		**236**	**45.6%**	**1.02 [0.48, 2.16]**
Total events	22		23			
Heterogeneity: Tau² = 0.19; Chi² = 4.38, df = 3 (P = 0.22); I² = 31%						
Test for overall effect: Z = 0.04 (P = 0.97)						
1.3.2 Dexamethasone						
Dexiprom 1999	4	102	7	102	12.1%	0.57 [0.17, 1.89]
Qublan 2001	9	72	2	67	8.8%	4.19 [0.94, 18.68]
Silver 1996	11	39	5	36	16.0%	2.03 [0.78, 5.28]
Taeusch 1979	11	52	7	66	17.6%	1.99 [0.83, 4.79]
Subtotal (95% CI)		**265**		**271**	**54.4%**	**1.71 [0.86, 3.43]**
Total events	35		21			
Heterogeneity: Tau² = 0.19; Chi² = 4.84, df = 3 (P = 0.18); I² = 38%						
Test for overall effect: Z = 1.52 (P = 0.13)						
Total (95% CI)		**496**		**507**	**100.0%**	**1.35 [0.81, 2.25]**
Total events	57		44			
Heterogeneity: Tau² = 0.19; Chi² = 10.97, df = 7 (P = 0.14); I² = 36%						
Test for overall effect: Z = 1.15 (P = 0.25)						
Test for subgroup differences: Chi² = 0.99, df = 1 (P = 0.32), I² = 0%						

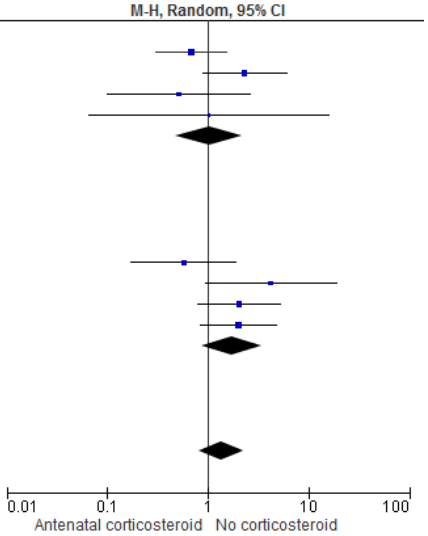

Figure 5: Subgroup analysis: Pyrexia after trial entry by type of antenatal corticosteroid administered

Study or Subgroup	Antenatal corticosteroid Events	Total	No corticosteroid Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.4.1 Betamethasone						
Amorim 1999	11	110	14	108	32.0%	0.77 [0.37, 1.62]
Nelson 1985	1	22	4	22	10.5%	0.25 [0.03, 2.06]
Schutte 1980	4	50	6	51	21.7%	0.68 [0.20, 2.27]
Subtotal (95% CI)		**182**		**181**	**64.2%**	**0.68 [0.37, 1.25]**
Total events	16		24			
Heterogeneity: Tau² = 0.00; Chi² = 0.98, df = 2 (P = 0.61); I² = 0%						
Test for overall effect: Z = 1.24 (P = 0.21)						
1.4.2 Dexamethasone						
Taeusch 1979	21	52	13	66	35.8%	2.05 [1.14, 3.69]
Subtotal (95% CI)		**52**		**66**	**35.8%**	**2.05 [1.14, 3.69]**
Total events	21		13			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.39 (P = 0.02)						
Total (95% CI)		**234**		**247**	**100.0%**	**0.95 [0.43, 2.06]**
Total events	37		37			
Heterogeneity: Tau² = 0.35; Chi² = 7.65, df = 3 (P = 0.05); I² = 61%						
Test for overall effect: Z = 0.14 (P = 0.89)						
Test for subgroup differences: Chi² = 6.54, df = 1 (P = 0.01), I² = 84.7%						

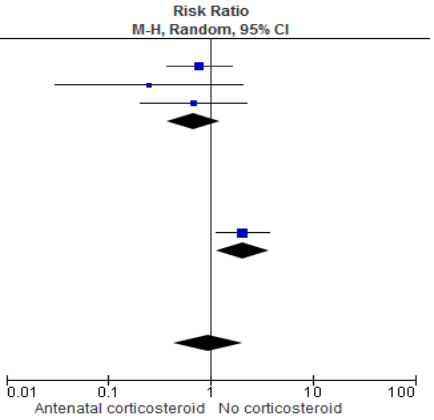

Figure 6: Subgroup analysis: Postnatal pyrexia by type of antenatal corticosteroid administered

Study or Subgroup	Antenatal cortiocsteroid Events	Total	No corticosteroid Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.5.1 Betamethasone						
Amorim 1999	9	110	13	108	24.2%	0.68 [0.30, 1.52]
Fekih 2002	2	59	2	59	3.7%	1.00 [0.15, 6.87]
Schutte 1980	5	50	3	51	5.5%	1.70 [0.43, 6.74]
Subtotal (95% CI)		**219**		**218**	**33.4%**	**0.88 [0.46, 1.68]**
Total events	16		18			
Heterogeneity: Chi² = 1.29, df = 2 (P = 0.53); I² = 0%						
Test for overall effect: Z = 0.38 (P = 0.70)						
1.5.2 Dexamethasone						
Collaborative 1981	27	342	29	340	53.7%	0.93 [0.56, 1.53]
Dexiprom 1999	7	102	7	102	12.9%	1.00 [0.36, 2.75]
Subtotal (95% CI)		**444**		**442**	**66.6%**	**0.94 [0.60, 1.47]**
Total events	34		36			
Heterogeneity: Chi² = 0.02, df = 1 (P = 0.89); I² = 0%						
Test for overall effect: Z = 0.27 (P = 0.79)						
Total (95% CI)		**663**		**660**	**100.0%**	**0.92 [0.64, 1.33]**
Total events	50		54			
Heterogeneity: Chi² = 1.34, df = 4 (P = 0.85); I² = 0%						
Test for overall effect: Z = 0.44 (P = 0.66)						
Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.88), I² = 0%						

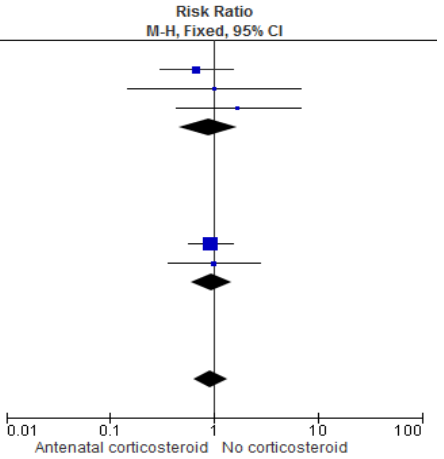

Figure 7: Subgroup analysis: Perinatal death by type of antenatal corticosteroid administered

Study or Subgroup	Antenatal corticosteroids Events	Antenatal corticosteroids Total	No corticosteroids Events	No corticosteroids Total	Weight	Risk Ratio M-H, Random, 95% CI
1.6.1 Betamethasone						
Amorim 1999	24	110	36	108	12.3%	0.65 [0.42, 1.02]
Block 1977	4	60	6	54	2.9%	0.60 [0.18, 2.01]
Doran 1980	5	81	14	63	4.2%	0.28 [0.11, 0.73]
Gamsu 1989	15	131	22	137	8.4%	0.71 [0.39, 1.31]
Garite 1992	12	36	12	41	7.5%	1.14 [0.59, 2.21]
Liggins 1972	108	601	122	617	19.4%	0.91 [0.72, 1.15]
Parsons 1988	0	23	1	22	0.5%	0.32 [0.01, 7.45]
Schutte 1980	6	65	12	58	4.6%	0.45 [0.18, 1.11]
Subtotal (95% CI)		**1107**		**1100**	**59.9%**	**0.72 [0.55, 0.94]**
Total events	174		225			
Heterogeneity: Tau² = 0.04; Chi² = 9.90, df = 7 (P = 0.19); I² = 29%						
Test for overall effect: Z = 2.38 (P = 0.02)						
1.6.2 Dexamethasone						
Collaborative 1981	47	378	47	379	14.3%	1.00 [0.69, 1.46]
Dexiprom 1999	4	105	10	103	3.3%	0.39 [0.13, 1.21]
Kari 1994	5	95	6	94	3.1%	0.82 [0.26, 2.61]
Qublan 2001	21	72	41	67	13.3%	0.48 [0.32, 0.72]
Taeusch 1979	10	56	12	71	6.2%	1.06 [0.49, 2.27]
Subtotal (95% CI)		**706**		**714**	**40.1%**	**0.72 [0.46, 1.11]**
Total events	87		116			
Heterogeneity: Tau² = 0.12; Chi² = 9.11, df = 4 (P = 0.06); I² = 56%						
Test for overall effect: Z = 1.49 (P = 0.14)						
Total (95% CI)		**1813**		**1814**	**100.0%**	**0.72 [0.58, 0.89]**
Total events	261		341			
Heterogeneity: Tau² = 0.05; Chi² = 19.21, df = 12 (P = 0.08); I² = 38%						
Test for overall effect: Z = 2.99 (P = 0.003)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.98), I² = 0%						

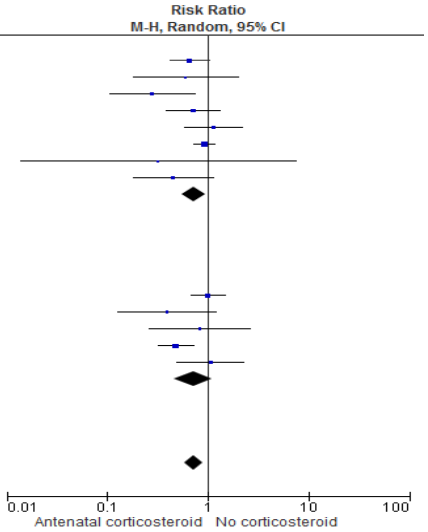

Figure 8: Subgroup analysis: Neonatal death by type of antenatal corticosteroid administered

Study or Subgroup	Antenatal corticosteroids Events	Antenatal corticosteroids Total	No corticosteroids Events	No corticosteroids Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.7.1 Betamethasone						
Amorim 1999	14	100	28	100	9.1%	0.50 [0.28, 0.89]
Block 1977	1	57	5	53	1.7%	0.19 [0.02, 1.54]
Doran 1980	4	80	11	60	4.1%	0.27 [0.09, 0.81]
Fekih 2002	9	63	21	68	6.5%	0.46 [0.23, 0.93]
Gamsu 1989	14	130	17	132	5.5%	0.84 [0.43, 1.63]
Garite 1992	9	33	11	40	3.2%	0.99 [0.47, 2.10]
Goodner 1979	4	47	7	45	2.3%	0.55 [0.17, 1.74]
Lewis 1996	1	38	1	39	0.3%	1.03 [0.07, 15.82]
Liggins 1972	61	554	72	567	23.1%	0.87 [0.63, 1.19]
Lopez 1989	6	20	6	20	1.9%	1.00 [0.39, 2.58]
Morales 1989	7	87	8	78	2.7%	0.78 [0.30, 2.06]
Nelson 1985	1	22	1	22	0.3%	1.00 [0.07, 15.00]
Parsons 1988	0	23	1	22	0.5%	0.32 [0.01, 7.45]
Porto 2011	0	163	2	157	0.8%	0.19 [0.01, 3.98]
Schutte 1980	3	62	12	58	4.0%	0.23 [0.07, 0.79]
Subtotal (95% CI)		**1479**		**1461**	**66.1%**	**0.67 [0.54, 0.81]**
Total events	134		203			
Heterogeneity: Chi² = 14.90, df = 14 (P = 0.39); I² = 6%						
Test for overall effect: Z = 3.97 (P < 0.0001)						
1.7.2 Dexamethasone						
Collaborative 1981	34	365	32	364	10.4%	1.06 [0.67, 1.68]
Dexiprom 1999	4	105	8	101	2.6%	0.48 [0.15, 1.55]
Kari 1994	4	91	6	88	2.0%	0.64 [0.19, 2.21]
Qublan 2001	19	70	39	65	13.1%	0.45 [0.29, 0.70]
Silver 1996	7	54	8	42	2.9%	0.68 [0.27, 1.73]
Taeusch 1979	8	54	10	69	2.8%	1.02 [0.43, 2.41]
Subtotal (95% CI)		**739**		**729**	**33.9%**	**0.72 [0.55, 0.94]**
Total events	76		103			
Heterogeneity: Chi² = 8.29, df = 5 (P = 0.14); I² = 40%						
Test for overall effect: Z = 2.43 (P = 0.02)						
Total (95% CI)		**2218**		**2190**	**100.0%**	**0.68 [0.58, 0.80]**
Total events	210		306			
Heterogeneity: Chi² = 22.98, df = 20 (P = 0.29); I² = 13%						
Test for overall effect: Z = 4.64 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.21, df = 1 (P = 0.65), I² = 0%						

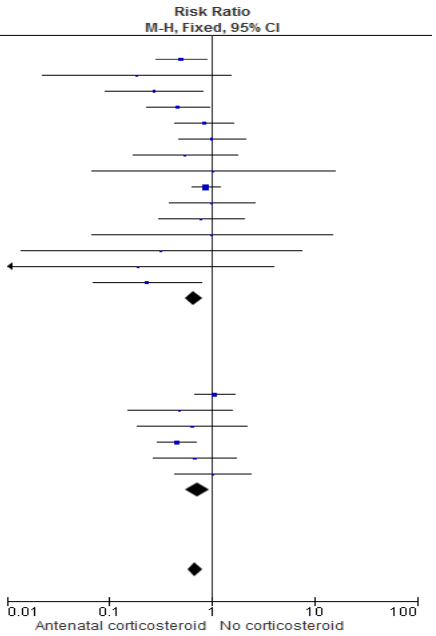

Figure 9: Subgroup analysis: Fetal death by type of antenatal corticosteroid administered

Study or Subgroup	Antenatal corticosteroids Events	Antenatal corticosteroids Total	No corticosteroids Events	No corticosteroids Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.8.1 Betamethasone						
Amorim 1999	10	110	8	108	8.2%	1.23 [0.50, 2.99]
Block 1977	3	60	1	54	1.1%	2.70 [0.29, 25.19]
Doran 1980	1	81	3	63	3.4%	0.26 [0.03, 2.43]
Gamsu 1989	1	131	5	137	4.9%	0.21 [0.02, 1.77]
Garite 1992	3	36	1	41	0.9%	3.42 [0.37, 31.41]
Liggins 1972	47	601	50	617	49.9%	0.97 [0.66, 1.41]
Parsons 1988	0	23	0	22		Not estimable
Schutte 1980	3	65	0	58	0.5%	6.26 [0.33, 118.64]
Subtotal (95% CI)		**1107**		**1100**	**69.0%**	**1.01 [0.73, 1.39]**
Total events	68		68			
Heterogeneity: Chi² = 7.13, df = 6 (P = 0.31); I² = 16%						
Test for overall effect: Z = 0.05 (P = 0.96)						
1.8.2 Dexamethasone						
Collaborative 1981	13	378	15	379	15.2%	0.87 [0.42, 1.80]
Dexiprom 1999	0	105	2	103	2.6%	0.20 [0.01, 4.04]
Kari 1994	1	95	0	94	0.5%	2.97 [0.12, 71.96]
Qublan 2001	2	72	2	67	2.1%	0.93 [0.13, 6.42]
Taeusch 1979	10	56	12	71	10.7%	1.06 [0.49, 2.27]
Subtotal (95% CI)		**706**		**714**	**31.0%**	**0.92 [0.56, 1.50]**
Total events	26		31			
Heterogeneity: Chi² = 1.67, df = 4 (P = 0.80); I² = 0%						
Test for overall effect: Z = 0.35 (P = 0.73)						
Total (95% CI)		**1813**		**1814**	**100.0%**	**0.98 [0.75, 1.28]**
Total events	94		99			
Heterogeneity: Chi² = 8.85, df = 11 (P = 0.64); I² = 0%						
Test for overall effect: Z = 0.15 (P = 0.88)						
Test for subgroup differences: Chi² = 0.10, df = 1 (P = 0.75), I² = 0%						

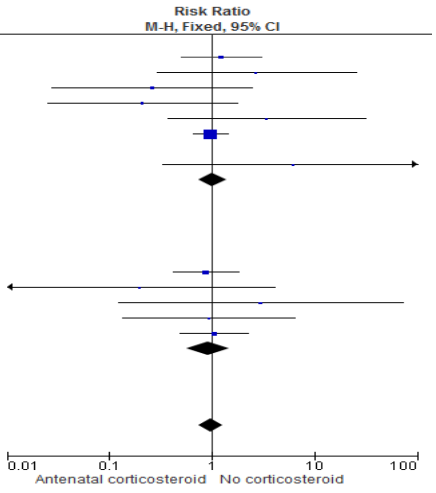

Figure 10: Subgroup analysis: Respiratory distress syndrome by type of antenatal corticosteroid administered

Study or Subgroup	Antenatal corticosteroids Events	Total	No corticosteroids Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.9.1 Betamethasone						
Amorim 1999	23	100	43	100	6.5%	0.53 [0.35, 0.82]
Balci 2010	2	50	8	50	1.2%	0.25 [0.06, 1.12]
Block 1977	5	57	12	53	2.4%	0.39 [0.15, 1.03]
Carlan 1991	1	11	4	13	0.7%	0.30 [0.04, 2.27]
Doran 1980	4	80	10	60	2.0%	0.30 [0.10, 0.91]
Fekih 2002	3	63	19	68	1.8%	0.17 [0.05, 0.55]
Gamsu 1989	7	130	16	132	3.0%	0.44 [0.19, 1.04]
Garite 1992	21	33	28	40	7.7%	0.91 [0.65, 1.26]
Goodner 1979	5	47	11	45	2.4%	0.44 [0.16, 1.15]
Lewis 1996	7	38	17	39	3.5%	0.42 [0.20, 0.90]
Liggins 1972	53	542	89	550	7.8%	0.60 [0.44, 0.83]
Lopez 1989	9	20	10	20	4.2%	0.90 [0.47, 1.73]
Morales 1989	23	87	41	78	6.7%	0.50 [0.33, 0.76]
Nelson 1985	10	22	11	22	4.5%	0.91 [0.49, 1.69]
Parsons 1988	3	23	3	22	1.2%	0.96 [0.22, 4.24]
Porto 2011	2	163	1	157	0.5%	1.93 [0.18, 21.03]
Schutte 1980	11	62	17	58	4.1%	0.61 [0.31, 1.18]
Teramo 1980	3	38	3	42	1.1%	1.11 [0.24, 5.15]
Subtotal (95% CI)		**1566**		**1549**	**61.2%**	**0.59 [0.48, 0.72]**
Total events	192		343			
Heterogeneity: Tau² = 0.04; Chi² = 23.88, df = 17 (P = 0.12); I² = 29%						
Test for overall effect: Z = 5.27 (P < 0.00001)						
1.9.2 Dexamethasone						
Collaborative 1981	46	361	65	359	7.4%	0.70 [0.50, 1.00]
Dexiprom 1999	32	102	27	100	6.4%	1.16 [0.75, 1.79]
Kari 1994	34	91	46	90	7.6%	0.73 [0.52, 1.02]
Qublan 2001	14	70	24	65	5.0%	0.54 [0.31, 0.95]
Silver 1996	43	54	34	42	9.3%	0.98 [0.81, 1.20]
Taeusch 1979	7	54	14	69	3.1%	0.64 [0.28, 1.47]
Subtotal (95% CI)		**732**		**725**	**38.8%**	**0.81 [0.65, 1.02]**
Total events	176		210			
Heterogeneity: Tau² = 0.04; Chi² = 10.08, df = 5 (P = 0.07); I² = 50%						
Test for overall effect: Z = 1.80 (P = 0.07)						
Total (95% CI)		**2298**		**2274**	**100.0%**	**0.66 [0.55, 0.78]**
Total events	368		553			
Heterogeneity: Tau² = 0.07; Chi² = 47.47, df = 23 (P = 0.002); I² = 52%						
Test for overall effect: Z = 4.79 (P < 0.00001)						
Test for subgroup differences: Chi² = 4.59, df = 1 (P = 0.03), I² = 78.2%						

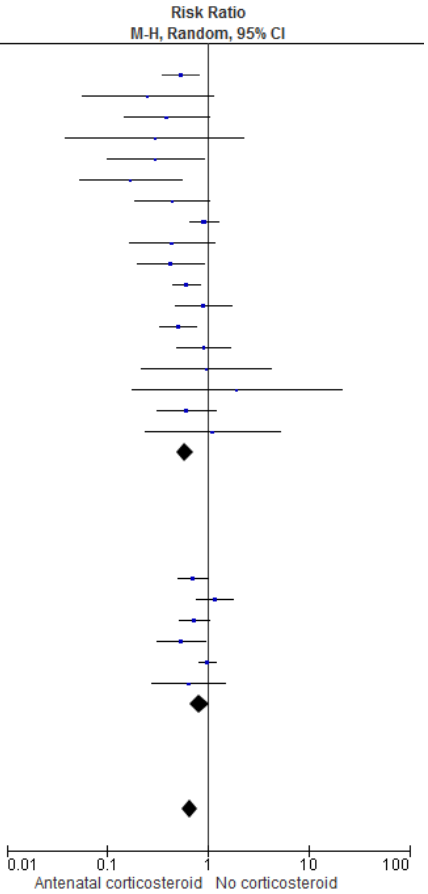

Figure 11 Subgroup analysis: intraventricular haemorrhage by type of antenatal corticosteroid administered

Study or Subgroup	Antenatal corticosteroids Events	Total	No corticosteroids Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.10.1 Betamethasone						
Amorim 1999	6	100	17	100	9.0%	0.35 [0.15, 0.86]
Doran 1980	1	80	4	60	2.0%	0.19 [0.02, 1.63]
Fekih 2002	5	63	14	68	8.0%	0.39 [0.15, 1.01]
Gamsu 1989	2	130	4	132	3.2%	0.51 [0.09, 2.72]
Garite 1992	10	33	19	40	14.2%	0.64 [0.35, 1.18]
Lewis 1996	0	38	3	39	1.1%	0.15 [0.01, 2.74]
Liggins 1972	16	554	27	567	14.3%	0.61 [0.33, 1.11]
Morales 1989	13	87	20	78	13.8%	0.58 [0.31, 1.09]
Subtotal (95% CI)		**1085**		**1084**	**65.8%**	**0.52 [0.39, 0.71]**
Total events	53		108			
Heterogeneity: Tau² = 0.00; Chi² = 3.54, df = 7 (P = 0.83); I² = 0%						
Test for overall effect: Z = 4.20 (P < 0.0001)						
1.10.2 Dexamethasone						
Dexiprom 1999	0	105	0	101		Not estimable
Kari 1994	8	77	18	66	11.0%	0.38 [0.18, 0.82]
Qublan 2001	2	70	8	65	3.9%	0.23 [0.05, 1.05]
Silver 1996	25	54	17	42	18.2%	1.14 [0.72, 1.82]
Taeusch 1979	0	54	4	69	1.2%	0.14 [0.01, 2.57]
Subtotal (95% CI)		**360**		**343**	**34.2%**	**0.48 [0.18, 1.26]**
Total events	35		47			
Heterogeneity: Tau² = 0.60; Chi² = 10.72, df = 3 (P = 0.01); I² = 72%						
Test for overall effect: Z = 1.49 (P = 0.14)						
Total (95% CI)		**1445**		**1427**	**100.0%**	**0.54 [0.39, 0.74]**
Total events	88		155			
Heterogeneity: Tau² = 0.09; Chi² = 16.25, df = 11 (P = 0.13); I² = 32%						
Test for overall effect: Z = 3.80 (P = 0.0001)						
Test for subgroup differences: Chi² = 0.03, df = 1 (P = 0.86), I² = 0%						

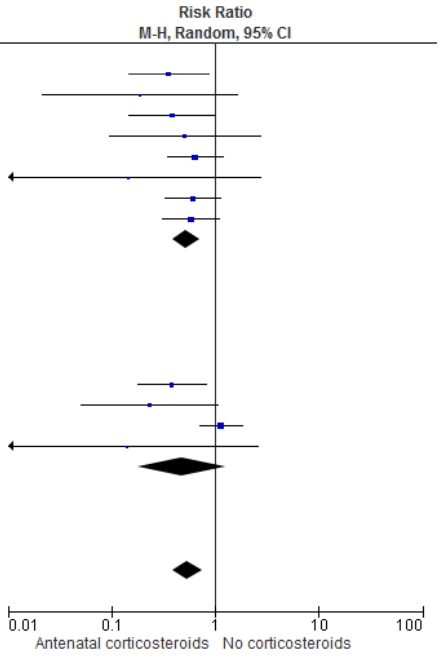

Figure 12: Subgroup analysis – Chorioamnionitis betamethasone regimens

Study or Subgroup	Betamethasone Events	Betamethasone Total	No corticosteroid Events	No corticosteroid Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.11.1 12mg immediately						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.11.2 12mg in 12 hours						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.11.3 24mg in 12 hours						
Lopez 1989	0	20	1	20	2.1%	0.33 [0.01, 7.72]
Subtotal (95% CI)		**20**		**20**	**2.1%**	**0.33 [0.01, 7.72]**
Total events	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.69 (P = 0.49)						
1.11.4 24mg in 24 hours						
Amorim 1999	2	110	1	108	1.4%	1.96 [0.18, 21.34]
Carlan 1991	0	11	3	13	4.5%	0.17 [0.01, 2.91]
Fekih 2002	1	59	0	59	0.7%	3.00 [0.12, 72.18]
Garite 1992	1	33	2	38	2.6%	0.58 [0.05, 6.07]
Lewis 1996	6	38	6	39	8.3%	1.03 [0.36, 2.90]
Liggins 1972	28	556	37	580	51.0%	0.79 [0.49, 1.27]
Morales 1989	9	87	16	78	23.7%	0.50 [0.24, 1.08]
Subtotal (95% CI)		**894**		**915**	**92.3%**	**0.74 [0.52, 1.05]**
Total events	47		65			
Heterogeneity: Chi² = 3.91, df = 6 (P = 0.69); I² = 0%						
Test for overall effect: Z = 1.69 (P = 0.09)						
1.11.5 24mg in 36 hours or more						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.11.6 28mg in 24 hours						
Schutte 1980	1	50	4	51	5.6%	0.26 [0.03, 2.20]
Subtotal (95% CI)		**50**		**51**	**5.6%**	**0.26 [0.03, 2.20]**
Total events	1		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.24 (P = 0.21)						
Total (95% CI)		**964**		**986**	**100.0%**	**0.70 [0.49, 0.99]**
Total events	48		70			
Heterogeneity: Chi² = 5.06, df = 8 (P = 0.75); I² = 0%						
Test for overall effect: Z = 2.01 (P = 0.04)						
Test for subgroup differences: Chi² = 1.13, df = 2 (P = 0.57), I² = 0%						

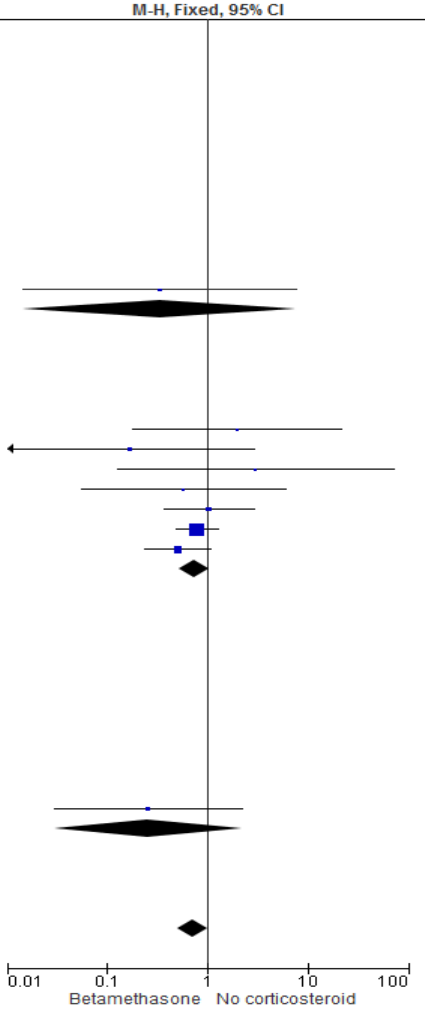

Figure 13: Subgroup analysis Chorioamnionitis dexamethasone regimen

Study or Subgroup	Dexamethasone Events	Dexamethasone Total	No corticosteroids Events	No corticosteroids Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.12.1 20mg in 36 hours						
Silver 1996	13	39	12	36	39.7%	1.00 [0.53, 1.90]
Subtotal (95% CI)		**39**		**36**	**39.7%**	**1.00 [0.53, 1.90]**
Total events	13		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
1.12.2 24mg in 24 hours						
Dexiprom 1999	11	102	8	102	25.4%	1.38 [0.58, 3.28]
Subtotal (95% CI)		**102**		**102**	**25.4%**	**1.38 [0.58, 3.28]**
Total events	11		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.72 (P = 0.47)						
1.12.3 24mg in 36 hours						
Kari 1994	13	77	8	80	25.0%	1.69 [0.74, 3.85]
Qublan 2001	6	72	3	67	9.9%	1.86 [0.48, 7.15]
Subtotal (95% CI)		**149**		**147**	**34.8%**	**1.74 [0.86, 3.51]**
Total events	19		11			
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.90); I² = 0%						
Test for overall effect: Z = 1.54 (P = 0.12)						
1.12.4 24mg in 40 hours						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**290**		**285**	**100.0%**	**1.35 [0.89, 2.05]**
Total events	43		31			
Heterogeneity: Chi² = 1.35, df = 3 (P = 0.72); I² = 0%						
Test for overall effect: Z = 1.42 (P = 0.16)						
Test for subgroup differences: Chi² = 1.31, df = 2 (P = 0.52), I² = 0%						

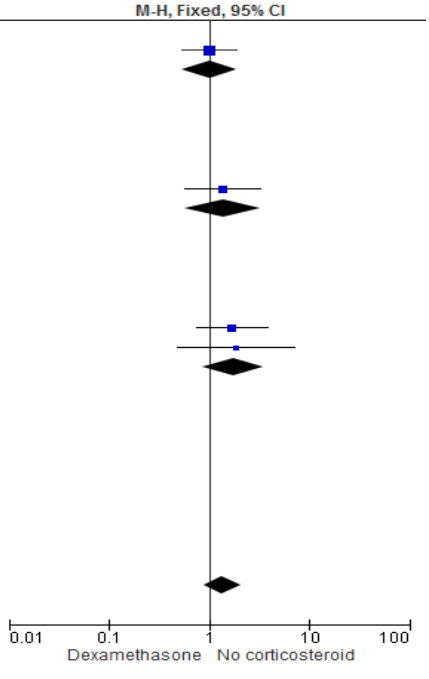

Figure 14: Subgroup analysis Puerperal sepsis betamethasone regimen

Study or Subgroup	Betamethasone Events	Betamethasone Total	No corticosteroid Events	No corticosteroid Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.13.1 12mg immediately						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.13.2 12mg in 12 hours						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.13.3 24mg in 12 hours						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.13.4 24mg in 24 hours						
Amorim 1999	9	110	13	108	57.8%	0.68 [0.30, 1.52]
Garite 1992	10	33	5	38	20.5%	2.30 [0.88, 6.06]
Lewis 1996	2	38	4	39	17.4%	0.51 [0.10, 2.64]
Subtotal (95% CI)		**181**		**185**	**95.6%**	**1.00 [0.57, 1.73]**
Total events	21		22			
Heterogeneity: Chi² = 4.38, df = 2 (P = 0.11); I² = 54%						
Test for overall effect: Z = 0.01 (P = 0.99)						
1.13.5 24mg in 36 hours or more						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.13.6 28mg in 24 hours						
Schutte 1980	1	50	1	51	4.4%	1.02 [0.07, 15.86]
Subtotal (95% CI)		**50**		**51**	**4.4%**	**1.02 [0.07, 15.86]**
Total events	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.01 (P = 0.99)						
Total (95% CI)		**231**		**236**	**100.0%**	**1.00 [0.58, 1.72]**
Total events	22		23			
Heterogeneity: Chi² = 4.38, df = 3 (P = 0.22); I² = 31%						
Test for overall effect: Z = 0.01 (P = 0.99)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.99), I² = 0%						

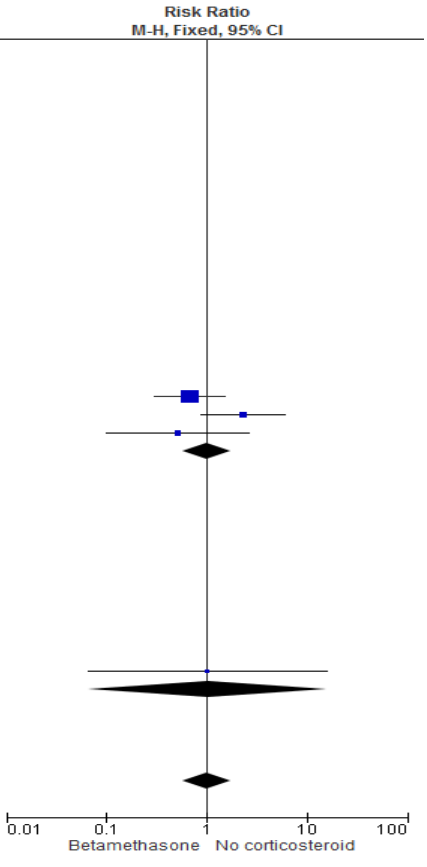

Figure 15: Subgroup analysis Puerperal sepsis dexamethasone regimen

Study or Subgroup	Dexamethasone Events	Dexamethasone Total	No corticosteroid Events	No corticosteroid Total	Weight	Risk Ratio M-H, Random, 95% CI
1.14.1 20mg in 36 hours						
Silver 1996	11	39	5	36	29.3%	2.03 [0.78, 5.28]
Subtotal (95% CI)		**39**		**36**	**29.3%**	**2.03 [0.78, 5.28]**
Total events	11		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.45 (P = 0.15)						
1.14.2 24mg in 24 hours						
Dexiprom 1999	4	102	7	102	22.2%	0.57 [0.17, 1.89]
Subtotal (95% CI)		**102**		**102**	**22.2%**	**0.57 [0.17, 1.89]**
Total events	4		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.92 (P = 0.36)						
1.14.3 24mg in 36 hours						
Qublan 2001	9	72	2	67	16.2%	4.19 [0.94, 18.68]
Subtotal (95% CI)		**72**		**67**	**16.2%**	**4.19 [0.94, 18.68]**
Total events	9		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.88 (P = 0.06)						
1.14.4 24mg in 40 hours						
Taeusch 1979	11	52	7	66	32.2%	1.99 [0.83, 4.79]
Subtotal (95% CI)		**52**		**66**	**32.2%**	**1.99 [0.83, 4.79]**
Total events	11		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.55 (P = 0.12)						
Total (95% CI)		**265**		**271**	**100.0%**	**1.71 [0.86, 3.43]**
Total events	35		21			
Heterogeneity: Tau² = 0.19; Chi² = 4.84, df = 3 (P = 0.18); I² = 38%						
Test for overall effect: Z = 1.52 (P = 0.13)						
Test for subgroup differences: Chi² = 4.84, df = 3 (P = 0.18), I² = 38.0%						

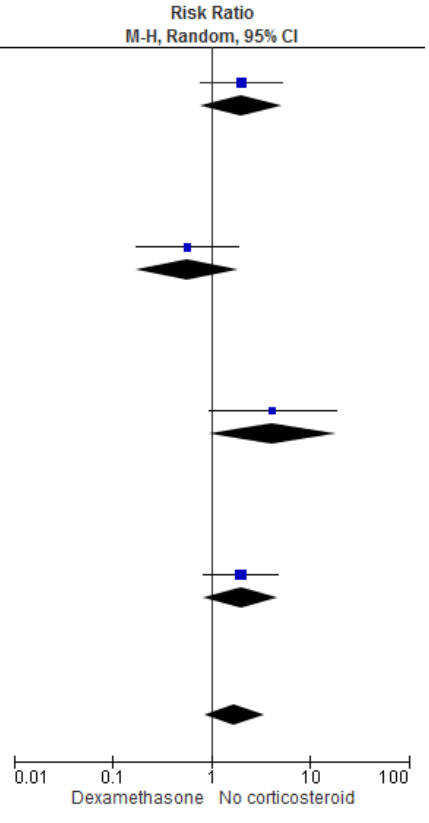

Figure 16: Subgroup analysis Neonatal death – Betamethasone regimens

Study or Subgroup	Betamethasone Events	Betamethasone Total	No corticosteroids Events	No corticosteroids Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.15.1 12mg immediately						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.15.2 12mg in 12 hours						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.15.3 24mg in 12 hours						
Lopez 1989	6	20	6	20	3.0%	1.00 [0.39, 2.58]
Nelson 1985	1	22	1	22	0.5%	1.00 [0.07, 15.00]
Parsons 1988	0	23	1	22	0.8%	0.32 [0.01, 7.45]
Subtotal (95% CI)		**65**		**64**	**4.3%**	**0.88 [0.37, 2.07]**
Total events	7		8			
Heterogeneity: Chi² = 0.48, df = 2 (P = 0.79); I² = 0%						
Test for overall effect: Z = 0.30 (P = 0.77)						
1.15.4 24mg in 24 hours						
Amorim 1999	14	100	28	100	14.2%	0.50 [0.28, 0.89]
Block 1977	1	57	5	53	2.6%	0.19 [0.02, 1.54]
Fekih 2002	9	63	21	68	10.3%	0.46 [0.23, 0.93]
Garite 1992	9	33	11	40	5.1%	0.99 [0.47, 2.10]
Lewis 1996	1	38	1	39	0.5%	1.03 [0.07, 15.82]
Liggins 1972	61	554	72	567	36.2%	0.87 [0.63, 1.19]
Morales 1989	7	87	8	78	4.3%	0.78 [0.30, 2.06]
Porto 2011	0	163	2	157	1.3%	0.19 [0.01, 3.98]
Subtotal (95% CI)		**1095**		**1102**	**74.4%**	**0.71 [0.56, 0.90]**
Total events	102		148			
Heterogeneity: Chi² = 7.47, df = 7 (P = 0.38); I² = 6%						
Test for overall effect: Z = 2.89 (P = 0.004)						
1.15.5 24mg in 36 hours or more						
Doran 1980	4	80	11	60	6.4%	0.27 [0.09, 0.81]
Gamsu 1989	14	130	17	132	8.6%	0.84 [0.43, 1.63]
Subtotal (95% CI)		**210**		**192**	**15.0%**	**0.60 [0.34, 1.03]**
Total events	18		28			
Heterogeneity: Chi² = 2.96, df = 1 (P = 0.09); I² = 66%						
Test for overall effect: Z = 1.84 (P = 0.07)						
1.15.6 28mg in 24 hours						
Schutte 1980	3	62	12	58	6.3%	0.23 [0.07, 0.79]
Subtotal (95% CI)		**62**		**58**	**6.3%**	**0.23 [0.07, 0.79]**
Total events	3		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.35 (P = 0.02)						
Total (95% CI)		**1432**		**1416**	**100.0%**	**0.67 [0.55, 0.82]**
Total events	130		196			
Heterogeneity: Chi² = 14.74, df = 13 (P = 0.32); I² = 12%						
Test for overall effect: Z = 3.85 (P = 0.0001)						
Test for subgroup differences: Chi² = 3.67, df = 3 (P = 0.30), I² = 18.2%						

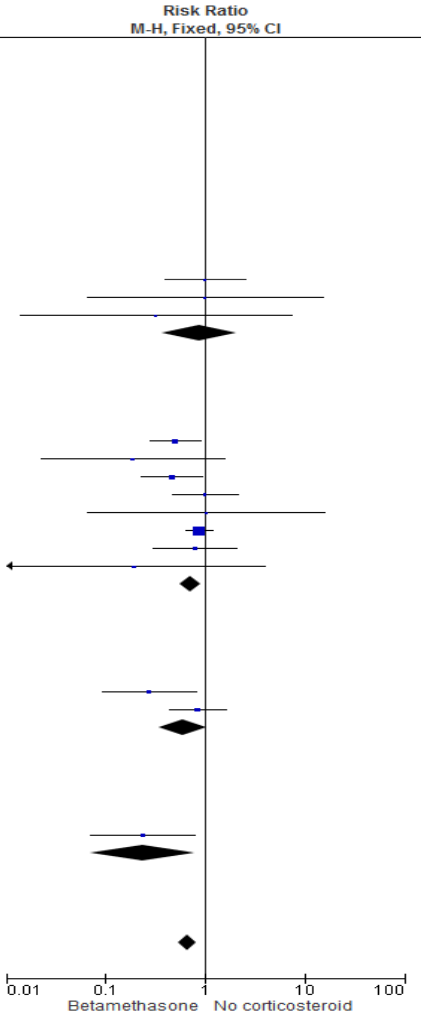

Figure 17: Subgroup analysis Neonatal death – dexamethasone regimens

Study or Subgroup	Dexamethasone Events	Dexamethasone Total	No corticosteroids Events	No corticosteroids Total	Weight	Risk Ratio M-H, Random, 95% CI
1.16.1 20mg in 36 hours						
Collaborative 1981	34	365	32	364	27.6%	1.06 [0.67, 1.68]
Silver 1996	7	54	8	42	12.5%	0.68 [0.27, 1.73]
Subtotal (95% CI)		**419**		**406**	**40.1%**	**0.97 [0.64, 1.47]**
Total events	41		40			
Heterogeneity: Tau² = 0.00; Chi² = 0.70, df = 1 (P = 0.40); I² = 0%						
Test for overall effect: Z = 0.14 (P = 0.89)						
1.16.2 24mg in 24 hours						
Dexiprom 1999	4	105	8	101	8.8%	0.48 [0.15, 1.55]
Subtotal (95% CI)		**105**		**101**	**8.8%**	**0.48 [0.15, 1.55]**
Total events	4		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.23 (P = 0.22)						
1.16.3 24mg in 36 hours						
Kari 1994	4	91	6	88	8.1%	0.64 [0.19, 2.21]
Qublan 2001	19	70	39	65	29.0%	0.45 [0.29, 0.70]
Subtotal (95% CI)		**161**		**153**	**37.1%**	**0.47 [0.31, 0.71]**
Total events	23		45			
Heterogeneity: Tau² = 0.00; Chi² = 0.29, df = 1 (P = 0.59); I² = 0%						
Test for overall effect: Z = 3.63 (P = 0.0003)						
1.16.4 24mg in 40 hours						
Taeusch 1979	8	54	10	69	14.0%	1.02 [0.43, 2.41]
Subtotal (95% CI)		**54**		**69**	**14.0%**	**1.02 [0.43, 2.41]**
Total events	8		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.05 (P = 0.96)						
Total (95% CI)		**739**		**729**	**100.0%**	**0.70 [0.47, 1.03]**
Total events	76		103			
Heterogeneity: Tau² = 0.09; Chi² = 8.29, df = 5 (P = 0.14); I² = 40%						
Test for overall effect: Z = 1.82 (P = 0.07)						
Test for subgroup differences: Chi² = 7.20, df = 3 (P = 0.07), I² = 58.4%						

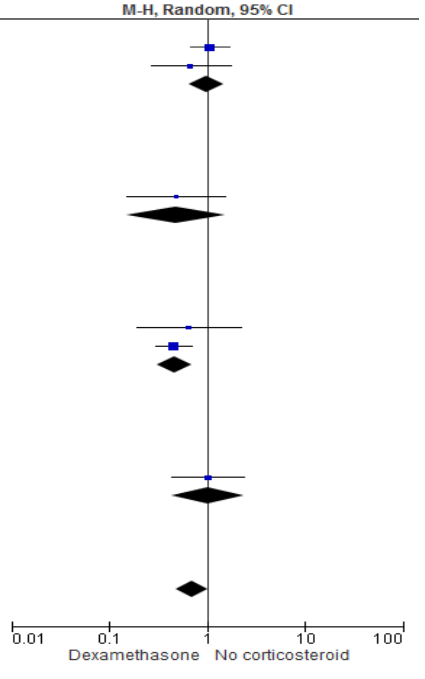

Figure 18: Subgroup analysis Respiratory distress syndrome – Betamethasone regimens

Study or Subgroup	Betamethasone Events	Betamethasone Total	No corticosteroid Events	No corticosteroid Total	Weight	Risk Ratio M-H, Random, 95% CI
1.17.1 12mg immediately						
Balci 2010	2	50	8	50	1.7%	0.25 [0.06, 1.12]
Subtotal (95% CI)		**50**		**50**	**1.7%**	**0.25 [0.06, 1.12]**
Total events	2		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.81 (P = 0.07)						
1.17.2 12mg in 12 hours						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.17.3 24mg in 12 hours						
Lopez 1989	9	20	10	20	6.9%	0.90 [0.47, 1.73]
Nelson 1985	10	22	11	22	7.4%	0.91 [0.49, 1.69]
Parsons 1988	3	23	3	22	1.8%	0.96 [0.22, 4.24]
Subtotal (95% CI)		**65**		**64**	**16.1%**	**0.91 [0.59, 1.40]**
Total events	22		24			
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 2 (P = 1.00); I² = 0%						
Test for overall effect: Z = 0.43 (P = 0.66)						
1.17.4 24mg in 24 hours						
Amorim 1999	23	100	43	100	11.5%	0.53 [0.35, 0.82]
Block 1977	5	57	12	53	3.7%	0.39 [0.15, 1.03]
Carlan 1991	1	11	4	13	1.0%	0.30 [0.04, 2.27]
Fekih 2002	3	63	19	68	2.7%	0.17 [0.05, 0.55]
Garite 1992	21	33	28	40	14.4%	0.91 [0.65, 1.26]
Lewis 1996	7	38	17	39	5.6%	0.42 [0.20, 0.90]
Liggins 1972	53	542	89	550	14.7%	0.60 [0.44, 0.83]
Morales 1989	23	87	41	78	11.9%	0.50 [0.33, 0.76]
Porto 2011	2	163	1	157	0.7%	1.93 [0.18, 21.03]
Teramo 1980	3	38	3	42	1.7%	1.11 [0.24, 5.15]
Subtotal (95% CI)		**1132**		**1140**	**67.9%**	**0.57 [0.43, 0.74]**
Total events	141		257			
Heterogeneity: Tau² = 0.07; Chi² = 16.18, df = 9 (P = 0.06); I² = 44%						
Test for overall effect: Z = 4.12 (P < 0.0001)						
1.17.5 24mg in 36 hours or more						
Doran 1980	4	80	10	60	3.0%	0.30 [0.10, 0.91]
Gamsu 1989	7	130	16	132	4.6%	0.44 [0.19, 1.04]
Subtotal (95% CI)		**210**		**192**	**7.6%**	**0.38 [0.20, 0.76]**
Total events	11		26			
Heterogeneity: Tau² = 0.00; Chi² = 0.30, df = 1 (P = 0.58); I² = 0%						
Test for overall effect: Z = 2.77 (P = 0.006)						
1.17.6 28mg in 24 hours						
Schutte 1980	11	62	17	58	6.7%	0.61 [0.31, 1.18]
Subtotal (95% CI)		**62**		**58**	**6.7%**	**0.61 [0.31, 1.18]**
Total events	11		17			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.47 (P = 0.14)						
Total (95% CI)		**1519**		**1504**	**100.0%**	**0.59 [0.48, 0.73]**
Total events	187		332			
Heterogeneity: Tau² = 0.05; Chi² = 23.37, df = 16 (P = 0.10); I² = 32%						
Test for overall effect: Z = 5.00 (P < 0.00001)						
Test for subgroup differences: Chi² = 6.75, df = 4 (P = 0.15), I² = 40.7%						

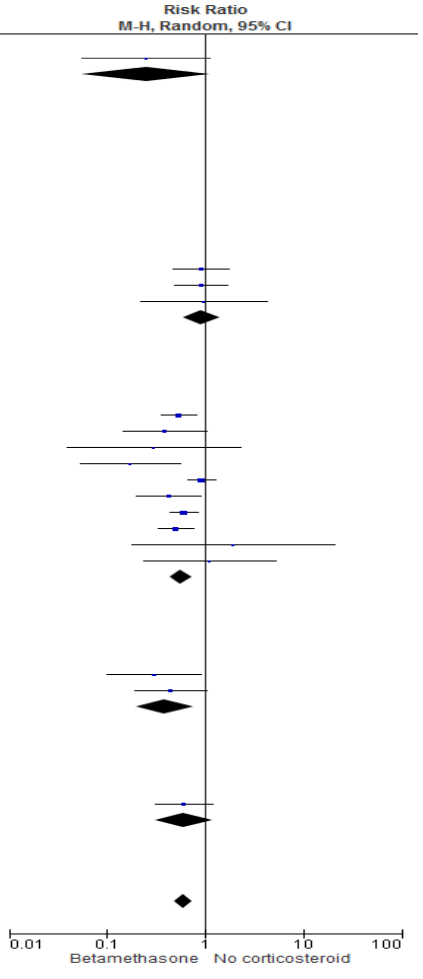

Figure 19: Subgroup analysis Respiratory distress syndrome - Dexamethasone regimens

Study or Subgroup	Dexamethasone Events	Dexamethasone Total	No corticosteroids Events	No corticosteroids Total	Weight	Risk Ratio M-H, Random, 95% CI
1.18.1 20mg in 36 hours						
Collaborative 1981	46	361	65	359	19.3%	0.70 [0.50, 1.00]
Silver 1996	43	54	34	42	28.2%	0.98 [0.81, 1.20]
Subtotal (95% CI)		**415**		**401**	**47.5%**	**0.85 [0.56, 1.29]**
Total events	89		99			
Heterogeneity: Tau² = 0.07; Chi² = 4.37, df = 1 (P = 0.04); I² = 77%						
Test for overall effect: Z = 0.77 (P = 0.44)						
1.18.2 24mg in 24 hours						
Dexiprom 1999	32	102	27	100	15.5%	1.16 [0.75, 1.79]
Subtotal (95% CI)		**102**		**100**	**15.5%**	**1.16 [0.75, 1.79]**
Total events	32		27			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.50)						
1.18.3 24mg in 36 hours						
Kari 1994	34	91	46	90	20.1%	0.73 [0.52, 1.02]
Qublan 2001	14	70	24	65	10.9%	0.54 [0.31, 0.95]
Subtotal (95% CI)		**161**		**155**	**31.0%**	**0.68 [0.51, 0.90]**
Total events	48		70			
Heterogeneity: Tau² = 0.00; Chi² = 0.81, df = 1 (P = 0.37); I² = 0%						
Test for overall effect: Z = 2.66 (P = 0.008)						
1.18.4 24mg in 40 hours						
Taeusch 1979	7	54	14	69	6.0%	0.64 [0.28, 1.47]
Subtotal (95% CI)		**54**		**69**	**6.0%**	**0.64 [0.28, 1.47]**
Total events	7		14			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.05 (P = 0.29)						
Total (95% CI)		**732**		**725**	**100.0%**	**0.81 [0.65, 1.02]**
Total events	176		210			
Heterogeneity: Tau² = 0.04; Chi² = 10.08, df = 5 (P = 0.07); I² = 50%						
Test for overall effect: Z = 1.80 (P = 0.07)						
Test for subgroup differences: Chi² = 4.53, df = 3 (P = 0.21), I² = 33.8%						

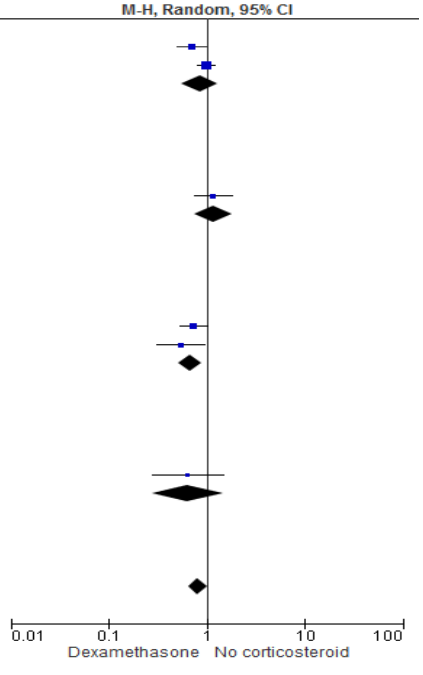

Figure 20: Subgroup analysis Repeat antenatal corticosteroids - Chorioamnionitis

Study or Subgroup	Repeat course Events	Repeat course Total	Single course Events	Single course Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.19.1 12mg completed immediately (no repeat doses)						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.19.2 11.4 mg completed immediately (repeat doses allowed)						
Crowther 2006	44	489	41	493	34.2%	1.08 [0.72, 1.62]
Subtotal (95% CI)		**489**		**493**	**34.2%**	**1.08 [0.72, 1.62]**
Total events	44		41			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.38 (P = 0.70)						
1.19.3 24mg in 24 hours (no repeat doses)						
Garite 2009	6	223	9	214	7.7%	0.64 [0.23, 1.77]
Subtotal (95% CI)		**223**		**214**	**7.7%**	**0.64 [0.23, 1.77]**
Total events	6		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.86 (P = 0.39)						
1.19.4 24mg in 24 hours (repeat doses allowed)						
Aghajafari 2002	0	6	0	6		Not estimable
Guinn 2002	60	249	42	236	36.1%	1.35 [0.95, 1.92]
Murphy 2008	22	935	20	918	16.9%	1.08 [0.59, 1.97]
Wapner 2006	8	250	6	242	5.1%	1.29 [0.45, 3.66]
Subtotal (95% CI)		**1440**		**1402**	**58.1%**	**1.27 [0.95, 1.70]**
Total events	90		68			
Heterogeneity: Chi² = 0.41, df = 2 (P = 0.81); I² = 0%						
Test for overall effect: Z = 1.60 (P = 0.11)						
Total (95% CI)		**2152**		**2109**	**100.0%**	**1.16 [0.92, 1.46]**
Total events	140		118			
Heterogeneity: Chi² = 2.27, df = 4 (P = 0.69); I² = 0%						
Test for overall effect: Z = 1.24 (P = 0.22)						
Test for subgroup differences: Chi² = 1.79, df = 2 (P = 0.41), I² = 0%						

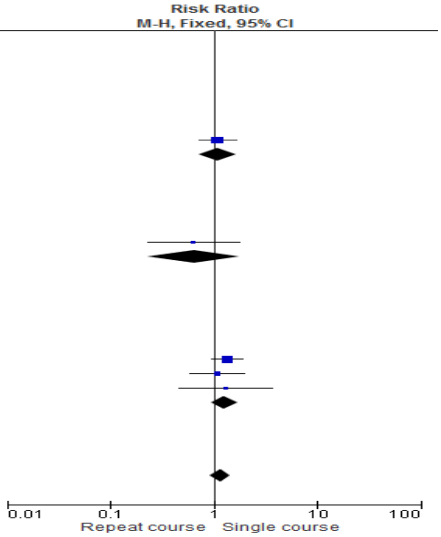

Figure 21: Subgroup analysis Repeat antenatal corticosteroids - Puerperal sepsis

Study or Subgroup	Repeat course Events	Repeat course Total	Single course Events	Single course Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.20.1 12mg completed immediately (no repeat courses)						
Peltoniemi 2007	19	125	12	124	19.5%	1.57 [0.80, 3.10]
Subtotal (95% CI)		**125**		**124**	**19.5%**	**1.57 [0.80, 3.10]**
Total events	19		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.30 (P = 0.19)						
1.20.2 11.4mg completed immediately (repeat doses allowed)						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.20.3 24 mg in 24 hours (no repeat doses)						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.20.4 24mg in 24 hours (repeat doses allowed)						
Aghajafari 2002	0	6	0	6		Not estimable
Guinn 2002	13	249	14	236	23.3%	0.88 [0.42, 1.83]
Murphy 2008	34	935	25	918	40.8%	1.34 [0.80, 2.22]
Wapner 2006	6	250	10	242	16.4%	0.58 [0.21, 1.57]
Subtotal (95% CI)		**1440**		**1402**	**80.5%**	**1.05 [0.72, 1.54]**
Total events	53		49			
Heterogeneity: Chi² = 2.44, df = 2 (P = 0.30); I² = 18%						
Test for overall effect: Z = 0.25 (P = 0.80)						
Total (95% CI)		**1565**		**1526**	**100.0%**	**1.15 [0.83, 1.60]**
Total events	72		61			
Heterogeneity: Chi² = 3.46, df = 3 (P = 0.33); I² = 13%						
Test for overall effect: Z = 0.83 (P = 0.40)						
Test for subgroup differences: Chi² = 1.03, df = 1 (P = 0.31), I² = 2.9%						

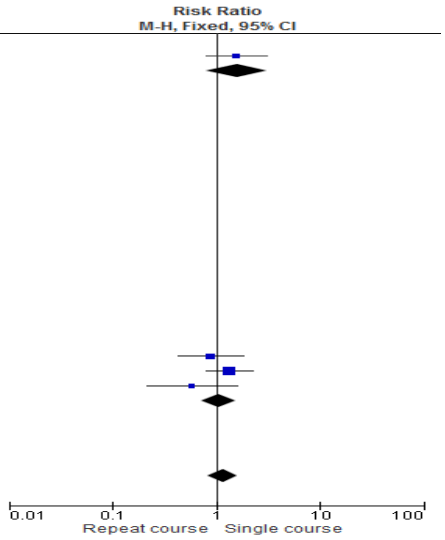

Figure 22: Subgroup analysis Repeat antenatal corticosteroids – Neonatal death

Study or Subgroup	Repeat course Events	Repeat course Total	Single course Events	Single course Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.21.1 12mg completed immediately (no repeat course)						
Peltoniemi 2007	8	159	3	167	5.6%	2.80 [0.76, 10.37]
Subtotal (95% CI)		**159**		**167**	**5.6%**	**2.80 [0.76, 10.37]**
Total events	8		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.54 (P = 0.12)						
1.21.2 11.4mg completed immediately (repeat doses allowed)						
Crowther 2006	26	567	28	577	53.0%	0.94 [0.56, 1.59]
Subtotal (95% CI)		**567**		**577**	**53.0%**	**0.94 [0.56, 1.59]**
Total events	26		28			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.21 (P = 0.83)						
1.21.3 24mg in 24 hours (no repeat doses allowed)						
Garite 2009	4	275	6	281	11.3%	0.68 [0.19, 2.39]
McEvoy 2010	1	56	0	56	1.0%	3.00 [0.12, 72.10]
Subtotal (95% CI)		**331**		**337**	**12.3%**	**0.86 [0.28, 2.66]**
Total events	5		6			
Heterogeneity: Chi² = 0.73, df = 1 (P = 0.39); I² = 0%						
Test for overall effect: Z = 0.26 (P = 0.80)						
1.21.4 24mg in 24 hours (repeat doses allowed)						
Aghajafari 2002	0	9	0	7		Not estimable
Guinn 2002	4	248	8	235	15.7%	0.47 [0.14, 1.55]
Mazumder 2008	4	38	7	38	13.4%	0.57 [0.18, 1.79]
Subtotal (95% CI)		**295**		**280**	**29.1%**	**0.52 [0.23, 1.18]**
Total events	8		15			
Heterogeneity: Chi² = 0.05, df = 1 (P = 0.82); I² = 0%						
Test for overall effect: Z = 1.56 (P = 0.12)						
Total (95% CI)		**1352**		**1361**	**100.0%**	**0.91 [0.62, 1.34]**
Total events	47		52			
Heterogeneity: Chi² = 5.40, df = 5 (P = 0.37); I² = 7%						
Test for overall effect: Z = 0.46 (P = 0.65)						
Test for subgroup differences: Chi² = 4.64, df = 3 (P = 0.20), I² = 35.4%						

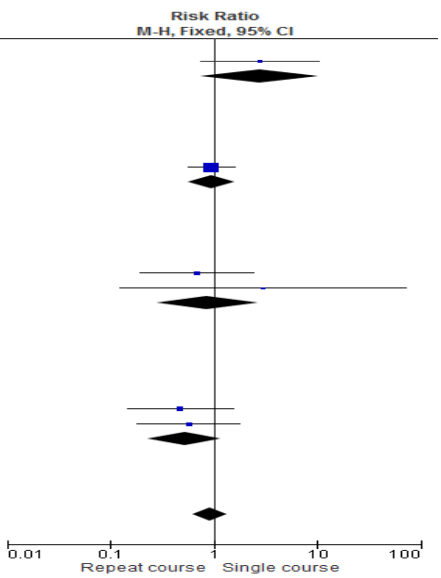

Figure 23: Subgroup analysis Repeat antenatal corticosteroids - Respiratory distress syndrome

Study or Subgroup	Repeat course Events	Repeat course Total	Single course Events	Single course Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.22.1 12mg completed immediately (no repeat dose)						
Peltoniemi 2007	82	159	80	167	13.9%	1.08 [0.87, 1.34]
Subtotal (95% CI)		**159**		**167**	**13.9%**	**1.08 [0.87, 1.34]**
Total events	82		80			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.66 (P = 0.51)						
1.22.2 11.4mg completed immediately (repeat doses allowed)						
Crowther 2006	186	567	239	577	42.1%	0.79 [0.68, 0.92]
Subtotal (95% CI)		**567**		**577**	**42.1%**	**0.79 [0.68, 0.92]**
Total events	186		239			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.00 (P = 0.003)						
1.22.3 24mg in 24 hours (no repeat doses allowed)						
Garite 2009	83	275	116	281	20.4%	0.73 [0.58, 0.92]
McEvoy 2010	15	56	23	56	4.1%	0.65 [0.38, 1.11]
Subtotal (95% CI)		**331**		**337**	**24.5%**	**0.72 [0.58, 0.89]**
Total events	98		139			
Heterogeneity: Chi² = 0.15, df = 1 (P = 0.70); I² = 0%						
Test for overall effect: Z = 3.10 (P = 0.002)						
1.22.4 24mg in 24 hours (repeat doses allowed)						
Aghajafari 2002	2	9	2	7	0.4%	0.78 [0.14, 4.23]
Guinn 2002	69	248	69	235	12.6%	0.95 [0.71, 1.26]
Mazumder 2008	2	37	4	37	0.7%	0.50 [0.10, 2.56]
Wapner 2006	24	252	32	243	5.8%	0.72 [0.44, 1.19]
Subtotal (95% CI)		**546**		**522**	**19.5%**	**0.86 [0.68, 1.10]**
Total events	97		107			
Heterogeneity: Chi² = 1.35, df = 3 (P = 0.72); I² = 0%						
Test for overall effect: Z = 1.22 (P = 0.22)						
Total (95% CI)		**1603**		**1603**	**100.0%**	**0.83 [0.75, 0.91]**
Total events	463		565			
Heterogeneity: Chi² = 9.34, df = 7 (P = 0.23); I² = 25%						
Test for overall effect: Z = 3.78 (P = 0.0002)						
Test for subgroup differences: Chi² = 7.72, df = 3 (P = 0.05), I² = 61.2%						

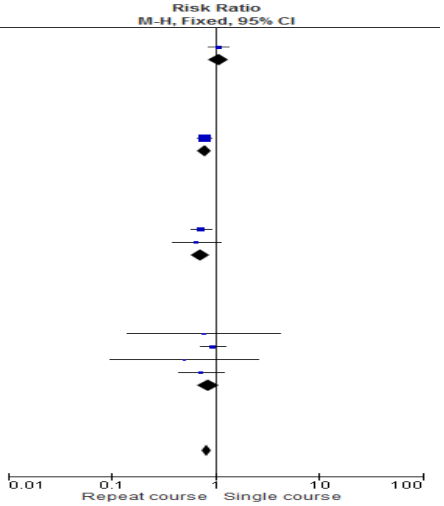

Figure 24: Subgroup analysis Repeat antenatal corticosteroids - Composite of serious infant outcomes

Study or Subgroup	Repeat course Events	Repeat course Total	Single course Events	Single course Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.23.1 12mg completed immediately (no repeat doses allowed)						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.23.2 11.4mg completed immediately (repeat doses allowed)						
Crowther 2006	114	567	150	577	28.6%	0.77 [0.62, 0.96]
Subtotal (95% CI)		**567**		**577**	**28.6%**	**0.77 [0.62, 0.96]**
Total events	114		150			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.35 (P = 0.02)						
1.23.3 24mg in 24 hours (no repeat doses allowed)						
Garite 2009	88	276	120	282	22.8%	0.75 [0.60, 0.93]
Subtotal (95% CI)		**276**		**282**	**22.8%**	**0.75 [0.60, 0.93]**
Total events	88		120			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.58 (P = 0.010)						
1.23.4 24mg in 24 hours (repeat doses allowed)						
Aghajafari 2002	4	9	5	7	1.1%	0.62 [0.26, 1.48]
Guinn 2002	56	256	66	246	12.9%	0.82 [0.60, 1.11]
Mazumder 2008	6	37	13	38	2.5%	0.47 [0.20, 1.11]
Murphy 2008	150	1164	143	1140	27.8%	1.03 [0.83, 1.27]
Wapner 2006	20	252	22	243	4.3%	0.88 [0.49, 1.56]
Subtotal (95% CI)		**1718**		**1674**	**48.6%**	**0.92 [0.78, 1.08]**
Total events	236		249			
Heterogeneity: Chi² = 4.72, df = 4 (P = 0.32); I² = 15%						
Test for overall effect: Z = 1.00 (P = 0.32)						
Total (95% CI)		**2561**		**2533**	**100.0%**	**0.84 [0.75, 0.94]**
Total events	438		519			
Heterogeneity: Chi² = 7.24, df = 6 (P = 0.30); I² = 17%						
Test for overall effect: Z = 3.06 (P = 0.002)						
Test for subgroup differences: Chi² = 2.80, df = 2 (P = 0.25), I² = 28.5%						

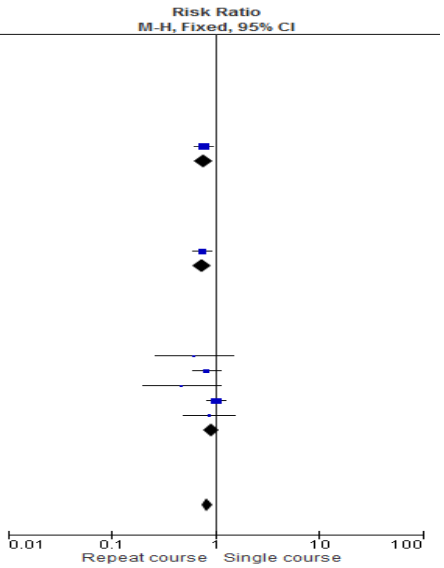

Figure 25: Subgroup analysis Repeat antenatal corticosteroids Birthweight

Study or Subgroup	Repeat course Mean	Repeat course SD	Repeat course Total	Single course Mean	Single course SD	Single course Total	Weight	Mean Difference IV, Fixed, 95% CI
1.24.1 12mg completed immediately (no repeat doses allowed)								
Peltoniemi 2007	1,460	500	159	1,558	487	167	15.2%	-98.00 [-205.22, 9.22]
Subtotal (95% CI)			**159**			**167**	**15.2%**	**-98.00 [-205.22, 9.22]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.79 (P = 0.07)								
1.24.2 11.4mg completed immediately (repeat doses allowed)								
Crowther 2006	1,867	824	567	1,877	816	577	19.4%	-10.00 [-105.04, 85.04]
Subtotal (95% CI)			**567**			**577**	**19.4%**	**-10.00 [-105.04, 85.04]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.21 (P = 0.84)								
1.24.3 24mg in 24 hours (no repeat doses allowed)								
Garite 2009	1,905	738	275	1,920	667	281	12.8%	-15.00 [-132.00, 102.00]
McEvoy 2010	1,806	778	56	1,830	657	56	2.5%	-24.00 [-290.70, 242.70]
Subtotal (95% CI)			**331**			**337**	**15.2%**	**-16.45 [-123.60, 90.69]**
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.95); I² = 0%								
Test for overall effect: Z = 0.30 (P = 0.76)								
1.24.4 24mg in 24 hours (repeat doses allowed)								
Guinn 2002	2,009.1	858.7	248	2,138.8	875.8	235	7.3%	-129.70 [-284.49, 25.09]
Mazumder 2008	1,553.4	441.4	37	1,645.6	627	37	2.9%	-92.20 [-339.27, 154.87]
McEvoy 2002	1,767	659	18	1,975	740	19	0.9%	-208.00 [-659.00, 243.00]
Murphy 2008	2,216	966	1164	2,330	970	1140	28.0%	-114.00 [-193.06, -34.94]
Wapner 2006	2,194.3	762.3	296	2,289.6	791.8	294	11.1%	-95.30 [-220.73, 30.13]
Subtotal (95% CI)			**1763**			**1725**	**50.2%**	**-112.51 [-171.58, -53.44]**
Heterogeneity: Chi² = 0.32, df = 4 (P = 0.99); I² = 0%								
Test for overall effect: Z = 3.73 (P = 0.0002)								
Total (95% CI)			**2820**			**2806**	**100.0%**	**-75.79 [-117.63, -33.96]**
Heterogeneity: Chi² = 4.99, df = 8 (P = 0.76); I² = 0%								
Test for overall effect: Z = 3.55 (P = 0.0004)								
Test for subgroup differences: Chi² = 4.67, df = 3 (P = 0.20), I² = 35.7%								

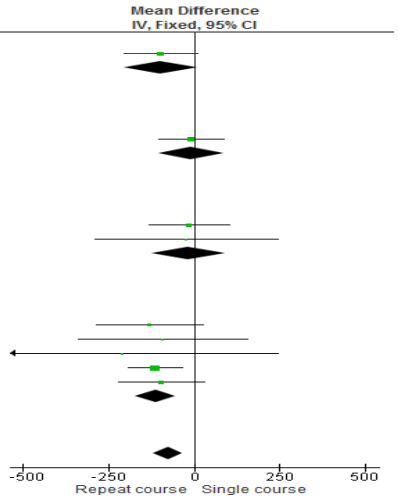

Figure 26: Interval between single and repeat antenatal corticosteroid courses - Chorioamnionitis

Study or Subgroup	Repeat course Events	Repeat course Total	Single course Events	Single course Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.25.1 Between 7 to 14 days						
Aghajafari 2002	0	6	0	6		Not estimable
Crowther 2006	44	489	41	493	34.2%	1.08 [0.72, 1.62]
Guinn 2002	60	249	42	236	36.1%	1.35 [0.95, 1.92]
Wapner 2006	8	250	6	242	5.1%	1.29 [0.45, 3.66]
Subtotal (95% CI)		**994**		**977**	**75.4%**	**1.23 [0.95, 1.59]**
Total events	112		89			
Heterogeneity: Chi² = 0.68, df = 2 (P = 0.71); I² = 0%						
Test for overall effect: Z = 1.55 (P = 0.12)						
1.25.2 >/= 14 days						
Garite 2009	6	223	9	214	7.7%	0.64 [0.23, 1.77]
Murphy 2008	22	935	20	918	16.9%	1.08 [0.59, 1.97]
Subtotal (95% CI)		**1158**		**1132**	**24.6%**	**0.94 [0.56, 1.57]**
Total events	28		29			
Heterogeneity: Chi² = 0.76, df = 1 (P = 0.38); I² = 0%						
Test for overall effect: Z = 0.23 (P = 0.82)						
Total (95% CI)		**2152**		**2109**	**100.0%**	**1.16 [0.92, 1.46]**
Total events	140		118			
Heterogeneity: Chi² = 2.27, df = 4 (P = 0.69); I² = 0%						
Test for overall effect: Z = 1.24 (P = 0.22)						
Test for subgroup differences: Chi² = 0.81, df = 1 (P = 0.37), I² = 0%						

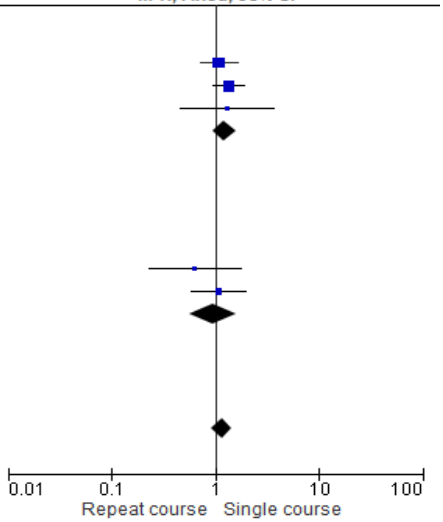

Figure 27: Interval between single and repeat antenatal corticosteroid courses - Puerperal sepsis

Study or Subgroup	Repeat course Events	Repeat course Total	Single course Events	Single course Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.26.1 Between 7 to 14 days						
Aghajafari 2002	0	6	0	6		Not estimable
Guinn 2002	13	249	14	236	23.3%	0.88 [0.42, 1.83]
Peltoniemi 2007	19	125	12	124	19.5%	1.57 [0.80, 3.10]
Wapner 2006	6	250	10	242	16.4%	0.58 [0.21, 1.57]
Subtotal (95% CI)		**630**		**608**	**59.2%**	**1.02 [0.66, 1.59]**
Total events	38		36			
Heterogeneity: Chi² = 2.93, df = 2 (P = 0.23); I² = 32%						
Test for overall effect: Z = 0.11 (P = 0.91)						
1.26.2 >/= 14 days						
Murphy 2008	34	935	25	918	40.8%	1.34 [0.80, 2.22]
Subtotal (95% CI)		**935**		**918**	**40.8%**	**1.34 [0.80, 2.22]**
Total events	34		25			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.11 (P = 0.26)						
Total (95% CI)		**1565**		**1526**	**100.0%**	**1.15 [0.83, 1.60]**
Total events	72		61			
Heterogeneity: Chi² = 3.46, df = 3 (P = 0.33); I² = 13%						
Test for overall effect: Z = 0.83 (P = 0.40)						
Test for subgroup differences: Chi² = 0.60, df = 1 (P = 0.44), I² = 0%						

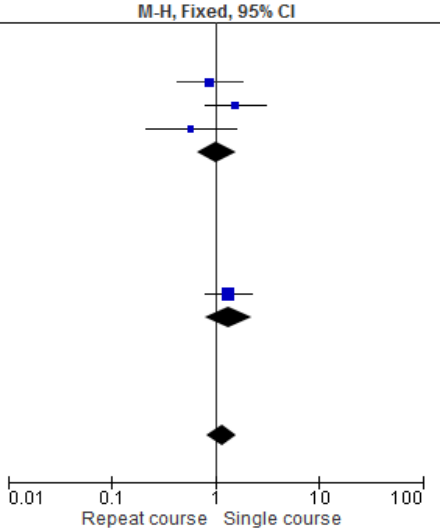

Figure 28: Interval between single and repeat antenatal corticosteroid courses – Perinatal death

Study or Subgroup	Repeat course Events	Repeat course Total	Single course Events	Single course Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.27.1 Between 7 to 14 days						
Aghajafari 2002	8	159	3	167	2.8%	2.80 [0.76, 10.37]
Crowther 2006	27	568	29	578	27.2%	0.95 [0.57, 1.58]
Guinn 2002	5	256	9	246	8.7%	0.53 [0.18, 1.57]
Mazumder 2008	4	38	8	38	7.6%	0.50 [0.16, 1.52]
Peltoniemi 2007	8	159	3	167	2.8%	2.80 [0.76, 10.37]
Wapner 2006	3	252	6	243	5.8%	0.48 [0.12, 1.91]
Subtotal (95% CI)		**1432**		**1439**	**54.7%**	**0.96 [0.67, 1.37]**
Total events	55		58			
Heterogeneity: Chi² = 8.56, df = 5 (P = 0.13); I² = 42%						
Test for overall effect: Z = 0.23 (P = 0.82)						
1.27.2 >/= 14 days						
Garite 2009	5	289	7	288	6.6%	0.71 [0.23, 2.22]
McEvoy 2010	1	56	0	56	0.5%	3.00 [0.12, 72.10]
Murphy 2008	43	1164	40	1140	38.2%	1.05 [0.69, 1.61]
Subtotal (95% CI)		**1509**		**1484**	**45.3%**	**1.02 [0.69, 1.51]**
Total events	49		47			
Heterogeneity: Chi² = 0.85, df = 2 (P = 0.65); I² = 0%						
Test for overall effect: Z = 0.12 (P = 0.91)						
Total (95% CI)		**2941**		**2923**	**100.0%**	**0.99 [0.76, 1.29]**
Total events	104		105			
Heterogeneity: Chi² = 9.50, df = 8 (P = 0.30); I² = 16%						
Test for overall effect: Z = 0.09 (P = 0.93)						
Test for subgroup differences: Chi² = 0.06, df = 1 (P = 0.81), I² = 0%						

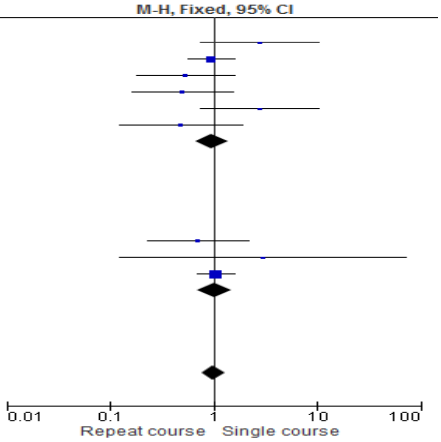

Figure 29: Interval between single and repeat antenatal corticosteroid courses – Fetal death

Study or Subgroup	Repeat course Events	Repeat course Total	Single course Events	Single course Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.28.1 Between 7 to 14 days						
Aghajafari 2002	0	9	0	7		Not estimable
Crowther 2006	1	568	1	578	22.0%	1.02 [0.06, 16.23]
Guinn 2002	1	256	1	246	22.6%	0.96 [0.06, 15.28]
Mazumder 2008	0	38	1	38	33.2%	0.33 [0.01, 7.93]
Subtotal (95% CI)		**871**		**869**	**77.8%**	**0.71 [0.14, 3.57]**
Total events	2		3			
Heterogeneity: Chi² = 0.33, df = 2 (P = 0.85); I² = 0%						
Test for overall effect: Z = 0.42 (P = 0.68)						
1.28.2 >/= 14 days						
Garite 2009	1	289	1	288	22.2%	1.00 [0.06, 15.86]
McEvoy 2010	0	56	0	56		Not estimable
Subtotal (95% CI)		**345**		**344**	**22.2%**	**1.00 [0.06, 15.86]**
Total events	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
Total (95% CI)		**1216**		**1213**	**100.0%**	**0.77 [0.19, 3.11]**
Total events	3		4			
Heterogeneity: Chi² = 0.36, df = 3 (P = 0.95); I² = 0%						
Test for overall effect: Z = 0.36 (P = 0.72)						
Test for subgroup differences: Chi² = 0.04, df = 1 (P = 0.83), I² = 0%						

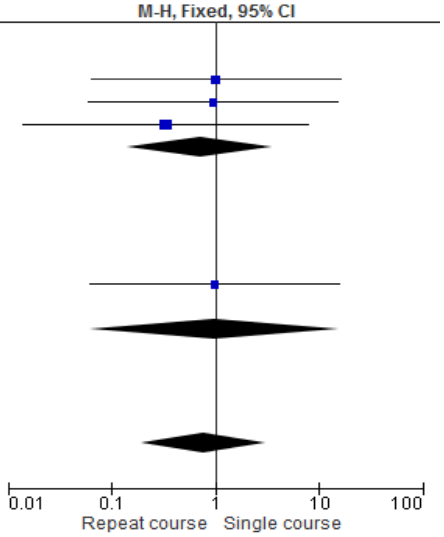

Figure 30: Interval between single and repeat antenatal corticosteroid courses – Neonatal death

Study or Subgroup	Repeat course Events	Repeat course Total	Single course Events	Single course Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.29.1 Between 7 to 14 days						
Aghajafari 2002	0	9	0	7		Not estimable
Crowther 2006	26	567	28	577	53.0%	0.94 [0.56, 1.59]
Guinn 2002	4	248	8	235	15.7%	0.47 [0.14, 1.55]
Mazumder 2008	4	38	7	38	13.4%	0.57 [0.18, 1.79]
Peltoniemi 2007	8	159	3	167	5.6%	2.80 [0.76, 10.37]
Subtotal (95% CI)		**1021**		**1024**	**87.7%**	**0.92 [0.61, 1.38]**
Total events	42		46			
Heterogeneity: Chi² = 4.66, df = 3 (P = 0.20); I² = 36%						
Test for overall effect: Z = 0.39 (P = 0.70)						
1.29.2 >/= 14 days						
Garite 2009	4	275	6	281	11.3%	0.68 [0.19, 2.39]
McEvoy 2010	1	56	0	56	1.0%	3.00 [0.12, 72.10]
Subtotal (95% CI)		**331**		**337**	**12.3%**	**0.86 [0.28, 2.66]**
Total events	5		6			
Heterogeneity: Chi² = 0.73, df = 1 (P = 0.39); I² = 0%						
Test for overall effect: Z = 0.26 (P = 0.80)						
Total (95% CI)		**1352**		**1361**	**100.0%**	**0.91 [0.62, 1.34]**
Total events	47		52			
Heterogeneity: Chi² = 5.40, df = 5 (P = 0.37); I² = 7%						
Test for overall effect: Z = 0.46 (P = 0.65)						
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.91), I² = 0%						

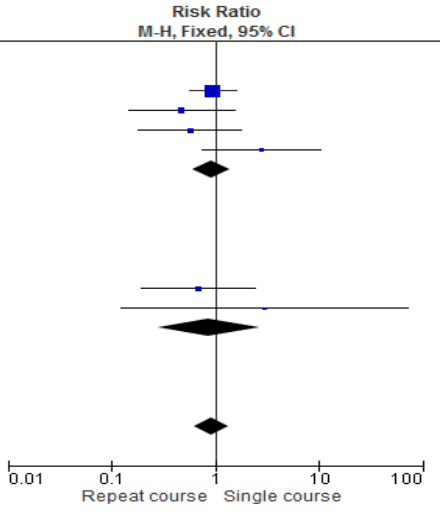

Figure 31: Interval between single and repeat antenatal corticosteroid courses - Respiratory distress syndrome

Study or Subgroup	Repeat course Events	Repeat course Total	Single course Events	Single course Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.30.1 Between 7 to 14 days						
Aghajafari 2002	2	9	2	7	0.4%	0.78 [0.14, 4.23]
Crowther 2006	186	567	239	577	42.1%	0.79 [0.68, 0.92]
Guinn 2002	69	248	69	235	12.6%	0.95 [0.71, 1.26]
Mazumder 2008	2	37	4	37	0.7%	0.50 [0.10, 2.56]
Peltoniemi 2007	82	159	80	167	13.9%	1.08 [0.87, 1.34]
Wapner 2006	24	252	32	243	5.8%	0.72 [0.44, 1.19]
Subtotal (95% CI)		**1272**		**1266**	**75.5%**	**0.86 [0.77, 0.96]**
Total events	365		426			
Heterogeneity: Chi² = 6.51, df = 5 (P = 0.26); I² = 23%						
Test for overall effect: Z = 2.60 (P = 0.009)						
1.30.2 >/= 14 days						
Garite 2009	83	275	116	281	20.4%	0.73 [0.58, 0.92]
McEvoy 2010	15	56	23	56	4.1%	0.65 [0.38, 1.11]
Subtotal (95% CI)		**331**		**337**	**24.5%**	**0.72 [0.58, 0.89]**
Total events	98		139			
Heterogeneity: Chi² = 0.15, df = 1 (P = 0.70); I² = 0%						
Test for overall effect: Z = 3.10 (P = 0.002)						
Total (95% CI)		**1603**		**1603**	**100.0%**	**0.83 [0.75, 0.91]**
Total events	463		565			
Heterogeneity: Chi² = 9.34, df = 7 (P = 0.23); I² = 25%						
Test for overall effect: Z = 3.78 (P = 0.0002)						
Test for subgroup differences: Chi² = 2.28, df = 1 (P = 0.13), I² = 56.2%						

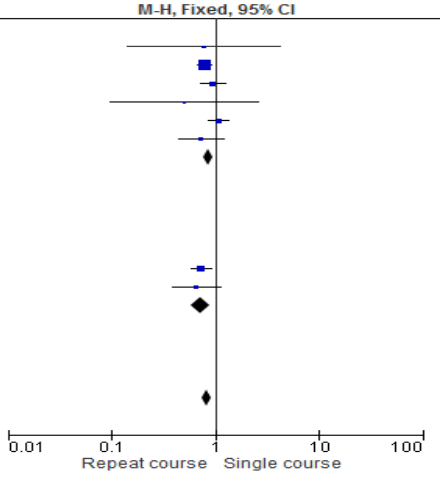

Figure 32: Interval between single and repeat antenatal corticosteroid courses - Composite of serious infant outcomes

Study or Subgroup	Repeat course Events	Repeat course Total	Single course Events	Single course Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.31.1 Between 7 to 14 days						
Aghajafari 2002	4	9	5	7	1.1%	0.62 [0.26, 1.48]
Crowther 2006	114	567	150	577	28.6%	0.77 [0.62, 0.96]
Guinn 2002	56	256	66	246	12.9%	0.82 [0.60, 1.11]
Mazumder 2008	6	37	13	38	2.5%	0.47 [0.20, 1.11]
Wapner 2006	20	252	22	243	4.3%	0.88 [0.49, 1.56]
Subtotal (95% CI)		**1121**		**1111**	**49.4%**	**0.78 [0.66, 0.91]**
Total events	200		256			
Heterogeneity: Chi² = 1.79, df = 4 (P = 0.77); I² = 0%						
Test for overall effect: Z = 3.06 (P = 0.002)						
1.31.2 >/= 14 days						
Garite 2009	88	276	120	282	22.8%	0.75 [0.60, 0.93]
Murphy 2008	150	1164	143	1140	27.8%	1.03 [0.83, 1.27]
Subtotal (95% CI)		**1440**		**1422**	**50.6%**	**0.90 [0.77, 1.05]**
Total events	238		263			
Heterogeneity: Chi² = 4.17, df = 1 (P = 0.04); I² = 76%						
Test for overall effect: Z = 1.31 (P = 0.19)						
Total (95% CI)		**2561**		**2533**	**100.0%**	**0.84 [0.75, 0.94]**
Total events	438		519			
Heterogeneity: Chi² = 7.24, df = 6 (P = 0.30); I² = 17%						
Test for overall effect: Z = 3.06 (P = 0.002)						
Test for subgroup differences: Chi² = 1.75, df = 1 (P = 0.19), I² = 42.8%						

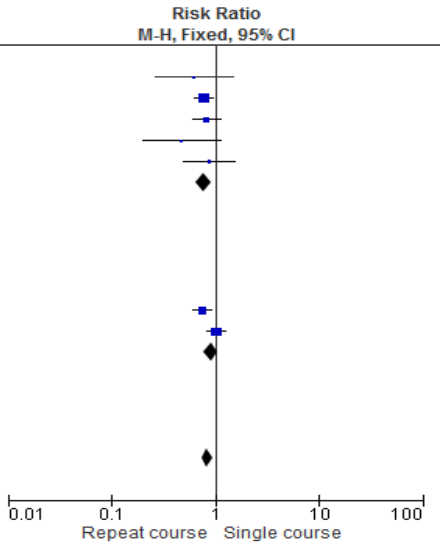

Figure 33: Interval between single and repeat antenatal corticosteroid courses – Birthweight

Study or Subgroup	Repeat course Mean	Repeat course SD	Repeat course Total	Single course Mean	Single course SD	Single course Total	Weight	Mean Difference IV, Fixed, 95% CI
1.32.1 Between 7 to 14 days								
Crowther 2006	1,867	824	567	1,877	816	577	19.4%	-10.00 [-105.04, 85.04]
Guinn 2002	2,009.1	858.7	248	2,138.8	875.8	235	7.3%	-129.70 [-284.49, 25.09]
Mazumder 2008	1,553.4	441.4	37	1,645.6	627	37	2.9%	-92.20 [-339.27, 154.87]
McEvoy 2002	1,767	659	18	1,975	740	19	0.9%	-208.00 [-659.00, 243.00]
Peltoniemi 2007	1,460	500	159	1,558	487	167	15.2%	-98.00 [-205.22, 9.22]
Wapner 2006	2,194.3	762.3	296	2,289.6	791.8	294	11.1%	-95.30 [-220.73, 30.13]
Subtotal (95% CI)			**1325**			**1329**	**56.8%**	**-72.88 [-128.42, -17.35]**
Heterogeneity: Chi² = 2.90, df = 5 (P = 0.72); I² = 0%								
Test for overall effect: Z = 2.57 (P = 0.01)								
1.32.2 >/= 14 days								
Garite 2009	1,905	738	275	1,920	667	281	12.8%	-15.00 [-132.00, 102.00]
McEvoy 2010	1,806	778	56	1,830	657	56	2.5%	-24.00 [-290.70, 242.70]
Murphy 2008	2,216	966	1164	2,330	970	1140	28.0%	-114.00 [-193.06, -34.94]
Subtotal (95% CI)			**1495**			**1477**	**43.2%**	**-79.61 [-143.23, -16.00]**
Heterogeneity: Chi² = 2.07, df = 2 (P = 0.36); I² = 3%								
Test for overall effect: Z = 2.45 (P = 0.01)								
Total (95% CI)			**2820**			**2806**	**100.0%**	**-75.79 [-117.63, -33.96]**
Heterogeneity: Chi² = 4.99, df = 8 (P = 0.76); I² = 0%								
Test for overall effect: Z = 3.55 (P = 0.0004)								
Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.88), I² = 0%								

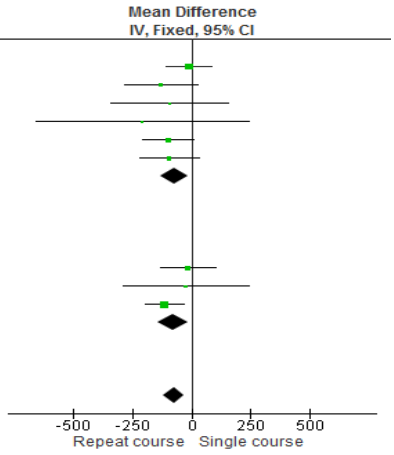

Figure 34: Interval between single and repeat antenatal corticosteroid courses – Birthweight z score

Study or Subgroup	Repeat course Mean	Repeat course SD	Repeat course Total	Single course Mean	Single course SD	Single course Total	Weight	Mean Difference IV, Fixed, 95% CI
1.33.1 >/= 7 and up to 14 days								
Crowther 2006	-0.4	1.05	567	-0.27	1.14	577	87.9%	-0.13 [-0.26, -0.00]
Subtotal (95% CI)			**567**			**577**	**87.9%**	**-0.13 [-0.26, -0.00]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.01 (P = 0.04)								
1.33.2 >/= 14 days								
McEvoy 2010	-0.14	0.86	56	-0.14	0.98	56	12.1%	0.00 [-0.34, 0.34]
Subtotal (95% CI)			**56**			**56**	**12.1%**	**0.00 [-0.34, 0.34]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.00 (P = 1.00)								
Total (95% CI)			**623**			**633**	**100.0%**	**-0.11 [-0.23, 0.00]**
Heterogeneity: Chi² = 0.49, df = 1 (P = 0.48); I² = 0%								
Test for overall effect: Z = 1.88 (P = 0.06)								
Test for subgroup differences: Chi² = 0.49, df = 1 (P = 0.48), I² = 0%