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



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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		gth of endation GRADE	Chapter
In a woman at risk of early pretern, [*] imminent [#] birth use a single course of antenatal corticosteroids. ^{\$}	А	STRONG	3 to 5
*when gestational age is 34 weeks' and 6 days or less.	Practic	e point	12
[#] when preterm birth is planned or expected within the next seven days, even if birth is likely within 24 hours.	А	STRONG	11
^{\$} regardless of the reason the woman is considered at risk of preterm birth. [%]	Practic	e point	14
The optimal time to administer antenatal corticosteroids is when preterm birth is planned or expected within the next 48 hours.	Practic	Practice Point	
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.	А	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.	А	STRONG	10
Administer dexamethasone phosphate ^{##} intramuscularly, in four doses of 6 mg, 12 hours apart.	Practic	e 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	А	STRONG	6 to 8
corticosteroids. [^] \$			
*when gestational age is 32 weeks' and 6 days or less.	Practic	e point	12
[#] when preterm birth is planned or expected within the next seven days, even if birth is likely within 24 hours.	А	STRONG	11
[^] not less than seven days following a single course of antenatal corticosteroids.	А	STRONG	11
^{\$} regardless of the reason the woman is considered at risk of preterm birth. [%]	Practic	e point	14
The clinical decision to use a repeat dose should be based on an assessment of ongoing risk for preterm birth.	Practic	Practice point	
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.	А	STRONG	10 and 11
Administer Celestone $\ensuremath{\mathbb{R}}$ Chronodose $\ensuremath{\mathbb{R}}^{**}$ 11.4 mg, intramuscularly as one dose.	Practic	e 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.	А	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.	А	STRONG	10 and 11
Do not give any further repeat courses.	А	STRONG	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.	Practic	e 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

	Strength of		
Clinical recommendations	recomme	recommendation	
	NHMRC	GRADE	
For elective caesarean section at term, where possible, plan at \geq 39 weeks' gestation.	Practice point 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.			13

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

	Strength of		
Clinical recommendations	recommendation		Chapter
	NHMRC	GRADE	
Use a single course of antenatal corticosteroids for women with	Practic	e point	14.7
diabetes in pregnancy or gestational diabetes at risk of preterm birth			
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.	Practic	e 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.	Practic	e 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.	Practic	e Point	14.7

At term

	Streng	gth of	
Clinical recommendations	recomme	recommendation	
	NHMRC	GRADE	
There is insufficient evidence currently to make a recommendation for	Practic	e point	15
the use of antenatal corticosteroids at term (\geq 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 in women with diabetes in	Practic	e point	15
pregnancy or with gestational diabetes if there is known fetal lung			
immaturity.			
If antenatal corticosteroids are used, monitor maternal blood glucose	Practic	e point	15
concentrations and treat if elevated.			

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

	Streng	Strength of	
Clinical recommendations	recommendation		Chapter
	NHMRC	GRADE	
Use a single course of antenatal corticosteroids for women with a	Practic	e point	14.6
multiple pregnancy at risk of preterm birth.			
Repeat antenatal corticosteroids for a woman with a multiple pregnancy	Practic	Practice point	
at risk of preterm birth.	•		
Where appropriate, estimate the risk of preterm birth by considering			
the use of adjunct prediction tests including fetal fibronectin and	Practic	e point	14.6
assessment of cervical length.			
Where appropriate, monitor women with a multiple pregnancy at risk			11.6
of preterm birth for signs of puerperal sepsis when antenatal	Practic	e point	14.6
corticosteroids have been given.			

With additional risk factor(s) for preterm birth

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

	Strength of		
Clinical recommendations	recomme	recommendation	
	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.	Practic	e 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.	Practic	e 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 <i>in utero</i> exposure to a single	3 to 5
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;	3 to 5
• report on the risk factors for preterm birth of the included participants;	14
• an assessment of the degree and health impact, if any, of changes in maternal blood glucose control.	
Randomised trials are needed to:	
• compare betamethasone and dexamethasone to assess the effect on the short term and long term outcomes for the infant;	9
• 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;	11
 investigate the neonatal benefits of antenatal corticosteroids administered to 	12
women at less than 24 weeks' gestation;	
• investigate if smaller doses are needed at lower gestational ages;	12
• investigate the neonatal benefits of antenatal corticosteroids administered late preterm (34 weeks' and 6 days to <37 weeks' gestation);	12
• review the effect of a single course of antenatal corticosteroids on women with systemic infection at risk of preterm birth;	14
• 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.	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;	10
 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. 	14
 establish the optimal timing of birth following administration of antenatal 	
corticosteroids to women with a fetus with intrauterine growth restriction.	

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 <i>in utero</i> exposure to repeat antenatal	6 to 8
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, 	
psychological health,the later risk of developing diabetes in adulthood.	
Social outcomes:	
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.	6 to 8
	14
• 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.	
Randomised trials are needed to:	9
• evaluate dexamethasone as the repeat antenatal corticosteroid;	-
• compare the use of different timing of administration of repeat antenatal	11
corticosteroids prior to preterm birth where preterm birth is definitely expected or	
planned;	
• investigate the effects of repeat antenatal corticosteroids in women \geq 32 weeks' and 6	12
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	14
chorioamnionitis;	
• assess the impact, if any, of repeat antenatal corticosteroids in women with systemic	14
infection at risk of preterm birth;	
 evaluate in settings where repeat prophylactic antenatal corticosteroids are being used 	14
for women with a multiple pregnancy and no other identified risk of preterm birth.	14
Conduct an individual patient data meta-analysis to explore key outcomes.	11
	10
Further research is required to explore betamethasone and dexamethasone as the repeat antenatal corticosteroid for:	10
the optimal dose	
• the optimal number of dose(s) in a course	
• the optimal interval between courses	
the effect of multiple repeat doses/courses.	
Establish the best management of women with diabetes in pregnancy given repeat	14
antenatal corticosteroids.	16
Conduct a decision analysis / economic analysis for antenatal corticosteroids	10

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	13
rates when antenatal corticosteroids are administered to women prior to planned caesarean	
section at term gestation (\geq 37 weeks') where their infants are at increased risk of neonatal	
respiratory disease.	

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	15
corticosteroids at term gestation (\geq 37 weeks') in women with diabetes in pregnancy.	

Glossary of terms

	Grossary of terms
Antenatal	Occurring before birth; concerned with the care and treatment of the unborn child and pregnant women.
Antenatal	Betamethasone and dexamethasone are corticosteroids, also called glucocorticoids, given
corticosteroids	before birth (antenatally) to improve lung development and function in the fetus at risk of preterm birth.
Antepartum	Bleeding from the vagina during pregnancy from 20 weeks gestation to birth.
haemorrhage	
Apgar score	A measure of the physical condition of a newborn infant at one and five minutes after
10	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 /	A systematic review of the evidence usually from randomised controlled trials relating to a
Cochrane Systematic	particular health problem or healthcare intervention, produced by the Cochrane
Review	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
1 ,	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	The central collection, validation and re-analysis of 'raw' data from existing trials
data	addressing the same research question to allow further exploration of patient factors or
T., t., 11.,	groups that are more or less likely to benefit from treatment.
Intellectual	A condition where powers of comprehension and information processing abilities are
Impairment Intraventricular	affected to the point where it impairs a persons' ability to perform.
	Bleeding inside or around the ventricles, the spaces in the brain containing the
haemorrhage	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
M 1 1	associated with neurologic disability.
Mechanical	To mechanically assist or replace spontaneous breathing.
ventilation	
Necrotising	A medical condition primarily seen in premature infants, where portions of the bowel
enterocolitis	undergo tissue death (necrosis).
Neonatal	Pertaining to the neonatal period which is the first four weeks after birth.
Neurologic	A group of disorders that relate to the central nervous system (brain and spinal cord).
impairment	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	The number of patients who need to be treated with the new or intervention treatment
treat to benefit	(rather than the control treatment) for one patient to benefit from the new treatment.

Periventricular	A form of brain injury characterised by the death of white matter near the cerebral
leucomalacia	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	A comparative study in which participants are randomly allocated to intervention and
controlled trial	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
D '	not receiving the treatment of interest.
Regimens	A pattern of treatment such as dose or frequency of a drug.
Respiratory distress	Respiratory distress usually in preterm babies, caused by developmental insufficiency of
syndrome	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 \geq 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	Tachypnoea (fast breathing) immediately or within two hours of birth along with other
of the newborn	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 (<u>Appendix A</u>). 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 (<u>Appendix A</u>).

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 <u>Appendix B</u>.

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

- o Mortality
- o Hypertension
- o Mode of birth
- o Postpartum haemorrhage
- o Breastfeeding at hospital discharge
- o Breastfeeding at 6 months postnatally
- o Postnatal depression symptoms
- o 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)
- o Gestational diabetes mellitus diagnosis after antenatal corticosteroid treatment
- o Insulin use after antenatal corticosteroid treatment

Additional maternal outcomes for women with diabetes and gestational diabetes:

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

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

Other respiratory morbidity outcomes:

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

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

Other infant morbidity outcomes for these Clinical Practice Guidelines:

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

Neonatal anthropometry:

- o Birthweight
- o Birth length
- o Birth head circumference
- o z scores at birth for weight, height, length, head circumference
- o Small for gestational age
- o 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

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

- o Blood pressure
- o Age at puberty

Infant as an adult secondary outcomes for these Clinical Practice Guidelines

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

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

- o Length of antenatal hospitalisation for the women
- Length of postnatal hospitalisation for the women
- o Maternal admission to intensive care
- o Baby admission to neonatal intensive care
- o Length of stay in neonatal intensive care
- o 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 <u>Appendix C</u>. 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). <u>Appendix C</u> 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 (<u>Appendix M</u>).

Summary of timeline

29th November 2012First Panel meeting in Auckland, New Zealand.15th September 2014Second Panel meeting in Auckland, New Zealand.20th October 2014Third Panel meeting/teleconference to confirm clinical
recommendations, research recommendations and practice points.January – February 2015Consultation period and endorsement by stakeholders.
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 <u>Appendix D</u>, <u>Appendix E</u> and <u>Appendix F</u>.

 "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 <u>Appendix G</u>, <u>Appendix H</u> and <u>Appendix I</u>.

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 <u>Appendix J</u>.

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**).

Author (Year)	Random	Allocation	Blinding of	Blinding of	Incomplete	Selective	Other bias
	sequence	concealment	participants/	outcome	outcome data	reporting	
	generation		personnel	assessment			
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)							

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

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

Author (Year)	Country	Intervention	Control	Outcomes reported				
		(number of women/infants)	(number of women/ infants)	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)	N	V	V	Х	
Balci (2010)	Turkey	1 x 12 mg betamethasone (Celestone®) (n=50 mothers and infants)	No treatment (n=50 mothers and infants)	V	V	Х	X	
Block (1977)	USA	2 x 12 mg betamethasone (Celestone® Soluspan®) 24 hours apart (n=60 infants)	Placebo (normal saline) (n=54 infants)	Х	V	Х	X	
Cararach (1991)	Spain	Type and dose not specified (n=12 infants)	Expectant management (n=6 infants)	Х		Х	Х	
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)	V	V	Х	Х	
Collaborative (1981)	USA	4×5 mg dexamethasone phosphate 12 hours apart (n=378 infants)	Placebo (n=379 infants)	Х	V	V	Х	
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)	V	V	Х	Х	
Doran (1980)	Canada	4 x 3 mg betamethasone acetate and 3mg betamethasone sodium phosphate 12 hourly (n=81 infants)	Placebo (n=63 infants)	Х	V	Х	Х	
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)			V	Х	Х	
Gamsu (1989)	UK	6 x 4 mg betamethasone phosphate 8 hourly (n=131 infants)	Placebo (n=137 infants)	Х	V	Х	Х	
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)		V	X	Х	
Goodner (1979)	USA	Betamethasone (no further details) (n=45 infants)	Placebo (saline) (n=47 infants)	Х		Х	Х	
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)	\checkmark	V	V	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)	\checkmark	V	Х	Х	
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)	V	V	V	N	
Lopez (1989)	Colombia	$2 \ge 12$ mg betamethasone (no further details) 12 hours apart (n=20 mothers and infants)	No treatment (n=20 mothers and infants)		V	Х	Х	

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

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)		\checkmark	X	Х	
Nelson (1985)			Delivery 24 to 48 hours after PPROM (n=22 mothers and infants)	V	V	X	Х	
Parsons (1988)	USA	2 x 12 mg betamethasone (no further details) 12 hours apart^ (n=23 infants)	Expectant management (n=22 infants)	Х		Х	Х	
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)			\checkmark	X	Х	
Qublan (2001)	Jordan	$4 \ge 6 \mod 4 \ge 6 \mod 12 \mod $	Expectant management (n=67 mothers and infants)		V	Х	Х	
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)		V	N		
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)	V	X	X	Х	
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)		V	Х	Х	
Taeusch (1979)	USA	6 x 4 mg dexamethasone phosphate (Decadron) 8 hours apart (n=39 mothers, 54 infants)	Placebo (n=36 mothers, 42 infants)		V	Х	Х	
Teramo (1980)	Finland	2 x 12 mg betamethasone (Celestone®) 24 hours apart (n=38 infants)	Placebo (n=42 infants)	Х	V	X	Х	

* 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 <u>Appendix K</u>.

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 \geq 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 \geq 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.

Author,	Country	Pre-intervention	Intervention if at risk of preterm birth after first course	Control	Ou	atcomes	reporte	d
Year		treatment for both intervention and control group			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	V	V	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)	V	\checkmark	\checkmark	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)	V	V	Х	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)	N	V	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 33 rd week of gestation (n=38 infants)	Expectant management (n=38 infants)	X	V	Х	N/A
McEvoy	USA	2 x 12 mg betamethasone	Undelivered one week after initial course.	Placebo (n=19	\checkmark	\checkmark	Х	N/A

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*#

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

*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

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)						

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

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 <u>Appendix L</u>.

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**).

				Outcome	s repoi	rted		
Author/year	Country	Betamethasone (number of women/infants)	Dexamethasone or other compar (number of women/infants)	ison	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 1 (n=76 infants)^	not specified) 12 hourly	Х	V	Х	X
Danesh (2012)	Iran	Betamethasone sodium (Exir Pharmaceutical Lab., Tehran, Iran) 2 x 12 mg 24 hourly (n=120 women, 120 infants)	Dexamethasone phosphate (Iranl Pharmaceutical Lab., Tehran, Iran (n=120 women, 120 infants)		X	V	X	X
Elimian (2007)	USA	Betamethasone (Celestone® Soluspan®), 2 x 12 mg 24 hourly (n= 150 women, 181 infants)	Dexamethasone sodium phospha 4x 6 mg 12 hourly (n=149 wome	n, 178 infants)	Х	V	Х	Х
Khandelwal (2012)	USA	Betamethasone (brand not specified) 2 x 12mg 12 hourly (n=161 women, 180 infants)	Betamethasone (brand not specific (n=67 women, 80 infants)	ied) 2 x 12mg 24 hourly			Х	Х
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)		Х		Х	Х
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)		Х	V	Х	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	V	X	Х
Romejo-Wolniewicz (2013)	Poland	Betamethasone (brand not specified)6 x 4mg 8 hourly (n=45 women)	Betamethasone (brand not specif (n=76 women)	ied) 2 x 12mg24 hourly	Х	V	Х	X
Rotmensch (1999)	Israel & Italy	Betamethasone (Bentalan®) 2 x 12 mg 24 hourly (n=22 women, 22 infants)	Dexamethasone (Decadron®) 2 x (n=24 women, 24 infants)	x 12 mg, 24 hourly	Х	V	Х	Х
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	V	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	V	V	Х
Urban (2005)	Poland	Betamethasone (Diprophos®) 2x 12 mg 24 hourly (n=33 women, 33 infants)	Dexamethasone (Dexaven®) 4x (women, 34 infants)	6 mg 12 hourly (n=34	Х		Х	Х

* 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.

 $\sqrt{reported}$, X not reported

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)							

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

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 $2 \ge 12 \mod 24$ 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)			1				
Ahmed (2014)							
Low risk of bias Unclear risk of bias High ri					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.

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

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

* 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 \geq 72 hours after the first dose of antenatal corticosteroids using a 100 g, 3 hour oral glucose tolerance test (Fasting plasma glucose \geq 5.8 mmol/L; 1 hour \geq 10.6 mmol/L; 2 hour \geq 9.2 mmol/L; 3 hour \geq 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 <u>Appendix E</u> and childhood and adulthood outcomes in <u>Appendix F</u>. 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).

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

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

* 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 (Chi² = 1.68, p = 0.19, I² = 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 (<u>Appendix N</u>, 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 (<u>Appendix E</u>).

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 (<u>Appendix E</u>).

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).

Outcome	Risk ratio (RR),	Number	Trials contributing data	Number
	Mean difference (MD) (95% Confidence Interval)	of trials		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

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

* 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 \leq 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 (<u>Appendix E</u>).

• 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.

Outcome in	Risk ratio (RR)	Number	Trials contributing	Number	Proportion
childhood	(95% Confidence	of trials	data	of	of infants
	Interval)			infants	followed
					up
Cerebral palsy	RR 0.60 (0.34 to 1.03)	5	Amorim, 1999;	904	36%
			Collaborative 1981;		
			Kari 1994; Liggins		
			1972; Schutte 1980		
Learning/behavioural	RR 0.86 (0.35 to 2.09)	1	Schutte 1980	90	73%
difficulties			(Schmand 1990)		
Developmental delay	RR 0.49 (0.24 to 1.00)	2	Amorim, 1999;	518	53%
			Collaborative 1981		
Neurodevelopmental	RR 0.64 (0.14 to 2.98)	1	Kari, 1994	82	43%
delay					
Visual impairment	RR 0.55 (0.24 to 1.23)	2	Kari 1994; Schutte	166	53%
			1980		
Hearing impairment	RR 0.64 (0.04 to 9.87)	2	Kari 1994; Schutte	166	53%
			1980		
* Source Doborto CDC roo	. 001 F		1		

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

* 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).

Outcome in adulthood	Risk ratio (RR)/ mean	Number	Trials	Number
	difference (MD)	of trials	contributing	of adults
	(95% Confidence Interval)		data	
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;	538
retuit weight (kg)	MIB 0.00 (2.02 to 5.02)	-	Schutte 1980	550
Adult height (cm)	MD 0.91 (-0.28 to 2.10)	2	Liggins 1972;	537
Reduct height (eni)	MID 0.91 (-0.20 to 2.10)	2	Schutte 1980	557
Skinfold thickness (cm)			Schutte 1700	
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 Liggins 1972	441
Subscapillar Suprailiac	MD -0.01 (-0.12 to 0.10)	1	Liggins 1972 Liggins 1972	452
*	MD -0.01 (-0.12 to 0.10)	1	Liggins 1972	432
Respiratory outcomes	$MD_{0.70}(2.16 \pm 1.76)$	1	Time 1072	202
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,	OR 1.36 (0.67 to 2.76)	1	Liggins 1972	534
upper airway conditions, bronchitis)				
Mean systolic blood pressure (mm/Hg)	MD -0.87 (-2.81 to 1.07)	2	Liggins 1972;	545
			Schutte 1980	
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	MD 18.00 (-151.30 to	1	Liggins 1972	174
content	187.30)			
Adult total body (g/cm3) areal bone	MD 0.00 (-0.03 to 0.03)	1	Liggins 1972	174
mineral density	, , , , , , , , , , , , , , , , , , ,			
Adult femoral neck (g/cm2) areal bone	MD 0.02 (-0.03 to 0.07)	1	Liggins 1972	174
mineral density	, , , , , , , , , , , , , , , , , , ,			
Adult femoral trochanter (g/cm^2) areal	MD 0.02 (-0.02 to 0.06)	1	Liggins 1972	174
bone mineral density	· · · · · · · · · · · · · · · · · · ·		00	
Adult femoral shaft (g/cm2) areal bone	MD 0.01 (-0.04 to 0.06)	1	Liggins 1972	174
mineral density		_		
Total proximal femur areal bone mineral	MD 0.02 (-0.03 to 0.07)	1	Liggins 1972	174
density (g/cm2)		_		
Hypothalamic pituitary adrenal axis	MD 0.06 (-0.02, 0.14)	1	Liggins 1972	444
function (fasting plasma cortisol [log	1.112 0.000 (0.02, 0.11)	1	Ligginis 1772	
values])				
Fasting plasma glucose concentration	MD 0.01 (-0.09, 0.11)	1	Liggins 1972	432
(mmol/L)		1	Liggins 1972	434
	MD -0.27 (-0.52, -0.02)	1	Liquina 1072	410
Plasma glucose concentration (mmol/L)	MID -0.27 (-0.52, -0.02)	1	Liggins 1972	410
after 2 hour 75g oral glucose tolerance test	MD 010(027.007)	1	Line: 4070	420
Plasma insulin concentration [log values]	MD -0.10 (-0.27, 0.07)	1	Liggins 1972	428
after 2 hour 75g oral glucose tolerance test * Source Roberts CPG version 2015				

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

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 <u>Appendix M1</u> – 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	А	STRONG
of antenatal corticosteroids.		

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:
 - o the hypothalamic-pituitary adrenal axis of the infant, child and adult.
 - o the glucose-insulin axis in childhood
 - o 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.

<u>Chapter 2</u> 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 <u>Appendix G</u>.

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.

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

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

*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) (<u>Appendix G</u>).
- 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.

<u>Chapter 2</u> 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 <u>Appendix H</u>. Details of all early childhood and adulthood outcomes can be found in <u>Appendix I</u>. 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 (Chi²=1.14, p=0.28, I²=12.6%). This can be interpreted as indicating that the overall treatment effect was similar regardless of the severity of respiratory disease (<u>Appendix N</u> - **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)	Number	Trials contributing data	Number
	(95% Confidence	of trials		of infants
	Interval)			
Perinatal death	RR 0.94 (0.71 to 1.23)	9	Aghajafari 2002; Crowther 2006;	5554
			Garite 2009; Guinn 2001; Mazumder	
			2008; McEvoy 2010; Murphy 2008;	
			Peltoniemi 2007; Wapner 2006	
Fetal death	RR 0.82 (0.24 to 2.84)	7	Aghajafari 2002; Crowther 2006;	2755
			Garite 2009; Guinn 2001; Mazumder	
			2008; McEvoy 2010; Peltoniemi 2007	
Neonatal death	RR 0.91 (0.62 to 1.34)	7	Aghajafari 2002; Crowther 2006;	2713
			Garite 2009; Guinn 2001; Mazumder	
			2008; McEvoy 2010; Peltoniemi 2007	
Respiratory distress	RR 0.83 (0.75 to 0.91)	8	Aghajafari 2002; Crowther 2006;	3206
syndrome			Garite 2009; Guinn 2001; Mazumder	
			2008; McEvoy 2002; Peltoniemi 2007;	
			Wapner 2006	
Composite serious	RR 0.84 (0.75 to 0.94)	7	Aghajafari 2002; Crowther 2006;	5094
outcome			Garite 2009; Guinn 2001; Mazumder	
			2008; Peltoniemi 2007; Wapner 2006	

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

* 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 (<u>Appendix H</u>). 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) (<u>Appendix H</u>).

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).

Outcome	Mean difference (MD)	Number	Trials contributing data	Number			
	(95% Confidence Interval)	of trials		of infants			
Mean measurem	Mean measurements at birth						
Weight	MD -75.79 (-117.63 to -33.96)	9	Crowther 2006; Garite 2009; Guinn	5626			
(grams)			2001; Mazumder 2008; McEvoy				
			2002; McEvoy 2010; Murphy 2008;				
			Peltoniemi 2007; Wapner 2006				
Head	MD -0.32 (-0.49 to -0.15)	9	Crowther 2006; Garite 2009; Guinn	5625			
circumference			2001; Mazumder 2008; McEvoy				
(centimetres)			2002; McEvoy 2010; Murphy 2008;				
			Peltoniemi 2007; Wapner 2006				
Length	MD -0.56 (-0.89 to -0.23)	6	Crowther 2006; Mazumder 2008;	4550			
(centimetres)			McEvoy 2010; Murphy 2008;				
			Peltoniemi 2007; Wapner 2006				
z scores at birth			•	•			
Weight	MD -0.11 (0.23 to 0.00)	2	Crowther 2006; McEvoy 2010	1256			
Head	MD -0.14 (-0.27 to 0.00)	2	Crowther 2006; McEvoy 2010	1256			
circumference							
Length	MD -0.05 (-0.19 to 0.09)	2	Crowther 2006; McEvoy 2010	1256			
* Source: Crowthe	(2011)		,				

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

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

* 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 (<u>Appendix H</u>).
- *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 \leq 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 (<u>Appendix I</u>).

Outcome at early childhood follow-up	Risk ratio (RR) (95% Confidence Interval)	Number of trials	Trials contributing data	Numbe r 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

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

* 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 sensitity, 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 \geq 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.

Outcome at early childhood follow-up	arly childhood Risk ratio (RR) or Number of Mean Difference (MD) (95% trials Confidence Interval)		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 childhoo	d			
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 associa	ted with small for age (as defined by tri	als)	· ·	
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	
Height	RR 1.12 (0.63 to 2.02)	2	Crowther 2006; Wapner 2006	1441

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)*

* 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 <u>Appendix M2</u> – 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	А	STRONG
early preterm, imminent birth following a single course of		
antenatal corticosteroids.		

Research recommendations:

- There is a need to better assess the impact, if any, of *in utero* exposure to repeat antenatal corticosteroids on:
 - o the glucose-insulin axis in childhood,
 - o hypothalamic-pituitary adrenal axis,
 - o bone mass,
 - o body size and body composition,
 - o neurosensory impairments,
 - o respiratory function,
 - o cardiovascular disease,
 - o metabolic disease,
 - o diabetes,
 - o psychological health,
 - o the later risk of developing diabetes in adulthood,
 - o educational attainment,
 - o behaviour,
 - o cognitive ability,
- Any future research to investigate the effects of treatment with repeat antenatal corticosteroids should:
 - o include outcomes for maternal quality of life.
 - o Report on the risk factors for preterm birth of the included participants.
 - o 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 (Chi²=5.63; p=0.02, I²=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 (Chi²=0.99, p=0.32, I²=0%) (<u>Appendix N</u>, 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 (Chi² = 6.54; p=0.01; I²=84.7%) (<u>Appendix N</u> - 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 (Chi² = 0.02; p=0.88; I²= 0%) (<u>Appendix N</u>, **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.

0		th no antenatal con		
Outcome	Betamethasone		Dexamethasone	
	Risk ratio (RR)	Trials	Risk ratio (RR)	Trials
	(95% Confidence	contributing data	(95% Confidence	contributing
	Interval)		Interval)	data
Chorioamnionitis	RR 0.70 (0.49 to 0.99);	Amorim 1999;	RR 1.35 (0.89 to 2.05);	Dexiprom
	9 trials, n=1950	Carlan 1991; Fekih	4 trials, n=575 women	1999; Kari
	women	2002; Garite 1992;		1994; Qublan
		Lewis 1996;		2001; Silver
		Liggins 1972;		1996
		Lopez 1989;		
		Morales 1989;		
		Schutte 1980		
Subgroup	Chi ² =5.63; p=0.02, I ² =	82.2%; 13 trials, n=2	2525 women	
interaction test				
Puerperal sepsis	RR 1.00 (0.58 to 1.72);	Amorim 1999;	RR 1.74 (1.04 to 2.89);	Dexiprom
	4 trials, n=467 women	Garite 1992; Lewis	4 trials, n=536 women	1999; Qublan
		1996; Schutte 1980		2001; Silver
				1996; Taeusch
				1979
Subgroup	Chi ² =0.99, p=0.32, I ² =	0%; 8 trials, n=1003	women	
interaction test				
Pyrexia after trial	RR 0.68 (0.37 to 1.25);	Amorim 1999;	RR 2.05 (1.14 to 3.69),	Taeusch 1979
entry*^	3 trials, n=363 women	Schutte 1980;	1 trial, n=118 women	
		Nelson 1985		
Subgroup	Chi ² = 6.54; p=0.01; I^{2}	=84.7%; 4 trials, n=4	81 women	L
interaction test	-			
Intrapartum	RR 0.60 (0.15 to 2.49);	Amorim 1999;	Not reported	-
pyrexia*^	2 trials, n=319 women	Schutte 1980	-	
Subgroup	Not performed			1
interaction test				
Postnatal pyrexia*^	RR 0.88 (0.46 to 1.68);	Amorim 1999;	RR 0.94 (0.60 to 1.47);	Collaborative
	3 trials, n=437 women	Fekih 2002;	2 trials, n=886 women	1981;
		Schutte 1980		Dexiprom 1999
Subgroup	Chi ² =0.02; p=0.88; I ² =		women	-
interaction test		. ,		
SC D 1 / CDC	. 2015 *			

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

^{\$} 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.

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

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

*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 (Chi²=0.00, p=0.98, I²=0%) (Table 22) (<u>Appendix N</u> - 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 (Chi²=0.1, p=0.15, I²=0%) (Table 22) (<u>Appendix N</u> - 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 (Chi²=0.21, p=0.65, I²=0%) (Table 22). (<u>Appendix N</u> - 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.

Outcome	Betamethasone		Dexamethasone		
	Risk ratio (RR)	Trials	Risk ratio (RR)	Trials	
	(95% Confidence	contributing data	(95% Confidence	contributing data	
	Interval)	0	Interval)	0	
Perinatal	RR 0.72 (0.55 to 0.94);	Amorim 1999;	RR 0.72 (0.46 to 1.11);	Collaborative,	
death	8 trials, n=2207 infants	Block, 1977; Doran,	5 trials, $n=1420$ infants	1981; Dexiprom,	
ucatii	0 thats, $n=2207$ milants	1980; Gamsu, 1989;	5 thats, 11–1420 infants	1999; Kari, 1994;	
		Garite, 1992;		Qublan, 2001;	
		Liggins, 1972;		Taeusch, 1979	
		Parsons, 1988;			
		Schutte, 1980			
Subgroup	Chi ² =0.00, p=0.98, I ² =00	%; 13 trials, n=3627 inf	ants		
interaction					
test					
Fetal death	RR 1.01 (0.73 to 1.39);	Amorim 1999;	RR 0.92 (0.56 to 1.50); 5	Collaborative,	
	8 trials, n=2207 infants	Block, 1977; Doran,	trials, n=1420 infants	1981; Dexiprom,	
		1980; Gamsu, 1989;		1999; Kari, 1994;	
		Garite, 1992;		Qublan, 2001;	
		Liggins, 1972;		Taeusch, 1979	
		Parsons, 1988;		,,,	
		Schutte, 1980			
Subgroup	Chi ² =0.1, p=0.15, I ² =0%		nte		
interaction	$c_{11} = 0.1, p = 0.13, 1 = 0.70$, 15 mass, m=5027 mma	ints		
test	DD 0 (7 (0 54 + 0 02)	4		C 11 1	
Neonatal	RR 0.67 (0.54 to 0.82);	Amorim 1999;	RR 0.72 (0.55 to 0.94); 6	Collaborative,	
death	15 trials, n=2940 infants	Block, 1977; Doran,	trials, n=1468 infants	1981; Dexiprom,	
		1980; Fekih, 2002;		1999; Kari, 1994;	
		Gamsu, 1989;		Qublan, 2001;	
		Garite, 1992;		Silver, 1996;	
		Goodner, 1979;		Taeusch, 1979	
		Lewis, 1996; Liggins,			
		1972; Lopez, 1989;			
		Morales, 1989,			
		Nelson, 1985;			
		Parsons, 1988;			
		Porto, 2011; Schutte,			
		1980			
Subgroup	Chi ² =0.21, p=0.65, I ² =09		ante		
interaction	Sin -0.21, p=0.03, 1 -0,	o, 21 (11415, 11-4400 IIII	u1110		
Respiratory	PP 0 50 (0 49 to 0 72) \diamond	Amorim 1000, Dal-:	DD $0.91 (0.65 \pm 0.102)$	Collaborativa	
Respiratory	RR 0.59 (0.48 to 0.72) [,]	Amorim 1999; Balci, 2010; Plack 1977;	RR 0.81 (0.65 to 1.02) [,] ;	Collaborative,	
distress	18 trials, n=3115 infants	2010; Block, 1977;	6 trials, n=1457 infants	1981; Dexiprom,	
syndrome		Carlan, 1991; Doran,		1999; Kari, 1994;	
		1980; Fekih, 2002;		Qublan, 2001;	
		Gamsu, 1989;		Silver, 1996;	
		Garite, 1992;		Taeusch, 1979	
		Goodner, 1979;			
		Lewis, 1996; Liggins,			
		1972; Lopez, 1989;			
		Morales, 1989,			
		Nelson, 1985;			
		Parsons, 1988;			
		Porto, 2011; Schutte,			
0.1		1980; Teramo, 1980			
Subgroup	Chi ² =4.59, p=0.03; I ² =78	3.2%; 24 trials, n=4490	infants		
-					
interaction test					

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

*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 (Chi²=4.59, p=0.03; I²=78.2%) (Table 22) (<u>Appendix N</u> - 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 (Chi²=0.24, p=0.62; I²=0%) (<u>Appendix N</u>, 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 <u>Appendix M3</u> – 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	А	STRONG
antenatal corticosteroid in women at risk of preterm birth.		

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 <u>Chapter 2</u> 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 <u>Chapter 6</u> and <u>Chapter 7</u> of these Clinical Practice Guidelines. A summary of the evidence is found in <u>Chapter 8</u> 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 <u>Appendix M4</u> –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	А	STRONG
in women at continued risk of preterm birth regardless of the		
corticosteroid preparation used in the first course.		

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 25. Regimens of thats using a single course of antenatal betamethasone compared with no				
		antenatal corticostero	ids*	
Total dose	Time to	Betamethasone regimen	Number	Trials contributing data

Table 22: Pagimona of trials using a single source of antonatal betamethesone compared with no

Total dose	Time to	Betamethasone regimen	Number	Trials contributing data
	complete course		of trials	
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	Time to	Dexamethasone regimen	Number	Trials contributing data
dose	complete course		of trials	
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 \geq 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 (Chi²=1.13, p=0.57, I²=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 (Chi²=1.31, p=0.52, I²=0%) (<u>Appendix N</u> - 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, $I^2=0\%$) (<u>Appendix N</u> - **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 \geq 36 hours, 24 mg completed in \geq 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 (I²=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, I²=38%) (<u>Appendix N</u> - Figure 15). This can be interpreted as indicating that these dexamethasone regimens did not differentially influence the risk of puerperal sepsis.

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

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

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

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

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

*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 \geq 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%) (<u>Appendix N</u> - 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 (Chi²=7.20, p=0.07, I²=58.4%) (<u>Appendix N</u> - Figure 17). This can be interpreted as indicating that each of these regimens had the same effect against neonatal death.

		thasone compared			-
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 treatmen	t effect	0.67 (0.55 to 0.82);	C	0.59 (0.48 to 0.73) [^] ;	
				17 trials, n= 3013 infants	
Subgroup interac	ction tests	Chi ² =3.67, p=0.39,	$1^2 = 18.2\%$	Chi ² =6.75, p=0.15, I ² =40.7%	

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

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

dexametriasone versus no antenatar controsteroids					
Total dose	Time to	Neonatal death		Respiratory distress	syndrome
dexamethasone	complete				
	course		r		
		Risk ratio RR	Trials	Risk ratio RR (95%	Trials
		(95% Confidence	contributing	Confidence	contributing data
		Interval)	data	Interval)	_
20 mg	36 hours	0.97 (0.64 to 1.47);	Collaborative	0.85 (0.56 to 1.29);	Collaborative 1981;
_		2 trials, $n = 825$	1981; Silver	2 trials, n=816	Silver 1996
		infants	1996	infants	
24 mg	24 hours	0.48 (0.15 to 1.55);	Dexiprom	1.16 (0.75 to 1.79);	Dexiprom 1999
		1 trial, n=206	1999	1 trial, n=202	
		infants		infants	
24 mg	36 hours	0.47 (0.31 to 0.71);	Kari 1994;	0.68 (0.51 to 0.90);	Kari 1994; Qublan
_		2 trials, $n=314$	Qublan 2001	2 trials, $n=316$	2001
		infants	-	infants	
24 mg	40 hours	1.02 (0.43 to 2.41);	Taeusch 1979	0.64 (0.28, 1.47);	Taeusch 1979
_		1 trial, n=123		1 trial, n=123	
		infants		infants	
Overall treatment effect		0.70 (0.47 to 1.03) [^] ;		0.81 (0.65 to 1.02);	
		6 trials, n=1468 inf	ants	6 trials, n=1457 infants	
Subgroup interac	ction tests	Chi ² =7.20, p=0.07,	$I^2 = 58.4\%$	Chi ² =4.53, p=0.21, I ² =33.8%	

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

*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 (Chi²=6.75, p=0.15, I²=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 (Chi²=4.53, p=0.21, I²=33.8%) (<u>Appendix N</u> - **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 \geq 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 \geq 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	А	STRONG	
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.	А	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 (<u>Chapter 2</u> - **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 2002, Mazumder 2008, Murphy 2008, 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.

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

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

*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 (chorioannionitis 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:

- $\leq 12 \text{ mg completed immediately}$
- 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 $\leq 12 \text{ mg}$

• 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 (Chi² = 1.79, p = 0.41, I² = 0%) (<u>Appendix N</u> - **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 $\leq 12 \text{ mg}$

• 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 (Chi²=1.03, p=0.31, I²=2.9%) (<u>Appendix N</u> - **Figure 21**). This can be interpreted as indicating that there was no difference between the regimens for the risk of puerperal sepsis.

Total dose of	Time to	Chorioam	nionitis	Puerpe	eral sepsis
betamethasone	complete	Risk ratio RR (95%	Trials	Risk ratio RR	Trials
	course	Confidence	contributing	(95%	contributing data
		Interval)	data	Confidence	
				Interval)	
≤12 mg betamet	hasone				
12 mg	Immediate	NR		1.57 (0.80 to	Peltoniemi 2007
	(no repeat			3.10),	
	doses)			1 trial, n= 249	
				women	
11.4 mg	Immediate	1.08 (0.72 to 1.62),	Crowther 2006	NR	
	(repeat	1 trial, n=982			
	dose(s)	women			
	allowed)				
24 mg betametha	asone				
24 mg	24 hours	0.64 (0.23 to 1.77);	Garite 2009	NR	
	(no repeat	1 trial, n= 437			
	doses)	women			
24 mg	24 hours	1.27 (0.95 to 1.70),	Aghajafari 2002;	1.05 (0.72 to	Aghajafari 2002;
_	(repeat	4 trials, n= 2842	Guinn 2001;	1.54),	Guinn 2001;
	doses	women	Murphy 2008;	4 trials, n= 2842	Murphy 2008;
	allowed)		Wapner 2006	women	Wapner 2006
Overall treatment	t effect	1.16 (0.92 to 1.46); 6 trials, n=4261		1.15 (0.83 to 1.60); 5 trials, n=3091	
		women		women	
Subgroup interac	ction tests	Chi ² =1.79, p=0.41, I ²		Chi ² =1.03, p=0.3	51, $I^2=2.9\%$

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

*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:

- $\leq 12 \text{ mg completed immediately}$
- 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 $\leq 12 \text{ mg}$

- 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 (Chi²=4.64, p=0.20, I²=35.4%) (<u>Appendix N</u>, **Figure 22**). This can be interpreted as indicating that there were no differential effects between the regimens for the risk of neonatal death.

	antenatal corticosteroids*					
Total dose of	Time to	Neon	atal death	Respiratory dis	stress syndrome	
betamethasone	complete	Risk ratio RR	Trials	Risk ratio RR	Trials	
	course	(95%	contributing data	(95% Confidence	contributing data	
		Confidence	_	Interval)	_	
		Interval)				
≤12 mg betamet	hasone					
12 mg	Immediate	2.80 (0.76 to	Peltoniemi 2007	1.08 (0.87 to 1.34);	Peltoniemi 2007	
	(no repeat	10.37);		1 trial, n=326		
	courses)	1 trial, n=326		infants		
		infants				
11.4 mg	Immediate	0.94 (0.56 to	Crowther 2006	0.79 (0.68 to 0.92);	Crowther 2006	
	(repeat	1.59);		1 trial, n=1144		
	courses	1 trial, n=1144		infants		
	allowed)	infants				
24 mg betametha	asone					
24 mg	24 hours	0.86 (0.28 to	Garite 2009;	0.72 (0.58 to 0.89);	Garite 2009;	
	(no repeat	2.66);	McEvoy 2010	2 trials, n=668	McEvoy 2010	
	doses)	2 trials, n=668		infants		
		infants				
24 mg	24 hours	0.52 (0.23 to	Aghajafari 2002;	0.86 (0.68 to 1.10);	Aghajafari 2002;	
	(repeat	1.18);	Guinn 2001;	4 trials, n=1068	Guinn 2001;	
	doses	3 trials, n=575	Mazumder 2008	infants	Mazumder 2008	
	allowed)	infants				
Overall treatment	t effect	0.91 (0.62 to 1.34));	0.83 (0.75 to 0.91);		
		7 trials, n=2713 i	nfants	s 8 trials, n=3206 infants		
Subgroup interac	ction tests	Chi ² =4.64, p=0.2	20, I ² =35.4%	Chi ² =7.72, p=0.05,	I ² =61.2%	
	1 1 1	1 1 1 1	and Clinical Drastics Cui	1 1' '11'		

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

*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 $\leq 12 \text{ mg}$

- 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 (Chi²=7.72, p=0.05, I²=61.2%) (<u>Appendix N</u> - **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 $\leq 12 \text{ mg}$

• 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 (Chi²=2.80, p=0.25, I²=28.5%) (<u>Appendix N</u> - **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 $\leq 12 \text{ mg}$

• 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 $\leq 12 \text{ mg}$ 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	Time to complete course	Mean difference MD (95% Confidence Interval)
betamethasone		Birthweight
≤12 mg betametl	nasone	
12 mg	Immediate	-98 g (-205. 22 to 9.22); 1 trial, n=326 infants
	(no repeat courses)	
11.4 mg^	Immediate	-10 g (-105.04 to 85.04); 1 trial, n=1144 infants
	(repeat courses allowed)	
24 mg betametha	asone	
24 mg	24 hours	-16.45 g (-123.60 to 90.69); 2 trials, n=668 infants
	(no repeat doses)	
24 mg	24 hours	-112.51 g (-171.58 to -53.44); 5 trials, n=3488 infants
	(repeat doses allowed)	
Overall mean diffe	rence	-75.79 g (-117.63 to -33.96); 9 trials, n=5626 infants
Interaction test res	sult	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 (Chi²=4.67, p=0.20, I²=36%) (<u>Appendix N</u>, **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 $\leq 12 \text{ mg}$

• 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 $\leq 12 \text{ mg}$

- 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 <u>Appendix M6</u> – 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		lation
	NHMRC	GRADE	Refer to
EITHER			Chapter
ETTHER <u>Use a single repeat dose(s)</u> 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 <u>Use a single repeat course</u> 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	А	STRONG	Chapter 10

Practice Points:

As repeat antenatal corticosteroid use

EITHER

<u>A single repeat dose</u> of Celestone[®] Chronodose^{®**} 11.4 mg, intramuscularly as one dose. Use up to a maximum of three, single, repeat doses only.

OR

<u>A single repeat course</u> 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 (<u>Appendix D</u>).

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 (<u>Appendix D</u>).

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.

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				<u>.</u>
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

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

*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) (<u>Appendix E</u>).
- <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) (<u>Appendix E</u>).

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 <u>Appendix M7</u> – 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	А	STRONG	
of preterm birth when birth is planned or expected within the			
next seven days even if birth is likely within 24 hours.			

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 <u>Appendix M8</u> – 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	А	STRONG	
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			

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 (Chi²=0.81, p=0.37, I²=0%) (<u>Appendix N</u> 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 (Chi² = 0.60, p=0.44, I²=0%) (<u>Appendix N</u> 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 \geq 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	Number of trials	Authors	Number of women
>7 1	Interval)^			
\geq 7 and up to 14 days f				
Chorioamnionitis	RR1.23 (0.95 to 1.59)	4	Aghajafari 2002;	1971
			Crowther 2006;	
			Guinn 2001; Wapner	
			2006	
Puerperal sepsis	RR 1.02 (0.66 to 1.59)	4	Aghajafari 2002;	1238
* *			Guinn 2001;	
			Peltoniemi 2007;	
			Wapner 2006	
Postnatal pyrexia*	RR 0.87 (0.55 to 1.38)	1	Crowther, 2006	982
≥14 days following fir	st course			
Chorioamnionitis	RR 0.94 (0.56 to 1.57)	2	Garite 2009; Murphy	2290
			2007	
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 \geq 7 and up to 14 days or \geq 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 (Chi²=0.06, p=0.81, I²=0%) (<u>Appendix N</u> - 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 \geq 7 and up to 14 days or \geq 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 (Chi²=0.04, p=0.83, I²=0%) (<u>Appendix N</u> - 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 \geq 7 and up to 14 days or \geq 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 (Chi²=0.01, p=0.91, I²=0%) (<u>Appendix N</u>, 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 (Chi²=2.28, p=0.13, I²=56.2%) (<u>Appendix N</u> 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 (Chi²=1.75, p=0.19, I²=42.8%) (<u>Appendix N</u> 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

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

$(\geq 7 \text{ days up to } 14 \text{ days and } \geq 14 \text{ days})^*$

*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 \geq 7 and up to 14 days and \geq 14 days the subgroup interaction test was not significant (Chi²=0.02, p=0.88, I²=0%) (Appendix N - Figure 33). This can be interpreted as indicating no difference for birthweight between the timing intervals (\geq 7 and up to 14 days and \geq 14 days). Infants in both timing intervals (\geq 7 and up to 14 days and \geq 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 (Chi²=0.49, p=0.48, I²=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 \geq 7 days and up to 14 days or \geq 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 \geq 7 days and up to 14 days or \geq 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 \geq 7 days and up to 14 days or when the interval was \geq 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 \geq 7 days and up to 14 days or when the interval was \geq 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 \geq 7 days and up to 14 days and when the interval was \geq 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 \geq 7 days and up to 14 days and \geq 14 days was not significant. This can be interpreted as indicating that there was no differential effect between the timing intervals (\geq 7 days and up to 14 days and \geq 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 \geq 7 days and up to 14 days, and when the interval between dose(s) was \geq 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 \geq 7 days and up to 14 days, and when the interval between dose(s) was \geq 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 \geq 7 days and up to 14 days or \geq 14 days of the single course and those with no repeat exposure.

An interval between the single course and repeat antenatal corticosteroids of \geq 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 <u>Appendix M9</u> – 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.	А	STRONG		
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	А	STRONG		
fourteen days following a single course and preterm birth is still				
expected within the next seven days. Do not give further repeat				
courses.				

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 (we	eeks ^{+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
- \geq 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 <u>not mutually exclusive</u>.

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 \geq 34 weeks' and 0 days

No trials that recruited and randomised women with a gestation at trial entry \geq 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* \geq 34 weeks' and 0 days No trials that recruited and randomised women with a gestation at trial entry \geq 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* \geq 34 weeks' and 0 days No trials that recruited and randomised women with a gestation at trial entry \geq 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]) (Clinical Trials.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 \leq 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 \geq 34 weeks' and 0 days.

For the infant

When gestational age at trial entry was \leq 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 \geq 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 \geq 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 <u>Appendix M10</u> - 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: \leq 31 weeks' and 6 days;

 \leq 32 weeks' and 6 days;

 \leq 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**).

corticosteroids included the Crowther (2011) systematic review*								
Gestational age range for inclusion in trial (weeks ^{+days})								
Author	Year	Minimum	Maximum					
		(weeks ^{+days})	(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					

Table 37: Gestational age range for inclusion in randomised controlled trials of repeat antenatal corticosteroids included the Crowther (2011) systematic review*

*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).
- \leq 33 weeks' and 6 days No data were reported when the gestational age at trial entry was \leq 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.

Outcome Risk Ratio (RR)		Trials contributing data	Number of					
Gestational age at trial	(95% Confidence		women					
entry (weeks ^{+days})	Interval)							
Chorioamnionitis								
≤31+6	1.11 (0.76 to 1.62), 3 trials	Aghajafari 2002; Crowther 2006; Wapner 2007	1486					
≤32+6	1.19 (0.89 to 1.59), 3 trials	Garite 2009; Guinn 2001; Murphy 2008	2775					
≤33+6	Not reported	Not reported	Not reported					
Puerperal sepsis								
≤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					
≤33+6	1.57 (0.80 to 3.10), 1 trial	Peltoniemi 2007	249					

Table 38: Maternal primary outcomes for these Clinical Practice Guidelines by gestational age at
trial entry: repeat antenatal corticosteroids\$*

\$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).

- ≤31 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 ≤31 weeks' 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).

• \leq 31 weeks' 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 Risk Ratio (RR) Trials contributing data Number of							
Gestational age at	Risk Ratio (RR)	Number of					
trial entry	(95% Confidence Interval)		infants				
(weeks ^{+ days})							
Perinatal death							
$\leq 31^{+6}$	0.87 (0.54 to 1.39), 3 trials	Aghajafari 2002; Crowther 2006; Wapner 2007	1657				
$\leq 32^{+6}$	0.87 (0.62 to 1.24), 4 trials	Garite 2009; Guinn 2001; Mazumder 2008; Murphy 2008	3459				
$\leq 33^{+6}$	2.83 (0.84 to 9.49), 2 trials	McEvoy 2010; Peltoniemi 2007	438				
Fetal death							
$\leq 31^{+6}$	1.02 (0.06 to 16.23); 2 trials	Aghajafari 2002; Crowther 2006	1162				
$\leq 32^{+6}$	0.70 (0.14 to 3.55); 3 trials	Garite 2009; Guinn 2001; Mazumder 2008	1155				
$\leq 33^{+6}$	1.05 (0.07 to 16.65); 2 trials						
Neonatal death							
$\leq 31^{+6}$	0.94 (0.56 to 1.59), 2 trials	Aghajafari 2002; Crowther 2006	1160				
$\leq 32^{+6}$	0.56 (0.28 to 1.12), 3 trials	Garite 2009; Guinn 2001; Mazumder 2008	1115				
$\leq 33^{+6}$	2.83 (0.84 to 9.49), 2 trials	McEvoy 2010; Peltoniemi 2007	438				
Respiratory distress	syndrome						
$\leq 31^{+6}$	0.78 (0.68 to 0.91); 3 trials	Aghajafari 2002; Crowther 2006; Wapner 2007	1655				
$\leq 32^{+6}$	0.81 (0.68 to 0.96); 3 trials	Garite 2009; Guinn 2001; Mazumder 2008	1113				
$\leq 33^{+6}$	0.98 (0.80 to 1.20); 2 trials	McEvoy 2010; Peltoniemi 2007	438				
Composite serious in	nfant outcome	-	1				
$\leq 31^{+6}$	0.78 (0.64 to 0.95); 3 trials Aghajafari 2002; Crow Wapner 2007		1655				
$\leq 32^{+6}$	0.83 (0.67 to 1.03)** 4 trials	Garite 2009; Guinn 2001; Mazumder 2008; Murphy 2008	3439				
$\leq 33^{+6}$	Not reported	Not reported	Not reported				
,	1	1 1	1 1				

\$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).
- \leq 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 \leq 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).
- \leq 33 weeks' and 6 days No difference was seen in birthweight when the gestational age at trial entry was \leq 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* -

 \leq 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 \leq 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 \leq 31 weeks' and 6 days (RR 1.02, 95%CI 0.92 to 1.12; 1 trial, n=1060 children).

 \leq 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 \leq 32 weeks' and 6 days (RR 1.01, 95%CI 0.97 to 1.04; 1 trial, n=2095 children) (Asztalos 2010).

 \leq 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 \leq 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 (<u>Appendix I</u>).

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 \leq 31 weeks' and 6 days, \leq 32 weeks' and 6 days or \leq 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 \leq 31 weeks' and 6 days, \leq 32 weeks' and 6 days or \leq 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 \leq 31 weeks' and 6 days and \leq 32 weeks' and 6 days. There was no difference in the risk for respiratory distress syndrome when the gestational age at trial entry was \leq 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 \leq 31 weeks' and 6 days but there was no difference when the gestational age at trial entry was \leq 32 weeks' and 6 days compared with no repeat exposure. No data were reported when the gestational age at trial entry was \leq 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 <u>Appendix M11</u> – 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 <u>Chapter 2</u> 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 (I²=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 (I²=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 (\geq 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 <u>Appendix M12</u> – 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 \geq 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
- 1) 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 <u>Appendix J</u>) and the Crowther CPG version 2015 systematic review for repeat antenatal corticosteroids (**Table 41** and <u>Appendix K</u>). 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.

Author (Year)	Women wit of previous birth		Women in p labour	oreterm	Preterm pre rupture of n at trial entry	nembranes	Women with chorioamnie		Women with antepartum haemorrhag		Women wit pregnancies higher orde	s (twins and
	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	-

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

- = not reported; NS = not stated; *eligibility as per individual trial criteria (<u>Appendix J</u>)

Author (Year)	diabe	en with etes in nancy	pretern	for whom n birth is y indicated	Women systemic in trial e	fection at	Women pregnancy a hyperter	ssociated	intrauteri	n with ne growth ction	cervical s	en with hortening nelling		pronectin est
	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	-

Table 40: (continued): Women with specific risk factors for preterm birth* reported in trials included in the Roberts CPG version 2015 systematic review

NR = not reported; NS = not stated; *eligibility as per individual trial criteria (<u>Appendix J</u>), ^ diabetes mellitus, ^^ gestational diabetes mellitus, #pre-eclampsia, \$ severe hypertension, \$\$ pregnancy induced hypertension

Author (Year)	Women with history of previous preterm birth		previous preterm birth		erm birth 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		

Table 41: Women at risk of preterm birth with specific risk factors for preterm birth* reported included in the Crowther 2011, Cochrane systematic review

NR = not reported; NS = not stated; *eligibility as per individual trial criteria (<u>Appendix K</u>), ^ triplets were not eligible

Study ID	Women with diabetes mellitus or gestational diabetes		Women f preterm medically	birth is	systemic	n with infection l entry	pregi assoc	n with nancy ciated ension	Wome intrauterii restri	ne growth	cervical s	n with hortening telling		pronectin est
	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	-

Table 41 (continued	l): Women at risk of	preterm birth with s	pecific risk factors for	preterm birth* re	ported included in the C	Crowther 2011, C	Cochrane systematic review
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NR = not reported; NS = not stated; *eligibility as per individual trial criteria (<u>Appendix K</u>), ^ 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 (<u>Appendix</u>]). 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: 0	Comparison of the overa	all effect estim	nate for use of a single	course of antena	tal corticoste	croids with trials that re	ported includi	ing a
	proportion	of women wi	ith a history of a previo	us preterm birth	– Maternal p	orimary outcomes*		
Primary outcome	nary outcome Single course of antenatal corticosteroid* Trials known to include women with a history of a previous preterm birth^							
	Trials contributing data	Number of	Overall risk ratio (RR)	Trials	Number of	Risk ratio (RR)	Actual	Actual

	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

Primary outcome	Single course of antenatal corticosteroid*			Trials known t birth^	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		

 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*

*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 <u>Appendix M13</u> – 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 (<u>Appendix</u> <u>K</u>). 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**).

Primary outcome	Repeat course of antenatal	d*	Trials known to have	included won	nen with a history of a previou	s 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

 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

*Source: Crowther (2011); ^meta-analyses conducted for these Clinical Practice Guidelines

Primary	Repeat course of antenata	l corticosteroid*		Trials known to have i	ncluded wome	n with a history of a previou	s preterm birth	^
outcome	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

 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

*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 <u>Appendix M14</u> – 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 (<u>Appendix I</u>).

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.

Primary outcome	Single course of antenat	al corticoster	oid*	Trials known to	have included w	omen 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	-	-

 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

*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.

Primary	Single course of antenatal corticosteroid	*		Trials known to have included women in preterm labour^					
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; 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	

 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

*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 <u>Appendix M15</u> – 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 (<u>Appendix K</u>). 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.

Primary outcome	Repeat course of antenat	al corticoste	roid*	Trials known to have in	ncluded 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

 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

*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**).

Primary	Repeat course of antenatal co	orticosteroid*		Trials known to have	e included v	vomen in preterm labour^		
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; 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

 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

*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 <u>Appendix M16</u> – 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.

Primary outcome	Single course of antenatal con	ticosteroid*	k	Trials known to have inclue entry [^]	ided women	with preterm prelabour r	upture of membra	nes at trial
	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	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
	1996			**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	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
	1980; Silver 1996; Taeusch 1979			**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

 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

*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.

Primary outcome	Single course of antenatal cortico	steroid*		Trials known to have incluentry^	ided womer	n with preterm prelabour	rupture of membrane	es at trial
	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;	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
	Schutte 1980; Taeusch 1979			**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;	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
	Schutte 1980; Taeusch 1979			**Dexiprom 1999; Parsons 1988	253	RR 0.20 (0.01 to 4.04), 2 trials, n=253 infants		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;	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
	Taeusch 1979			**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

 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

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 ** 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	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;	538
				Nelson 1985; Parsons 1988;	

*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 (<u>Appendix K</u>). 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**).

	Repeat course of ante	natal cortico	steroid*	Trials known to have	included wo	omen with preterm prelabour r	upture of membranes a	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

 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

*Source: Crowther (2011); ^meta-analyses conducted for these Clinical Practice Guidelines

	Repeat course of antenata	al corticoster	oid*	Trials known to have include	led women v	with preterm prelabour ruptu	ire 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

 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

*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 <u>Appendix M18</u> – 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.

Primary outcome	Single course of antena	atal corticos	teroid*	Trials known to have	included wor	men with chorioamnionitis at tria	ıl 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

 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

*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 h	nave included w	omen with chorioamnionit	s 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 <u>Appendix M19</u> – 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 <u>Appendix M20</u> – 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.

Primary	Single course of antenat	al corticoster	oids*	Trials known to have i	included a propo	ortion of women with antepa	rtum haemorrhage	٨
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	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	-	-	-	-

 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

*Source: Roberts CPG version 2015; ^meta-analyses conducted for these Clinical Practice Guidelines

Primary outcome	Single course of antenatal corticosteroids			Trials known to haemorrhage	have include	d a proportion of women	with antepartum	
	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

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

*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 <u>Appendix M21</u> – 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**).

Primary outcome	Repeat antenatal corticoster	roids*		Trials known to have	e included a p	proportion of women with an	tepartum haemorr	hage^
	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

 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

*Source: Crowther (2011); ^meta-analyses conducted for these Clinical Practice Guidelines

Primary	Repeat antenatal corticosteroids*			Trials known to have	e included a	proportion of women w	ith antepartum haemo	rrhage^
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; 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

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

*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 <u>Appendix M22</u>– 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 (<u>Appendix I</u>).

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.

Primary outcome	Single course of antenatal	•		preterm birth		ortion of women with a 1		
	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

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

*Source: Roberts CPG version 2015 ; ^meta-analyses conducted for these Clinical Practice Guidelines

	Single course of antenatal corticosteroids		Trials known to have preterm birth			th a multiple pregnancy	at risk of	
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

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

*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 <u>Appendix M23</u>- 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 (<u>Appendix K</u>). 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 corticostero	ids and trials known to	have included a proportion of wome	n with a multiple pregnancy at ris	k of preterm birth*
	Trials contributing data	Number of women	Risk ratio (RR)	Actual proportion detailed in	Actual number of
			(95% Confidence Interval)	trials	women
Chorioamnionitis	Aghajafari 2002; Crowther 2006; Garite	4261	RR 1.16 (0.92 to 1.46), 6 trials,	Aghajafari 2002; Crowther 2006;	637
	2009; Guinn 2001; Murphy 2008;		n=4261 women	Garite 2009; Guinn 2001;	
	Wapner 2006			Murphy 2008; Wapner 2006	
Puerperal sepsis	Aghajafari 2002; Guinn 2001; Murphy	3091	RR 1.15 (0.83 to 1.60), 5 trials,	Aghajafari 2002; Guinn 2001;	412
	2008; Peltoniemi 2007; Wapner 2006		n=3091 women	Murphy 2008; Peltoniemi 2007;	
				Wapner 2006	
Pyrexia after trial entry	NR	NR	NR	-	-
requiring treatment					
Intrapartum pyrexia	NR	NR	NR	-	-
requiring treatment					
Postnatal pyrexia requiring	Crowther 2006	982	RR 0.87 (0.55 to 1.38), 1 trial,	Crowther 2006	157
treatment			n=982 women		

*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 include	ed a proportion of women with	a multiple pregnancy at risk of preterm birth*	
	Trials contributing data	Number	Risk ratio (RR)	Actual proportion detailed in trials	Actual
		of	(95% Confidence Interval)		number of
		infants			infants
Perinatal death	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn	5554	RR 0.94 (0.71 to 1.23),	Aghajafari 2002; Crowther 2006; Garite 2009;	865
	2001; Mazumder 2008; McEvoy 2010; Murphy 2008;		9 trials, n=5554 infants	Guinn 2001; McEvoy 2010; Murphy 2008;	
	Peltoniemi 2007; Wapner 2006			Peltoniemi 2007; Wapner 2006	
Fetal death	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn	2755	RR 0.82 (0.24 to 2.84),	Aghajafari 2002; Crowther 2006; Garite 2009;	513
	2001; Mazumder 2008; McEvoy 2010; Peltoniemi 2007		7 trials, n=2755 infants	Guinn 2001; McEvoy 2010; Peltoniemi 2007	
Neonatal death	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn	2713	RR 0.91 (0.62 to 1.34),	Aghajafari 2002; Crowther 2006; Garite 2009;	505
	2001; Mazumder 2008; McEvoy 2010; Peltoniemi 2007		7 trials, n=2713 infants	Guinn 2001; McEvoy 2010; Peltoniemi 2007	
Respiratory distress	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn	3206	RR 0.83 (0.75 to 0.91),	Aghajafari 2002; Crowther 2006; Garite 2009;	604
syndrome	2001; Mazumder 2008; McEvoy 2010; Peltoniemi 2007;		8 trials, n=3206 infants	Guinn 2001; McEvoy 2010; Peltoniemi 2007;	
	Wapner 2006			Wapner 2006	
Composite outcome of	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn	3959	RR 0.84 (0.75 to 0.94),	Aghajafari 2002; Crowther 2006; Garite 2009;	754
serious infant outcomes	2001; Mazumder 2008; Murphy 2008; Wapner 2006		7 trials, n=3959 infants	Guinn 2001; Murphy 2008; Wapner 2006	

*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 <u>Appendix M24</u> – 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 (<u>Appendix I</u>).

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 (<u>Appendix I</u>).

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 (<u>Appendix K</u>).

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 (<u>Appendix K</u>).

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 <u>Appendix M26</u> – 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 prespecified 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 (<u>Appendix J</u>).

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 <u>Chapter 3</u> 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.

Primary outcome	Single course of antenatal corticoster	oids		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	

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*

*Source : Roberts CPG version 2015; ^meta-analyses conducted for these Clinical Practice Guidelines

Primary outcome	Single course of antenatal corticosteroids			or gestational d		ed a proportion of wom	en with diabe	tes mellitus
	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; Tacusch 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; Tacusch 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; Tacusch 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; Tacusch 1979	783	RR 0.54 (0.38 to 0.76) 4 trials n=783 infants	Amorim 1999; Doran 1980; Porto 2011; Taeusch 1979	51

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*

*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 <u>Appendix M27</u> - 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 (<u>Appendix K</u>). 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 <u>Chapter 6</u> 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**).

Primary outcome	Repeat antenatal corticost	teroids		Trials known to have diabetes^	e included a pro	oportion of women with diabet	es mellitus or gest	ational
	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	-	-

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

Source: Crowther (2011); ^meta-analyses conducted for these Clinical Practice Guidelines

	Repeat antenatal corticosteroids	3		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	

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

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 <u>Appendix M28</u> – 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 <u>Appendix M29</u> – 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 <u>Appendix M30</u> – 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 \geq ominous sign (proteinuria $\geq 3^+$ by dipstick, creatinine $\geq 1.2 \text{ mg/dL}$, platelet count < 100,000 cells/mm3, epigastric pain, visual disturbances). All subjects had $\geq 2^+$ 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.

Primary outcome	Single course of antenatal co	•		hypertension^	•	ided a proportion of wom		-
	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

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*

*Source: Roberts CPG version 2015; ^meta-analyses conducted for these Clinical Practice Guidelines

Primary outcome	Single course of antenatal corticostero	ids		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	

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*

*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**).

Primary outcome	Repeat course of a	antenatal co		Trials known to ha hypertension^	ve included a p	proportion of women wit	h pregnancy assoc	ciated
	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

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*

*Source: Crowther (2011); ^meta-analyses conducted for these Clinical Practice Guidelines

Primary outcome	Repeat course of antenatal			hypertension^	9 I					
	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		

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*

*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 <u>Appendix M32</u>– 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 (<u>Appendix I</u>).

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.

Primary outcome	Single course of anten	atal corticost		Trials known to have restriction [^]	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	-	-			

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*

* Source: Roberts CPG version 2015; ^meta-analyses conducted for these Clinical Practice Guidelines

Primary outcome	Single course of antenatal corticostero	oids	^		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		

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*

*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) (<u>Appendix K</u>). 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.

Primary outcome	Repeat antenatal	corticostero	ids	Trials known to have includ restriction [^]	ed a proportio	on of women with a fetus wi	th intrauterine	growth
	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

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*

*Source: Crowther (2011); ^meta-analyses conducted for these Clinical Practice Guidelines

Primary outcome	Repeat antenatal corticosteroids	3		restriction	ncluded a prop	ortion of women with a f	etus with intrauter	rine growth
	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

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*

*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	0.88 (0.84 to 0.91)	0.89 (0.85 to 0.92)
interval)		

*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 (\geq 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 (<u>Appendix J</u>; <u>Appendix K</u>).

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 <u>Appendix M36</u> – 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 <u>Appendix M37</u> – 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 <u>Appendix M38</u> – 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).

Outcome	0	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		

Table 77: Significant health outcomes and resource use following administration of antenatal corticosteroids for women at risk of preterm birth*

*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.

Methods/ Stages of change Predisposing	Awareness Launch of the guideline Ensure health practitioners have access to the guideline in both New Zealand and Australia.	Agreement 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.	Adoption Undertake a current practice review in a select number of units to identify the gap between existing practice and the guidelines.	Adherence 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	/PRECEDE Model (David 2	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 .

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.

Adapted from the Pathman/PRECEDE Model (David 2003)

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Members	Expertise	Affiliation	Role on the panel
Caroline	Maternal fetal medicine	Liggins Institute, The	Chairperson of
Crowther	subspecialist.	University of Auckland	the Guideline
			Panel
Julie Brown	Research Synthesis and	The Liggins Institute,	Member of the
	Clinical Guideline	University of Auckland	Executive Group,
	Development		member for the
			Guideline Panel
			and Project
			Officer
Jane Alsweiler	Neonatologist	Senior Lecturer, Department of	Member of the
		Paediatrics: Child and Youth	Executive Group,
		Health, University of Auckland	member for the
		Consultant Neonatologist,	Guideline Panel
		NICU, National Women's	
		Health, Auckland City Hospital	
		Honorary Senior Lecturer,	
		Liggins Institute, University of	
21.11		Auckland	
Philippa	Perinatal Epidemiologist,	Executive Director of ARCH	Member of the
Middleton	Research Methodologist	within Robinson Institute,	Executive Group,
		University of Adelaide	member for the
K C			Guideline Panel
Katie Groom	Maternal fetal medicine	Consultant Obstetrician and	Royal Australian
	subspecialist.	Gynaecologist at National Women's Health, Auckland	and New Zealand
		City Hospital	College of Obstetrics and
		Senior Lecturer in Department	Gynaecology
		of Obstetrics and Gynaecology,	Gynaecology
		University of Auckland	
Euan Wallace*	Obstetrician and	Director of Obstetric Services	Perinatal Society
Eduir Wanace	Gynaecologist	for Southern Health,	of Australia and
	o y muceo logist	Department of Obstetrics &	New Zealand
		Gynaecology Monash	r to w Bounding
		University,	
		Director of the Ritchie Centre,	
		Monash University	
Dell Horey*	Consumer Advocate	Faculty of Health Sciences,	Consumer
,		School of Health Sciences	representative
		Research, Melbourne	· · · · · · · · · · · · · · · · · · ·
		University	
Liz van Dort	Consumer	Australia	Consumer
			representative
Cara Wasywich	Consumer	New Zealand	Consumer
-			representative
Christine East	Midwifery	Co-Director of Maternity	Perinatal Society
		Services, Southern Health	of Australia and
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		of Nursing and Midwifery,	
		Monash University	

		Associate Editor for the	
		Cochrane Pregnancy and	
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Vicki Flenady	Perinatal Epidemiologist	Director, Translational Health,	Chair of Perinatal
		Mater Institute,	Society of
		International Stillbirth Alliance,	Australia and
		WHO Research Network	New Zealand
			Policy Group
Kay Gamble	Midwifery	Delivery Unit, National	College of
	Diabetes Nurse Specialist	Women's Health, Auckland	Midwives New
		City Hospital	Zealand
Brenda Hughes	Specialist Paediatric	Auckland City Hospital	Pharmacists
	Pharmacist		
Bill Jeffries	General Physician,	Head of Department of	Expert in
	Endocrinologist	Medicine, Lyell McEwin	obstetric
		Hospital,	medicine
		Head of Obstetric Medicine at	
		Flinders University	
Mahia Winder	Maori Midwifery Advisor,	Regional Committee of the	Māori (New
	Auckland District Health	New Zealand College of	Zealand)
	Board	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	
Annie Marshall	Neonatal Nurse,	Chairperson of the Neonatal	Neonatal Nurses
		Nurses College of Aotearoa	College of
		(NNCA)	Aotearoa
Sally Jeston	Neonatal Nurse	Australian College of Neonatal	Australian
55		Nurses	College of
			Neonatal Nurses
Chris McKinlay	Neonatologist	Liggins Institute, University of	Expert on
,	INCOLLATOROUSIST		1
	reonatologist	Auckland. New Zealand	antenatal
	neonatologist		antenatal corticosteroids
Tineke Crawford	Research Officer	Auckland. New Zealand	corticosteroids
Tineke Crawford		Auckland. New Zealand Liggins Institute, University of	corticosteroids Management
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Emma		Auckland. New Zealand Liggins Institute, University of Auckland. New Zealand Liggins Institute, University of	corticosteroids Management Group Management
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*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:
Garonice Glownice	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.
	Study Group. Australasian randomized trial to evaluate the role of maternal intramuscular
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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: Crowther C, Harding JE, Middleton PF, Andersen CC, Ashwood P, Robinson JS; A*STEROID
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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	\checkmark		\checkmark	
requiring antibiotics *				
Chorioamnionitis*	\checkmark			
Intrapartum fever requiring	\checkmark		\checkmark	
antibiotics*				
Post-natal pyrexia*	\checkmark		\checkmark	
Puerperal sepsis*			\checkmark	
Quality of life*				
Glucose tolerance*				
Mortality			\checkmark	
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 diabete.	s 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				

Fetal, Neonatal and Infant outcomes for these Clinical Practice Guidelines	Fetal, Neonatal and Infant or	outcomes for these	Clinical Practice Guidelines
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Fetal, Neonatal and Infant outcomes	Roberts 2006	Crowther 2011	Brownfoot 2013	Sotriadis 2009
Fetal, neonatal or later death*		\checkmark		
Respiratory distress syndrome*	\checkmark		\checkmark	\checkmark
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	\checkmark		\checkmark	
grade				
Severe IVH (Grade 3 or 4)			\checkmark	
Cystic periventricular			\checkmark	
leucomalacia/white matter injury				
Neonatal encephalopathy in term babies				
Patent ductus arteriosus as defined,			\checkmark	
requiring treatment				
Transient tachypnoea of the neonate				
(term)				
Hypoglycaemia requiring treatment				
Hyperglycaemia requiring treatment				
Chronic lung disease	\checkmark		\checkmark	
Necrotising enterocolitis	\checkmark		\checkmark	
Retinopathy of prematurity			\checkmark	
Gestational age at birth				
Interval between antenatal	\checkmark		\checkmark	
corticosteroid exposure and birth				
Small for gestational age as defined				
Birthweight				
Birth length				
Birth head circumference	\checkmark	\checkmark	\checkmark	
Placental weight	\checkmark		\checkmark	
Low Apgar (<7 at 5 minutes)	\checkmark		\checkmark	
Use and duration of respiratory support	\checkmark		\checkmark	
Use and duration of oxygen	\checkmark		\checkmark	
supplementation				
Use of surfactant	\checkmark		\checkmark	
Air leak syndrome	N		N	
Pulmonary hypertension		1		
Inotropic support				
Use of nitric oxide for respiratory		N		
support				
Early neonatal infection (< 48 hours)				
Late neonatal infection (\geq 48 hours)			V	
Use of post-natal corticosteroids		V		
Neonatal blood pressure				
Anthropometry at hospital discharge		V		
HPA axis suppression, including cortisol		Ń		
*primary outcomes for these Guidelines	· ·	1	1	1

Child outcomes for these Clinical Practice Guidelines

Child outcomes	Roberts 2006	Crowther 2011	Brownfoot 2013	Sotriadis 2009
Survival free of neurosensory		\checkmark		
disability*				
Neurosensory disability		\checkmark		
(composite of impairments:				
cerebral palsy, blindness, deafness,				
developmental delay)*				
Total mortality				
Cerebral palsy	\checkmark	\checkmark		
Developmental delay / IQ	\checkmark	\checkmark		
Visual impairment		\checkmark		
Hearing impairment		\checkmark		
Motor dysfunction		\checkmark		
Anthropometry				1
Child behaviour				
Respiratory disease/lung function	\checkmark			1
Blood pressure		\checkmark		
Impairment of insulin / glucose				
axis or insulin sensitivity				
Cognitive ability		\checkmark		
Learning disability		\checkmark		
Hypothalamic pituitary adrenal		\checkmark		
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	\checkmark			
Hearing impairment	\checkmark			
Bone density	\checkmark	\checkmark		
Respiratory function	\checkmark			
Anthropometry	\checkmark			
Blood pressure	\checkmark			
Hypothalamic pituitary adrenal	\checkmark			
axis suppression				

Health service use outcomes	Roberts 2006	Crowther 2011	Brownfoot 2013	Sotriadis 2009
Duration of respiratory support*				
Length of neonatal		\checkmark	\checkmark	
hospitalisation				
Length of stay in NICU Admission to NICU		N		N
		N		V
Maternal admission to ICU		N		
Length of postnatal hospitalisation for the women	V	v	v	
Length of antenatal		\checkmark	\checkmark	
hospitalisation for the women				

Health service use outcomes for these Clinical Practice 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:

- o Medline
- o Embase
- o CENTRAL
- o Cochrane Database of Systematic Reviews
- o HTA database
- o National Guideline Clearing House
- o Guidelines International Network Database
- o Clinical Trials Register
- o 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 ($I^2 \ge 30\%$) a random effects model was used. All data are presented as effect estimates 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 (<u>Appendix M</u>).

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)
- 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:

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)

Outcome	Effect Size	95%CI	Р	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 1 st dose	0.77	0.37 to 1.62	0.49	1	218
Premature ROM at 1 st 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 1 st dose	0.92	0.38 to 2.27	0.86	2	239
Delivery <48 hours after 1 st dose	0.78	0.38 to 1.60	0.49	1	341
Delivery 1-7 days after 1 st dose	0.55	0.27 to 1.11	0.096	1	482
Delivery >7 days after 1^{st} dose	1.59	0.63 to 4.03	0.33	1	461
Intact membranes at 1 st dose	0.83	0.50 to 1.40	0.49	4	1243
Premature ROM at 1 st 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 1 st dose	2.18	0.62 to 7.69	0.22	1	46
Between 26 and <30 weeks' at 1 st dose	1.06	0.55 to 2.06	0.85	1	242
Between 30 and <33 weeks' at 1 st dose	0.19	0.04 to 0.86	0.031	1	294
Between 33 and <35 weeks' at 1 st dose	0.47	0.12 to 1.80	0.27	1	333
Between 35 and <37 weeks' at 1 st 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 1 st dose	0.68	0.30 to 1.52	0.35	1	218
Premature ROM at 1 st 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 1 st dose	0.13	0.01 to 2.58	0.18	1	46
Intact membranes at 1 st dose	1.10	0.61 to 2.00	0.74	2	289

Appendix D: Single course of antenatal corticosteroids maternal outcomes (Roberts CPG version 2015)

Premature ROM at 1 st 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 1 st dose	0.98	0.06 to 15.50	0.99	1	218
Premature ROM at 1 st 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				
Mode of birth	reported				
Desteration la service d'ADDLD	Not				
Postpartum haemorrhage (PPH)	reported				
Breastfeeding at hospital discharge	Not				
breastreeding at nospital discharge	reported				
Breastfeeding at 6 months	Not				
breastreeding at 6 months	reported				
Postnatal depression symptoms	Not				
r ostnatar depression symptoms	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	Р	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 1 st dose	0.60	0.39 to 0.94	0.024	3	293
Delivery <48 hours after 1 st dose	0.59	0.41 to 0.86	0.0061	1	373
Delivery 1-7 days after 1 st dose	0.81	0.60 to 1.09	0.16	3	606
Delivery >7 days after 1^{st} dose	1.42	0.91 to 2.23	0.12	3	598
Intact membranes at 1 st dose	0.87	0.70 to 1.08	0.21	4	1332
Premature ROM at 1 st 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 1 st dose	1.00	0.66 to 1.50	0.99	1	49
Between 26 and <30 weeks' at 1 st dose	0.80	0.59 to 1.08	0.14	1	261
Between 30 and <33 weeks' at 1 st dose	0.59	0.35 to 1.01	0.052	1	319
Between 33 and <35 weeks' at 1 st dose	1.10	0.59 to 2.05	0.76	1	353
Between 35 and <37 weeks' at 1 st 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 1 st dose	0.68	0.34 to 1.38	0.29	3	293
Delivery <48 hours after 1 st dose	0.78	0.40 to 1.51	0.46	1	373
Delivery 1-7 days after 1 st dose	1.01	0.58 to 1.76	0.98	3	606
Delivery >7 days after 1^{st} dose	1.36	0.73 to 2.53	0.34	3	598
Intact membranes at 1 st dose	1.09	0.73 to 1.64	0.66	4	1332
Premature ROM at 1 st 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 1 st dose	0.65	0.33 to 1.25	0.20	1	49
Between 26 and <30 weeks' at 1 st dose	1.23	0.65 to 2.34	0.52	1	261
Between 30 and <33 weeks' at 1 st dose	0.67	0.31 to 1.46	0.31	1	319
Between 33 and <35 weeks' at 1 st 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:	1010 0.000	0.50 10 0.00	-0.00001	21	1100
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	0.55 to 1.12	0.12	2	89
Delivery <30 weeks'	0.79	0.50 to 1.12	0.19	2	150
Delivery <32 weeks'	0.59	0.43 to 0.80	0.19	3	378
Delivery <34 weeks'	0.59	0.52 to 0.92	0.000805	2	715
Delivery <36 weeks'				2	
Delivery <36 weeks' Delivery at least at 34 weeks'	0.68	0.50 to 0.92 0.71 to 3.50	0.013		869
5	1.58		0.26	2	808
Delivery at least at 36 weeks'	2.62	0.77 to 8.96		3	514
Delivery <24 hours after 1 st dose	0.53	0.29 to 0.96	0.035	4	295
Delivery <48 hours after 1 st dose	0.49	0.30 to 0.81	0.0057	1	339
Delivery 1-7 days after 1 st dose	0.74	0.51 to 1.07	0.11	3	563
Delivery >7 days after 1 st dose	1.45	0.75 to 2.80	0.27	3	561
Intact membranes at 1 st dose	0.77	0.58 to 1.03	0.077	4	1236
Premature ROM at 1 st 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 1 st dose	1.87	0.61 to 5.72	0.27	1	27
Between 26 and <30 weeks' at 1 st dose	0.67	0.45 to 0.99	0.046	1	227
Between 30 and <33 weeks' at 1 st dose	0.51	0.23 to 1.11	0.090	1	295
Between 33 and <35 weeks' at 1 st dose	1.11	0.49 to 2.48	0.81	1	339
Between 35 and <37 weeks' at 1 st 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 meeks'	0.67	0.52 to 0.87	0.0022	4	218
Delivery <32 meeks'	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'	0.52	0.38 to 1.16	0.15	5	1261
Delivery at least at 36 weeks'	0.86	0.03 to 2.67	0.13	5	557
$\frac{1}{1} \frac{1}{1} \frac{1}$	0.90	0.66 to 1.15	0.28	9	517
		0.66 to 1.15 0.49 to 0.93		3	374
Delivery <48 hours after 1^{st} dose	0.67		0.017		
Delivery 1-7 days after 1 st dose	0.46	0.35 to 0.60	<0.00001	9	1110
$Delivery > 7 \ days \ after \ 1^{st} \ dose$	0.82	0.53 to 1.28	0.39	8	988
Intact membranes at 1 st dose	0.62	0.51 to 0.74	<0.00001	5	1527
Premature ROM at 1 st 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 1 st dose	2.86	0.37 to 21.87	0.31	1	24
Between 26 and <30 weeks' at 1 st dose	0.49	0.34 to 0.72	0.00026	2	242
Between 30 and <33 weeks' at 1 st dose	0.56	0.36 to 0.87	0.011	2	361
Between 33 and <35 weeks' at 1 st dose	0.53	0.31 to 0.91	0.021	2	434
Between 35 and <37 weeks' at 1 st 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
·	KK 0.55	0.45 to 0.71	<0.00001	0	1000
Sub group analysis for moderate/severe RDS:	0.50	0.27 . 4.27	0.24		100
Delivery <24 hours after 1 st dose	0.69	0.37 to 1.27	0.24	1	182
Delivery <48 hours after 1 st dose	0.45	0.27 to 0.73	0.0014	1	326
Delivery 1-7 days after 1 st dose	0.37	0.22 to 0.62	0.00020	1	462
Delivery >7 days after 1^{st} 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:	0.10		0.00/0	-	
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 1 st dose	0.54	0.21 to 1.36	0.19	3	264
Delivery <48 hours after 1 st dose	0.26	0.09 to 0.75	0.012	1	339
Delivery 1-7 days after 1 st dose	0.51	0.23 to 1.13	0.096	1	482
Delivery >7 days after 1 st dose	2.01	0.37 to 10.86	0.42	1	453
Intact membranes at 1 st dose	0.50	0.35 to 0.72	0.00017	4	1200
Premature ROM at 1 st 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 1 st dose	1.20	0.24 to 6.06	0.83	1	27
Between 26 and <30 weeks' at 1 st dose	0.45	0.21 to 0.95	0.036	2	229
Between 30 and <33 weeks' at 1 st 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 1 st 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 1 st dose	1.13	0.27 to 4.74	0.65	3	434
Premature ROM at 1 st dose	0.50	0.27 10 4.74 0.33 to 0.76	0.65) 1	434
	0.30	0.33 to 0.76 0.02 to 1.68	0.00099	1	200
Pregnancies with hypertension syndromes	0.20	0.02 10 1.08	0.14	/	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 1 st dose	0.61	0.15 to 2.48	0.49	2	257
Premature ROM at 1 st 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	0.05 10 2.07	0.72	,	200
Cystic periventricular leucomalacia	Not reported				
V L	*				
White matter injury	Not reported				
Patent ductus arteriosus as defined, requiring	Not reported				
treatment					
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,	Not reported				
retinopathy of prematurity, cystic	*				
periventricular leucomalacia, patent ductus					
arteriosus, neonatal encephalopathy)					
Gestational age at birth	Not reported				
	MD 0.23	-1.86 to 2.32	0.83	3	1513
Interval between trial entry and birth				-	
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 1 st dose	46.52	-94.26 to 187.29	0.52	2	242
Delivery <48 hours after 1 st dose	-5.90	-131.95 to 120.15	0.93	1	373
Delivery 1-7 days after 1 st dose	-105.92	-212.52 to 0.68	0.051	1	520
Delivery >7 days after 1^{st} dose	-147.01	-291.97 to -2.05	0.047	1	486
Intact membranes at 1 st dose	-59.09	-157.84 to 39.67	0.24	3	1107
Premature ROM at 1 st 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 1 st dose	63.14	-607.37 to 733.65	0.85	1	49
Between 26 and <30 weeks' at 1 st dose	26.41	-215.55 to 268.37	0.83	1	261
Between 30 and <33 weeks' at 1 st dose	-190.64	-359.98 to -21.30	0.027	1	319
Between 33 and <35 weeks' at 1 st 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:	ivor reported				
Apgar <7 at five minutes	RR 0.84	0.69 to 1.01	0.06	8	2072
Use and duration of respiratory support:	KK 0.04	0.09 10 1.01	0.00	0	2072
1 7 11					
Use of respiratory support	RR 0.73	0.59 to 0.92	0.006	7	1021
*mechanical ventilation/CPAP					
Sub group analysis for need for mechanical ventilation/CPAP:					
Intact membranes at 1 st dose	0.70	0.52 to 0.93	0.016	2	253
Premature ROM at 1 st dose	0.70	0.32 to 0.33 0.47 to 1.73	0.076	2	206
ROM > 24 hours	0.50	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)	0.02	0.12 10 0.91	0.075	,	200
*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 1 st dose	3.80	-20.79 to 28.39	0.76	1	33
Premature ROM at 1 st dose	-3.50	-5.12 to -1.88	0.000022	1	165
Use and duration of oxygen supplementation	2.20	2012101100	0.000022		
Use of oxygen supplementation	Not reported				
Duration of oxygen supplementation	rtor reported				
(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
	RR 0.69	0.32 to 1.03 0.19 to 2.47	0.10	4	138
Air leak syndrome		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:	0.44		0.040		200
Intact membranes at 1 st dose	0.46	0.26 to 0.84	0.012	1	200
Premature ROM at 1 st dose	0.97	0.45 to 2.06	0.93	3	291
ROM >24 hours Pregnancies with hypertension syndromes	0.97	0.40 to 2.39	0.95	1	157
· · ·	0.46	0.26 to 0.84	0.012	/	200
Late neonatal infection (≥48 hours):					-
Proven infection while in the neonatal	RR 0.82	0.66 to 1.02	0.07	12	2927
intensive care unit					
Sub group analysis for infection in first 48 hours of					
life: Intact membranes at 1 st dose	0.69	0.51 to 0.95	0.023	3	1057
Premature ROM at 1 st dose	1.26	0.86 to 1.85	0.023	7	796
ROM >24 hours	1.34	0.82 to 2.21	0.23	2	363
ROM > 24 hours	1.15	0.68 to 1.95	0.24	2	258
Pregnancies with hypertension syndromes	0.55	0.34 to 0.87	0.012	2	278
Use of post-natal corticosteroids	Not reported	5.51 10 0.07	0.012	-	270
Neonatal blood pressure	Not reported				
Anthropometry at hospital discharge	Not reported				
	not reported				
HPA axis suppression, including cortisol:		2.10	0.07	1	27
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):	0.00	11.02 += 20.02	0.40	1	6
Delivery <24 hours after 1 st dose	9.00	-11.93 to 29.93	0.40	1	6

Delivery $24 - 48$ hours after 1^{st} dose	0.00	-8.68 to 8.68	1.00	1	10
Delivery >48 hours after 1 st 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)

	1 / (-			
Childhood Outcome	Effect Size	95%CI	Р	No of studies	n
Total mortality	RR 0.68	0.36 to 1.27	0.22	4	1010
Neurosensory disability (composite of	Not				
impairments: cerebral palsy, blindness,	reported				
deafness, developmental delay)	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:	DD 0.04		0.17	2	770
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	Р	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	Р	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

Outcome	Effect Size	95%CI	Р	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				

Appendix G: Repeat antenatal corticosteroids - Maternal outcomes (Crowther 2011)

Mental anxiety	Not reported				
Quality of life	Not reported				
Adverse effects of therapy (Gastrointestinal	RR 0.97	0.24 to 3.90	0.96	2	1474
upset, glucose intolerance, insomnia, pain at					
injection site, bruising at injection site, infection					
at injection site, weight gain, Cushing					
syndrome)					
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	Not reported
treatment	
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	Р	No of	n
				studies	
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	0.86	0.76 to 0.98	0.021	2	1470
or less	0.00	01/01/01/0	0.002.	-	
Planned dose per treatment course >12 to	0.78	0.67 to 0.92	0.0023	6	1736
24 mg				Ť	.,,,,
Planned repeat drug exposure was 12 mg	0.79	0.68 to 0.92	0.0027	1	1144
or less/week					
Planned repeat drug exposure was >12	0.86	0.68 to 1.10	0.22	4	1068
mg/week to 24 mg/week					
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	0.98	0.77 to 1.26	0.89	5	2519
days or less	0.77	0.43 to 1.36	0.26	1	EAC
A minimum interval of 14 days or more	0.77	0.43 to 1.36 0.69 to 1.42	0.36	1	546 872
One repeat course				2	
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	0.89	0.57 to 1.38	0.60	1	1144
or less/week					
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:	100	0.07 00 1.00	0.01		0070
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	0.97	0.78 to 1.21	0.78	6	2538
days or less	0.57	0.7 0 70 7.27	0.70	Ŭ	2000
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	0.97	0.65 to 1.44	0.87	4	1068
mg/ week to 24 mg/ week					
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	RR 0.80	0.64 to 0.98	0.036	6	4356
treatment					
Neonatal encephalopathy in term babies	Not reported				
Composite serious outcome (may include fetal,	RR 0.84	0.75 to 0.94	0.0022	7	5094
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)					
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	0.78	0.66 to 0.91	0.0022	5	2232
days or less	0.70	0.00 10 0.51	0.0022)	2292
A minimum interval of between 8 and			<u> </u>		
<14 days					
ŭ	0.90	0.77 to 1.05	0.19	2	2862
A minimum interval of 14 days or more	0.90	0.77 to 1.03 0.60 to 0.93			
One repeat course			0.0099	1	558
Planned dose per treatment course 12 mg	0.77	0.62 to 0.96	0.019	1	1144
or less	0.07	0.74 0.00	0.022		2050
Planned dose per treatment course >12 to	0.87	0.76 to 0.99	0.032	6	3950
24 mg					
Planned dose per treatment course >24					
mg	0.00	0.77 4.07	0.47		2440
Planned repeat drug exposure was 12 mg	0.90	0.77 to 1.05	0.17	2	3448
or less/week	0.70				1000
Planned repeat drug exposure was >12	0.78	0.60 to 1.00	0.050	4	1088
mg/week to 24 mg/week					
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	1.38	1.04 to 1.82	0.025	4	1006
days or less					
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	1.33	0.92 to 1.94	0.13	1	326
or less					
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:			0.02	-	

Use of oxygen supplementation	RR 0.92	0.85 to 0.99	0.025	2	3448
Duration of oxygen supplementation	MD 3.30	-2.31 to 8.91	0.25	1	37
(days)					
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	MD 0.70	-2.47 to 3.87	0.67	1	175
after birth					
Mean neonatal blood pressure 6 weeks'	MD -1.40	-5.06 to 2.26	0.45	1	175
after birth					
Anthropometry at hospital discharge:					
Mean weight at primary hospital	MD -1.00	-77.15 to 75.15	0.98	1	1090
discharge (grams)					
Weight z score at primary hospital	MD -0.05	-0.16 to 0.06	0.38	2	1195
discharge					
Mean head circumference at primary	MD 0.12	-0.10 to 0.35	0.27	2	1195
hospital discharge (cm)					
Head circumference z score at primary	MD -0.03	-0.15 to 0.10	0.68	2	1195
hospital discharge					
Mean length at primary hospital	MD 0.02	-0.44 to 0.47	0.94	2	1189
discharge (cm)					
Length z score at primary hospital	MD -0.06	-0.23 to 0.10	0.46	2	1189
discharge					
HPA axis suppression, including cortisol:					
Mean basal cortisol concentrations	MD -44.90	-78.41 to -	0.0086	1	67
(nmol/L) at birth		11.39			

Childhood Outcome	Effect Size	95%CI	Р	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

Appendix I: Repeat antenatal corticosteroids - Child/adult (follow up) (Crowther 2011)

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	Р	No of	n
				studies	
Length of antenatal hospitalisation for the	Not reported				
woman					
Length of postnatal hospitalisation for the	MD 0.0	-0.22 to 0.22	1.00	1	483
woman					
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	Women with preeclampsia
	elective preterm delivery	Women for whom steroids are contraindicated on medical grounds.
	24 to 34 weeks' gestation	
Fekih 2002	Women in preterm labour	Gestational diabetes
	26 to 34 weeks'	>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	Contraindication to corticosteroids
	<34 weeks' gestation	Contraindications to postponing delivery
		Diabetes
		Suspected intrauterine infection
Garite 1992	Women likely to deliver between 24 hours and 7 days with	PROM
	spontaneous preterm labour or planned preterm delivery	Clinical or laboratory evidence of infection
	24 to 27 weeks' and 6 days gestation	Contraindication to previously given corticosteroids
		Diabetes
Goodner 1979	Any pregnant woman expected to deliver prior to 34 weeks'	Not stated
	gestation	
Kari 1994	Women with preterm labour or threatened preterm delivery due to	Rupture of membranes
	pre eclampsia	Chorioamnionitis
		Congenital abnormalities
		Proven lung maturity
		Insulin treated diabetes
		Previously treated with corticosteroids
Lewis 1996	Singleton pregnancy	Evidence of infection
	PROM	Vaginal examination
	24 to 34 weeks' gestation	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	Imminent delivery
	24 to 36 weeks'	Contraindication to corticosteroids
Lopez 1989	27 to 35 weeks'	Not stated
	Premature rupture of membranes (confirmed using speculoscopy	
	and ultrasound)	
	No signs of infection	
	Not in labour at time of hospitalisation	
	•	

Morales 1989	PROM	PROM <12 hours before onset of labour
	Singleton pregnancy	Uterine tenderness
	26 to 34 weeks' gestation	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	Fetal distress
	28 to 34 weeks' gestation	Active labour
	Ŭ	Cervical dilatation >3 cm
		Sensitivity to tocolytics
		PROM >24 hours
		Existing infection
Parsons 1988	PROM and <4 cm of cervical dilatation	Infection
	25 to 32 weeks' gestation	Fetal distress
	0	Fetal anomalies
		Contraindication to tocolysis
Porto 2011	34 to 36 weeks' and 6 days gestation	Multiple pregnancy
	At risk of imminent premature delivery (either spontaneously or if	Major congenital malformations
	early delivery is recommended as a result of problems with mother	Haemorrhage symptoms with active bleeding
	or fetus)	Clinical evidence of chorioamnionitis
		Previous use of antenatal corticosteroids
		Need for immediate resolution of pregnancy for maternal or fetal reasons
Qublan 2001	PROM	Lethal congenital abnormality
	Singleton pregnancy	Fetal death
	27 to 34 weeks' gestation	Infection
		Expected delivery within 12 hours
Schutte 1980	Women with preterm labour in whom it was possible to delay	No contraindications to the use of corticosteroids or ociprenaline (insulin treated
	delivery by at least 12 hours	diabetes, hyperthyroidism, infection, severe hypertension, cardiac disease, marked
	26 to 32 weeks' gestation	fetal growth retardation or fetal distress)
Shanks 2010	Singleton pregnancy	Multiple gestation
	34 to 36 weeks' and 6 days gestation	Ruptured membranes
	Immature TDx-FLM-II test (<45 mg/g) (surfactant to albumin	Uncertain gestational ages
	ratio) after clinically indicated amniocentesis to test for fetal lung	Previous steroid treatment in current pregnancy
	maturity	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	Indication for immediate delivery
	<5cm at 33 weeks' or less	Obstetrician objection
	Women with an L/S ratio <2 if >33 weeks' or who had a previous	Pre eclampsia
	infant with RDS	Previously received corticosteroids
Teramo 1980	Women with preterm labour and cervical dilatation <4 cm without	Pre eclampsia
	progression of labour upon initial observation of up to 12 hours.	Diabetes
	28 to 35 weeks' gestation	

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. 	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.

Mazumder 2008 McEvoy 2002	 restriction <10th percentile, oligohydramnios, abnormal antepartum testing, progression of fetal anomaly compatible with life; twin to twin transfusion syndrome). 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. 25 to 33 weeks' gestation; 	Unreliable gestational age; Frank chorioamnionitis; Major fetal malformation. Insulin dependent diabetes;
	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.	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';	Not stated.
	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).	
Danesh 2012	Pregnant women of low parity;	Evidence of fetal distress;
	16 to 45 years of age;	Substantial abnormalities in neurological, psychiatric, cardiac,
	Between 24 and 34 weeks' gestation;	endocrinological, haematologic, hepatic, renal or metabolic function;
	Hospitalised because of high risk of preterm birth that justified preventative	Signs of infection;
	corticosteroid therapy;	Positive urine culture;
	With or without intact membranes;	Vaginal bleeding due to placental praevia or abruption.
	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).	
Egerman 1998	Preterm birth between 24 to 33 weeks' gestation;	Received corticosteroids during pregnancy (except immediately before
	Preterm labour;	transfer);
	Preterm rupture of membranes;	Anticonvulsant therapy;
	Medical indication for delivery.	Rifampin;

	(Preterm labour was defined as contractions with either cervical change, 2 cm	Infection other than cystitis or cervicitis;
	dilatation, 80% effacement).	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;	Not stated.
	At risk of preterm birth between 26 to 34 weeks' gestation;	
	Has not received steroids in the preceding week.	
Mulder 1997	Women with premature contractions or at risk of preterm labour;	Cervical dilatation >5 cm;
	Between 26 to 33 weeks' gestation;	Signs of intrauterine infection;
	Small for gestational age (estimated fetal size <5th centile);	Ritodrine hydrochloride treatment for <4 days at the start of the study.
	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	
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	Women with preterm birth <35 weeks' gestation.	Not stated.
(2013)		
Rotmensch 1999	Women with preterm birth at 27 to 34 weeks' gestation;	Not stated.
	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.	
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;	Imminent birth;
	27 to 35 weeks' gestation;	Multiple pregnancy;
	Singleton pregnancy.	Previously participated in the protocol;
		Received corticosteroid therapy <10 days prior.
Urban 2005	Preterm contractions of the uterus;	Fetal major structural malformation or abnormal karyotype.
	Preterm premature rupture of membranes;	
	Cervical length less than 20 mm;	
	Placenta praevia before 34 weeks';	
	Singleton pregnancy.	

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 ev	idence and risk of bias in the included	d studies)					
Maternal The Roberts CPG version 2015 systematic :		А	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias				
randomised controlled trials involving 4469 (Level I).	women and 4853 infants	В	One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias				
Infant		С	One or two Level III studies with a low risk of bias or Level I or II studies with moderate risk of bias				
The Roberts CPG version 2015 systematic controlled trials involving 4469 women and		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 sin corticosteroids does not increase the risk of		А	All studies consistent				
chorioamnionitis, or puerperal sepsis, pyrex fever or postnatal pyrexia. Evidence is cons corticosteroid administration increases mate	ia after trial entry, intrapartum istent that antenatal	В	Most studies consistent and inconsistency can be explained				
concentrations.		С	Some inconsistency, reflecting genuine uncertainty around question				
Evidence is consistent that a single course of associated with significant reductions in feta	ll and neonatal death,	D	Evidence is not consistent				
respiratory distress syndrome, intra-ventricu enterocolitis, systemic infection, and overall	need for respiratory support.	NA	Not applicable (one study only)				
3. Clinical impact (<i>indicate if the study results intervention could not be determined</i>)	varied according to some unknown fa	ector (not si	mply study quality or sample size) and thus the clinical impact of the				
Maternal The benefit of improved neonatal outcome	s probably outweighs the	А	Very large				
impact of a transient elevation in maternal b	lood glucose.	В	Substantial				
Infant High quality, precise evidence with large eff	ect sizes demonstrating	С	Moderate				
reduction in a number of outcomes.		D	Slight/Restricted				
4. Generalisability (how well does the body of e	* *	nical setting	,				
The systematic review included one large tr		А	Evidence directly generalisable to target population				
majority of other studies were conducted in were conducted in women at risk of pretern		В	Evidence directly generalisable to target population with some caveats				
the authors). Some of the trials allowed repo	eat courses of antenatal	С	Evidence not directly generalisable to target population but				
corticosteroids if the woman remained at ris	sk of preterm birth.	0	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 h	ealthcare c	ontext in terms of health services / delivery of care and cultural factors?)				
The results are directly applicable to the Ne	w Zealand / Australian	А	Evidence directly applicable to New Zealand / Australian				
healthcare context. Betamethasone and dex		11	healthcare context				
available and already in use in Australia and	New Zealand.	В	Evidence applicable to New Zealand / Australian healthcare context with few caveats				
		С	Evidence probably applicable to New Zealand / Australian healthcare context with some caveats				
		D	Evidence not applicable to New Zealand / Australian healthcare context				
	at you took into account when assessin	ng the evide	newhence context				
upgrade the recommendation)							
	(summarise the development group's s	ynthesis of	the evidence relating to the key question, taking all the above factors into				
account) Component Rating	Description						
1. Evidence base A		with a lo	w risk of bias, or several Level II studies with a low risk of				
2. Consistency A	All studies consistent						
3. Clinical Impact A	Very large						
4. Generalisability A	Evidence directly generalisat						
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)	OVERALL GRADE OF RECOMMENDATION					
does the guideline development group draw from this	A Body of evidence can be trusted to guide practice					
evidence? Use action statements where possible)	В	Body of evidence can be trusted to guide practice in most situ	ations			
In women at risk of preterm birth use a single	С	c Body of evidence provides some support for recommendations(s) but care should be taken in its application				
course of antenatal corticosteroids.	D	Body of evidence is weak and recommendation must be applied with caution				
	PP	Practice Point				
UNRESOLVED ISSUES (If needed, keep a note of spe	ecific issues th	hat arise when each recommendation is formulated and that require follow u	þ)			
Nil						
IMPLEMENTATION OF RECOMMENDATI	ON (Pleas	e indicate yes or no to the following questions. Where the answer is yes, plea	se provide explanatory			
information about this. This information will be used to develo	op the implen	mentation plan for the guidelines)				
Will this recommendation result in changes in usual	in usual care? YES					
	NO					
Are there any resource implications associated with implementing this recommendation? YES						
			<u>NO</u>			
Will the implementation of this recommendation requ	luire chang	es in the way care is currently organised?	YES			
			<u>NO</u>			
Are the guideline development group aware of any b	arriers to i	mplementation of this recommendation?	YES			
			NO			

M1 GRADE 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. Outcome measures: Quality of evidence							
1. Outcome measures:		Quality of	evidence	37		n making a deci	ision
Maternal Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
D ₁ Chorioamnionitis	1				1		
D ₂ Puerperal sepsis		1			1		
D ₃ Pyrexia after entry to trial		1				1	
D4 Intrapartum fever requiring antibiotics		*				*	
D5 Post natal pyrexia	4					4	
D ₆ Maternal quality of life				NR	4		
Infant Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
D ₁ Combined fetal and neonatal death	1			2011	1		Important
D2 Neonatal death							
D3 Fetal death			4				
D4 RDS	*	1			*		
O ₅ Composite of serious outcomes	•	1		NR			
for the infant O6 Neurosensory disability (composite of mpairments) for infant as a child				NR	1		
O7 Survival free of neurosensory disability for the				NR			
nfant as a child Os Survival free of metabolic disease for the infant as a child				NR	~	√	
D ₉ Neurosensory disability (composite of mpairments) for infant as an adult				NR	4		
O10 Survival free of neurosensory disability for the				NR	4		
nfant as an adult O ₁₁ Survival free of metabolic disease for the					•		
nfant as an adult 2. Is there is insufficient evidence to ma		1		NR		1	
Evidence statement Maternal The evidence for maternal infection is based on nine Infant There is a large volume of high quality evidence for r disability is less, but is of high quality. Evidence com 3. What benefit will the proposed interver Evidence statement Maternal - There do not appear to be any direct be aimed at improving maternal health but is directed as other clinical questions that indicates significant bence Infant - The evidence shows significant reductions in	nortality outc es from the B ention/actio enefits report t improving i efit to the infa	comes and re Roberts CPC n have? ted for mate fetal lung m ant.	espiratory d G version 20 ernal health aturation. T	istress synd)15 systemation n. The inter There is the	rome. The evi tic review. vention is no evidence from	dence for neuro Quality t n MOD	
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. High							
4. What harm might the proposed interv	ention/actio	on do?					
Evidence statement Maternal - The randomised controlled trials included i Found no increased risk of maternal infection (variou requiring the use of antibiotics, intrapartum fever rec hat women exposed to corticosteroids were more lik hose women in the control arm. This trial used a reg had not been born and comment was made that it wi	sly reported a puiring antibio cely to have g gimen of weel	as puerperal otics, or pos lucose intole kly repeat de	sepsis, pyre tnatal fever) erance (not oses in eligil	exia after tri). Amorim clearly defin ble women i	al entry 1999 did find ned) than f the infant	Quality of o	evidence DERATE
outcome. Infant - There is some evidence indicating that intraut						мор	ERATE

Judging the harms in context						
<i>Maternal</i> - 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?						
	ood and namn?					
Evidence statement				Overall		
<i>Maternal</i> - There does not appear to be an increased transient maternal glucose intolerance. Any effects	quality of evidence					
transient maternal glucose intolerance. Any effects on maternal health are probably outweighed by the significant benefits to the infant (Chapter 4).						
Infant - There are clear benefits to the infant in terms	ed risk of respiratory distress syndrome.					
The evidence for HPA axis suppression is limit		ere are no differences in	developmental	HIGH		
outcomes. The benefits are likely to outweigh the ha Judging the balance of benefits and harms in co						
Maternal - There do not appear to be any direct healt		other. Evidence indicates	an increased risk o	f maternal glucose		
intolerance following exposure to antenatal corticost						
research. This increased risk for the mother is outwe	eighed by the eviden	ce of clear and large benef	its for the neonate			
Infant - Benefits clearly outweigh harms	<u> </u>					
Benefits clearly outweigh harms	Recommend			<u>STRONG</u>		
Benefits probably outweigh harms	Consider			CONDITIONAL		
Not known	Make a recommendation for research (see 8 below)		WEAK			
Benefits probably don't outweigh harms	CONDITIONAL					
Harms probably outweigh benefits		make no recommendation				
Benefits clearly don't outweigh harms				(TTDO) IO		
Harms clearly outweigh benefits	Recommend again	nst		STRONG		
6. Is the intervention/action implement	table in the New Z	ealand and Australian co	ontext?			
Summary statement						
Antenatal corticosteroids are already widely in use in	New Zealand and A					
Yes		Recommend/conside	<u>r</u>			
Not known		Consider economic eval	uation			
No		Recommend/consider a	against			
7. Final recommendation						
			Strength of rec	commendation		
	с .		TRONG			
In women at risk of preterm birth use a single course	e of antenatal cortice	osteroids.	<u>STRONG</u> CONDITION	AT		
			WEAK			
8. Recommendations for research						
There is a need to better assess the degree				e control from		
administration of a single course of anter						
There is a need to better assess the impact		1 0	e of antenatal corti	costeroids on:		
 the hypothalamic-pituitary ad the glucose-insulin axis in chi 		ant, child and adult.				
		adulthood.				
 the later risk of the infant developing diabetes in adulthood. Events research that investigates the use of a single course of actionated continuous and maternal quality of 						

• 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	А	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias					
systematic review (level 1 study) reported on maternal outcomes (Crowther 2011).	В	One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias					
Infant	С	One or two Level III studies with a low risk of bias or Level I or II studies with moderate risk of bias					
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.		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	А	All studies consistent					
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.	В	Most studies consistent and inconsistency can be explained					
Infant Evidence is consistent that repeat antenatal corticosteroids are	С	Some inconsistency, reflecting genuine uncertainty around question					
associated with a reduction in composite serious outcome, a significant reduction in respiratory distress and several other key clinical outcomes.	D	Evidence is not consistent					
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.		Not applicable (one study only)					
3. Clinical impact (indicate if the study results varied according to some unken intervention could not be determined)	ıown fact	or (not simply study quality or sample size) and thus the clinical impact of the					
Maternal There are no obvious detrimental effects on the mother of repeat antenatal corticosteroids.	А	Very large					
Infant High quality, precise evidence with large effect sizes demonstrating reduction in a number of clinical health outcomes for infants	В	Substantial					
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.	С	Moderate					
There was no difference between groups in birthweight at hospital discharge. The benefits for the neonate are likely to outweigh any health harms.	D	Slight / Restricted					
4. Generalisability (how well does the body of evidence match the population a	and clinic	al settings being targeted by the guideline?)					
The Crowther (2011) review includes one study from Australia,	А	Evidence directly generalisable to target population					
and one from New Zealand, that are generalisable to this guidelines target population. The other studies were conducted in	В	Evidence directly generalisable to target population with some caveats					
the United States/ India/ Canada and the UK. All studies were conducted in women at risk of preterm birth	С	Evidence not directly generalisable to target population but could be sensibly applied					
(variously defined by the authors). All administered betamethasone.	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 / Austr	alian hea	ulthcare 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	А	Evidence directly applicable to New Zealand / Australian healthcare context					
and betamethasone are readily available and already in use in Australia and New Zealand.	В	Evidence applicable to New Zealand / Australian healthcare context with few caveats					
	С	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 upgrade the recommendation)	assessing	the evidence base (for example, issues that might cause the group to downgrade or					

account)	MAIRIX (summaris	e the development grou	p's synthesis of the ei	idence relating to the key question, taking all the above factors into		
Component	Rating	Description				
1. Evidence base	А	risk of bias				
2. Consistency	А	All studies consistent				
3. Clinical Impact	В	Substantial				
4. Generalisability	А	Evidence directly	y generalisable to	target population		
5. Applicability	А	Evidence directly applicable to New Zealand / Australian healthcare context				
antenatal corticosteroids is for fe Infant The evidence is based on random suggest decrease birthweight but	nised controlled tria	ls, and suggests sig	nificant respirator	y benefits to the neonate. There is some evidence to		
RECOMMENDATION (What				RALL GRADE OF RECOMMENDATION		
development group draw from this evide				ly of evidence can be trusted to guide practice		
Use repeat antenatal corticosteroids in women at risk of early preterm, imminent birth following a single course of antenatal corticosteroids.			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			
				ication		
			D Bod appl	ication y of evidence is weak and recommendation must be ted with caution		
			D Bod appl PP Prac	ication y of evidence is weak and recommendation must be ted with caution tice Point		
UNRESOLVED ISSUES (If ne	eeded, keep a note of sp.	ecific issues that arise 1	D Bod appl PP Prac	ication y of evidence is weak and recommendation must be ted with caution		
IMPLEMENTATION OF RI information about this. This informati	ECOMMENDAT	ON (Please indicate) op the implementation	D Bod appl PP Prac when each recommend yes or no to the follo	ication y of evidence is weak and recommendation must be ied with caution tice Point dation is formulated and that require follow up) wing questions. Where the answer is yes, please provide explanator es)		
IMPLEMENTATION OF RI	ECOMMENDAT	ON (Please indicate) op the implementation	D Bod appl PP Prac when each recommend yes or no to the follo	ication y of evidence is weak and recommendation must be ied with caution tice Point dation is formulated and that require follow up) wing questions. Where the answer is yes, please provide explanator		
IMPLEMENTATION OF RI information about this. This informati	ECOMMENDAT	ON (Please indicate) op the implementation	D Bod appl PP Prac when each recommend yes or no to the follo	ication y of evidence is weak and recommendation must be ied with caution tice Point dation is formulated and that require follow up) wing questions. Where the answer is yes, please provide explanator es)		
IMPLEMENTATION OF RI <i>information about this. This information</i> Will this recommendation result	ECOMMENDAT	ON (Please indicate op the implementation care?	D Bod appl PP Prac when each recommend yes or no to the follo plan for the guidelin	ication y of evidence is weak and recommendation must be ied with caution tice Point lation is formulated and that require follow up) wing questions. Where the answer is yes, please provide explanator es) YES in some practices NO YES		
IMPLEMENTATION OF RI information about this. This information Will this recommendation result Are there any resource implication	ECOMMENDAT ion will be used to devel in changes in usual ons associated with i	ON (Please indicate op the implementation care? mplementing this r	D Bod appl PP Prace when each recommend yes or no to the follo plan for the guidelin recommendation?	ication y of evidence is weak and recommendation must be ied with caution tice Point lation is formulated and that require follow up) wing questions. Where the answer is yes, please provide explanator es) YES in some practices NO		
IMPLEMENTATION OF RI information about this. This information Will this recommendation result Are there any resource implicatio Will the implementation of this r	ECOMMENDAT ion will be used to devel in changes in usual ons associated with i	ON (Please indicate op the implementation care? mplementing this r	D Bod appl PP Prace when each recommend yes or no to the follo plan for the guidelin recommendation?	ication y of evidence is weak and recommendation must be ied with caution tice Point lation is formulated and that require follow up) wing questions. Where the answer is yes, please provide explanator es) YES in some practices NO YES		
IMPLEMENTATION OF RI information about this. This informati	ECOMMENDAT ion will be used to devel in changes in usual ons associated with i	ON (Please indicate op the implementation care? mplementing this r	D Bod appl PP Prace when each recommend yes or no to the follo plan for the guidelin recommendation?	ication y of evidence is weak and recommendation must be ted with caution tice Point dation is formulated and that require follow up) wing questions. Where the answer is yes, please provide explanator es) YES in some practices NO YES NO		
IMPLEMENTATION OF RI information about this. This information Will this recommendation result Are there any resource implicatio Will the implementation of this r	ECOMMENDAT ion will be used to develo in changes in usual ons associated with i recommendation rec	ON (Please indicate op the implementation care? mplementing this r quire changes in the	D Bod appl PP Prac when each recommend yes or no to the follo plan for the guidelin recommendation?	ication y of evidence is weak and recommendation must be ted with caution tice Point dation is formulated and that require follow up) wing questions. Where the answer is yes, please provide explanator es YES in some practices NO YES NO YES YES YES		
IMPLEMENTATION OF RI information about this. This information Will this recommendation result Are there any resource implication Will the implementation of this r currently organised?	ECOMMENDAT ion will be used to develo in changes in usual ons associated with i recommendation rec	ON (Please indicate op the implementation care? mplementing this r quire changes in the	D Bod appl PP Prac when each recommend yes or no to the follo plan for the guidelin recommendation?	ication y of evidence is weak and recommendation must be ted with caution tice Point dation is formulated and that require follow up) wring questions. Where the answer is yes, please provide explanator es YES in some practices NO YES NO YES NO YES NO YES 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		-	portance of out making a deci	king a decision	
Maternal Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important	
D ₁ Chorioamnionitis	4				*			
O2 Puerperal sepsis	4				✓			
O ₃ Pyrexia after entry to trial				NR		1		
O ₄ Intrapartum fever requiring antibiotics				NR				
O_5 Post natal pyrexia								
O ₆ Maternal quality of life				NR		1		
Infant Outcomes	HIGH	MOD	LOW	V.	✓ Critical	Important	Not	
O1 Combined fetal and neonatal death	×			LOW			Importan	
O2 Neonatal death	· ·				· ·			
O3 Fetal death	*	1						
O4 RDS		~			✓			
O ₅ Composite of serious outcomes					1			
for the infant	✓				1			
O ₆ Neurosensory disability (composite of impairments) for infant as a child		1			~			
O7 Survival free of neurosensory disability for the infant as a child			1		~			
O_8 Survival free of metabolic disease for the								
nfant as a child				NR		1		
O ₉ Neurosensory disability (composite of mpairments) for infant as an adult				NR	1			
O ₁₀ Survival free of neurosensory disability for				NR				
the infant as an adult O ₁₁ Survival free of metabolic disease for the			-	INK	1			
infant as an adult				NR		1		
2. Is there is insufficient evidence to	make a recon	nmendatio	n?					
Evidence statement Maternal - Evidence for puerperal sepsis is based over 3000 women. Evidence for postnatal pyrexi over 900 women. Infant - There is a large volume of evidence from involving 5554 infants. Data for longer term follow 3. What benefit will the proposed int	a is based on o the Crowther i ow-up was iden	one trial, incl 2011 Cochra ntified in the	luded in the ane systema	Crowther 2 tic review in	2011 Cochrane s	vystematic review randomised con	, conducted o	
Evidence statement						Ouality	of evidence	
Maternal - There appear to be no direct health b						of		
maternal infection. Evidence from one random postnatal pyrexia for women exposed to repeat of							IIGH	
puerperal sepsis for women exposed to repeat								
randomised controlled trials including 3091 wom	en.							
<i>Infant</i> - There was a 16% reduction in the risk of								
respiratory distress syndrome for those infants on no statistically significant difference in risk of f							IIGH	
			· ·	*	·			
infants exposed to repeat courses of antenatal corticosteroids compared to those exposed to placebo. 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 in	· ·							
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 MODERATE								

compared with no repeat antenatal corticosteroids. The duration and clinical significance are not discussed by the	MODERATE
trials reporting this outcome. One trial found no significant differences in glucose tolerance among women	
exposed to repeat antenatal corticosteroids.	
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 repe						
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 O Maternal - There are no clear direct health benefits for the mother exposed to repeat antenatal corticosteroids. O 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. H Infant - The benefit of reduction in risk of composite serious outcome and respiratory distress syndrome outweigh any potential harms. H						
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			<u>STRONG</u>		
Benefits probably outweigh harms	Consider			CONDITIONAL		
Not known	Make a recommen	ndation for research (see 8	below)	WEAK		
Benefits probably don't outweigh harms						
Harms probably outweigh benefits	 Consider against/1 	make no recommendation		CONDITIONAL		
Benefits clearly don't outweigh harms	Decommond again	a t		STRONG		
Harms clearly outweigh benefits	 Recommend again 	ist		STRONG		
6. Is the intervention/action implemen	table in the New Ze	ealand and Australian co	ntext?			
Summary statement Antenatal corticosteroids are already widely in use in	- Now Zooland and A	Ametralia				
Antenatal concosteroids are arready widely in use in Yes	in New Zealand and A	Recommend/conside	<u>r</u>			
Not known		Consider economic eval	uation			
No		Recommend/consider a	gainst			
7. Final recommendation						
Use repeat antenatal corticosteroids in women at ris a single course of antenatal corticosteroids.	commendation IAL					
8. Recommendations for research						
 There is a need to better assess the impact, if any, of <i>in utero</i> 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 latter 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 inclu	ded studi	es)				
Maternal The Brownfoot CPG version 2015 systematic review included trials of	А	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias				
a single course of antenatal corticosteroids and different regimens (Level I). The trials of different regimens did not report maternal	в	One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias				
outcomes.	С	One or two Level III studies with a low risk of bias or Level I				
Infant Evidence from two systematic reviews that were updated in the Brownfoot CPG version 2015 and Roberts CPG version 2015 (Level I).	D	or II studies with moderate risk of bias 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 apple	icable')					
Maternal	,					
No differential effect was seen for intrapartum pyrexia, postnatal syrexia requiring treatment with antibiotics, and puerperal sepsis between treatment with betamethasone or dexamethasone compared with no antenatal corticosteroids. Subgroup interaction tests		All studies consistent				
conducted for the purposes of these Clinical Practice Guidelines indicated that betamethasone has a protective effect against chorioarmionitis 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.	В	Most studies consistent and inconsistency can be explained				
Infant Subgroup interaction tests conducted for the purposes of these Clinical Practice Guidelines indicated no differential effect between a single	С	Some inconsistency, reflecting genuine uncertainty around question				
ractice 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	D	Evidence is not consistent				
compared with no antenatal corticosteroids, although the direction of the treatment effect was towards reduced risk for both types of antenatal corticosteroid.		Not applicable (one study only)				
3. Clinical impact (indicate if the study results varied according to some unknown intervention could not be determined)	factor (n	ot simply study quality or sample size) and thus the clinical impact of the				
Maternal The benefit of improved infant outcomes outweighs the impact of	А	Very large				
potential increase in risk of pyrexia after trial entry, ensuring access to antibiotics, if required, is readily available.	В	Substantial				
	С	Moderate				
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.	D	Slight / Restricted				
4. Generalisability (how well does the body of evidence match the population and	clinical se	ttings 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	А	Evidence directly generalisable to target population				
New Zealand. All studies were conducted in women at risk of preterm labour	В	Evidence directly generalisable to target population with some caveats				
(variously defined by the authors).	С	Evidence not directly generalisable to target population but could be sensibly applied				
		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	n healthca	re 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	А	Evidence directly applicable to New Zealand / Australian healthcare context				
available and already in use in Australia and New Zealand.	В	Evidence applicable to New Zealand / Australian healthcare context with few caveats				
	С	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 assesupgrade the recommendation)	ssing the o					

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	А	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	А	All studies consistent
3. Clinical Impact	А	Very large
4. Generalisability	А	Evidence directly generalisable to target population
5. Applicability	А	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.

	OVERALL GRADE OF RECOMMENDATION						
RECOMMENDATION (What recommendation(s) does the	Α	Body of evidence can be trusted to guide practice					
guideline development group draw from this evidence? Use action statements where possible) Use betamethasone or dexamethasone as a single course of	В	Body of evidence can be trusted to guide practice in most situations					
	С	Body of evidence provides some support for recommendations(s) but care should be taken in its application					
antenatal corticosteroid in women at risk of preterm birth.		Body of evidence is weak and recommendation must be applied with caution					
		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						
		<u>NO</u>					
Are there any resource implications associated with implementing	YES						
		<u>N0</u>					
Will the implementation of this recommendation require change	YES						
organised?			NO				
Are the guideline development group aware of any barriers to in	nplement	ation of this	YES				
recommendation?			<u>NO</u>				

M3 GRADE Evidence Summary

Do benefits or harms in the mother, fetus, infant	red Judgem					hasone is adm	inistered as a
single course of antenatal corticosteroids?	, child, adui	t vary by w	nether beta	amethason			
1. Outcome measures:				portance of ou making a dec			
Maternal Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O1 Chorioamnionitis	1				1		
O ₂ Puerperal sepsis	1				1		
O ₃ Pyrexia after entry to trial				NR		1	
O4 Intrapartum fever requiring antibiotics				NR		4	
O5 Post natal pyrexia				NR		1	
O6 Maternal quality of life				NR	4		
Infant Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O1 Combined fetal and neonatal death		1		10 1	4		Importan
O2 Neonatal death	4	· ·			*		
O₃ Fetal death	 ✓				*		
O4 RDS	 ↓						
O5 Composite of serious outcomes	•			NR			
for the infant O6 Neurosensory disability (composite of impairments) for infant as a child			4	IVK			
O7 Survival free of neurosensory disability for the				NR			
infant as a child O ₈ Survival free of metabolic disease for the infant					4		
as a child O9Neurosensory disability (composite of				NR		4	
impairments) for infant as an adult				NR	1		
O ₁₀ Survival free of neurosensory disability for the infant as an adult				NR	4		
O11 Survival free of metabolic disease for the				NR			
infant as an adult 2. Is there is insufficient evidence to mal	ke a recomn	nendation?	l			1	
 Evidence statement Maternal - The evidence for maternal outcomes follow chorioamnionitis, and four randomised controlled tri four randomised controlled trials involving 575 wom puerperal sepsis (Roberts CPG version 2015). Maternal outcomes were not reported in any of the tri Infant - The evidence for the infant is based on up to involving 753 infants, which compared dexamethaso included up to 18 randomised controlled trials, involve reported on infant outcomes. 3. What benefit will the proposed intervention 	als involving en for choric rials included five randomi ne with betar ving 3115 inf	467 women pamnionitis, in the Brow ised controll nethasone h iants, which	for puerpe and four ra vnfoot (201. ed trials inc ead to head	ral sepsis. T ndomised c 3) systemati luded in the I. The Robe	he evidence f ontrolled trial c review. Brownfoot (rts CPG versi	or dexamethason s involving 536 v 2013) systematic on 2015 systema	ne is based on women for review atic review
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, HIGH							
no statistically significant differences in neonatal de exposed to betamethasone or dexamethasone when of children followed up at 18 months of age sugges between those exposed to betamethasone compared	compared he ted there is r	ead to head	(Brownfoot e in the rate	, 2013). A s	mall subgroup) H	IIGH
Judging the benefits in context Maternal - The evidence is based on well designed and The populations included women from Brazil, the U: Infant - The evidence is based on a number of well de most outcomes. The populations included women fr New Zealand, Brazil, France, The Netherlands, Jorda	nited States, signed and c om a wide va m, Finland a	the Netherla onducted ra rriety of cou nd Tunisia.	nds, South ndomised c	Africa, Jord ontrolled tr	an. ials with large	combined samp	le sizes for
4. What harm might the proposed interv	ention/action/	on do?				1.5	
Evidence statement Maternal - The evidence from the Roberts CPG version significantly increases the risk of puerperal sepsis. The guideline and was found to be non-significant (RD 0)	e absolute ris	sk difference	e was calcul			Quality of MOI	evidence DERATE

dexamethasone was identified. There does not appea differences seen between those exposed to betameth disability.	HIGH					
Judging the harms in context Maternal - The evidence of greater risk of puerperal s lack of data on maternal outcomes from head to hea Infant - Both betamethasone and dexamethasone hav of age suggests no statistically significant differences There is no evidence to suggest that one is clinically 5. What is the likely balance between go	d comparison of dif re demonstrated ben in neurosensory disa superior to the other	ferent types of corticoster efits on neonatal outcome ability between those expo	oids. s. A small subgrou	ip followed up at 18 months		
Evidence statement Overall 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. Overall Infant - Both direct and indirect evidence suggest neither is clinically superior to the other. HIGH Judging the balance of benefits and harms in context HIGH 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.						
<i>Infant</i> - 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			<u>STRONG</u>		
Benefits probably outweigh harms	Consider			CONDITIONAL		
Not known	Make a recommen	ndation for research (see 8	below)	WEAK		
Benefits probably don't outweigh harms	Consider against/make no recommendation			CONDITIONAL		
Harms probably outweigh benefits	consider against/ make no recommendation			Gordannorum		
Benefits clearly don't outweigh harms	Deserved second			STRONG		
Harms clearly outweigh benefits	Recommend against			3110110		
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						
Use betamethasone or dexamethasone as a single course of antenatal corticosteroid in women at risk of preterm birth. Strength of recommendation 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?						
		of evidence and risk of bias in the incl	uded stud	lies)		
Maternal				One or more Level I studies with a low risk of bias, or several		
The systematic review on repeat courses only included trials that used				Level II studies with a low risk of bias		
betamethasone as no trials that used dexamethasone were identified (Crowther 2011). The systematic review on different regimens did not			В	One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias		
report maternal outcomes			С	One or two Level III studies with a low risk of bias or Level I		
Infant			C	or II studies with moderate risk of bias		
	Frownfoot 201	3) (Crowther 2011) (Level I).	D	Level IV studies or Level I to III studies/SRs with a high risk of bias		
2. Consistency (if only one	study was availd	able, rank this component as 'not app	licable')			
Maternal	5	, 1 11	,			
There is no current trial evidence that directly compares			А	All studies consistent		
betamethasone and dexam		ne repeat antenatal ompares betamethasone as a				
		I finds no differences for any	В	Most studies consistent and inconsistency can be explained		
of the maternal primary ou	atcomes of the	e Clinical Practice Guidelines.				
Infant			С	Some inconsistency, reflecting genuine uncertainty around question		
Currently, no randomised	controlled tria	lls have reported on the		1		
effects of repeat course(s) (Brownfoot 2013) found n		sone. One systematic review	D	Evidence is not consistent		
between those exposed to						
		oup followed up at 18 months	NA	Not applicable (one study only)		
of age. No other childhood			n factor (not simply study quality or sample size) and thus the clinical impact of the		
intervention could not be determ		nus varieta actoriante lo some antenon.	<i>in juuron</i> (i	nor simply sincy quality of sample size, and time time at impact of the		
Maternal			А	Very large		
with no evidence of health		lear benefit for the neonate e mother.	В	Substantial		
* 4						
Infant The evidence for repeat an	tenatal cortic	osteroids is mainly found in	С	Moderate		
		s significant neonatal benefits				
when compared with a sing $(Charten 7.0)$. There are a			D	Slight / Restricted		
dexamethasone as the repe		ns for betamethasone versus orticosteroid.				
4. Generalisability (how w	vell does the body	of evidence match the population and	clinical s	ettings being targeted by the guideline?)		
All studies were conducted						
(variously defined by the a			А	Evidence directly generalisable to target population		
evidence is generalisable for currently no evidence for t	the use of repo	eat dexamethasone on	В	Evidence directly generalisable to target population with some caveats		
maternal or infant health o				Evidence not directly generalisable to target population but		
			С	could be sensibly applied		
			D	Evidence not directly generalisable to target population and		
F A 1 1 1 1 1 7 7 7 7 7 7 7	C • 1 1		1 1.1	hard to judge whether sensible to apply		
	v		an nealth	care context in terms of health services / delivery of care and cultural factors?)		
The results are likely to be Australian healthcare conte		nasone and betamethasone are	А	Evidence directly applicable to New Zealand / Australian healthcare context		
readily available and alread	ly in use in Au	istralia and New Zealand.	В	Evidence applicable to New Zealand / Australian healthcare		
				context with few caveats Evidence probably applicable to New Zealand / Australian		
			С	healthcare context with some caveats		
			D	Evidence not applicable to New Zealand / Australian		
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	А		vith a lo	w risk of bias, or several Level II studies with a low risk of bias		
2. Consistency 3. Clinical Impact	A A	All studies consistent Very large				
4. Generalisability	A	Evidence directly generalisable to target population				
5. Applicability	А	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

Indicate any dissenting opinions		
RECOMMENDATION (What recommendation(s) does the		OVERALL GRADE OF RECOMMENDATION
guideline development group draw from this evidence? Use action	Α	Body of evidence can be trusted to guide practice
statements where possible)	В	Body of evidence can be trusted to guide practice in most situations
Use betamethasone as the repeat course antenatal corticosteroid in women at continued risk of preterm birth	С	Body of evidence provides some support for recommendations(s) but care should be taken in its application
regardless of the corticosteroid preparation used in the first course.	D	Body of evidence is weak and recommendation must be applied with caution
	PP	Practice Point
RECOMMENDATION (What recommendation(s) does the		OVERALL GRADE OF RECOMMENDATION
guideline development group draw from this evidence? Use action	А	Body of evidence can be trusted to guide practice
statements where possible)	В	Body of evidence can be trusted to guide practice in most situations
If betamethasone is not available use dexamethasone.	С	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 the	hat arise when	each recommendation is formulated and that require follow up)
IMPLEMENTATION OF RECOMMENDATION (Pleas	se indicate yes o	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 implem Will this recommendation result in changes in usual care?	neniaiion pian	YES
win uns recommendation result in changes in usual care?		1123

win this recommendation result in changes in usual care.	120
	NO
Are there any resource implications associated with implementing this recommendation?	YES
	<u>NO</u>
Will the implementation of this recommendation require changes in the way care is currently	YES
organised?	<u>NO</u>
Are the guideline development group aware of any barriers to implementation of this	YES
recommendation?	<u>N0</u>

M4 GRADE Evidence Summary

1. Outcome measures:		Quality of (NR = not		Importance of outcome in making a decision				
Maternal Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not	
O1 Chorioamnionitis								
O2 Puerperal sepsis	1							
O ₃ Pyrexia after entry to trial				NR		4		
O4 Intrapartum fever requiring antibiotics				NR		~		
O ₅ Post natal pyrexia	1					4		
O6 Maternal quality of life				NR	+			
Infant Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Importan	
O1 Combined fetal and neonatal death	1				1			
O2 Neonatal death	1				~			
O3 Fetal death		4			~			
O4 RDS	-				1			
Os Composite of serious outcomes for the infant	1							
O ₆ Neurosensory disability (composite of impairments) for infant as a child		*			*			
O7 Survival free of neurosensory disability for the infant as a child			1		*			
O ₈ Survival free of metabolic disease for the infant as a child				NR		*		
O ₂ Neurosensory disability (composite of impairments) for infant as an adult				NR	*			
O10 Survival free of neurosensory disability for the infant as an adult				NR	*			
O ₁₁ Survival free of metabolic disease for the				NR		1		
infant as an adult 2. Is there is insufficient evidence to a		mondation				· · ·		

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
<i>Maternal</i> - 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 control	
Crowther (2011) systematic review, that involve a total of 4261 women from a range of healthcare settings. There are	e 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	
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	HIGH
antenatal corticosteroids (betamethasone) compared to those not exposed to repeat antenatal corticosteroids.	
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	.1 6 1	1 . 1' . '1	6 . 1. 1	1	
Maternal - The evidence for lack of harm is direct evi with antenatal betamethasone, or placebo, after remain				exposed to repeat treatment	
<i>Infant</i> - The evidence for lack of harm is direct evide				eat exposure to	
betamethasone at the antenatal corticosteroid, or pla					
5. What is the likely balance between ge					
Evidence statement				Overall	
Maternal - There are no clear direct health benef		exposed to repeat cour	ses of antenatal	quality of evidence	
corticosteroids. There is no increased risk of infecti-		1 1 .			
Infant - The benefit of a reduction in risk of resoutweigh any potential harms. There is no evidence				HIGH	
outweigh any potential name. There is no evidence	tor ongoing marin in	to early and fate emidinood		HIGH	
Judging the balance of benefits and harms in co					
<i>Maternal</i> - Repeat exposure to betamethasone as the					
Infant - Repeat exposure to betamethasone as the antis high.	tenatal corticosteroid	is nightly likely to be bene	encial for the infan	t. The impact of the benefit	
Benefits clearly outweigh harms	Recommend			<u>STRONG</u>	
Benefits probably outweigh harms	Consider	CONDITIONAL			
Not known	Make a recommen	Make a recommendation for research (see 8 below)			
Benefits probably don't outweigh harms	Consider against/1	CONDITIONAL			
Harms probably outweigh benefits	Consider against/1	nake no recommendation	CONDITIONAL		
Benefits clearly don't outweigh harms	Recommend again		STRONG		
Harms clearly outweigh benefits	Ű			Sinono	
6. Is the intervention/action implement	table in the New Ze	ealand and Australian co	ontext?		
Summary statement					
Antenatal corticosteroids are already widely in use in Yes	n New Zealand and A	ustralia. Recommend/conside	er		
Not known		Consider economic eva			
No		Recommend/consider	against		
7. Final recommendation			0		
			Strongth of ro	commendation	
			Strength of lea	commendation	
Use betamethasone as the repeat course antenatal co			STRONG		
preterm birth regardless of the corticosteroid prepar	ration used in the first	t course.	CONDITION	JAL	
			WEAK		
If betamethasone is not available use dexamethasone	e.		STRONG		
			CONDITION	JAL	
			WEAK (Practi	ice point)	
8. Recommendations for research					
• A randomised trial of dexamethasone as the re-	epeat corticosteroid is	s 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 antenatal corticosteroids?	optima	al interval between doses when using a single course of
1. Evidence base (number of studies, level of evidence and risk of bias in the in	cluded sta	udies)
Two systematic reviews updated in the Roberts CPG version 2015 and Brownfoot CPG version 2015systematic review (Level I).	А	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias
	В	One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias
	С	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 ap	plicable')	
Maternal Current evidence supports the administration of 24 mg of etamethasone completed in 24 hours. This regimen showed ignificantly reduced risk of chorioamnionitis and no difference in isk of puerperal sepsis in women treated with a single course ompared with no antenatal corticosteroids. Evidence for		All studies consistent
compared with no antenatal corticosteroids. Evidence for chorioannionitis 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 chorioannionitis, and a significantly increased risk of puerperal sepsis following treatment with dexamethasone compared with no treatment.	В	Most studies consistent and inconsistency can be explained
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	С	Some inconsistency, reflecting genuine uncertainty around question
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	D	Evidence is not consistent
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.	NA	Not applicable (one study only)
3. Clinical impact (indicate if the study results varied according to some unkno intervention could not be determined)	wn factor	(not simply study quality or sample size) and thus the clinical impact of the
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	А	Very large
dexamethasone showed no difference in risk of chorioamnionitis, but did show significantly increased risk of puerperal sepsis when compared with no antenatal corticosteroids.	В	Substantial
Infant There are significant benefits for the neonate with the use of 24 mg	С	Moderate
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.	D	Slight / Restricted
4. Generalisability (how well does the body of evidence match the population and	ıd clinical	l 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	А	Evidence directly generalisable to target population
(variously defined by the trial authors).	В	Evidence directly generalisable to target population with some caveats
	С	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 / Austra	lian heali	theare 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.	А	Evidence directly applicable to New Zealand / Australian healthcare context

				1	Evidence applic	able to New Zealand / Australian healthcare		
			F	В	context with few	v caveats		
				_	Evidence proba	bly applicable to New Zealand / Australian		
				С		ext with some caveats		
			Г			pplicable to New Zealand / Australian healthcare		
					context	• •		
	ny other factors .	that you took into account	when assess	sing th	the evidence base (for a	example, issues that might cause the group to downgrade or		
upgrade the recommendation)								
		7/ • 1 1 •			1			
	NT MATRIX	(summarise the developm	ent group's .	synth	besis of the evidence re	elating to the key question, taking all the above factors into		
account) Component	Rating	Description						
1. Evidence base	A		studies w	vith a	a low risk of bias.	or several Level II studies with a low risk of bias		
2. Consistency	В	Most studies consiste						
3. Clinical Impact	А	Very large			,			
4. Generalisability	А	Evidence directly gen						
5. Applicability	А	Evidence directly ap	plicable to	Ne	w Zealand / Aust	ralian healthcare context		
Evidence statement			,		1 1: 0/1			
						nours and 24 mg of dexamethasone completed in		
Jo nours. Evidence for othe	1 regimens is	milled to a small num	uer or trial	is an	ici caution advised	before generalising any observed benefits.		
For women at risk of preter	m birth use:				OVERALL GR	ADE OF RECOMMENDATION		
in the second proton			Α	E		can be trusted to guide practice		
EITHER a single course of			В			can be trusted to guide practice in most situations		
divided doses completed bet	tween 12 and	36 hours	С	E	Body of evidence	provides some support for recommendations(s)		
	C 1 .		ι L			taken in its application		
OR a single course of 24 mg doses completed between 24			D			is weak and recommendation must be applied		
doses completed between 24	+ and 40 nour	5.	DD		with caution Practice Point			
RECOMMENDATION	AV71 -4	detienter des	PP			ADE OF DECOMMENDATION		
RECOMMENDATION (guideline development group dram			А			ADE OF RECOMMENDATION can be trusted to guide practice		
statements where possible)	J10m 11515 craw	ne: Ost union	B			can be trusted to guide practice in most situations		
······						provides some support for recommendations(s)		
Administer Celestone® Chr		as two intramuscular	С			care should be taken in its application		
doses of 11.4 mg, 24 hours a	apart.		D	E	Body of evidence i	is weak and recommendation must be applied		
OR Administrat dovementhese and	abourtes ## ·	atua mana ca-la ala			with caution			
Administer dexamethasone p four doses of 6 mg, 12 hour		nutamuscularly, in						
1001 00303 01 0 mg, 12 noun	s apart.							
** Celestone® Chronodos	e® Injection	, available in New						
Zealand and Australia, is	a sterile a	iqueous suspension						
containing betamethason		phosphate and						
betamethasone acetate. A s								
Celestone Chronodose Injec mg, as betamethasone sodiu								
and betamethasone acetate								
aqueous vehicle containir	ng sodium	phosphate, sodium	РР	F	Practice Point			
phosphate monobasic, di								
chloride and water for Inject	tions.							
##Downersthesesses also 1	to in11							
##Dexamethasone phospha injection which contains 4	ue is availab 137 mg dev	amethasone sodium						
phosphate, in addition pro								
sodium hydroxide and water								
New Zealand is Dexametha	asone-Hamelr	n and in Australia is						
Dexamethasone Sodium Ph	nosphate - H	ospira Australia Pty						
Ltd Australia.	Al mand- 1 1. 1	a note of shortly in a	at anice		ah maamma Jata	formulated and that require follow wet		
UINKESULVED ISSUES	(1) needed, keep	a nove of specific issues the	u urrse When	n eac	in recommendation is	formulated and that require follow up)		
IMPLEMENTATION O	F RECOMM	ENDATION (Please	indicate ves	orn	to the following and	estions. Where the answer is yes, please provide explanatory		
information about this. This info								
Will this recommendation re			1	1	0 /	YES		
	0					NO		
Are there any recourse in all	cations assoc	ated with implementin	a this room	ome	nendation	YES		
Are there any resource impli	ications associ	accu with implementin	ig uns reco	omm	nenuation:			
						NO		
Will the implementation of t	this recommen	ndation require change	s in the wa	ay ca	are is currently	YES		
organised?						NO		
Are the guideline developme	ent group awa	re of any barriers to in	nolementat	tion	of this	YES		
recommendation?	8-0 ap awa		r			NO		

M5 GRADE Evidence Summary

	sidered Judg		-			n using a cir	ale course of
What is the most effective dose, number of or antenatal corticosteroids? 1. Outcome measures:	loses in a co	Quality of		rval betwee		mportance o	-
		(NR = not)	in making a	Not			
Maternal Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Importan	t Important
O1 Chorioamnionitis	1				1		
O ₂ Pyrexia after entry to trial				NR		1	
O ₃ Intrapartum fever requiring antibiotics				NR		1	
O4 Post natal pyrexia				NR		4	
O5 Puerperal sepsis	1				1		
O6 Maternal quality of life				NR	4		
Infant Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Importan	t Not Important
D1 Combined fetal and neonatal death		4			1		
D2 Neonatal death		4			1		
O3 Fetal death			~				
O4 RDS		· ·			× •		
O ₅ Composite of serious outcomes		*					
for the infant O6 Neurosensory disability (composite of impairments) for infant as a child				NR NR	*		
O7 Survival free of neurosensory disability for the infant as a child				NR			
Os Survival free of metabolic disease for the nfant as a child				NR		4	
O ₉ Neurosensory disability (composite of mpairments) for infant as an adult O ₁₀ Survival free of neurosensory disability				NR	1		
for the infant as an adult				NR	1		
O ₁₁ Survival free of metabolic disease for the nfant as an adult				NR		1	
 Evidence statement Maternal - The Roberts CPG version 2015 system both in varying dosages and intervals. As not all Guidelines. Infant - The Roberts CPG version 2015 systema both in varying dosages and intervals. Meta-anai (Brownfoot CPG version 2015). What benefit will the proposed in 	the trials rep- tic review fou lyses were con	orted mater nd included nducted for	nal outcom 18 trials th these Clinic	es, meta-ana at used beta	dyses were con methasone an	nducted for th d 6 trials that	e Clinical Practice used dexamethasone
Evidence statement			•			Q	uality of evidence
Maternal - Current evidence supports the admir regimen showed significantly reduced risk of women treated with a single course compared and puerperal sepsis following treatment with l'hese trials found no difference in the risk o sepsis following treatment with dexamethasone <i>ln[ant</i> - Current evidence supports the adminis regimen was found to significantly reduce the to with no antenatal corticosteroids. Evidence	chorioamnior with no ante a single cour f chorioamni- compared wi- stration of 24 risk of neonat	itis and no enatal cortic se of dexan onitis, and a th no treatm mg of bet tal death an	difference costeroids. nethasone i a significan nent. amethasone d respirator	in risk of Evidence for s limited to tly increased e completed y distress sy	puerperal sep or chorioamni o one or two d risk of puer l in 24 hours. yndrome com	sis in onitis trials. peral This pared	HIGH
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.							
udging the benefits in context The evidence is based randomised controlled tri and respiratory distress syndrome. There was no aarm. The trials included in the Roberts CPG v women at risk of preterm birth. The benefit of a complete course of antenatal corticosteroids. Ev pefore generalising findings.	o evidence of version 2015 s an interval of vidence for ot	direct health ystematic re 12 hours be her dosing 1	n benefits to eview were tween dose	o the mothe conducted in s rather than	r, although the n a variety of l n 24 hours is t	ere was no evi nealthcare sett he increased l	dence of increase in ings, and involved ikelihood of a
4. What harm might the proposed in Evidence statement	ntervention/	action do?					lity of evidence

distress syndrome, with no evidence of increased ris	k of harms. There is	no evidence that increasing the dose	MOD		
improves outcomes for the infant.					
Judging the harms in context			•		
Maternal - Evidence from the Roberts CPG version 2					
and those exposed to no antenatal corticosteroids, at $P_{1} = \frac{1}{2} \left(\frac{1}{2} \right)^{1/2}$			antenatal corticosteroids.		
Evidence from the Brownfoot (2013) review is direct Infant - Evidence from the Roberts CPG version 201			woosod to botomothesono		
and those exposed to no antenatal corticosteroids, a					
Evidence from the Brownfoot (2013) review is direct					
5. What is the likely balance between go					
Evidence statement			Overall		
Maternal - There is no increased risk of maternal infe	0	0	quality of evidence		
completed in 24 hours compared with no antenatal	0		HIGH		
difference in risk of chorioamnionitis, but did show	significantly increase	d risk of puerperal sepsis when compared	111011		
with no antenatal corticosteroids.					
Infant - There are significant benefits for the neonathours, such as reduced neonatal death and re					
corticosteroids. A regimen of 24 mg of dexamethase					
against neonatal death, although no difference was s			MOD		
Judging the balance of benefits and harms in co	1 2	,			
Maternal - The likelihood of harm to the mother is m		act is low. There is no evidence of direct hea	lth benefits for the mother.		
	,				
Infant - The likelihood of good for the infant is highl	y likely, and the impa	act is high. There is no evidence of harm.	1		
Benefits clearly outweigh harms	Recommend		STRONG		
Benefits probably outweigh harms	Consider		CONDITIONAL		
Not known	Make a recommen	ndation for research (see 8 below)	WEAK		
Benefits probably don't outweigh harms		× ,			
Harms probably outweigh benefits	Consider against/	CONDITIONAL			
Benefits clearly don't outweigh harms					
, 0	Recommend again	Recommend against			
Harms clearly outweigh benefits					
6. Is the intervention/action implement	table in the New Ze	ealand and Australian context?			
Summary statement Antenatal corticosteroids are already widely in use in	Now Zooland and A	Viatralia			
Yes	Thew Zealand and A	Recommend/consider			
Not known		Consider economic evaluation			
No					
		Recommend/consider against			
7. Final recommendation			Strength of		
For women at risk of preterm birth use:			recommendation		
For women at lisk of preterin birth use.					
EITHER a single course of 24 mg of betamethasone OR a single course of 24 mg of dexamethasone in d		*	<u>STRONG</u> CONDITIONAL WEAK		
Administer Celestone® Chronodose®,** as two intr	amuscular doses of 1	1.4 mg, 24 hours apart.	STRONG		
OR			CONDITIONAL		
Administer dexamethasone phosphate## intramuscu	larly, in four doses of	f 6 mg , 12 hours apart.	WEAK (Practice point)		
^{**} Celestone® Chronodose® Injection, available in N containing betamethasone sodium phosphate and be Celestone Chronodose Injection contains betametha solution) and betamethasone acetate 6 mg (in susper sodium phosphate monobasic, disodium edetate, be	etamethasone acetate asone 11.4 mg, as bet nsion) in an aqueous	A single dose provided in 2 mL of camethasone sodium phosphate 7.8 mg (in vehicle containing sodium phosphate,			
 ##Dexamethasone phosphate is available as a 4 mg/ phosphate in addition propylene glycol, disodium ed preparation in New Zealand is Dexamethasone-Han Hospira Australia Pty Ltd Australia. 8. Recommendations for research 	letate, sodium hydrox	xide and water for injections. The			
8. Recommendations for research To maximise benefit and minimise harm to the moth	her and infant there i	is a need to establish:			
 the minimally effective dose per course of both 					
- are minimary effective dose per course of both					
the optimal timing interval por course between	doses for both both	methasone and devemethasone			
 the optimal timing interval per course between the optimal number of doese per course for he 		methasone and dexamethasone;			
 the optimal timing interval per course between the optimal number of doses per course for be the optimal number of doses per course for do 	etamethasone;	methasone and 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 of corticosteroids?	•	-
Is a single repeat dose/course (or rescue dose(s)/course) more effect. Evidence base (number of studies, level of evidence and risk of bias in the incluance dose (number of studies) and the incluance dose of the studies of the stu		
	ieu simene	, ,
One systematic review (Crowther 2011) (Level 1)	А	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias
	В	One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias
	С	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 applic	able')	01 0143
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	А	All studies consistent
were two doses of 12 mg betamethasone, 24 hours apart, and no trials reported data for more than one repeat course of antenatal corticosteroids.	В	Most studies consistent and inconsistency can be explained
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	С	Some inconsistency, reflecting genuine uncertainty around question
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.	D	Evidence is not consistent
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.	NA	Not applicable (one study only)
3. Clinical impact (indicate if the study results varied according to some unknown) intervention could not be determined)	factor (no	t simply study quality or sample size) and thus the clinical impact of the
Maternal No statistically significant differences were seen for chorioamnionitis or	А	Very large
puerperal sepsis. Infant	В	Substantial
There were no differences in perinatal, neonatal or fetal death reported in the three trials included in the Crowther systematic review	С	Moderate
(Crowther, 2011) that compared one planned repeat course of antenatal betamethasone with no repeat antenatal corticosteroids. Results for respiratory distress syndrome had significant heterogeneity.	D	Slight / Restricted
4. Generalisability (how well does the body of evidence match the population and co	linical set	tings 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	А	Evidence directly generalisable to target population
labour (variously defined by the authors). There are currently no randomised controlled trials of a repeat course of dexamethasone.	В	Evidence directly generalisable to target population with some caveats
r	С	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	healthca	re 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	А	Evidence directly applicable to New Zealand / Australian healthcare context
available and already in use in Australia and New Zealand.	В	Evidence applicable to New Zealand / Australian healthcare context with few caveats
	С	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 asses. upgrade the recommendation)	sing the e	vidence base (for example, issues that might cause the group to downgrade or

				ing to the key question taking all the above factors in					
uccount)		\mathbf{X} (summarise the development group's synthesis of the evo	uienie reidit	ng w we key question, taking at the avove factors in					
Component	Rating	Description							
. Evidence base	A		f bigs or	several Level II studies with a low risk of his					
	В	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias Most studies consistent and inconsistency can be explained							
Consistency		· · · · · · · · · · · · · · · · · · ·	i be expla	ined					
Clinical Impact	В	Substantial							
Generalisability	А	Evidence directly generalisable to target popu							
. Applicability	А	Evidence directly applicable to New Zealand	/ Austral	ian healthcare context					
nd puerperal sepsis for the r	mother, or pe to repeat cou	repeat course of antenatal corticosteroids is limi erinatal, neonatal and fetal death, or respiratory o rses of antenatal corticosteroids.							
		ndation(s) does the guideline development group draw	OVER	ALL GRADE OF RECOMMENDATIO					
from this evidence? Use action stat				Body of evidence can be trusted to guide					
EITHER	ements more p		Α	practice					
) of 12 mg b	etamethasone following a single course of		Body of evidence can be trusted to guide					
		ys prior, where the woman is still at risk of	В						
preterm birth within the next		yo prior, where the woman is suit at lisk Of		practice in most situations					
After this dose, if the woman	1 has not give	en birth seven or more days and less than 14 repeat dose and is still considered to be at risk	С	Body of evidence provides some support for recommendations(s) but care should b					
		ys a further repeat dose(s) of 12 mg		taken in its application					
betamethasone can be admin		ys a rurtifer repeat (USE(S) OF 12 Hig	-	Body of evidence is weak and					
oetamethasone can be admin DR	istered.		D	recommendation must be applied with					
	-604 1			caution					
Jse a single repeat course	of 24 mg be	tamethasone in divided doses completed							
		of antenatal corticosteroids seven or more	РР	Practice Point					
		s of preterm birth within the next seven days		Tractice Font					
Do not give further repeat co									
RECOMMENDATION (1	What recommen	ndation(s) does the guideline development group draw	OVER	ALL GRADE OF RECOMMENDATIO					
rom this evidence? Use action star	tements where t	possible)		Body of evidence can be trusted to guide					
As repeat antenatal corticoste		,	Α	practice					
1				Body of evidence can be trusted to guide					
EITHER			В	practice in most situations					
	estone® Chr	onodose®** 11.4 mg, intramuscularly as one		Body of evidence provides some support					
lose.			С	for recommendations(s) but care should b					
Use up to a maximum of three	ee single rer	peat doses only	C						
ese up to a maximum of this	ee, single, rep	cat doses only.		taken in its application					
OR				Body of evidence is weak and					
	`-l	h	D	recommendation must be applied with					
	.elestone® C	hronodose®** 11.4 mg, as two intramuscular		caution					
loses, 24 hours apart.									
Do not give any further repe	at courses.								
Zealand) is a sterile aqueous s and betamethasone acetate. A injection contains betamethas in solution) and betamethas	suspension c A single dose isone 11.4 mg one acetate 6 e, sodium ph	he only currently registered product in New ontaining betamethasone sodium phosphate provided in 2 mL of Celestone Chronodose g, as betamethasone sodium phosphate 7.8 mg mg (in suspension) in an aqueous vehicle osphate monobasic, disodium edetate, ction.	РР	Practice Point					
UNRESOLVED ISSUES	(If needed keet	a note of specific issues that arise when each recommend	ation is for	mulated and that require follow up)					
		IENDATION (Please indicate yes or no to the follow							
		used to develop the implementation plan for the guideline							
nformation about this This infor				TES					
	sure in change								
	0		1	<u>NO</u>					
	0								
Will this recommendation res		iated with implementing this recommendation?	N N	YES					
Vill this recommendation res		iated with implementing this recommendation?		YES					
Vill this recommendation res		iated with implementing this recommendation?		XES NO					
Will this recommendation res	cations assoc		1	NO					
Will this recommendation resource implication for the theorem of the templementation of templementation	cations assoc	iated with implementing this recommendation? ndation require changes in the way care is curren	ntly Y	NO VES					
Will this recommendation res Are there any resource implic Will the implementation of th	cations assoc		ntly Y	NO					
Will this recommendation res Are there any resource implic Will the implementation of th organised?	cations assoc		ntly Y	NO VES					

M6 GRADE Evidence Summary

Consi	idered Judge	ment - Stre	ngth of rec	ommenda	tion				
What is the most effective dose, number of do	oses in a cour	rse, and opt	timal interv	al betwee	n courses for r	epeat antenatal			
corticosteroids?		oo, and op		ar seenee.		epeur unternatur			
Is a single repeat dose/course (or rescue dose	e(s)/course)	more effect	ive than m	ultiple rep	eat dose(s)/c	ourses?			
	portance of out	come							
1. Outcome measures:		Quality of (NR = not					naking a decision		
Maternal Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important		
O1 Chorioamnionitis	1				1				
O ₂ Puerperal sepsis	1				1				
O ₃ Pyrexia after entry to trial				NR		1			
O4 Intrapartum fever requiring antibiotics				NR		1			
O ₅ Post natal pyrexia				NR					
O ₆ Maternal quality of life				NR		•			
Infant Outcomes	HIGH	MOD	LOW	V. LOW	✓ Critical	Important	Not Important		
O1 Combined fetal and neonatal death	1				1				
O2 Neonatal death	4				1				
O3 Fetal death									
O ₄ RDS	· ·								
O ₅ Composite of serious outcomes		1			1				
for the infant		1			1				
O6 Neurosensory disability (composite of				NR					
impairments) for infant as a child				INK	1				
O7 Survival free of neurosensory disability for the infant as a child				NR	1				
O_8 Survival free of metabolic disease for the									
infant as a child				NR		~			
O9 Neurosensory disability (composite of				NR					
impairments) for infant as an adult				INK	1				
O ₁₀ Survival free of neurosensory disability for the infant as an adult				NR	1				
O ₁₁ Survival free of metabolic disease for the									
infant as an adult				NR		1			
2. Is there is insufficient evidence to r	make a recon	nmendation	n?						
Evidence statement									
Maternal and infant - All of the randomised trials in									
more than one repeat course of antenatal corticos			nal or infant	t outcomes	for the Clinica	l Practice Guideli	nes.		
3. What benefit will the proposed inte	ervention/act	tion have?							
Evidence statement							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,	1	, ,							
compared with no repeat courses. Similarly, no di							IIGH		
planned repeat course (1 dose of 12 mg betameth with no repeat courses.	iasone, i trial,	279 WOINEI	i or antena	tai corticos	teroius compar				
Infant - A reduction in composite serious outcome	e was seen in	one trial inc	luded in the	Crowther	(2011) systema	tic			
review, following treatment with one planned re					· / ·				
No difference was seen in perinatal, fetal or neon									
for gestational age in the trials that compared o							IIGH		
with no repeat antenatal corticosteroid. At early survival free of major disability and major disability									
planned repeat dose compared with placebo.	nty at childho	ou tonow-u	p were seef	i ior inrant	s exposed to o	iic			
planned repeat dose compared with placebo.									

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.

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 significant		d to four or more courses	of antenatal	MODERATE
corticosteroids born below the 5 th percentile for Judging the harms in context				
Maternal - There was no evidence of harm to the Infant - There was no evidence of increase in risk one planned repeat course of antenatal corticoste courses is based on one trial that was stopped ea reduced birthweight is unclear and there is evider	of mortality, respiratory eroids. The evidence of r rly due to concerns abou	distress syndrome or disa reduction in birthweight fo at the reduced birthweight	bility at early child ollowing exposure outcomes. The cli	to four or more repeat nical significance of the
5. What is the likely balance between	n good and harm?			
Evidence statement Maternal - Exposure to one planned repeat co			ease the risk of	Overall quality of evidence
chorioamnionitis or puerperal sepsis compared w Infant - Exposure to one planned repeat course composite of serious neonatal outcomes, wi	of antenatal corticoster th no difference in n	oids was associated with nortality, respiratory dist	ress syndrome,	HIGH
birthweight, small for gestational age, or major antenatal corticosteroids.		thood tollow-up compar-	ed to no repeat	HIGH
Judging the balance of benefits and harms in Maternal - The likelihood of harm to the mother a	a context is minimal, and the impa	ct is low. There is no evid	ence of direct heal	th benefits for the mother.
Infant - The likelihood of benefit for the infant is antenatal corticosteroids.	high, and the impact is l	nigh. There is no evidence	of harm for one p	lanned repeat course of
Benefits clearly outweigh harms	Recommend			STRONG
Benefits probably outweigh harms	Consider			CONDITIONAL
Not known	Make a recommen	dation for research (see 8	below)	WEAK
Benefits probably don't outweigh harms Harms probably outweigh benefits	Consider against/1	make no recommendation		CONDITIONAL
Benefits clearly don't outweigh harms Harms clearly outweigh benefits	Recommend again	ist		STRONG
6. Is the intervention/action implem	entable in the New Ze	ealand and Australian co	ontext?	
Summary statement Antenatal corticosteroids are already widely in us	e in New Zealand and A	ustralia		
Yes		Recommend/conside	r	
Not known		Consider economic eval		
No		Recommend/consider a		
7. Final recommendation		,	0	
Use a single repeat dose(s) of 12 mg betameth corticosteroid seven or more days prior, where the the next seven days. After this dose, if the woman has not given birth administration of the previous repeat dose and is within the next seven days a further repeat dose(OR Use a single repeat course of 24 mg betamethe hours following a single course of antenatal corti woman is still at risk of preterm birth within the courses.	<u>STRONG</u> CONDITION WEAK	AL		
	give further repeat			
As repeat antenatal corticosteroid use			Strength of rec	ommendation
As repeat antenatal corticosteroid use EITHER <u>A single repeat dose</u> of Celestone® Chronodox Use up to a maximum of three, single, repeat dos			Strength of rec STRONG CONDITION <u>WEAK</u>	
EITHER <u>A single repeat dose</u> of Celestone® Chronodos Use up to a maximum of three, single, repeat dos OR <u>A single repeat course</u> of Celestone® Chronoc hours apart. Do not give any further repeat courses. ** Celestone® Chronodose® Injection (the only a sterile aqueous suspension containing betameth acctate. A single dose provided in 2 mL of Celess betamethasone 11.4 mg, as betamethasone sodiu betamethasone acetate 6 mg (in suspension) in ar sodium phosphate monobasic, disodium edetates	ses only. lose®** 11.4 mg, as two currently registered pro- nasone sodium phosphat tone Chronodose Injecti m phosphate 7.8 mg (in n aqueous vehicle contai	cularly as one dose. intramuscular doses, 24 duct in New Zealand) is e and betamethasone on contains solution) and ning sodium phosphate,	STRONG CONDITION	
EITHER <u>A single repeat dose</u> of Celestone® Chronodos Use up to a maximum of three, single, repeat dos OR <u>A single repeat course</u> of Celestone® Chronoc hours apart. Do not give any further repeat courses. ** Celestone® Chronodose® Injection (the only a sterile aqueous suspension containing betameth acetate. A single dose provided in 2 mL of Celess betamethasone 11.4 mg, as betamethasone sodiu betamethasone acetate 6 mg (in suspension) in ar sodium phosphate monobasic, disodium edetate, 8. Recommendations for research	ses only. lose®** 11.4 mg, as two currently registered pro- nasone sodium phosphat tone Chronodose Injecti m phosphate 7.8 mg (in n aqueous vehicle contai benzalkonium chloride	cularly as one dose. intramuscular doses, 24 duct in New Zealand) is e and betamethasone on contains solution) and ning sodium phosphate, and water for injection.	STRONG CONDITION WEAK	
EITHER <u>A single repeat dose</u> of Celestone® Chronodos Use up to a maximum of three, single, repeat dos OR <u>A single repeat course</u> of Celestone® Chronoc hours apart. Do not give any further repeat courses. ** Celestone® Chronodose® Injection (the only a sterile aqueous suspension containing betameth acetate. A single dose provided in 2 mL of Celess betamethasone a11.4 mg, as betamethasone sodiu betamethasone acetate 6 mg (in suspension) in ar sodium phosphate monobasic, disodium edetate, <u>8.</u> Recommendations for research Further research is required to explore betameth	ses only. lose®** 11.4 mg, as two currently registered pro- nasone sodium phosphat tone Chronodose Injecti m phosphate 7.8 mg (in n aqueous vehicle contai benzalkonium chloride	cularly as one dose. intramuscular doses, 24 duct in New Zealand) is e and betamethasone on contains solution) and ning sodium phosphate, and water for injection.	STRONG CONDITION WEAK	
EITHER <u>A single repeat dose</u> of Celestone® Chronodos Use up to a maximum of three, single, repeat dos OR <u>A single repeat course</u> of Celestone® Chronoc hours apart. Do not give any further repeat courses. ** Celestone® Chronodose® Injection (the only a sterile aqueous suspension containing betameth acetate. A single dose provided in 2 mL of Celess betamethasone a1.4 mg, as betamethasone sodiu betamethasone acetate 6 mg (in suspension) in an sodium phosphate monobasic, disodium edetate, <u>8. Recommendations for research</u> Further research is required to explore betameth • the optimal dose;	ses only. lose®** 11.4 mg, as two currently registered pro hasone sodium phosphat tone Chronodose Injecti m phosphate 7.8 mg (in n aqueous vehicle contai benzalkonium chloride	cularly as one dose. intramuscular doses, 24 duct in New Zealand) is e and betamethasone on contains solution) and ning sodium phosphate, and water for injection.	STRONG CONDITION WEAK	
EITHER <u>A single repeat dose</u> of Celestone® Chronodos Use up to a maximum of three, single, repeat dos OR <u>A single repeat course</u> of Celestone® Chronoc hours apart. Do not give any further repeat courses. ** Celestone® Chronodose® Injection (the only a sterile aqueous suspension containing betameth actate. A single dose provided in 2 mL of Celes betamethasone 11.4 mg, as betamethasone sodiu betamethasone acetate 6 mg (in suspension) in an sodium phosphate monobasic, disodium edetate, 8. Recommendations for research Further research is required to explore betameth • the optimal dose; • the optimal number of dose(s) in a co	ses only. lose®** 11.4 mg, as two currently registered pro- nasone sodium phosphat tone Chronodose Injecti m phosphate 7.8 mg (in n aqueous vehicle contai , benzalkonium chloride asone and dexamethasor purse;	cularly as one dose. intramuscular doses, 24 duct in New Zealand) is e and betamethasone on contains solution) and ning sodium phosphate, and water for injection.	STRONG CONDITION WEAK	
EITHER <u>A single repeat dose</u> of Celestone® Chronodos Use up to a maximum of three, single, repeat dos OR <u>A single repeat course</u> of Celestone® Chronod hours apart. Do not give any further repeat courses. ** Celestone® Chronodose® Injection (the only a sterile aqueous suspension containing betameth actetate. A single dose provided in 2 mL of Celess betamethasone a1.4 mg, as betamethasone sodiu betamethasone actetate 6 mg (in suspension) in an sodium phosphate monobasic, disodium edetate, <u>8. Recommendations for research</u> Further research is required to explore betameth • the optimal dose;	ses only. lose®** 11.4 mg, as two currently registered pro hasone sodium phosphat tone Chronodose Injecti m phosphate 7.8 mg (in n aqueous vehicle contai , benzalkonium chloride asone and dexamethasor purse;	cularly as one dose. intramuscular doses, 24 duct in New Zealand) is e and betamethasone on contains solution) and ning sodium phosphate, and water for injection.	STRONG CONDITION WEAK	

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 in	cluded stu	(dies)			
Maternal Roberts CPG version 2015 systematic review for a single course of antenatal corticosteroids (Level 1) included two randomised	А	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias			
controlled trials that reported on chorioamnionitis and puerperal sepsis in relation to time interval from administration of first dose to	В	One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias			
birth. Infant	С	One or two Level III studies with a low risk of bias or Level I or II studies with moderate risk of bias			
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.	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 ap	plicable')				
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	А	All studies consistent			
systematic review (<24 hours before birth, <48 hours before birth, between one to seven days before birth, \geq 7 days before birth). A single trial reported no difference in puerperal sepsis for women	В	Most studies consistent and inconsistency can be explained			
giving birth <24 hours from receiving the first dose, no data were reported for other time points for this outcome. Infant	С	Some inconsistency, reflecting genuine uncertainty around question			
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	D	Evidence is not consistent			
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.	NA	Not applicable (one study only)			
3. Clinical impact (indicate if the study results varied according to some unknot intervention could not be determined)	wn factor	(not simply study quality or sample size) and thus the clinical impact of the			
Maternal benefits or harms were associated with the timing of administration.	А	Very large			
Infant	В	Substantial			
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	С	Moderate			
birth, with significant reductions in mortality and RDS seen at this time.	D	Slight / Restricted			
4. Generalisability (how well does the body of evidence match the population and	d 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	А	Evidence directly generalisable to target population			
preterm birth (variously defined by the trial authors), in a variety of countries and healthcare settings.	В	Evidence directly generalisable to target population with some caveats			
O.	С	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 / Austra	lian health	bcare context in terms of health services / delivery of care and cultural factors?)			
Evidence is applicable to the New Zealand and Australian health care setting	А	Evidence directly applicable to New Zealand / Australian healthcare context			
	В	Evidence applicable to New Zealand / Australian healthcare context with few caveats			
	С	Evidence probably applicable to New Zealand / Australian healthcare context with some caveats			
	D	Evidence not applicable to New Zealand / Australian healthcare context			

	MENT MATRI	${f X}$ (summarise the development grou	up's synthes	sis of the evidence rea	lating to the key question, taking all the above factors into	
account) Component	Rating	Description				
1. Evidence base	A		es with a	low risk of bias.	or several Level II studies with a low risk of bias	
2. Consistency	А	All studies consistent				
3. Clinical Impact	А	Very large				
4. Generalisability	А	Evidence directly generalis	able to ta	rget population		
5. Applicability	A	Evidence directly applicable			alian healthcare context	
Evidence statement The evidence indicates t anticipated to occur wit	hin 7 days from t	me prior to birth to administe			atal corticosteroids is when preterm birth is	
		ndation(s) does the guideline		1	RADE OF RECOMMENDATION	
development group draw from	m this evidence? Use	action statements where	Α		ence can be trusted to guide practice	
possible)			В	situations	nce can be trusted to guide practice in most	
Use a single course of a	ntenatal corticost	eroids in women at risk of	0	Body of evider	nce provides some support for	
preterm birth when birt			recommendations(s) but care should be taken in its application			
seven days even if birth	is likely within 24	hours.	D Body of evidence is weak and recommendation must be applie with caution			
			PP Practice Point			
RECOMMENDATIO	DN (What recomme	ndation(s) does the guideline	OVERALL GRADE OF RECOMMENDATION			
development group draw from			А		nce can be trusted to guide practice	
possible)			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			
the use of adjunct predi	ction tests includ	reterm birth by considering ng fetal fibronectin and				
assessment of cervical le	ength.		D	D Body of evidence is weak and recommendation must be applied with caution		
The optimal time to adr preterm birth is planned		corticosteroids is when hin the next 48 hours.	PP Practice Points			
UNRESOLVED ISSU	J ES (If needed, kee	b a note of specific issues that arise	when each	recommendation is j	formulated and that require follow up)	
IMPI EMENITATIO	N OF RECOM	AFNDATION (Please indicat	0 1105 04 110	to the following and	tions. Where the answer is yes, please provide explanator	
		used to develop the implementation				
Will this recommendation				. ,	YES	
					NO	
Are there any resource i	implications assoc	tiated with implementing this	recomme	endation?	YES	
2	-	. 0			NO	
Will the implementation	n of this recomme	endation require changes in th	e way car	e is currently	YES	
organised?		1		,	NO	
Are the mideline devol	pment group and	are of any harriers to impland	entation	of this	YES	
Are the guideline development group aware of any barriers to implementation of this recommendation?			110			

M7 GRADE Evidence summary

	onsidered Ju						
What is the optimal time prior to birth to	administer a			tal corticos		mportance of ou	itcome
1. Outcome measures:		Quality of o	evidence	T ==	-	in making a dec	cision
Matemal Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O1 Chorioamnionitis	1				1		
O ₂ Puerperal sepsis	1				1		
O ₃ Pyrexia after entry to trial				NR		4	
O ₄ Intrapartum fever requiring antibiotics				NR		4	
D5 Post natal pyrexia				NR		4	
O6 Maternal quality of life				NR			
Infant Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O1 Combined fetal and neonatal death	4			10 11	1		Important
D2 Neonatal death	4				1		
D ₃ Fetal death	✓		1		1		
O ₄ RDS	4				1		
O5 Composite of serious outcomes for the infant				NR	4		
O ₆ Neurosensory disability (composite of mpairments) for infant as a child				NR	1		
O ₇ Survival free of neurosensory disability for the infant as a child				NR	4		
O ₈ Survival free of metabolic disease for the infant as a child				NR		*	
O9 Neurosensory disability (composite of				NR	-		
mpairments) for infant as an adult D 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		4	
2. Is there is insufficient evidence	e to make a re	ecommendat	ion?				
 Evidence statement Maternal - Evidence for maternal outcomes is of antenatal corticosteroids that report on cho birth. Infant - Evidence for infant outcomes is based antenatal corticosteroids, which reported on a first dose to birth. 3. What benefit will the proposed 	orioamnionitis l on up to 9 tr mortality and	s and puerpers ials included i respiratory dis	al sepsis in 1 n the Rober stress syndro	elation to ti	me interval fro sion 2015 syst	om administration ematic review for	a single course of
Evidence statement						Quali	ity of evidence
<i>Maternal</i> - 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, between one to seven days before birth, ≥ 7 days before birth). <i>Infant</i> - 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 exposed to antenatal corticosteroids.	corticosteroid	ls between of	ne and 7 da	iys before b	wirth and those	e not	HIGH
Judging the benefits in context <i>Maternal</i> - The evidence is based on well desig Africa and New Zealand. Infant - Evidence for infant outcomes is base							
nortality and respiratory distress syndrome in n a variety of countries and health care settin	n relation to th lgs, and includ	ne time interva le up to 1110	al from adm infants.				
4. What harm might the proposed	1 intervention	n/action do?					A 11
E vidence statement Maternal - There was no increased risk of mat	ernal infection	n for those wh	no received	antenatal co	rticosteroids	Quality	of evidence
compared with those who did not received as						ours	HIGH

before birth, <48 hours before birth, between one te Infant - When the interval from first dose to birth wa among those infants exposed compared to infants n	HIGH				
Judging the harms in context <i>Maternal</i> - 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, \geq 7 days before birth). <i>Infant</i> - 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 go	bod and harm?				
Evidence statement Maternal - There are no direct health benefits to the mother of exposure to antenatal corticosteroids. There are significant benefits to the infant. 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.				Overall quality of evidence HIGH HIGH	
Judging the balance of benefits and harms in co Maternal - The likelihood of harm to the mother is m mother, there is also no evidence of harms. Infant - The likelihood of benefit for the infant is hig	ninimal, and the impa				
Benefits clearly outweigh harms	Recommend			<u>STRONG</u>	
Benefits probably outweigh harms	Consider			CONDITIONAL	
Not known	Make a recommen	dation for research (see 8	below)	WEAK	
Benefits probably don't outweigh harms		CONDITIONAL			
Harms probably outweigh benefits	Consider against/1	CONDITIONAL			
Benefits clearly don't outweigh harms	- Recommend again	st		STRONG	
Harms clearly outweigh benefits	0			omono	
6. Is the intervention/action implement	table in the New Ze	ealand and Australian co	ontext?		
Summary statement Antenatal corticosteroids are already widely in use in	New Zealand and A	ustralia			
Yes	rite w Bedduite and F	Recommend/conside	2 <u>r</u>		
Not known		Consider economic eval	luation		
No		Recommend/consider a	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 re STRONG CONDITION WEAK				commendation	
8. Recommendations for research					
 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 in	cluded sti	udies)	
Maternal None of the randomised controlled trials in the Crow systematic review reported post-randomisation subgr		А	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias	
optimal timing to administer repeat dose(s) antenata on maternal outcomes.		В	One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias	
Infant None of the randomised controlled trials identified in (2011) systematic review reported post-randomisation		С	One or two Level III studies with a low risk of bias or Level I or II studies with moderate risk of bias	
analysis of optimal timing to administer repeat dose(s corticosteroids for infant mortality, respiratory distre composite of serious infant outcomes. The evidence is equivalent to the overall effect of rep	mal timing to administer repeat dose(s) of antenatal for infant mortality, respiratory distress syndrome or erious infant outcomes.		Level IV studies or Level I to III studies/SRs with a high risk of bias	
corticosteroids summarised in Chapter 8				
2. Consistency (if only one study was available, rank this	component as 'not ap	plicable')		
See Chapter 8		А	All studies consistent	
		В	Most studies consistent and inconsistency can be explained	
		С	Some inconsistency, reflecting genuine uncertainty around	
		D	question Evidence is not consistent	
		NA	Not applicable (one study only)	
3 Clinical impact (indicate if the study results varied asso	rding to some unknow		(not simply study quality or sample size) and thus the clinical impact of the	
intervention could not be determined)	rung to some unknot	vn jacior	(noi simply sind) quadity of sample size) and time to cunical impact of the	
See Chapter 8		А	Very large	
		В	Substantial	
		С	Moderate	
		D	Slight / Restricted	
4. Generalisability (how well does the body of evidence ma	tch the population an	d clinical	settings being targeted by the guideline?)	
See Chapter 8		А	Evidence directly generalisable to target population	
		В	Evidence directly generalisable to target population with some caveats	
		С	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	v Zealand Austral	lian healt	to judge whether sensible to appry theare context in terms of health services / delivery of care and cultural factors?)	
See Chapter 8		А	Evidence directly applicable to New Zealand / Australian	
			healthcare context Evidence applicable to New Zealand / Australian healthcare	
		В	context with few caveats Evidence probably applicable to New Zealand / Australian	
		С	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 upgrade the recommendation)	into account when as	ssessing ti	he evidence base (for example, issues that might cause the group to downgrade or	
EVIDENCE STATEMENT MATRIX (summarise account)	the development grou	ıp's synth	vesis of the evidence relating to the key question, taking all the above factors into	
Component	Rating		ription	
1. Evidence base	А		or more Level I studies with a low risk of bias, or several Level II es with a low risk of bias	
2. Consistency	А		udies consistent	
3. Clinical Impact	В	Subst		
 Generalisability Applicability 	A		ence directly generalisable to target population ence directly applicable to New Zealand / Australian healthcare	
	11	conte	• * *	
Evidence statement				

RECOMMENDATION (What recommendation(s) does the		OVERALL GRADE OF RECOMMENDATION
guideline development group draw from this evidence? Use action	Α	Body of evidence can be trusted to guide practice
statements where possible)	В	Body of evidence can be trusted to guide practice in most situations
Use repeat antenatal corticosteroids in women at	С	Body of evidence provides some support for recommendations(s) but
continued risk of preterm birth where the antenatal		care should be taken in its application
corticosteroids were given seven or more days prior,	D	Body of evidence is weak and recommendation must be applied with
when birth is planned or expected within the next seven		caution
days, even if birth is likely within 24 hours	PP	Practice Point
RECOMMENDATION (What recommendation(s) does the		OVERALL GRADE OF RECOMMENDATION
guideline development group draw from this evidence? Use action	А	Body of evidence can be trusted to guide practice
statements where possible)	В	Body of evidence can be trusted to guide practice in most situations
Where appropriate, estimate the risk of preterm birth by	С	Body of evidence provides some support for recommendations(s) but
considering the use of adjunct prediction tests including	<u> </u>	care should be taken in its application
fetal fibronectin and assessment of cervical length.	D	Body of evidence is weak and recommendation must be applied with
If betamethasone is not available use dexamethasone.		caution
If betamethasone is not available use dexamethasone.	PP	Practice Point
UNRESOLVED ISSUES (If needed, keep a note of specific issues)	ues that arise	when each recommendation is formulated and that require follow up)
	D	
		te 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 in Will this recommendation result in changes in usual care?	rpiementation	n pian for the guadennes) YES
will this recommendation result in changes in usual care?		
		NO
Are there any resource implications associated with implem	enting this	recommendation? YES
		NO
Will the implementation of this recommendation require ch	langes in th	he way care is currently YES
organised?		NO
Are the guideline development group aware of any barriers	to impleme	entation of this YES
recommendation?	NO	

M8 GRADE Evidence summary

Cons	idered Judge	ment - Stre	ngth of rec	commenda	tion				
What is the optimal time prior to birth to adm	ninister a repo	eat dose(s)	of antenat	al corticost	eroids?				
1. Outcome measures:		Quality of	evidence				rtance of outcome aking a decision		
Maternal Outcomes	HIGH	MOD	LOW	V. LOW	Important	Not Important			
D1 Chorioamnionitis				NR	4				
D ₂ Puerperal sepsis				NR	4				
D ₃ Pyrexia after entry to trial				NR		4			
D4 Intrapartum fever requiring antibiotics				NR		4			
D5 Post natal pyrexia				NR		4			
D ₆ Maternal quality of life				NR	4				
Infant Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important		
D ₁ Combined fetal and neonatal death				NR	4				
D2 Neonatal death				NR					
D3 Fetal death				NR					
D4 RDS		1		NR	• •				
D ₅ Composite of serious outcomes				NR					
For the infant D ₆ Neurosensory disability (composite of					1				
mpairments) for infant as a child D7 Survival free of neurosensory disability for				NR	1				
he infant as a child				NR	1				
D ₈ Survival free of metabolic disease for the nfant as a child				NR		4			
D9 Neurosensory disability (composite of				NR	1				
mpairments) for infant as an adult D10 Survival free of neurosensory disability for					•				
he infant as an adult D ₁₁ Survival free of metabolic disease for the				NR	4				
nfant as an adult				NR		✓			
Evidence statement Maternal - None of the randomised controlled tria optimal timing to administer repeat dose(s) of an Infant - None of the randomised controlled trials is analysis of optimal timing to administer repeat do composite of serious infant outcomes. 3. What benefit will the proposed int	tenatal corticos identified in th ose(s) of antena	steroids on i e Crowther atal corticos	maternal ou (2011) syste	tcomes. ematic revie	w reported po	ost-randomisation	n subgroup		
r r r	ervention/ act	ion nave?					c · 1		
E vidence statement Maternal - Evidence is based on overall summary	of repeat anter	natal cortico	ste r oids sur	nmarised in	Chapter 8	Qualit	y of evidence		
<i>Infant</i> - Evidence is based on overall summary of Judging the benefits in context	repeat antenat	al corticoste	roids summ	narised in Ch	napter 8		HIGH		
Evidence is based on overall summary of repeat a	intenatal cortio	costeroids su	ımmarised i	n Chapter 8	3				
4. What harm might the proposed int	tervention/ac	tion do?							
Evidence statement	of repeat apter	atal cortico	eteroide eur	nmarised in	Chapter 8	Quality o	f evidence		
<i>Maternal</i> - Evidence is based on overall summary of repeat antenatal corticosteroids summarised in Chapter 8 <i>Infant</i> - Evidence is based on overall summary of repeat antenatal corticosteroids summarised in Chapter 8							HIGH		
<i>infant</i> - Evidence is based on overall summary of udging the harms in context									
infant - Evidence is based on overall summary of	good and ha	rm?							
<i>Infant</i> - Evidence is based on overall summary of udging the harms in context	of repeat anter	natal cortico				quality	Overall 7 of evidence HIGH		
infant - Evidence is based on overall summary of fudging the harms in context 5. What is the likely balance between Evidence statement Maternal - Evidence is based on overall summary of infant - Evidence is based on overall summary of udging the balance of benefits and harms in Maternal - Evidence is based on overall summary of the balance of based on overall summary of the balance of benefits and harms in Maternal - Evidence is based on overall summary of the balance of based on overall summary of the balance over a based on overall summary of the balance over a based on o	of repeat anter repeat antenat context of repeat anter	natal cortico al corticoste natal cortico	roids summ steroids sur	narised in Ch	Chapter 8	quality	of evidence		
infant - Evidence is based on overall summary of fudging the harms in context 5. What is the likely balance between Evidence statement Maternal - Evidence is based on overall summary of infant - Evidence is based on overall summary of sudging the balance of benefits and harms in Maternal - Evidence is based on overall summary of infant - Evide	of repeat anter repeat antenat context of repeat anter	natal cortico al corticoste natal cortico al corticoste	roids summ steroids sur	narised in Ch	Chapter 8	quality	y of evidence HIGH		
<i>infant</i> - Evidence is based on overall summary of udging the harms in context 5. What is the likely balance between Evidence statement <i>Maternal</i> - Evidence is based on overall summary	of repeat anter repeat antenat context of repeat anter repeat antenat	natal cortico al corticoste natal cortico al corticoste <u>nend</u>	roids summ steroids sur	narised in Ch	Chapter 8	quality STRON	y of evidence HIGH		

Benefits probably don't outweigh harms	Consider against/make no recommendation			CONDITIONAL			
Harms probably outweigh benefits	Consider against/1	make no recommendation		CONDITIONAL			
Benefits clearly don't outweigh harms	D 1 -						
Harms clearly outweigh benefits	Recommend again	st		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/conside	r				
Not known		Consider economic eval	uation				
No	No			Recommend/consider against			
7. Final recommendation							
Use repeat antenatal corticosteroids in women at cor antenatal corticosteroids were given seven or more of within the next seven days, even if birth is likely with		Strength of rec STRONG CONDITION WEAK	commendation				
Where appropriate, estimate the risk of preterm birti prediction tests including fetal fibronectin and assess If betamethasone is not available use dexamethasone	STRONG CONDITION WEAK (Practi						
8. Recommendations for research	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 definit	ely expected or plann	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 ind	cluded stu	dies)			
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	А	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias			
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		One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias			
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 Courter (2014) control is university in the provided of the second	С	One or two Level III studies with a low risk of bias or Level I or II studies with moderate risk of bias			
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.	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 ap	blicable')				
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.	А	All studies consistent			
Infant No differences were seen in measures of infant mortality among infants exposed to repeat antenatal corticosteroids between 7 and 14		Most studies consistent and inconsistency can be explained			
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	С	Some inconsistency, reflecting genuine uncertainty around question			
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.		Evidence is not consistent			
		Not applicable (one study only)			
3. Clinical impact (indicate if the study results varied according to some unknow intervention could not be determined)	vn factor	(not simply study quality or sample size) and thus the clinical impact of the			
Maternal There are no direct health benefits for the mother, and there do not appear to be any detrimental effects.	А	Very large			
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).	В	Substantial			
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	С	Moderate			
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.	D	Slight / Restricted			

4. Generalisability (how well does the	body of eviden	ice match the popula	ition an	d clinica	settings being targeted by the guideline?)		
Evidence is generalisable. All studies			1.	А	Evidence directly generalisable to target population		
(2011) systematic review were condu risk of preterm birth (variously defin	ed by the tr	rial authors)		В	Evidence directly generalisable to target population with some		
following an initial course of antenatal corticosteroids, in a variety of countries and healthcare settings.			С	caveats Evidence not directly generalisable to target population but could			
0				D	be sensibly applied Evidence not directly generalisable to target population and hard		
					to judge whether sensible to apply		
				ian heali	heare context in terms of health services / delivery of care and cultural factors?)		
Evidence is applicable to the New Z care settings	ealand and	Australian health	1	А	Evidence directly applicable to New Zealand / Australian healthcare context		
0				В	Evidence applicable to New Zealand / Australian healthcare context with few caveats		
				С	Evidence probably applicable to New Zealand / Australian		
					healthcare context with some caveats Evidence not applicable to New Zealand / Australian healthcare		
				D	context		
upgrade the recommendation)				-	he evidence base (for example, issues that might cause the group to downgrade or besis of the evidence relating to the key question, taking all the above factors into		
account)	(****** [<i>F</i> • 9			
Component	Rating	Description					
1. Evidence base	А	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk bias					
2. Consistency	А	All studies con	isistent	-			
3. Clinical Impact	В	Substantial					
4. Generalisability	А	Evidence direc	etly gen	neralisal	ble to target population		
5. Applicability	А	Evidence direc	tly app	olicable	to New Zealand / Australian healthcare context		
Evidence statement: More benefits : between 7 and up to 14 days.	are observe	d when the interv	val bet	ween th	the single course of antenatal corticosteroids and the repeat course is		
RECOMMENDATION (What rec	ommendation	(s) does the		(OVERALL GRADE OF RECOMMENDATION		
guideline development group draw from this statements where possible) EITHER	evidence? Us	e action	А	Body	of evidence can be trusted to guide practice		
Use a single repeat dose of repeat a corticosteroids if preterm has not oc days and less than fourteen days follo and preterm birth is still expected wi	curred seve owing a sing	gle course	В	Body of evidence can be trusted to guide practice in most situations			
days. If the woman has not given birth aft is still considered to be at risk of pre next seven days, a further repeat dos	term birth v		С	Body of evidence provides some support for recommendations(s) but care should be taken in its application			
betamethasone can be administered. OR			D	Body of evidence is weak and recommendation must be applied with caution			
Use a single repeat course of repeat corticosteroids if preterm birth has r more days and less than fourteen day course and preterm birth is still expe seven days. Do not give further repe	not occurred ys following cted within	g a single	рр	Practi	ice Point		
RECOMMENDATION (What rec				(OVERALL GRADE OF RECOMMENDATION		
guideline development group draw from this statements where possible)	eviaence? Us	se action	А	Body	of evidence can be trusted to guide practice		
Use up to a maximum of three single	e repeat dos	ses.	В	Body	of evidence can be trusted to guide practice in most situations		
If using a single repeat dose, use of a			С		of evidence provides some support for recommendations(s) but		
up to a maximum of three single rep evaluated after seven or more days a			D		hould be taken in its application of evidence is weak and recommendation must be applied with		
from administration of a previous re clinical decision to use a repeat dose			PP	cautio Pract	on ice 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
	<u>NO</u>
Will the implementation of this recommendation require changes in the way care is currently	YES
organised?	<u>NO</u>
Are the guideline development group aware of any barriers to implementation of this	YES
recommendation?	NO

M9 GRADE Evidence summary

What is the optimal timing between a first cours	e of antena	atal cortico	steroids ar	nd initiatin	g a repeat do	se(s)?	
1. Outcome measures:		Quality o	f evidence			nportance of or n making a de	
Matemal Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
D ₁ Chorioamnionitis	1			20 11	1		Important
D ₂ Puerperal sepsis	1						
D ₃ Pyrexia after entry to trial				NR	•	4	
D4 Intrapartum fever requiring antibiotics				NR			
D5 Post natal pyrexia				NR		4	
De Maternal quality of life						√	
A •		MOD	LOW	NR V.		T	Not
Infant Outcomes	HIGH	MOD	LOW	LOW	Critical	Important	Important
D1 Combined fetal and neonatal death		1			1		
D2 Neonatal death		1			~		
O3 Fetal death			1		1		
D4 RDS	1				1		
D ₅ Composite of serious outcomes	1				·		
for the infant D6 Neurosensory disability (composite of	•				•		
mpairments) for infant as a child		1			1		
D ₇ Survival free of neurosensory disability for the nfant as a child		1			1		
O ₈ Survival free of metabolic disease for the infant				NR		,	
as a child D9 Neurosensory disability (composite of						4	
mpairments) for infant as an adult				NR	1		
O_{10} Survival free of neurosensory disability for the nfant as an adult				NR	1		
O ₁₁ Survival free of metabolic disease for the				NR			
nfant as an adult 2. Is there is insufficient evidence to ma	ke a recorr	mendation	n?			4	
Maternal - The evidence for maternal outcomes follow repeat antenatal corticosteoids is based on four rande Evidence for maternal outcomes following exposure based on two randomised trials included in the Crow Infant - The evidence for infant outcomes following of dose(s) is based on six randomised trials included in outcomes following exposure to repeat antenatal cor randomised trials included in the Crowther (2011) re 3. What benefit will the proposed intervent	omised trial to repeat a yther (2011) exposure to the Crowth ticosteroids view involv	s included i ntenatal con review invo repeat ante er (2011) sy more than ing 2993 in	in the Crow rticosteroids olving 2290 enatal cortico ystematic rev 14 days bet	ther (2011) s more than women. osteroids fre view involvi	systematic rev 14 days betwe om 7 to 14 day ing up to 2871	iew involving up een single and re ys between singl infants. Eviden	to 1971 wome peat doses(s) is e and repeat ce for infant
Evidence statement							y of evidence
<i>Maternal</i> - No differences were seen in risk of chorid intenatal corticosteroids between 7 and 14 days, or r							HIGH
antenatal corticosteroids between 7 and 14 days, or more than 14 days from the single course compared with those with no repeat treatment. <i>Infant</i> - 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 between 4 and 16 days from 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.							
in a composite of serious infant outcomes when con- days or more from a single course had no effect on compared with no repeat exposure, however subgro effect between timing intervals. There was no ev	the incident up interaction ridence of	on test was increased r	risk of neu	rosensory c	lisability at ea	rly	
n a composite of serious infant outcomes when con- lays or more from a single course had no effect on compared with no repeat exposure, however subgro- ffect between timing intervals. There was no ev- hildhood follow up when the interval was between udging the benefits in context The evidence is based on a number of well conducted nvolving a large number of women who remained a	the inciden- up interacti- idence of 7 and 14 da d randomis t risk of pre	on test was increased r ys or greate ed controlle eterm birth	risk of neu er than 14 de ed trials, und	rosensory d ays from the dertaken in	lisability at ea e single course a variety of co	untries and heal	
n a composite of serious infant outcomes when con- lays or more from a single course had no effect on compared with no repeat exposure, however subgro- effect between timing intervals. There was no ev- childhood follow up when the interval was between fudging the benefits in context The evidence is based on a number of well conducted nvolving a large number of women who remained a 4. What harm might the proposed interv	the inciden- up interacti- idence of 7 and 14 da d randomis t risk of pre	on test was increased r ys or greate ed controlle eterm birth	risk of neu er than 14 de ed trials, und	rosensory d ays from the dertaken in	lisability at ea e single course a variety of co	rly untries and heal l corticosteroids	
n a composite of serious infant outcomes when con- lays or more from a single course had no effect on compared with no repeat exposure, however subgro- effect between timing intervals. There was no ev- childhood follow up when the interval was between fudging the benefits in context The evidence is based on a number of well conducted nvolving a large number of women who remained a	the inciden- up interacti idence of 7 and 14 da d randomis t risk of pre- rention/ac	on test was increased r ys or greate ed controlle term birth i tion do?	isk of neu er than 14 d ed trials, un following ar	rosensory d ays from the dertaken in	lisability at ea e single course a variety of co	rly untries and heal l corticosteroids	

	epeat antenatal corticosteroid was more than 14 da birthweight z scores. The clinical impact of this, if a		HIGH
udging the harms in context			
	mother. There do not appear to be any direct health		
	ed birthweight is unclear. There was no increase in		
	antenatal corticosteroids and the repeat dose(s) is b	etween / and up to	14 days.
5. What is the likely balance betwee	en good and harm?		
Evidence statement			Overall
Maternal - There is no evidence of harm to the n	mother. There do not appear to be any direct health	n benefits for the	quality of evidence
mother.			
5 0 1	y distress seen for infants exposed to a repeat dos	. /	HIGH
corticosteroids, at intervals of between 7 and 1			
	ween 7 and 14 days, outweighs the potential h	arm of reduced	HIGH
birthweight, and birthweight z scores. Judging the balance of benefits and harms i	in contact		
	e mother is minimal, and the impact is low. There c	o not appear to be	any detrimental effects for
the mother.	e mother is minimal, and the impact is low. There c	io not appear to be	any definitental effects for
	fant is high, and the impact is high for those infants	remaining at risk (of preterm birth following a
nitial single course.	tant is high, and the impact is high for those infant.	remaining at now	or preterini birtir tono wing 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	Consider against/malso no recommendation		CONDITIONAL
Harms probably outweigh benefits	Consider against/make no recommendation	1	CONDITIONAL
Benefits clearly don't outweigh harms	Recommend against		STRONG
Harms clearly outweigh benefits	Recommend against		SIKONG
6. Is the intervention/action implemented by the intervention of the second sec	mentable in the New Zealand and Australian c	ontext?	
Summary statement			
Antenatal corticosteroids are already widely in u	use in New Zealand and Australia.		
Yes	<u>Recommend/conside</u>	er in the second se	
Not known	Consider economic eva		
No	Recommend/consider	against	
7. Final recommendation			
		Strength of ree	commendation
EITHER			
Use a single repeat dose of repeat antenatal co	orticosteroids if preterm has not occurred seven		
or more days and less than fourteen days follow	ving 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		
	her repeat dose of 12 mg betamethasone can be	STRONG	
administered.	1 0	CONDITION	AL.
		WEAK	
OB		WEAK	
OR	corrigostaroids if pratarm birth has not occurred	WEAK	
<u>Use a single repeat course of repeat antenatal</u>	corticosteroids if preterm birth has not occurred	WEAK	
<u>Use a single repeat course</u> of repeat antenatal seven or more days and less than fourteen days	following a single course and preterm birth is	WEAK	
<u>Use a single repeat course</u> of repeat antenatal seven or more days and less than fourteen days	following a single course and preterm birth is	WEAK	
<u>Use a single repeat course</u> of repeat antenatal seven or more days and less than fourteen days	following a single course and preterm birth is	WEAK	
<u>Use a single repeat course</u> of repeat antenatal seven or more days and less than fourteen days	following a single course and preterm birth is	WEAK	
<u>Use a single repeat course</u> of repeat antenatal seven or more days and less than fourteen days still expected within the next seven days. Do no	following a single course and preterm birth is of give further repeat courses.		
Use a single repeat course of repeat antenatal seven or more days and less than fourteen days still expected within the next seven days. Do no Use up to a maximum of three single repeat do	following a single course and preterm birth is of give further repeat courses. ses.	STRONG	TAT
<u>Use a single repeat course</u> of repeat antenatal seven or more days and less than fourteen days till expected within the next seven days. Do no Use up to a maximum of three single repeat dow if using a single repeat dose, use of a further rep	following a single course and preterm birth is of give further repeat courses. ses. peat dose, up to a maximum of three single	STRONG CONDITION	
Use a single repeat course of repeat antenatal seven or more days and less than fourteen days still expected within the next seven days. Do not Use up to a maximum of three single repeat dow of using a single repeat dose, use of a further rep repeat doses, should be re-evaluated after seven	following a single course and preterm birth is of give further repeat courses. ses. peat dose, up to a maximum of three single or more days and less than 14 days from	STRONG	
<u>Use a single repeat course</u> of repeat antenatal seven or more days and less than fourteen days still expected within the next seven days. Do not Use up to a maximum of three single repeat dow if using a single repeat dose, use of a further rep repeat doses, should be re-evaluated after seven idministration of a previous repeat course. The	following a single course and preterm birth is of give further repeat courses. ses. peat dose, up to a maximum of three single or more days and less than 14 days from e clinical decision to use a repeat dose should be	STRONG CONDITION	
<u>Use a single repeat course</u> of repeat antenatal seven or more days and less than fourteen days still expected within the next seven days. Do no Use up to a maximum of three single repeat do If using a single repeat dose, use of a further re repeat doses, should be re-evaluated after seven	following a single course and preterm birth is of give further repeat courses. ses. peat dose, up to a maximum of three single or more days and less than 14 days from e clinical decision to use a repeat dose should be	STRONG CONDITION	
<u>Use a single repeat course</u> of repeat antenatal seven or more days and less than fourteen days still expected within the next seven days. Do no Use up to a maximum of three single repeat dow If using a single repeat dose, use of a further rep repeat doses, should be re-evaluated after seven administration of a previous repeat course. The based on an assessment of ongoing risk for pre-	following a single course and preterm birth is of give further repeat courses. ses. peat dose, up to a maximum of three single a or more days and less than 14 days from clinical decision to use a repeat dose should be term birth.	STRONG CONDITION	
Use a single repeat course of repeat antenatal seven or more days and less than fourteen days still expected within the next seven days. Do no Use up to a maximum of three single repeat dow If using a single repeat dose, use of a further rep repeat doses, should be re-evaluated after seven udministration of a previous repeat course. The based on an assessment of ongoing risk for pree Where appropriate, estimate the risk of preterm	following a single course and preterm birth is of give further repeat courses. ses. peat dose, up to a maximum of three single a or more days and less than 14 days from clinical decision to use a repeat dose should be term birth. a birth by considering the use of adjunct	STRONG CONDITION	
<u>Jse a single repeat course</u> of repeat antenatal even or more days and less than fourteen days till expected within the next seven days. Do no Jse up to a maximum of three single repeat doo f using a single repeat dose, use of a further rep epeat doses, should be re-evaluated after seven idministration of a previous repeat course. The pased on an assessment of ongoing risk for pre-	following a single course and preterm birth is of give further repeat courses. ses. peat dose, up to a maximum of three single a or more days and less than 14 days from clinical decision to use a repeat dose should be term birth. a birth by considering the use of adjunct	STRONG CONDITION	

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.		One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias		
		One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias		
Infant When gestational age at trial entry was \leq 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 \leq 34 weeks' and 6 days was reported in sixteen trials and 2 trials reported gestational age at trial entry of >34 weeks'.		One or two Level III studies with a low risk of bias or Level I or II studies with moderate risk of bias		
		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 ap	plicable')		
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 by wore not significant.	А	All studies consistent		
	В	Most studies consistent and inconsistency can be explained		
treatment effect, but were not significant. Infant Evidence is consistent that the risk of perinatal death, neonatal	С	Some inconsistency, reflecting genuine uncertainty around question		
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	D	Evidence is not consistent		
Solution to exposite when gestational age at that entry was \leq 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 (one study only)		
3. Clinical impact (indicate if the study results varied according to some unkno intervention could not be determined)	wn factor	r (not simply study quality or sample size) and thus the clinical impact of the		
Maternal The risk of maternal infection is not increased when a single course of antenatal corticosteroids is administered at \leq 34 weeks' and 6 days	А	Very large		
gestation. The significant benefits to the infant outweigh any risk of maternal infection.	В	Substantial		
Infant The evidence for reductions in risk of perinatal death, neonatal death and respiratory distress syndrome when gestational age at trial	С	Moderate		
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.	D	Slight / Restricted		
4. Generalisability (how well does the body of evidence match the population and	ıd clinica	l settings being targeted by the guideline?)		
Evidence from a variety of healthcare settings. Studies conducted in USA, France, Australia, and The Netherlands.	А	Evidence directly generalisable to target population		
	В	Evidence directly generalisable to target population with some caveats		
	С	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 / Austra	lian heal	theare 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.	А	Evidence directly applicable to New Zealand / Australian healthcare context
	В	Evidence applicable to New Zealand / Australian healthcare context with few caveats
	С	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 \leq 34 weeks' and 6 days. No trials reported data for maternal infection when gestation at trial entry was \geq 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 \geq 34 weeks'. No data was identified on the use of antenatal corticosteroids <24 weeks' gestation.

RECOMMENDATION (W hat recommendation(s) does the guideline development		OVERALL GRADE OF RECOMMENDATION			
group draw from this evidence? Use action statements where possible)	А	Body of evidence can be trusted to guide practice			
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.	В	Body of evidence can be trusted to guide practice in most situations			
	С	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			
	РР	Practice Point			
RECOMMENDATION (W hat recommendation(s) does the guideline development	OVERALL GRADE OF RECOMMENDATION				
group draw from this evidence? Use action statements	А	Body of evidence can be trusted to guide practice			
where possible)	В	Body of evidence can be trusted to guide practice in most situations			
If considering use of antenatal corticosteroids prior to 24 weeks' gestation, there should be	С	Body of evidence provides some support for recommendations(s) but care should be taken in its application			
careful consideration of benefit and risks with parental consultation.	D	Body of evidence is weak and recommendation must be applied with caution			
parentai consultation.	РР	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
	<u>N0</u>
Will the implementation of this recommendation require changes in the way care is currently	YES
organised?	<u>N0</u>
Are the guideline development group aware of any barriers to implementation of this	YES Educational requirement to change
recommendation?	practice if required
	NO

M10 GRADE Evidence summary

At what gestational age is a single course of antenata	l corticost	eroids effe	ctive?				
1. Outcome measures:			f evidence		-	ortance of out making a deci	
Maternal Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
D ₁ Chorioamnionitis	4				1		-
D ₂ Puerperal sepsis		1			4		
D ₃ Pyrexia after entry to trial		1				4	
O4 Intrapartum fever requiring antibiotics		1				1	
D ₅ Post natal pyrexia	4						
D ₆ Maternal quality of life	•			NR	4	•	
Infant Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Importar
D ₁ Combined fetal and neonatal death				LOW			Importai
D2 Neonatal death		√			✓		
D ₃ Fetal death		1			1		
D4 RDS			1		1		
O ₅ Composite of serious outcomes		*			1		
for the infant				NR	1		
O6 Neurosensory disability (composite of impairments) for infant as a child O7 Survival free of neurosensory disability for the				NR	1		
nfant as a child				NR	4		
O8 Survival free of metabolic disease for the infant as a child				NR		4	
Dy Neurosensory disability (composite of impairments) for infant as an adult D ₁₀ Survival free of neurosensory disability for the				NR	4		
nfant as an adult				NR	*		
O ₁₁ Survival free of metabolic disease for the infant as				NR		4	
Evidence statement - The evidence is based on a sub- selected are not mutually exclusive. Clinical recomm <i>Maternal</i> - No trials included in the Roberts CPG version is andomised women with a gestational age at trial entry > 3 was ≤ 34 weeks' and 6 days, ten trials reported on chorioa entry, one trial reported on intrapartum pyrexia, and three <i>Infant</i> - When gestational age at trial entry was ≤ 34 weeks' review for a single course of antenatal corticosteroids rep- reported on fetal death. One trial reported data for neona that recruited and randomised women with a gestation at For respiratory distress syndrome, gestational age at trial entry ≤ 34 weeks'.	endations 2015 system 34 weeks' re- mnionitis, s- e trials repo- and 6 days orted on pe- tal death in trial entry of entry of ≤ 3	cannot be natic review eported on six trials rep rted on por s, seven of t rinatal deat infants wh of >34 weel 4 weeks' an	made. v for a single maternal in ported on pre- tinatal pyres he 26 trials h, thirteen o had a ges ss' reported	e course of a fection outc uerperal sep xia requiring included in trials reporte tational age l on perinata	intenatal corti omes. When § treatment. the Roberts C ed on neonata >34 weeks' at l or fetal deat	costeroids that is gestational age a reported on pyr PG version 201 I death, and seve time of trial en h.	recruited and t trial entry exia after tria 5 systematic en trials try. No trials
3. What benefit will the proposed interventio		lave:				0 11	
Evidence statement Maternal - There is no increased risk of maternal infection weeks' and 6 days. The treatment effects for chorioan intrapartum pyrexia tended toward increased risk when significant. Infant - The risk of perinatal death, neonatal death and following exposure to a single course of antenatal cortico at trial entry was \leq 34 weeks' and 6 days. There was no di risk of neonatal death or respiratory distress syndrome wh	nnionitis, p compared respiratory steroids con fference in	to the over distress sy mpared wit risk of fetz	psis, pyrex rall treatme ndrome we h no exposi l death. Th	ia after tria ent effect, b ere significar ure when ge ere was no o	l entry, and ut were not ntly reduced stational age difference in	Quality of Not apj	
Judging the benefits in context The evidence is based overall on well designed and condu women at risk of preterm birth. The populations were dr 4. What harm might the proposed intervention	icted rando awn from a	mised cont a range of h	rolled trials	investigating	g the use of at	ntenatal corticos	teroids in
Evidence statement	,					Quality of ev	idence
Maternal - The risk of maternal infection is not increased values administered at \leq 34 weeks' and 6 days gestation. The sign						Quanty of ev Not apj	

Infant - There is no evidence of harm to the infant. There is evidence for reductions in a number of important

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 \leq 34 weeks' and 6 days.					
Judging the harms in context <i>Maternal</i> - The evidence is direct evidence from trials that recruited and randomised women at risk of preterm birth. <i>Infant</i> - 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 go	ood and harm?				
Evidence statementMaternal - 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'.Overall quality of evide Not applicableInfant - 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'.Not applicable					
Judging the balance of benefits and harms in co Maternal - The benefits to the infant are significant w Infant - The benefits to the infant are significant with	vith no obvious healt				
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				CONDITIONAL	
Harms probably outweigh benefits	Consider against/make no recommendation			CONDITIONAL	
Benefits clearly don't outweigh harms				STRONG	
Harms clearly outweigh benefits	Recommend agair	ISt		STRONG	
6. Is the intervention/action implement	able in the New Ze	ealand context?			
Summary statement Antenatal corticosteroids are already widely in use in	New Zealand and A	Instralia			
Yes		Recommend/conside	<u>r</u>		
Not known		Consider economic eval	uation		
No		Recommend/consider a	igainst		
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 paren		,			
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 in	cluded stu	(dies)		
Maternal Three trials included in the Crowther (2011) Cochrane systematic review randomised women up to a gestational age at trial entry of \leq 31 weeks' and 6 days. Three trials randomised women up to \leq 32 weeks' and 6 days gestation at trial entry, and one trial randomised women up to \leq 33 weeks' and 6 days at trial entry.		One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias		
		One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias		
Infant Three trials included in the Crowther (2011) Cochrane systematic review reported outcomes in infants exposed to repeat doses(s) of antenatal corticosteroids at \leq 31 weeks' and 6 days gestation at trial entry, four trials reported outcomes in infants exposed to repeat doses(s) of antenatal corticosteroids at \leq 32 weeks' and 6 days gestation at trial entry, two trials reported outcomes in infants exposed to repeat doses(s) of antenatal corticosteroids at \leq 33 weeks' and 6 days gestation at trial entry.		One or two Level III studies with a low risk of bias or Level I or II studies with moderate risk of bias		
		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 af	plicable')			
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 \leq 31 weeks' and 6 days or \leq 32 weeks' and 6 days. No data were		All studies consistent		
reported for \leq 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 \leq 31 weeks' and 6 days, \leq 32 weeks' and 6 days or \leq 33 weeks' and 6 days.	В	Most studies consistent and inconsistency can be explained		
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'	С	Some inconsistency, reflecting genuine uncertainty around question		
	D	Evidence is not consistent		
gestational age at that entry was ≤ 51 weeks and 6 day, ≤ 52 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.		Not applicable (one study only)		
3. Clinical impact (<i>indicate if the study results varied according to some unkno</i> <i>intervention could not be determined</i>)	wn factor	(not simply study quality or sample size) and thus the clinical impact of the		
Maternal 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.	А	Very large		
Infant Data for perinatal death following exposure to repeat antenatal corticosteroids at ≤33 weeks' and 6 days is imprecise with wide	В	Substantial		
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 coduced eich. Birthweicht was reduced in all these costational age	С	Moderate		
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.		Slight / Restricted		

4. Generalisability (how a	well does the bo	dy of evidence match the	population	and clinica	l settings being targel	ted by the guideline?)		
Evidence from a variety o USA, France, Australia, a			lucted in	А		tly generalisable to target population		
			В	caveats	tly generalisable to target population with some			
			С	Evidence not directly generalisable to target population but coul be sensibly applied				
				D	Evidence not d to judge wheth	irectly generalisable to target population and hard er sensible to apply		
5. Applicability (is the bod	dy of evidence re	levant to the New Zeala	nd Ausi	tralian heal		ns of health services / delivery of care and cultural factors?)		
Corticosteroids are readily and their use is feasible.	y available in	Australia and New Z	Cealand	А	Evidence direc healthcare cont	tly applicable to New Zealand / Australian		
				В		cable to New Zealand / Australian healthcare		
				С	Evidence prob	ably applicable to New Zealand / Australian text with some caveats		
				D		applicable to New Zealand / Australian healthcare		
	re any other fact	ors that you took into ac	count when	ı assessing t	the evidence base (for	example, issues that might cause the group to downgrade or		
				ubgroup	s cannot be exp	lored as the groups selected are not mutually		
exclusive. Clinical reco								
EVIDENCE STATEM account)	IENT MATI	RIX (summarise the der	velopment g	roup's synth	hesis of the evidence 1	elating to the key question, taking all the above factors into		
Component	Rating	Description						
1. Evidence base	NA	Not applicable	lot applicable					
2. Consistency	NA	Not applicable						
3. Clinical Impact	NA	Not applicable	Not applicable					
4. Generalisability	NA	Not applicable						
5. Applicability	NA	Not applicable	plicable					
Evidence statement Repeat exposure to antenatal corticosteroids does not appear to increase the risk of infection for the mother, while affording significant benefit for the infant in terms of reduced risk of mortality and respiratory distress syndrome.						or the mother, while affording significant benefits		
RECOMMENDATION guideline development group d				C	OVERALL GRA	DE OF RECOMMENDATION		
statements where possible)	A Body of evidence can be trusted to guide practice			trusted to guide practice				
Use repeat antenatal corti preterm birth (<32 weeks Chapter 10 of these Clinic	s' and 6 days §	gestation). Refer to	B Body of evidence can be trusted to guide practice in most situations			trusted to guide practice in most situations		
Chapter 10 of these Chin		Juidennes.	С	C Body of evidence provides some support for recommendations(s) but should be taken in its application				
				f evidence is weal	k and recommendation must be applied with			
PP Practice Point								
UNRESOLVED ISSUI	ES (If needed.)	keep a note of specific iss	ues that ar	ise when eau	ch recommendation is	s formulated and that require follow up)		
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			
,	and any resource any account was implementing this recommendation:					NO		
Will the implementation of	Will the implementation of this recommendation require changes in the way care is currently				are is currently	YES		
organised?		-				NO		
Are the guideline develop recommendation?	oment group a	aware of any barriers	to imple	mentation	of this	YES Education may be required to facilitate change if required		
recommendation:					NO			

M11 GRADE Evidence summary

Matemal Outcomes HIGH MOD LOW V. LOW Critical Important Important 01 Chorioannionitis / / / / / / / 02 Puerperal sepsis / / / / / / / / 03 Pyrexia after entry to trial /	At what gestational age is a repeat dose(s) of antenatal corticosteroids effective? 1. Outcome measures: Quality of evidence							
O1 Chorioamnionitis Image: Constraint of the second se	Matemal Outcomes	HIGH	MOD	LOW		Critical Important		Not Importan
O2 Puerperal sepsis NR	O1 Chorioamnionitis	1			20 11	1		Importan
O4 Intrapartum fever requiring antibiotics NR Image: Constraint of the second sec	O2 Puerperal sepsis							
O4 Intrapartum fever requiring antibiotics NR ✓ NR ✓ O5 Post natal pyrexia ✓ ✓ ✓ ✓ ✓ O6 Maternal quality of life NR ✓ ✓ ✓ ✓ Infant Outcomes HIGH MOD LOW V. LOW Critical Important	O ₃ Pyrexia after entry to trial				NR		1	
O5 Post natal pyrexia	O4 Intrapartum fever requiring antibiotics				NR			
O6 Maternal quality of life NR Important Impo	O5 Post natal pyrexia		1					
Infant Outcomes HIGH MOD LOW V. LOW Critical Important Important O1 Combined fetal and neonatal death / / / / / / O2 Neonatal death / / / / / / / O3 Fetal death / / / / / / / / O3 Fetal death / / / / / / / / / / O4 RDS / <td>O6 Maternal quality of life</td> <td></td> <td></td> <td></td> <td>NR</td> <td>1</td> <td></td> <td></td>	O6 Maternal quality of life				NR	1		
O2 Neonatal death ✓ ✓ ✓ ✓ O3 Fetal death ✓ ✓ ✓ ✓ O4 RDS ✓ ✓ ✓ ✓ O5 Composite of serious outcomes for the infant ✓ ✓ ✓ ✓ O5 Composite of serious outcomes for the infant ✓ ✓ ✓ ✓ O6 Neurosensory disability (composite of impairments) for infant as a child NR ✓ ✓ O7 Survival free of neurosensory disability for the infant as a child NR ✓ ✓ O8 Survival free of metabolic disease for the infant as a child NR ✓ ✓ O9 Neurosensory disability (composite of impairments) for infant as an adult NR ✓ ✓ O9 Neurosensory disability (composite of impairments) for infant as an adult NR ✓ ✓	Infant Outcomes	HIGH	MOD	LOW			Important	Not Importan
O3 Fetal death Y Y Y O4 RDS Y Y Y O5 Composite of serious outcomes for the infant Y Y Y O5 Composite of serious outcomes for the infant Y Y Y O6 Neurosensory disability (composite of impairments) for infant as a child NR Y Y O7 Survival free of neurosensory disability for the infant as a child NR Y Y O8 Survival free of metabolic disease for the infant as a child NR Y Y O9 Neurosensory disability (composite of impairments) for infant as an adult NR Y Y	O1 Combined fetal and neonatal death	*				1		
O4 RDS ✓ ✓ ✓ O5 Composite of serious outcomes for the infant ✓ ✓ ✓ O6 Neurosensory disability (composite of impairments) for infant as a child ✓ ✓ ✓ O7 Survival free of neurosensory disability for the infant as a child NR ✓ ✓ O8 Survival free of metabolic disease for the infant as a child NR ✓ ✓ O9 Neurosensory disability (composite of impairments) for infant as an adult NR ✓ ✓	O2 Neonatal death	4				4		
O5 Composite of serious outcomes ✓ ✓ ✓ for the infant ✓ ✓ ✓ O6 Neurosensory disability (composite of impairments) ✓ ✓ ✓ for infant as a child NR ✓ ✓ O7 Survival free of neurosensory disability for the NR ✓ ✓ O8 Survival free of metabolic disease for the infant as a child NR ✓ ✓ O9 Neurosensory disability (composite of impairments) NR ✓ ✓ O9 Neurosensory disability (composite of impairments) NR ✓ ✓ O10 Survival free of neurosensory disability for the NR ✓ ✓	O3 Fetal death					4		
O5 Composite of serious outcomes for the infant Image: Composite of serious outcomes for the infant O6 Neurosensory disability (composite of impairments) for infant as a child NR O7 Survival free of neurosensory disability for the infant as a child NR O8 Survival free of metabolic disease for the infant as a child NR O9 Neurosensory disability (composite of impairments) for infant as an adult NR	O4 RDS	1				4		
for infant as a child NR ✓ O7 Survival free of neurosensory disability for the infant as a child NR ✓ O8 Survival free of metabolic disease for the infant as a child NR ✓ O9 Neurosensory disability (composite of impairments) for infant as an adult NR ✓	for the infant	4				4		
infant as a child NR O8 Survival free of metabolic disease for the infant as a child NR O9 Neurosensory disability (composite of impairments) for infant as an adult NR O10 Survival free of neurosensory disability for the NR	for infant as a child				NR	*		
child NR ✓ O9 Neurosensory disability (composite of impairments) for infant as an adult NR ✓ O10 Survival free of neurosensory disability for the NR ✓					NR	+		
for infant as an adult NR O ₁₀ Survival free of neurosensory disability for the NR					NR		+	
	for infant as an adult				NR	4		
	infant as an adult				NR	1		
O ₁₁ Survival free of metabolic disease for the infant as an adult 2. Is there is insufficient evidence to make a recommendation?	an adult				NR		*	

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 \leq 31 weeks' and 6 days is based on 3 trials involving 1486 women, and gestational age at trial entry of \leq 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 \leq 33 weeks' and 6 days. The evidence for puerperal sepsis in women treated with repeat antenatal corticosteroids when gestational age at trial entry was \leq 31 weeks' and 6 days is based on 2 trials involving 504 women, gestational age at trial entry was \leq 31 weeks' and 6 days is based on 2 trials involving 504 women, gestational age at trial entry of \leq 32 weeks' and 6 days is based on 2 trials involving 2388 women, and gestational age at trial entry of \leq 33 weeks' and 6 days is based on 0 trial involving 249 women. One trial that randomised 972 women at \leq 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 \leq 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 \leq 31 weeks' and 6 days gestation at trial entry. Evidence for outcomes at \leq 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 \leq 32 weeks' and 6 days gestational age at trial entry. Evidence for outcomes at \leq 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 \leq 33 weeks' and 6 days gestation at trial entry.

255 weeks and 0 days gestation at that entry.	
3. What benefit will the proposed intervention/action have?	
	0 11 6 11
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	Not applicable
repeat antenatal corticosteroids with the gestational age at trial entry was ≤ 31 weeks' and 6 days, ≤ 32 weeks' and 6	
days or \leq 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 \leq 31 weeks' and 6	
days, \leq 32 weeks' and 6 days and \leq 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 \leq 31 weeks'	
and 6 days and \leq 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	

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 \leq 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 corticosteroid								
from a variety of healthcare settings worldwide.	us and exposed to rep	cat antenatar correcostero	les of placebo. In	e populations were unawn				
4. What harm might the proposed intervention/action do?								
	,							
Evidence statement			1. 6 .	Quality of evidence				
Maternal - There is no evidence of health harms for t Infant - There was evidence of reduced birthweight i				Not applicable				
repeat antenatal corticosteroids compared with no r		age at that entry categoin	es tonowing	Not applicable				
Judging the harms in context	epear exposure.			l				
Maternal - There was no evidence of harm to the mo	other.							
Infant - The clinical significance of reduced birthweig		re to repeat antenatal corti	costeroids is uncle	ear. Only two trials adjusted				
birthweight for gestational age using z scores, and th								
5. What is the likely balance between ge								
Evidence statement				Overall				
Maternal - The evidence suggests no increased risk o	f harm to the mother			quality of evidence				
Infant - The evidence for significant reductions in ri			and a composite	1				
of serious infant outcomes for infants exposed to				Not applicable				
infant. This outweighs the potential for reduced birt		significant of which is not	yet clear.					
Judging the balance of benefits and harms in co								
Maternal - There do not appear to be increased risk of								
Clinical Practice Guidelines. Although the evidence								
<i>Infant</i> - The benefits to the infant are significant, and HIGH it is indirect and a STRONG recommend			thweight. Althou	gn the evidence is ranked				
Benefits clearly outweigh harms	it is indirect and a STRONG recommendation cannot be made. clearly outweigh harms Recommend STRONG							
Benefits probably outweigh harms	Consider	CONDITIONAL						
Not known	Make a recomme	endation for research (se	ee 8 below)	<u>WEAK</u>				
Benefits probably don't outweigh harms	Consider assignt/	maka na maammaadatian		CONDITIONAL				
Harms probably outweigh benefits	Consider against/1	make no recommendation		CONDITIONAL				
Benefits clearly don't outweigh harms	D 1 .			CTR ON C				
Harms clearly outweigh benefits	Recommend again	STRONG						
6. Is the intervention/action implement	table in the New Ze	ealand context?						
Summary statement								
Antenatal corticosteroids are already widely in use in New Zealand and Australia. Yes Recommend/consider								
Yes								
Not known								
No Recommend/consider against								
7. Final recommendation								
Strength of 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. STRONG								
gestation. Refer to Grapter 10 or these Gillicar I fa	ence Outdennes.		WEAK (Practi					
8. Recommendations for research								
• Randomised trials are needed to investigate the effects of repeat antenatal corticosteroids in women \geq 32 weeks' and 6 days gestation.								

M12 Use of antenatal corticosteroids for women planning an elective caesarean section at term M12 NHMRC Evidence summary

1. Forkinger base (number of studies, level of machines and risk of bias in the included turbles) Maternal Not data or more larged 1 studies with a low risk of bias, or several Level II studies with a low risk of bias, or SR/several Level II studies with a low risk of bias, or SR/several Level II studies with a low risk of bias, or SR/several Level II studies with a low risk of bias, or SR/several Level II studies with a low risk of bias or Level I or through studies with a low risk of bias or Level I with studies with a low risk of bias or Level I with studies with a low risk of bias or Level I with studies with	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?							
No data on maternal outcomes was reported in the Sotiraidis (2007) A One or two Level II studies with a low risk of bias, or SR/several Level II studies with a low risk of bias, or SR/several Level II studies with a low risk of bias, or SR/several Level II studies with a low risk of bias, or SR/several Level II studies with a low risk of bias, or SR/several Level II studies with a low risk of bias, or SR/several Level II studies with a low risk of bias, or SR/several Level II studies with a low risk of bias, or SR/several Level II studies with a low risk of bias, or Level I or III studies with a low risk of bias, or Level I or III studies with a low risk of bias, or Level I or III studies with a low risk of bias, or Level I or III studies with a low risk of bias, or Level I or III studies with a low risk of bias. C Consistency (f) only one study rut available, rask this momented a low optimization of the studies with a low risk of bias. III studies with a low risk of bias. C Consistency (f) only one study rut available, rask this momented a low optimization of the studies consistent and inconsistency can be explained the studies in a low risk of bias. III studies consistent inconsistency can be explained the studies consistent and inconsistency can be explained the studies low rute as a significant discress in those exposed to anternate concess of perinstruk destribution of these as a significant discress in the source of perinstruk discress in the source of perinstruk discress in the source of perinstruk discress as low error burg and the studies consistent and inconsistency can be explained the source of perinstruk discress in the source of perinstruk discress in the control distruk the ways a significant discress in the control distruk the ways a significant discress in the control distruk the ways a significant discress in the control distruk the ways	1. Evidence base (number of studies, level of evidence and risk of bias in the included studies)							
Infant Infant The Solitable CPG version 2015 systematic review included one systematic review including one randomised controlled trial and one call including 423 women and 422 mfants, a follow-up report of that including 424 infants. C One or rev Level III studies with a low risk of bias or Level I or truthles with moderate risk of bias in both trials was unclear and there was no blinding of participants. Risk of bias in both trials was unclear and there was no blinding of participants. D Level III studies with moderate risk of bias. Constructory (if why on attay was analidable, much this component at wat apblicable? A All studies consistent. No data on matternal outcomes was reported in the Solitiadis (2PG version 2015. A All studies consistent. Infant Deve version cases of perinatal death in either group reported in the single cource of between sagnificant decrease in reportancy distress syndhome and respiratory distress in door exposed to a single cource of between sagnificant decrease in reportancy distress syndhome and respiratory distress reported in the work was asgedired decrease in door expiratory distress reported in the Solitable CPG were constant of the borning distress reported in the Solitable CPG were constant of the borning distress reported in the Solitable CPG were constant of the borning distress reported in the Solitable CPG were constant of the borning distres reported in the Solitable CPG were constant of the constant distress reported in the Solitable CPG were constant of the solitable CPG were constant of the constant decrease in the Solitable CPG were constast of the colitable mateer and wore review sa unchalemate diver	No data on maternal outcomes was reported in the Sotiriadis (2009)							
systematic review including one randomised controlled trial involving 43 sources 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 three was no blinding of participants 2. Consistency (f ush year andiable, nucl. this compound at inst applicable). 3. Consistency (f ush year andiable, nucl. this compound at inst applicable). 3. Consistency (f ush year andiable, nucl. this compound at inst applicable). 4. All studies consistent and inconsistency can be explained. There were no cases of permatal death in either group reported in the single rain lands (and net report on fead death, and there were no cases of permatal death in either group reported in the single rain lands (and net report on fead death, and there were no cases of permatal death. There was a subject review. The Ahmed (2014) raid data net report on fead death, and there were no cases of permatal death. There was a subject review. The bhere was a subject review as a significant review. The bhere was a subject review as a significant review. The bhere was a subject review as a significant review. The bhere was a subject review as a subject review as a significant review. The bhere was a subject review as a significant review. The bhere was a subject review as a underprovered to draw of differences in this outcome. Unclear if there are long term included in the Cochrane systematic review was underprovered to draw differences in this outcome. Unclear if there are long term included in a Cochrane systematic review. 4. Applicability (<i>in term</i> dub the thet of the trank the polation and there are	Infant	В						
Risk of bias in both trials was unclear and there was no bilinding of participants D Level IV studies or Level I to III studies/SRs with a high risk of bias 2. Consistency (if only one study was available, rank this component as 'not applicable') A AII studies consistent Naternal No data on maternal outcomes was reported in the SotiraidS CPG the single trial netuded in the SotiraidS (2009) systematic review. A AII studies consistent There were no cases of perinatal death in either group reported in the single trial netuded in the SotiraidS (2009) systematic review. B Most studies consistent C Some inconsistency, reflecting genuine uncertainty around question C Some inconsistency, reflecting genuine uncertainty around question D Evidence is not consistent D Evidence is not consistent Glow up (mediana gel 122 yers) for those born following resposed to attendentatione. However there was evidence that the children were low academic achievers reported in theoreting and also the demination. NA No data on maternal outcomes were reported in the SotiraidS CPG harmed A Very large B Substantial Infant C Moderate D Sight / Restricted Infant Event runs for respiratory distress were very low, and the trial included in the Cochrane systematic review was undeprovered to the demination A Evidence direcrly generalisable to target population were strian single	systematic review including one randomised controlled trial involving 943 women and 942 infants, a follow-up report of that	С						
2. Consistency (i) only one study must available, rank this component at inst applicable? Maternal No data on maternal outcomes was reported in the Sotinaids CPG to have been ocases of perinatal death in either group reported in the single trail ancluded in the Sotinaids (2009) systematic review. A All studies consistent There were no cases of perinatal death. in either group reported in the Sotinaids (2009) systematic review. B Most studies consistent and inconsistency can be explained The were no cases of neonatal death. There was a significant decrease in respiratory distress syndrome and respiratory distress in those exposure to a single course of beamethasona at term compared to controls who did not receive betamethasona. However there was evidence that the children were low academic achievers reported in only one trial Not applicable (one study only) Some inconsistent death. Not applicable (one study only) Not applicable (one study only) Not and an aternal outcomes were reported in the Sotinaids CPG were available in a cochrang to stream theorem future (not simply study quality or sample size) and thus the dialial impact of the intervention was underpowered to the cochrane systematic review was underpowered to a maternal outcomes. Unclear if there are long term in included in the Cohrane systematic review. No diarate included in the Cohrane systematic review. 4. Generalisability (now red) due to the by of cristme maternal outcomes in precise acces Asstartian and and was asstartiant and were zealish applicable. No applicable in target population with some caccess. B. Subtantia	Risk of bias in both trials was unclear and there was no blinding of	D	· · · · · · · · · · · · · · · · · · ·					
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detect differences in this outcome. Unclear if there are long term harms. D Slight / Restricted 4. Generalisability (how well does the body of eridence match the population and clinical settings being targeted by the guideline?) A Evidence from a single trial, conducted in the United Kingdom, included in a Cochrane systematic review. A Evidence directly generalisable to target population with some caveats B Evidence directly generalisable to target population with some caveats B 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 D Evidence ont directly generalisable to target population and hard to judge whether sensible to apply 5. Applicability (is the body of eridence relevant to the New Zealand / Australian bed/beare 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 applicable to New Zealand / Australian healthcare context with few caveats C Evidence not applicable to New Zealand / Australian healthcare context with some caveats Evidence applicable to New Zealand / Australian healthcare context with few caveats C Evidence applicable to New Zealand / Australian healthcare context with few caveats	Event rates for respiratory distress were very low, and the trial	С	Moderate					
Evidence from a single trial, conducted in the United Kingdom, A Evidence directly generalisable to target population included in a Cochrane systematic review. B Evidence directly generalisable to target population with some caveats C Evidence not directly generalisable to target population but could be sensibly applied D 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 ontext in terms of health services / delivery of care and cultural factors?) B Evidence ortext B Evidence context B Evidence ortext Evidence applicable to New Zealand / Australian healthcare context B Evidence applicable to New Zealand / Australian healthcare context B Evidence not applicable to New Zealand / Australian healthcare context B Evidence not applicable to New Zealand / Australian healthcare context B Evidence not applicable to New Zealand / Australian healthcare context with few caveats D Evidence not applicable to New Zealand / Australian healthcare context with few caveats D <td< td=""><td colspan="2">detect differences in this outcome. Unclear if there are long term</td><td>Slight / Restricted</td></td<>	detect differences in this outcome. Unclear if there are long term		Slight / Restricted					
included in a Cochrane systematic review. Image: Producte 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 but could be sensibly applied D Evidence not directly generalisable to target population but could be sensibly applied C 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 applicable to New Zealand / Australian healthcare context B Evidence probably applicable to New Zealand / Australian healthcare context with few caveats C Evidence context with few caveats C Evidence not applicable to New Zealand / Australian healthcare context D Evidence ont applicable to New Zealand / Australian healthcare context with few caveats D Evidence not applicable to New Zealand / Australian healthcare context D Evidence not applicable to New Zealand / Aust		nd clinical	settings being targeted by the guideline?)					
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 healtbcare 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 and their use of corticosteroids at term before elective caesarean section A Evidence directly applicable to New Zealand / Australian healthcare context New Zealand for use of corticosteroids at term before elective caesarean section C Evidence probably applicable to New Zealand / Australian healthcare context with few caveats B Evidence probably applicable to New Zealand / Australian healthcare context with few caveats C Evidence not applicable to New Zealand / Australian healthcare context with some caveats D Evidence not applicable to New Zealand / Australian healthcare context D Evidence not applicable to New Zealand / Australian healthcare context with some caveats D Evidence not applicable to New Zealand / Australian healthcare context New Zealand for use of inforces that you took into account when assessing the evidence not applicable to New Zealand / Au		А	Evidence directly generalisable to target population					
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 B C Evidence not applicable to New Zealand / Australian healthcare context with few caveats C Evidence applicable to New Zealand / Australian healthcare context with few caveats C Evidence not applicable to New Zealand / Australian healthcare context with few caveats D Evidence not applicable to New Zealand / Australian healthcare context D Evidence not applicable to New Zealand / Australian healthcare context D Evidence not applicable to New Zealand / Australian healthcare context D Evidence not applicable to New Zealand / Australian healthcare context D Evidence the reamy other factors that you took into account when assessing the evidence		В						
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 B Evidence applicable to New Zealand / Australian healthcare context C Evidence probably applicable to New Zealand / Australian healthcare context with few caveats C Evidence probably applicable to New Zealand / Australian healthcare context with few caveats D Evidence not applicable to New Zealand / Australian healthcare context with few caveats D Evidence not applicable to New Zealand / Australian healthcare context with few caveats D Evidence not applicable to New Zealand / Australian healthcare context D Evidence not applicable to New Zealand / Australian healthcare context D Evidence not applicable to New Zealand / Australian healthcare context D Evidence not applicable to New Zealand / Australian healthcare context D Evidence not applicable to New Zealand / Australian healthcare context <		С	Evidence not directly generalisable to target population but could					
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)		D	Evidence not directly generalisable to target population and hard					
and their use is feasible. Variations in practice across Australian and New Zealand for use of corticosteroids at term before elective caesarean section A 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	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?)							
caesarean section 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 with some caveats D Evidence not applicable to New Zealand / Australian healthcare context with some caveats D Evidence not applicable to New Zealand / Australian healthcare context D Evidence not applicable to New Zealand / Australian healthcare context Evidence is limited in volume and quality. Event rates are low and respiratory distress was not the primary outcome of one of the	and their use is feasible. Variations in practice across Australian and	А						
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		В						
D 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			healthcare context with some caveats					
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			context					
	upgrade the recommendation)	-						
children exposed to antenatal corticosteroids. A clinical recommendation cannot be made with the current lack of certainty	trials. Only one trial has reported on longer term childhood follo	w-up ar	d there is concern about lower academic achievement in					

I

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	В	All studies consistent
3. Clinical Impact	С	Moderate
4. Generalisability	D	Evidence directly generalisable to target population with some caveats
5. Applicability	С	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	OV	ERALL GRADE OF RECOMMENDATION				
development group draw from this evidence? Use action statements where	Α	Body of evidence can be trusted to guide practice				
possible)	В	Body of evidence can be trusted to guide practice in most situations				
For elective caesarean section at term, where possible, plan at \geq 39 weeks' gestation.	С	Body of evidence provides some support for recommendations(s) but care should be taken in its application				
Use antenatal corticosteroids 48 hours prior to caesarean birth planned beyond 34 weeks' and 6 days gestation if there is known	D	Body of evidence is weak and recommendation must be applied with caution				
fetal lung immaturity.	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				

	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	YES
organised?	NO
Are the guideline development group aware of any barriers to implementation of this	YES Giving steroids prior to caesarean
recommendation?	section is used around New Zealand and
	Australia
	NO

M12 GRADE Evidence summary

Considered J What are the benefits and harms for the mother, fetu	0	6			antenatal co	rticosteroids fo	r fetal lung
maturation to women planning an elective caesarean							Ũ
1. Outcome measures:		Quality o	f evidence			ortance of out making a deci	
Matemal Outcomes	HIGH MOD LOW V. LOW Critical			Important	Not Important		
O1 Chorioamnionitis				NR	1		
O2 Puerperal sepsis				NR	4		
O ₃ Pyrexia after entry to trial				NR			
O4 Intrapartum fever requiring antibiotics				NR		*	
O5 Post natal pyrexia				NR		*	
O6 Maternal quality of life				NR	4		
Infant Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Importan
O1 Combined fetal and neonatal death				NR	4		Importan
D ₂ Neonatal death				NR	1		
O3 Fetal death				NR	4		
O4 RDS		1					
O5 Composite of serious outcomes for the infant				NR	1		
O ₆ Neurosensory disability (composite of impairments) for infant as a child				NR	1		
O7 Survival free of neurosensory disability for the infant as a child				NR	4		
Os Survival free of metabolic disease for the infant as a child				NR		4	
O9 Neurosensory disability (composite of impairments) for infant as an adult				NR	4		
O ₁₀ Survival free of neurosensory disability for the infant as an adult				NR	1		
O11 Survival free of metabolic disease for the infant as				NR		4	
2. Is there is insufficient evidence to make a	recommen	ndation?				*	
Evidence statement - Evidence is limited in volume outcome of one of the trials. Only one trial has repor academic achievement in children exposed to antena lack of certainty Maternal - The one trial (Stutchfield, 2005) included in the (2014) trial did not report maternal outcomes. Infant - Infant mortality outcomes were not reported in ei distress syndrome was reported in Ahmed (2014) and Stu 3. What benefit will the proposed intervention	ted on long atal cortico e Sotiriadis (ther the Ah itchfield (20	ger term cl osteroids. A (2009) syste med (2014) 005) but ever	nildhood fo clinical re matic review trial, or the	ollow-up an ecommenda w did not re e Sotiriadis (d there is co ation cannot port maternal	ncern about lo be made with outcomes. The	wer the current Ahmed
Evidence statement						Quality of	evidence
<i>Maternal</i> - 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.						Not apj	plicable
<i>Infant</i> - 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 of	outcomes in	the Stutch	field (2005)	or Ahmed ((2014) trials.		
There was a significant reduction in transient tachypnoea and length of stay in neonatal intensive care for infants ex exposure following elective caesarean section at term.							
There were no adverse effects on behavioural, cognitive of exposure to a single course of betamethasone (2 x 12 mg, not receive betamethasone. No follow-up has as yet been	, 24 hours a	part) at terr	n compared	l to controls			

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 interv	vention/action do?						
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) trials did not pre-specify or report on any maternal outcomes. Quality of evidence Infant - School performance data was available from 352 children (37% of original study) followed-up from the Stuchfield (2005) trial. Children who had been exposed to antenatal corticosteroids <i>in utero</i> 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). Judging the harms in context 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 Overall quality of evidence 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							
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)			<u>WEAK</u>			
Benefits probably don't outweigh harms	Consider against/1	CONDITIONAL					
Harms probably outweigh benefits	_						
Benefits clearly don't outweigh harms	Recommend again	st		STRONG			
Harms clearly outweigh benefits							
6. Is the intervention/action implement	able in the New Ze	ealand and Australian co	ontext?				
Summary statement Antenatal corticosteroids are already widely in use in	New Zealand and A	ustralia.					
Yes		Recommend/conside	r				
Not known		Consider economic eval	luation				
No							
7. Final recommendation							
For elective caesarean section at term, where possible, plan at ≥39 weeks' gestation. Strength of recommendation 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 8. Recommendations for research WEAK (Practice Points) • 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 (\geq 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 (<i>number of studies, level of evidence and risk of bias in the inclu</i>	ded studi	ies)				
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.	А	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias				
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.	В	One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias				
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.	С	One or two Level III studies with a low risk of bias or Level I or II studies with moderate risk of bias				
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.	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 appli	cable')					
Maternal Within the subgroup of trials that included a proportion of women	А	All studies consistent				
who had had a previous preterm birth, there was no increased risk of chorioamnionitis or puerperal sepsis.	В	Most studies consistent and inconsistency can be explained				
Infant	С	Some inconsistency, reflecting genuine uncertainty around question				
The overall beneficial effect of reduced neonatal mortality and respiratory distress syndrome was absent from the subgroup of trials	D	Evidence is not consistent				
that reported the proportion of women with a history of preterm birth.	N A	Not applicable (one study only)				
3. Clinical impact (indicate if the study results varied according to some unknown intervention could not be determined)		ot simply study quality or sample size) and thus the clinical impact of the				
Maternal There was some imprecision in the confidence intervals for puerperal	А	Very large				
sepsis in the subgroup of trials that reported the proportion of women with previous history of preterm birth.	В	Substantial				
Infant Among those trials that reported the proportion of women with the history of preterm birth, the beneficial effect of reduced mortality and	С	Moderate				
respiratory distress syndrome was absent. The risk of these outcomes was not increased.	D	Slight / Restricted				
4. Generalisability (how well does the body of evidence match the population and a	linical se	ttings 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	А	Evidence directly generalisable to target population				
not generalizable, however the evidence can sensibly be applied to women at current risk.	В	Evidence directly generalisable to target population with some caveats				
	С	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	healthc	are 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	А	Evidence directly applicable to New Zealand / Australian healthcare context				
	В	Evidence applicable to New Zealand / Australian healthcare context with few caveats				
	С	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 a	any other factors tha	t you took into account whe	n assessing the	e evidence base (for ex	cample, issues that might cause the group to downgrade or	
upgrade the recommendation)						
					of women with a previous history of	
preterm birth. This level of	of evidence can	not be used to form a	clinical rec	commendation		
EVIDENCE STATEME	NT MATRIX (summarise the development	group's synthe	sis of the evidence rela	ating 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						
					evious history of preterm birth who are at	
			previous his	tory of preterm b	irth, there is no evidence of benefit.	
RECOMMENDATION development group draw from the				OVERALL GF	RADE OF RECOMMENDATION	
possible)			Α	Body of evidence can be trusted to guide practice		
Use a single course of anter history of a previous pretern factor(s) for preterm birth.			В	B Body of evidence can be trusted to guide practice in most situations		
Where appropriate, estimate	e the risk of preto	erm birth by	С	Body of evidence provides some support for recommendations(s) but care should be taken in its application		
considering the use of adjur fibronectin and assessment			D	Body of eviden with caution	ice is weak and recommendation must be applied	
			РР	Practice Point	ts	
UNRESOLVED ISSUES	(If needed, keep a	note of specific issues that a	rise when each	recommendation is fe	ormulated and that require follow up)	
					tions. Where the answer is yes, please provide explanatory	
information about this. This info						
Will this recommendation r	esult in changes	in usual care?			YES	
					NO	
Are there any resource impl	lications associate	ed with implementing th	his recomme	endation?	YES	
					NO	
Will the implementation of	this recommend	ation require changes in	the way can	e is currently	YES	
organised?					NO	
Are the guideline developm	ent group aware	of any barriers to imple	ementation of	of this	YES	
recommendation?						

M13 GRADE Evidence summary

What is the safety for the mother and fetus, infant with previous history of preterm birth?	, child, adult	of adminis	tering a si	ngle course	e of antenatal	l corticosteroid	ls to women
1. Outcome measures:		Quality of	evidence			oortance of out making a deci	
Matemal Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Importan
O1 Chorioamnionitis		1			1		
O2 Puerperal sepsis			1		1		
O ₃ Pyrexia after entry to trial				NR			
O4 Intrapartum fever requiring antibiotics				NR		4	
O5 Post natal pyrexia				NR		~	
O6 Maternal quality of life				NR	1		
Infant Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Importan
O1 Combined fetal and neonatal death				NR	1		
O2 Neonatal death	1						
O3 Fetal death				NR	-		
O4 RDS	1				4		
O5 Composite of serious outcomes	•			NR			
for the infant O6 Neurosensory disability (composite of impairments) for infant as a child				NR	· ·		
O7 Survival free of neurosensory disability for the infant as a child				NR	*		
O8 Survival free of metabolic disease for the infant as a child				NR		*	
O9 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		1	
Evidence statement - Evidence is based on a sub- previous history of preterm birth. This level of evi <i>Maternal</i> - No randomised controlled trial evidence wa history of preterm labour being the only risk factor fo for a single course of antenatal corticosteroids include and reported on maternal outcomes. Overall treatmen <i>Infant</i> - The Roberts CPG version 2015 systematic rev- outcomes that reported the proportion of women with compared with this subgroup of trials.	dence cannot s identified for r preterm birth d two trials the t effects for a iew for a single h a previous hi	t be used to r the prophy n in the curr at detailed the single cours e course of a istory of pre-	o form a cli vlactic use o ent pregnar he proporti- e were com antenatal co	inical record of antenatal of acy. The Ro on of wome opared with orticosteroid	nmendation corticosteroids berts CPG ver en with a previ this subgroup is included thr	s in women with rsion 2015 syste ious history of p of trials. ee trials reportii	n a previous matic review oreterm birth ng infant
3. What benefit will the proposed interver	ntion/action	have?					
Evidence statement <i>Maternal</i> - 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. <i>Infant</i> - 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.							f evidence plicable
Judging the benefits in context Maternal - The evidence for maternal outcomes is base of antenatal corticosteroids that reported including a p confidence intervals for puerperal sepsis. Infant - The evidence for infant outcomes is based on antenatal corticosteroids that involved 493 infants.	proportion of v	women with hin the Rob	a previous	preterm bin	th. There was	some imprecisi	on in the
4. What harm might the proposed interve	ntion/action	do?					
Evidence statement <i>Maternal</i> - There is no evidence of increased risk of cheprevious preterm birth following exposure to a single <i>Infant</i> - Although the beneficial effect for the infant of syndrome, seen in the overall treatment effect is not p	course of ante reduced neon	natal cortico atal mortalit	osteroids. y and respi	ratory distre	ess	Quality of ev Not ap	vidence plicable

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 go		orved up to 495 infants.				
Evidence statement <i>Maternal</i> - There is a lack of evidence for the use of a women whose only risk factor in the current pregna- health benefits for the mother, however there is no following a single course of antenatal corticosteroids preterm birth in the current pregnancy. <i>Infant</i> - There is no increased risk of harm for infants administered a single course of antenatal corticoster	Overall quality of evidence Not applicable					
Judging the balance of benefits and harms in co There was no evidence to contraindicate the use of a current risk of preterm birth. For women whose on	antenatal corticostero					
Benefits clearly outweigh harms	Recommend			STRONG		
Benefits probably outweigh harms	Consider			CONDITIONAL		
<u>Not known</u>	<u>Make a recommendation for research</u> (see 8 below)			<u>WEAK</u>		
Benefits probably don't outweigh harms	Consider against/	naka no recommendation		CONDITIONAL		
Harms probably outweigh benefits	Consider against/make no recommendation			CONDITIONAL		
Benefits clearly don't outweigh harms	- Recommend again	st		STRONG		
Harms clearly outweigh benefits	Ũ					
6. Is the intervention/action implement Summary statement Antenatal corticosteroids are already widely in use in			ontext?			
Antenatal concosteroids are already widely in use in Yes	I New Zealand and A	Recommend/conside	<u>er</u>			
Not known		Consider economic evaluation				
No		Recommend/consider a	against			
7. Final 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				IAL		
8. Recommendations for research						
 Any future randomised trials of a single course included participants. 	e of antenatal corticos	steroids should report on	the risk factors for	preterm birth of the		

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 ad women with a history of previous preterm birth?	ministe	ering a repeat course(s) of antenatal corticosteroids to
1. Evidence base (number of studies, level of evidence and risk of bias in the include	led studie	s)
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.	А	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias
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.	В	One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias
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.	С	One or two Level III studies with a low risk of bias or Level I or II studies with moderate risk of bias
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.	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 applied	able')	
Maternal There was no evidence of increased risk of chorioamnionitis, post-natal pyrexia requiring treatment, or puerperal sepsis from the trials that	А	All studies consistent
reported the proportion of women in their trial with a previous history of preterm birth.	В	Most studies consistent and inconsistency can be explained
Infant As per the overall treatment effect, there was no difference in neonatal death between exposure to repeat antenatal corticosteroids and no	С	Some inconsistency, reflecting genuine uncertainty around question
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	D	Evidence is not consistent
corticosteroids compared with no repeat exposure in the trials that reported including a proportion of women with a previous history of preterm birth.	NA	Not applicable (one study only)
3. Clinical impact (indicate if the study results varied according to some unknown intervention could not be determined)	factor (no	t simply study quality or sample size) and thus the clinical impact of the
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	А	Very large
preterm birth. Infant	В	Substantial
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	С	Moderate
birth. Although there was reduced risk of respiratory distress, there was no difference in composite serious outcome as observed in the overall treatment effect.	D	Slight / Restricted
4. Generalisability (how well does the body of evidence match the population and co	linical set	tings 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	А	Evidence directly generalisable to target population
not generalizable, however the evidence can sensibly be applied to women at current risk.	В	Evidence directly generalisable to target population with some caveats
	С	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	healthca	re 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	А	Evidence directly applicable to New Zealand / Australian healthcare context
	В	Evidence applicable to New Zealand / Australian healthcare context with few caveats
	С	Evidence probably applicable to New Zealand / Australian healthcare context with some caveats Evidence not applicable to New Zealand / Australian
	D	healthcare context

upgrade the recommendation)								
		om trials that reported they included a propo		women with a previous history of				
preterm birth. This leve	l of evidence car	not be used to form a clinical recommendat	1011					
EVIDENCE STATEM	ENT MATRIX	(summarise the development group's synthesis of the evide	nce relatinț	g to the key question, taking all the above factors int				
account)								
Component	Rating	Description						
1. Evidence base	NA	Not applicable						
2. Consistency	NA	Not applicable						
3. Clinical Impact	NA	Not applicable						
Generalisability	NA	Not applicable						
5. Applicability	NA	Not applicable						
Evidence statement								
There was no evidence to	contraindicate the	e use of antenatal corticosteroids in women with	a previo	ous history of preterm birth who are at				
		whose only risk factor is previous history of pret-	erm birth	, there is no evidence of benefit.				
		ation(s) does the guideline development group draw		OVERALL GRADE OF				
from this evidence? Use action	statements where pos	sible)		RECOMMENDATION				
				Body of evidence can be trusted to guide				
		in with a history of preterm birth and with an	Α	practice				
additional risk factor(s) fo	r preterm birth.			Body of evidence can be trusted to guide				
			В	practice in most situations				
Where appropriate, estimate	ate the risk of pret	erm birth by considering the use of adjunct		Body of evidence provides some support				
prediction tests including	fetal fibronectin a	nd assessment of cervical length.	С	for recommendations(s) but care should				
				be taken in its application				
			_	Body of evidence is weak and				
			D	recommendation must be applied with				
				caution				
			PP	Practice Points				
UNRESOLVED ISSUE	ES (If needed, keep a	note of specific issues that arise when each recommendate	on is form	ulated and that require follow up)				
			2					
IMPLEMENTATION	OF RECOMME	ENDATION (Please indicate yes or no to the following	g question.	s. Where the answer is yes, please provide explanator				
		ed to develop the implementation plan for the guidelines)						
Will this recommendation	result in changes	in usual care?	Y	YES				
	Ŭ		1	NO				
Are there any resource im	plications associat	ed with implementing this recommendation?	1	YES				
			l	NO				
Will the implementation of	of this recommend	lation require changes in the way care is currentl	v Y	YES				
organised?		1	·	NO				
			1					
č								
č	ment group aware	of any barriers to implementation of this	, I	YES				

M14 GRADE Evidence summary

women with a history of previous preterm birth?	,		0	r	e(s) of antena	atal corticoster	bids to
1. Outcome measures:		Quality o	f evidence			oortance of out making a decis	
Maternal Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Importan
D ₁ Chorioamnionitis	1				4		
D2 Puerperal sepsis	*				~		
D ₃ Pyrexia after entry to trial				NR		4	
D4 Intrapartum fever requiring antibiotics				NR			
D5 Post natal pyrexia		-				4	
D ₆ Maternal quality of life				NR	1		
Infant Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Importar
D ₁ Combined fetal and neonatal death	4			LOW	-		Importat
D2 Neonatal death	 ✓				· ·		
D3 Fetal death	•		,				
D4 RDS			1		1		
O ₅ Composite of serious outcomes	1				1		
for the infant O ₆ Neurosensory disability (composite of impairments)	1				1		
for infant as a child				NR	1		
O7 Survival free of neurosensory disability for the infant as a child				NR	4		
O ₈ Survival free of metabolic disease for the infant as a				NR		,	
child D9 Neurosensory disability (composite of impairments)						*	
for infant as an adult				NR	1		
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	recommen	ndation?	l		l		
previous history of preterm birth. This level of evider Maternal - No randomised controlled trial evidence was id history of preterm labour being the only risk factor for pr included four trials that detailed the proportion of womer treatment effects for a repeat course were compared with <i>lnfant</i> - The Crowther (2011) Cochrane systematic review with a previous history of preterm birth. Overall treatme	entified for eterm birth n with a pre- this subgro- included for nt effects for	the prophy in the curr evious histo oup of trials our trials rep or a repeat of	vlactic use o ent pregnar ry of preter oorting infat	f antenatal o ney. The Cro m birth and nt outcomes	corticosteroid owther (2011) reported on 1 s that reported	Cochrane system naternal outcom	natic review nes. Overall
		navez	Jourse were	compared	with this subg		of women
3. What benefit will the proposed intervention		nave?	louise were	compared	with this subg	roup of trials.	
3. What benefit will the proposed intervention Evidence statement Maternal - There was no increased risk of chorioamnion sepsis in the mother from the trials that reported that a pro- birth. Infant - In line with the overall treatment effect for a si- difference for neonatal death between those exposed to in the trials that detailed that a proportion of the womer for the overall treatment effect, there was a significant exposure to a repeat course compared to no repeat course	nitis, postr proportion or repeat cour a repeat co h in their tr nt reduction	natal pyrexis of women i rse of anter urse and th ial had a pr n in respire	a requiring n their trial natal cortice ose not exp evious prete atory distre	treatment of had a previous posteroids, the posed to a re- erm birth.	or puerperal ous preterm here was no epeat course As observed he following		evidence
3. What benefit will the proposed intervention Evidence statement Maternal - There was no increased risk of chorioamnio repsis in the mother from the trials that reported that a pointh. Infant - In line with the overall treatment effect for a st difference for neonatal death between those exposed to n the trials that detailed that a proportion of the womer for the overall treatment effect, there was a significant	nitis, postr proportion of repeat court a repeat court in their tr nt reduction se in the su n four trials with a prev s prior and of r trials, invo with a prev s prior and of	natal pyrexia of women i rse of anter urse and th ial had a pr n in respir ibgroup of s, involving ious preterr were at con blving up to ious preterr were at con	a requiring n their trial natal cortico ose not exp evious pret- atory distre- trials that r up to 3339 n birth in tl tinued risk - 3961 infan n birth in tl	treatment of had a previ osteroids, th ossed to a merm birth. ss syndrom eported a pro- women, inconcir trial. Th of preterm 1 ts, included meir trial. Th	or puerperal ous preterm here was no epeat course As observed he following roportion of cluded in the C women had birth. in the Crowth te women had	Quality of Not app Crowther (2011) already received	evidence blicable Cochrane l a single rane
3. What benefit will the proposed intervention Evidence statement Maternal - There was no increased risk of chorioamnio iepsis in the mother from the trials that reported that a p oirth. Infant - In line with the overall treatment effect for a s- difference for neonatal death between those exposed to n the trials that detailed that a proportion of the womer for the overall treatment effect, there was a significant exposure to a repeat course compared to no repeat course women in their trial with a previous preterm birth. Maternal - The evidence for maternal outcomes is based on systematic review that detailed the proportion of women sourse of antentala corticosteroids between 7 and 21 days to an explore the proportion of women course of antentalal corticosteroids between 7 and 21 days	nitis, postr proportion of repeat court a repeat court in their tr nt reduction se in the su n four trials with a prev s prior and of r trials, invo with a prev s prior and of	natal pyrexia of women i rse of anter urse and th ial had a pr n in respir ibgroup of s, involving ious preterr were at con blving up to ious preterr were at con	a requiring n their trial natal cortico ose not exp evious pret- atory distre- trials that r up to 3339 n birth in tl tinued risk - 3961 infan n birth in tl	treatment of had a previ osteroids, th ossed to a merm birth. ss syndrom eported a pro- women, inconcir trial. Th of preterm 1 ts, included meir trial. Th	or puerperal ous preterm here was no epeat course As observed he following roportion of cluded in the C women had birth. in the Crowth te women had	Quality of Not app Not app Crowther (2011) already received her (2011) Cochr already received	evidence blicable Cochrane I a single ane I a single
 What benefit will the proposed intervention Evidence statement Maternal - There was no increased risk of chorioamnion epsis in the mother from the trials that reported that a proportion. <i>infant</i> - In line with the overall treatment effect for a still ference for neonatal death between those exposed to an the trials that detailed that a proportion of the womer for the overall treatment effect, there was a significant exposure to a repeat course compared to no repeat course vomen in their trial with a previous preterm birth. Udging the benefits in context Maternal - The evidence for infant outcomes is based on ystematic review that detailed the proportion of women course of antenatal corticosteroids between 7 and 21 days <i>nfant</i> - The evidence for infant outcomes is based on four ystematic review that detailed the proportion of women course of antenatal corticosteroids between 7 and 21 days What harm might the proposed intervention 	nitis, postr proportion of repeat cour a repeat co n in their tr nt reduction se in the su n four trials with a prev s prior and of r trials, invo with a prev s prior and of on/action	hatal pyrexis of women i rse of anter urse and th ial had a pr n in respir ibgroup of s, involving ious preterr were at con blving up to ious preterr were at con do?	a requiring n their trial natal cortico ose not exp evious preta tory distre- trials that r up to 3339 n birth in the tinued risk of 3961 infan n birth in the tinued risk of source of the second n birth in the tinued risk of pyrexia required	treatment of had a previ osteroids, th ossed to a re- erm birth. ss syndrom eported a pro- women, inco neir trial. Th of preterm 1 ts, included neir trial. Th of preterm 1	or puerperal ous preterm nere was no epeat course As observed he following roportion of cluded in the C women had birth. in the Crowth women had birth. ent or	Quality of Not app Crowther (2011) already received	evidence blicable Cochrane I a single ane I a single

Infant - The beneficial effect of reduced composite se	erious 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			d alleady received a single			
5. What is the likely balance between go	<i>.</i> .	at contained how of preterint birth.				
, , , , , , , , , , , , , , , , , , , ,						
Evidence statement			Overall			
Maternal - There is a lack of evidence for the use of a			quality of evidence			
women whose only risk factor in the current pregna						
health benefits for the mother, however there is no			NT (
treatment or puerperal sepsis following a repeat cour		costeroids in women with a history of	Not applicable			
preterm birth who are at risk of preterm birth in the Infant - There is a significant reduction in respiratory		and no increased risk of herm for infants				
of women with a history of preterm birth who were						
risk of preterm birth in the current pregnancy.	administered a single	e course of antenatal conteosteroids for				
Judging the balance of benefits and harms in co	ntext					
There was no evidence to contraindicate the use of a		olds in women with a previous history of p	reterm birth who are at			
current risk of preterm birth. For women whose on						
Benefits clearly outweigh harms	Recommend		STRONG			
Benefits probably outweigh harms	Consider		CONDITIONAL			
	Make a recommen	idation for research				
Not known	(see 8 below)		<u>WEAK</u>			
Benefits probably don't outweigh harms	Consider assingt/	make no recommendation	CONDITIONAL			
Harms probably outweigh benefits	Consider against/1	make no recommendation	CONDITIONAL			
Benefits clearly don't outweigh harms	D 1 .		CTRONG			
Harms clearly outweigh benefits	Recommend again	ist	STRONG			
6. Is the intervention/action implement	able in the New Ze	ealand and Australian context?				
Summary statement						
Antenatal corticosteroids are already widely in use in	New Zealand and A					
Yes		Recommend/consider				
Not known		Consider economic evaluation				
No		Recommend/consider against				
7. Final recommendation						
		Г	Strength of			
			recommendation			
Repeat antenatal corticosteroids for a woman with a	history of preterm h	airth and with an additional risk factor(s)	STRONG			
for preterm birth.	motory of preterm b	and with an additional lisk factor(5)	CONDITIONAL			
P bittin			WEAK (Practice Points)			
Where appropriate, estimate the risk of preterm birth	h by considering the	use of adjunct prediction tests including				
fetal fibronectin and assessment of cervical length.	, 011	, 1 0				
8. Recommendations for research						
Any future randomised trials of repeat antenat	al corticosteroids sho	ould report on the risk factors for preterm	birth of the included			
participants.		r				

M15 Women in preterm labour – Single course of antenatal corticosteroids

M15 NHMRC Evidence summary

What is the safety for the mot preterm labour?	ther and the t	fetus, infant, child, adult of	fadmin	istering a single course of antenatal steroids to women in		
1. Evidence base (number of stud	dies, level of evid	ence and risk of bias in the include	ed studies,)		
Seven trials reporting on matern on infant outcomes included in			А	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias		
systematic review for a single co the proportion of women who		В	One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias			
women being in spontaneous la	bour, where r	eported.	С	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, ra	ank this component as 'not applica	ıble')			
All studies indicated that even a benefit to the neonate.	n incomplete	course could have potential	А	All studies consistent		
			В	Most studies consistent and inconsistency can be explained		
			С	Some inconsistency, reflecting genuine uncertainty around question		
			D	Evidence is not consistent		
			NA	Not applicable (one study only)		
intervention could not be determined)	e study results va	iried according to some unknown f	actor (not	simply study quality or sample size) and thus the clinical impact of the		
Maternal For the mother in spontaneous sepsis following a single course	of antenatal c	orticosteroids is suggested,	А	Very large		
although there is no evidence of or pyrexia at trial entry, intrapar requiring treatment.			В	Substantial		
Infant As with the overall treatment ef antenatal corticosteroids compa			С	Moderate		
there were significant reductions Respiratory distress syndrome w antenatal corticosteroids compa	s in perinatal a vas reduced fo	and neonatal death. Illowing a single course of	D	D Slight / Restricted		
4. Generalisability (how well doe	s the body of evi	dence match the population and cli	nical setti	ings being targeted by the guideline?)		
Evidence is probably generalizat health setting.	ble to the New	w Zealand and Australasian	А	Evidence directly generalisable to target population		
8.			В	Evidence directly generalisable to target population with some caveats		
			С	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 evi	idence relevant to	o the New Zealand / Australian	healthcare	e context in terms of health services / delivery of care and cultural factors?)		
The evidence is relevant and app	plicable to the	health care setting.	А	Evidence directly applicable to New Zealand / Australian healthcare context		
			В	Evidence applicable to New Zealand / Australian healthcare context with few caveats		
			С	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 of upgrade the recommendation)	ther factors that	you took into account when assess.	ing the evi	idence base (for example, issues that might cause the group to downgrade or		
Evidence is based on a subse evidence cannot be used to fo			ncluded	l a proportion of women in preterm labour. This level of		
EVIDENCE STATEMENT account)	MATRIX (st.	ummarise the development group's	synthesis (of the evidence relating to the key question, taking all the above factors into		
Component	Rating	Description				
1. Evidence base	NA	Not applicable				

2. Consistency	NA	Not applicable						
3. Clinical Impact	NA	Not applicable	Not applicable					
4. Generalisability	NA	Not applicable						
5. Applicability	NA	Not applicable						
Evidence statement								
The evidence suggests that ev preterm labour.	ven an incomple	ete course of antenatal corticosteroids may ha	ve benefit	s to the neonate when the mother is in				
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 antena	1	А	Body of evidence can be trusted to guide practice					
		erm birth by considering the use of adjunct ad assessment of cervical length.	В	Body of evidence can be trusted to guide practice in most situations				
Where appropriate, monitor when antenatal corticosteroid	women in prete	С	Body of evidence provides some support for recommendations(s) but care should be taken in its application					
	0		D	Body of evidence is weak and recommendation must be applied with caution				
			РР	Practice Points				
UNRESOLVED ISSUES	(If needed, keep a	note of specific issues that arise when each recommenda	ution is form	nulated and that require follow up)				
IMPLEMENTATION OF		NDATION (Please indicate yes or no to the follow d to develop the implementation plan for the guidelines		as. Where the answer is yes, please provide explanatory				
IMPLEMENTATION OF	mation will be used	d to develop the implementation plan for the guidelines)	us. Where the answer is yes, please provide explanatory ES				
IMPLEMENTATION OF information about this. This infor	mation will be used	d to develop the implementation plan for the guidelines	y Y					
IMPLEMENTATION OF <i>information about this. This inform</i> Will this recommendation res	mation will be used	d to develop the implementation plan for the guidelines	<u>y</u>	ES				
IMPLEMENTATION OF <i>information about this. This inform</i> Will this recommendation res	mation will be used	d to develop the implementation plan for the guidelines	<u>Y</u> <u>Y</u> <u>Y</u>	ES <u>10</u>				
IMPLEMENTATION OF information about this. This infor Will this recommendation res Are there any resource implic Will the implementation of th	mation will be used	d to develop the implementation plan for the guidelines	<u>Y</u> <u>Y</u> <u>Y</u> <u>N</u>	ES ES				
IMPLEMENTATION OF information about this. This infor Will this recommendation res Are there any resource implic	mation will be used	d to develop the implementation plan for the guidelines in usual care? ed with implementing this recommendation?	tly	ES ES 10 10				
IMPLEMENTATION OF information about this. This infor Will this recommendation res Are there any resource implic Will the implementation of th organised?	mation will be used sult in changes i cations associate his recommenda	d to develop the implementation plan for the guidelines in usual care? ed with implementing this recommendation?	1) Y Y Y tly Y	ES 10 ES 10 ES ES				

M15 GRADE Evidence summary

Considered Judgement - Strength of recommendation

Considered. What is the safety for the mother and fetus, infant, cl	, 0	0			e of antenatal	corticosteroid	s to women	
in preterm labour? 1. Outcome measures:	,		f evidence	0	Imp	ortance of outcome		
Maternal Outcomes	HIGH	MOD	LOW	V. LOW	Critical	making a deci Important	sion Not Important	
O ₁ Cho r ioamnionitis				LOW		_	Important	
O2 Puerperal sepsis	1				×			
O ₃ Pyrexia after entry to trial		*			1			
O4 Intrapartum fever requiring antibiotics		*				4		
		*				1		
D5 Post natal pyrexia		1				4		
O6 Maternal quality of life	HIGH	MOD	LOW	NR V.	✓ Critical	Important	Not	
O ₁ Combined fetal and neonatal death	mon	MOD	LOW	LOW	Cilicai	Important	Important	
O ₁ Combined retai and neonatal death	*				1			
	1				1			
O ₃ Fetal death		1			1			
O4 RDS O5 Composite of serious outcomes	1				1			
for the infant				NR	1			
O ₆ Neurosensory disability (composite of impairments) for infant as a child				NR	1			
O7 Survival free of neurosensory disability for the				NR	-			
infant as a child Os Survival free of metabolic disease for the infant as a child				NR	•	1		
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	4			
Ω_{11} Survival free of metabolic disease for the infant as an adult				NR				
2. Is there is insufficient evidence to make a	recommen	ndation?						
Evidence statement - Evidence is based on a subset labour. This level of evidence cannot be used to for <i>Maternal</i> – The Roberts CPG version 2015 systematic rev the proportion of women in preterm labour, up to seven women included in these trials were in spontaneous prete compared with this subgroup of trials that detailed the pr <i>Infant</i> - The Roberts CPG version 2015 systematic review proportion of women in preterm labour and reported on a single course of antenatal corticosteroids were compare trial who were in spontaneous preterm labour. 3. What benefit will the proposed intervention	n a clinical iew for a sin of which re erm labour. oportion of for a single infant outc d with this	I recomme ported mat Overall trea women ind course of a omes. Thes subgroup o	ndation of antenata ernal outco atment effec- cluded in th antenatal co e trials invo	l corticoster mes and inv cts for a sing leir trial who orticosteroid olved up to 2	roids included rolved 1797 we gle course of a o were in spon s included fift 3683 infants. C	thirteen trials th omen. An avera ntenatal cortico taneous pretern een trials that do Overall treatmer	nat detailed ge of 74% of steroids were n labour. etailed the nt effects for	
Evidence statement		_				Quality of	evidence	
<i>Maternal</i> - 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. <i>Infant</i> - 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.								
Judging the benefits in context						received a sime	0.000mmg - f	
<i>Maternal</i> - The evidence is based on seven trials involving antenatal corticosteroids (or placebo). <i>Infant</i> - The evidence is based on 15 trials involving 3683 mothers were in spontaneous preterm labour.	infants who	were expo	-			, i i i i i i i i i i i i i i i i i i i		
4. What harm might the proposed interventi	on/action	do?						
Evidence statement Maternal - There was an increased risk of puerperal sepsis	among wor	men t r eated	with anten	atal corticos	steroids in	Quality of ev	idence	
trials that included a proportion of women in spontaneou Infant - There was no evidence of harms for the infant fol	ıs preterm l	abour.				Not apj	plicable	

corticosteroids in the trials that reported including a	proportion of wome	en in spontaneous preterm	labou r .	
Judging the harms in context Maternal - The evidence is based on seven trials invo antenatal corticosteroids (or placebo). Infant - The evidence is based on 15 trials involving 3 mothers were in spontaneous preterm labour. 5. What is the likely balance between go	3683 infants who we			-
5. What is the likely balance between go	ood and namine			
Evidence statement <i>Maternal</i> - For the mother in spontaneous labour the course of antenatal corticosteroids although there pyrexia at trial entry, intrapartum pyrexia or postnata. <i>Infant</i> - As with the overall treatment effects for exprime with no antenatal corticosteroids, there were signified istress syndrome was reduced in infants of w corticosteroids compared with no antenatal corticosteroids. Judging the balance of benefits and harms in co	Overall quality of evidence Not applicable			
<i>Maternal</i> - The evidence is based on seven trials invo antenatal corticosteroids (or placebo). <i>Infant</i> - The evidence is based on 15 trials involving 3 mothers were in spontaneous preterm labour.	lving 1797 women w	1 1		0
Benefits clearly outweigh harms	Recommend			STRONG
Benefits probably outweigh harms	Consider			CONDITIONAL
Not known	Make a recomme	endation for research (se	e 8 below)	<u>WEAK</u>
Benefits probably don't outweigh harms	Consider coniect/			CONDITIONAL
Harms probably outweigh benefits	Consider against/	make no recommendation		CONDITIONAL
Benefits clearly don't outweigh harms	Recommend agair	nct.		STRONG
Harms clearly outweigh benefits	Ŭ			511(61(6
6. Is the intervention/action implement	table in the New Ze	ealand and Australian co	ntext?	
Summary statement	Now Zooland and	matualia		
Antenatal corticosteroids are already widely in use in Yes	Thew Zealand and P	Recommend/conside	r	
Not known		Consider economic eval		
No		Recommend/consider a		
7. Final recommendation				
			Strength of ro	commendation
Use a single course of antenatal corticosteroids in women in preterm labour. So C C C C C C C C C C C C C C C C C C			STRONG CONDITION <u>WEAK</u> (Practi	JAL
antenatal corticosteroids have been given. 8. Recommendations for research				

M16 Women in preterm labour – Repeat course of antenatal corticosteroids

M16 NHMRC Evidence summary

What is the safety for the more preterm labour?	ther and the	fetus, infant, child, adult of	f admin	istering repeat dose(s) of antenatal steroids to women in			
1. Evidence base (number of studies, level of evidence and risk of bias in the included studies)							
Six trials included in the Crowth reported on maternal outcomes	and detailed a	a proportion of women	А	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias			
who were in preterm labour wit labour, where reported.	h 49% of wor	nen being in spontaneous	В	One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias			
Eight trials included in the Crow reported on infant outcomes an were in preterm labour with 499	d detailed a p	roportion of women who	С	One or two Level III studies with a low risk of bias or Level I or II studies with moderate risk of bias			
labour, where reported	70 OI Women I	enig ili spontaneous	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, ra	ank this component as 'not applica	able')				
All studies indicated that even a	n incomplete	course could have potential	А	All studies consistent			
benefit to the neonate.			В	Most studies consistent and inconsistency can be explained			
			С	Some inconsistency, reflecting genuine uncertainty around question			
			D	Evidence is not consistent			
			NA	Not applicable (one study only)			
	e study results va	rried according to some unknown f	actor (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 ar evidence of an increased risk fo (chorioamnionitis, pyrexia at tri-	r any materna	infection	А	Very large			
pyrexia requiring treatment, pue			В	Substantial			
There were no differences betw corticosteroids for infant morta women in preterm labour. Resp following a repeat dose(s) of an	lity in trials th piratory distre	at reported a proportion of ss syndrome was reduced	С	Moderate			
repeat exposure. There was a sig serious infant outcomes followi corticosteroids compared with a	gnificant redu ng a repeat do	ction in a composite of ose(s) of antenatal	D	Slight / Restricted			
4. Generalisability (how well doe	es the body of evi	dence match the population and cli	inical setti	ings being targeted by the guideline?)			
Evidence is probably generaliza health setting	ble to the New	w Zealand and Australasian	А	Evidence directly generalisable to target population			
neutri setting			В	Evidence directly generalisable to target population with some caveats			
			С	Evidence not directly generalisable to target population but			
			D	could be sensibly applied Evidence not directly generalisable to target population and			
				hard to judge whether sensible to apply			
			healthcard	e context in terms of health services / delivery of care and cultural factors?)			
The evidence is relevant and ap	plicable to the	health care setting.	А	Evidence directly applicable to New Zealand / Australian healthcare context			
			В	Evidence applicable to New Zealand / Australian healthcare context with few caveats			
			С	Evidence probably applicable to New Zealand / Australian healthcare context with some caveats			
			D	Evidence not applicable to New Zealand / Australian			
Other factors (indicate here any o	ther factors that	you took into account when assess		healthcare context idence base (for example, issues that might cause the group to downgrade or			
upgrade the recommendation)			-	a proportion of women in preterm labour. This level of			
evidence cannot be used to fe			nciuded	a proportion of women in preterm labour. This level of			
	MATRIX (st.	mmarise 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					
 Generalisability Applicability 	NA NA	Not applicable Not applicable					

Evidence statement				
The evidence suggests that even an incomplete course of antenatal corticosteroids may ha	ve benefi	its to the neonate when the mother is in		
preterm labour.				
RECOMMENDATION (What recommendation(s) does the guideline development group draw		OVERALL GRADE OF		
from this evidence? Use action statements where possible)		RECOMMENDATION		
Repeat antenatal corticosteroids for a woman in preterm labour.	А	Body of evidence can be trusted to guide practice		
Where appropriate, estimate the risk of preterm birth by considering the use of adjunct prediction tests including fetal fibronectin and assessment of cervical length.	В	Body of evidence can be trusted to guide practice in most situations		
1	С	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		
		eaution		
	РР	Practice Points		
UNRESOLVED ISSUES (If needed, keep a note of specific issues that arise when each recommendated	tion is for	Practice Points mulated and that require follow up)		
IMPLEMENTATION OF RECOMMENDATION (Please indicate yes or no to the follow	ution is for ving questio	Practice Points mulated and that require follow up)		
	ution is for ing question)	Practice Points mulated and that require follow up)		
IMPLEMENTATION OF RECOMMENDATION (Please indicate yes or no to the follow information about this. This information will be used to develop the implementation plan for the guidelines	ution is for ing question ing	Practice Points mulated and that require follow up) ons. Where the answer is yes, please provide explanatory		
IMPLEMENTATION OF RECOMMENDATION (Please indicate yes or no to the follow information about this. This information will be used to develop the implementation plan for the guidelines	ution is for ing question i)	Practice Points mulated and that require follow up) ons. Where the answer is yes, please provide explanatory YES		
IMPLEMENTATION OF RECOMMENDATION (Please indicate yes or no to the follow 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?	ution is for ing questic	Practice Points mulated and that require follow up) ms. Where the answer is yes, please provide explanatory YES NO		
IMPLEMENTATION OF RECOMMENDATION (Please indicate yes or no to the follow 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? Are there any resource implications associated with implementing this recommendation? Will the implementation of this recommendation require changes in the way care is current.	ution is for ing question i)	Practice Points mulated and that require follow up) ons. Where the answer is yes, please provide explanatory YES NO YES		
IMPLEMENTATION OF RECOMMENDATION (Please indicate yes or no to the follow 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? Are there any resource implications associated with implementing this recommendation? Will the implementation of this recommendation require changes in the way care is current organised?	ttion is form	Practice Points mulated and that require follow up) ons. Where the answer is yes, please provide explanatory YES NO YES NO		
IMPLEMENTATION OF RECOMMENDATION (Please indicate yes or no to the follow 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? Are there any resource implications associated with implementing this recommendation? Will the implementation of this recommendation require changes in the way care is current.	ttion is for ing question i)	Practice Points mulated and that require follow up) ons. Where the answer is yes, please provide explanatory YES NO YES NO YES		

Considered	Judgement	- Strength	of recom	nendation			
What is the safety for the mother and fetus, infant, cl in preterm labour?	hild, adult	of adminis	tering rep	eat dose(s)	of antenatal	corticosteroids	to women
1. Outcome measures:					ortance of outcome making a decision		
Maternal Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Importan
D ₁ Chorioamnionitis	4			LOW	-		Importan
D2 Puerperal sepsis	 ✓				* *		
D ₃ Pyrexia after entry to trial	· ·			NR	· ·		
D4 Intrapartum fever requiring antibiotics				NR		1	
D5 Post natal pyrexia				INK		1	
De Maternal quality of life	1			NR		4	
	111011	MOD	LOW	V.		T	Not
Infant Outcomes	HIGH	MOD	LOW	LOW	Critical	Important	Importan
O1 Combined fetal and neonatal death	1				1		
O2 Neonatal death	1				1		
O3 Fetal death		1			1		
D4 RDS	1				1		
O5 Composite of serious outcomes for the infant	1				1		
O ₆ Neurosensory disability (composite of impairments)				NR			
for infant as a child D7 Survival free of neurosensory disability for the nfant as a child				NR			
D ₈ Survival free of metabolic disease for the infant as a shild				NR		*	
D ₉ Neurosensory disability (composite of impairments) for infant as an adult				NR	1		
O_{10} Survival free of neurosensory disability for the nfant as an adult				NR	1		
O ₁₁ Survival free of metabolic disease for the infant as				NR		1	
2. Is there is insufficient evidence to make a	recommer	ndation?		•		· ·	
Evidence statement - Evidence is based on a subset abour. This level of evidence cannot be used to form <i>Maternal</i> - Six trials included in the Crowther (2011) Coch women who were in preterm labour with 49% of women <i>nfant</i> - Eight trials included in the Crowther (2011) Coch with 49% of women being in spontaneous labour, and re	n a clinical rane system being in sp rane system	atic review ontaneous atic review	ndation reported o abour, whe included a	n maternal o ere reported	outcomes and	included a prop	ortion of
3. What benefit will the proposed intervention							
Evidence statement <i>Maternal.</i> -Following a repeat dose(s) of antenatal cortico maternal infection (chorioamnionitis, pyrexia at trial e treatment, puerperal sepsis). <i>Infant</i> - There were no differences between repeat and n trials that reported a proportion of women in preten following a repeat dose(s) of antenatal corticosteroids co reduction in a composite of serious infant outcomes compared with no repeat exposure.	ntry, intrap no repeat ar m labour. ompared wit	artum pyre ntenatal con Respirator th no repea	xia or pos ticosteroid y distress t exposure.	tnatal pyres s for infant syndrome v There was	mortality in was reduced a significant	Quality of Not apj	
udging the benefits in context Maternal - Evidence is based on six well conducted trials i to the New Zealand and Australian health care setting. Infant - Evidence is based on eight well conducted trials in New Zealand and Australian health care setting. 4. What harm might the proposed interventi	volving up	to 5228 inf		Ũ	0		
Evidence statement	any action					Quality of ev	idence
<i>Maternal</i> - There is no evidence of any increased risk of m ntrapartum pyrexia or postnatal pyrexia requiring treatme lose(s) of antenatal corticosteroids. <i>infant</i> - The evidence demonstrated significant reductions evidence of harm was identified.	ent, puerper	al sepsis) fo	ollowing ex	posure to a	repeat	Not apj	
Judging the harms in context Maternal - Evidence is based on six well conducted trials i to the New Zealand and Australian health care setting.	nvolving up	to 4261 w	omen, and	is generaliza	ble to the targ	et population a	nd applicable

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?						
	ood and namn:					
Evidence statement <i>Maternal</i> - Following a repeat dose(s) of antenatal cc maternal infection (chorioamnionitis, pyrexia at tr treatment, puerperal sepsis). <i>Infant</i> - There were no differences between repeat a trials that reported a proportion of women in pre women in pretern labour for a repeat dose(s) of There was a significant reduction in a composite of corticosteroids compared with no repeat exposure in	fant mortality in was reduced in repeat exposure.	Overall quality of evidence Not applicable				
Judging the balance of benefits and harms in co Maternal - No evidence of harm or benefit to the mo Infant - No evidence of harm for the infant and clear	other.					
Benefits clearly outweigh harms	Recommend			STRONG		
Benefits probably outweigh harms	Consider			CONDITIONAL		
Not known	Make a recomme	endation for research (se	ee 8 below)	WEAK		
Benefits probably don't outweigh harms	Consider against/	nake no recommendation		CONDITIONAL		
Harms probably outweigh benefits	Consider against/1	hake no recommendation		CONDITIONAL		
Benefits clearly don't outweigh harms	Recommend again	st		STRONG		
Harms clearly outweigh benefits	Ũ			511(6)(6)		
6. Is the intervention/action implementable in the New Zealand and Australian context?						
Summary statement Antenatal corticosteroids are already widely in use in	n New Zealand and A	ustralia.				
Yes		Recommend/conside	<u>er</u>			
Not known		Consider economic eval	luation			
No		Recommend/consider a	against			
7. Final recommendation						
	commendation					
Repeat antenatal corticosteroids for a woman in pre- Where appropriate, estimate the risk of preterm birt prediction tests including fetal fibronectin and assess	IAL ce 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 One or more Level I studies with a low risk of bias, or several The evidence for maternal infection is based the Roberts CPG А Level II studies with a low risk of bias version 2015 systematic review for a single course of antenatal corticosteroids that included sixteen trials that reported including a One or two Level II studies with a low risk of bias, or SR/several proportion of women with preterm prelabour rupture of В Level III studies with a low risk of bias membranes at trial entry, and seven trials that only included women with preterm prelabour rupture of membranes at trial entry. One or two Level III studies with a low risk of bias or Level I or С Infant II studies with moderate risk of bias 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 Level IV studies or Level I to III studies/SRs with a high risk of D proportion of women with preterm prelabour rupture of bias membranes at trial entry, and seven trials that only included women with preterm prelabour rupture of membranes at trial entry. 2. Consistency (if only one study was available, rank this component as 'not applicable') Maternal А All studies consistent 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 В Most studies consistent and inconsistency can be explained reported including a proportion of women with preterm prelabour rupture of membranes. Some inconsistency, reflecting genuine uncertainty around С Infant question Among trials that reported including a proportion of women with preterm prelabour rupture of membranes, treatment effects for D Evidence is not consistent 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 NA Not applicable (one study only) infants exposed to a single course of antenatal corticosteroids compared with no exposure. 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 Very large А potential risk of maternal infection. В Substantial Infant High quality evidence with large effect sizes that demonstrate significant reductions in measures of mortality, and respiratory С distress syndrome from trials that reported including a proportion Moderate 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 D Slight / Restricted probably due to the small number of babies. 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 А Evidence directly generalisable to target population USA, France, Australia, New Zealand. Evidence directly generalisable to target population with some В caveats Evidence not directly generalisable to target population but could С be sensibly applied Evidence not directly generalisable to target population and hard D 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 Evidence directly applicable to New Zealand / Australian А and their use is feasible. healthcare context Evidence applicable to New Zealand / Australian healthcare В context with few caveats Evidence probably applicable to New Zealand / Australian С healthcare context with some caveats Evidence not applicable to New Zealand / Australian healthcare D 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 (W hat recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible)		OVERALL GRADE OF RECOMMENDATION
	Α	Body of evidence can be trusted to guide practice
Use a single course of antenatal corticosteroids for women with preterm prelabour	В	Body of evidence can be trusted to guide practice in most situations
rupture of membranes.	С	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
	<u>N0</u>
Are there any resource implications associated with implementing this recommendation?	YES
	<u>NO</u>
Will the implementation of this recommendation require changes in the way care is currently	YES
organised?	NO
Are the guideline development group aware of any barriers to implementation of this	YES
recommendation?	<u>NO</u>

M17 GRADE Evidence summary

Considered J What is the safety for the mother and fetus, infant, ch with preterm prelabour rupture of membranes (at tria	nild, adult	of adminis	tering a sir	ngle course	of antenatal	corticosteroid	s to women
1. Outcome measures:	Quality of evidence			Importance of outcome in making a decision			
Matemal Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O1 Chorioamnionitis				NR	1		
O2 Puerperal sepsis		1			1		
O ₃ Pyrexia after entry to trial		*					
O4 Intrapartum fever requiring antibiotics				NR			
O ₅ Post natal pyrexia		1				4	
O ₆ Maternal quality of life				NR	4		
Infant Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O1 Combined fetal and neonatal death	*				4		
O2 Neonatal death	4				4		
O ₃ Fetal death	*				1		
O ₄ RDS		4			1		
O ₅ Composite of serious outcomes for the infant				NR	1		
O6 Neurosensory disability (composite of impairments) for infant as a child				NR	1		
O_7 Survival free of neurosensory disability for the infant as a child				NR	4		
Os Survival free of metabolic disease for the infant as a child				NR		+	
O ₂ Neurosensory disability (composite of impairments) for infant as an adult				NR	4		
O10 Survival free of neurosensory disability for the infant as an adult				NR	4		
O ₁₁ Survival free of metabolic disease for the infant as an adult				NR			

Evidence statement - Evidence is based on a subset of data from trials that reported they included a proportion of women w 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 entry. Eight trials involving 2748 infants 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. 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.	Not applicable
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.	
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.

Evidence statement			Quality of evidence		
Maternal - There was no evidence of harm to the where reported Infant - There was no evidence of harm to the in reduction in risk of a number of important clinic distress syndrome.	ed with a Not applicable				
Judging the harms in context					
Maternal - The evidence is direct evidence from t significant harms to the mother Infant - The evidence is direct evidence from tria significant harms to the infant.	trials that involved women with confirmed rupture of the second s				
5. What is the likely balance betwee	in good and harm?				
Evidence statement Maternal - The evidence suggests no increase corticosteroids in the presence of ruptured mem	ed risk of harms for the mother when treate	d with antenatal	Overall quality of evidence		
Infant - The evidence suggests clear benefits for respiratory distress syndrome, with no increase presence of ruptured membranes.	r the infant of reduced risk of fetal, neonatal and ed risk of harms when exposed to antenatal cort		Not applicable		
Judging the balance of benefits and harms in Maternal - The benefits to the infant are significa Infant - The benefits to the infant are significant	int with no obvious health harms to the mother				
Benefits clearly outweigh harms	Recommend				
Benefits probably outweigh harms	Consider		CONDITIONAL		
Not known	Make a recommendation for research (s	see 8 below)	<u>WEAK</u>		
		CONDITIONAL			
Benefits probably don't outweigh harms			CONDITIONAL		
1 . 0	Consider against/make no recommendatio	n	CONDITIONAL		
Harms probably outweigh benefits		n			
Harms probably outweigh benefits Benefits clearly don't outweigh harms Harms clearly outweigh benefits	Recommend against		CONDITIONAL		
Harms probably outweigh benefits Benefits clearly don't outweigh harms Harms clearly outweigh benefits					
Harms probably outweigh benefits Benefits clearly don't outweigh harms Harms clearly outweigh benefits 6. Is the intervention/action implen Summary statement	Recommend against				
Harms probably outweigh benefits Benefits clearly don't outweigh harms Harms clearly outweigh benefits 6. Is the intervention/action implen Summary statement Antenatal corticosteroids are already widely in u	Recommend against nentable in the New Zealand and Australian of se in New Zealand and Australia.	context?			
Harms probably outweigh benefits Benefits clearly don't outweigh harms Harms clearly outweigh benefits 6. Is the intervention/action implen Summary statement Antenatal corticosteroids are already widely in u Yes	Recommend against	context?			
Benefits clearly don't outweigh harms Harms clearly outweigh benefits 6. Is the intervention/action implem Summary statement Antenatal corticosteroids are already widely in u Yes Not known	Recommend against mentable in the New Zealand and Australian of se in New Zealand and Australia. Recommend/consid	context? er aluation			
Harms probably outweigh benefits Benefits clearly don't outweigh harms Harms clearly outweigh benefits 6. Is the intervention/action implen Summary statement Antenatal corticosteroids are already widely in u Yes Not known	Recommend against nentable in the New Zealand and Australian of use in New Zealand and Australia. Recommend/consider Consider economic ev	context? er aluation			
Harms probably outweigh benefits Benefits clearly don't outweigh harms Harms clearly outweigh benefits 6. Is the intervention/action implen Summary statement Antenatal corticosteroids are already widely in u Yes Not known No	Recommend against mentable in the New Zealand and Australian of se in New Zealand and Australia. Recommend/consider Recommend/consider	er aluation against	strong		

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 preterm prelabour rupture of membranes (at trial entry) at risk o				
1. Evidence base (number of studies, level of evidence and risk of bias in the in	ncluded sti	udies)		
Maternal The evidence for maternal infection is based on a systematic review (Crowther, 2011) that included six trials that reported including a	А	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias		
proportion of women with preterm prelabour rupture of membranes at trial entry.		One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias		
Infant The evidence for infant outcomes is based on a systematic review	С	One or two Level III studies with a low risk of bias or Level I or II studies with moderate risk of bias		
(Crowther, 2011) that included six trials that reported including a proportion of women with preterm prelabour rupture of membranes at trial entry.	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 ap	oplicable')			
Maternal There was no difference seen for chorioamnionitis, postnatal pyrexia and puerperal sepsis with treatment effects similar to the	А	All studies consistent		
overall treatment effect and no difference between groups, among trials that reported including a proportion of women with preterm prelabour rupture of membranes.	В	Most studies consistent and inconsistency can be explained		
Infant Among trials that reported including a proportion of women with preterm prelabour rupture of membranes, treatment effects for	С	Some inconsistency, reflecting genuine uncertainty around question		
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	D	Evidence is not consistent		
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.		Not applicable (one study only)		
3. Clinical impact (indicate if the study results varied according to some unkno intervention could not be determined)	own factor	(not simply study quality or sample size) and thus the clinical impact of the		
Maternal The benefit of improved infant outcomes probably outweighs any potential risk of maternal infection.	А	Very large		
Infant	В	Substantial		
High quality evidence with large effect sizes that demonstrates a significant reduction in risk of respiratory distress syndrome from	С	Moderate		
trials that reported including a proportion of women with preterm prelabour rupture of membranes.	D	Slight / Restricted		
4. Generalisability (how well does the body of evidence match the population and	nd clinical	settings being targeted by the guideline?)		
Evidence from a variety of healthcare settings. Studies conducted in USA, France, Australia, New Zealand.	А	Evidence directly generalisable to target population		
	В	Evidence directly generalisable to target population with some caveats		
	С	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 / Austra	ulian healt			
Corticosteroids are readily available in Australia and New Zealand and their use is feasible.	А	Evidence directly applicable to New Zealand / Australian healthcare context		
	В	Evidence applicable to New Zealand / Australian healthcare context with few caveats		
	С	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 a upgrade the recommendation)	ussessing th	he evidence base (for example, issues that might cause the group to downgrade or		

EVIDENCE STATEM	ENT MAT	RIX (summarise the develop	ment group's synth	besis of the evidence r	elating to the key question, taking all the above factors into			
Component	Rating	Description	Description					
1. Evidence base	NA	Not applicable	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 of membranes. This lev					on of women with preterm prelabour rupture n			
RECOMMENDATION guideline development group d				OVERALL GRA	ADE OF RECOMMENDATION			
statements where possible)	ruw jrom 1515 c.		Α	Body of evidence can be trusted to guide practice				
Repeat antenatal corticos prelabour rupture of men		woman with preterm	В	Body of evidence can be trusted to guide practice in most situations				
L L		Γ	С	Body of evidence provides some support for recommendations(s) but care should be taken in its application				
			D	Body of evide with caution	ence is weak and recommendation must be applied			
			РР	Practice Poi	nt			
UNRESOLVED ISSUE	E S (If needed, .	keep a note of specific issues th	bat arise when eac	h recommendation is	formulated and that require follow up)			
IMPLEMENTATION information about this. This i					estions. Where the answer is yes, please provide explanatory			
Will this recommendation	n result in cha	anges in usual care?			YES			
					NO			
Are there any resource im	nplications as	sociated with implementi	ng this recomn	nendation?	YES			
					NO			
Will the implementation organised?	of this recom	mendation require chang	es in the way c	are is currently	YES			
Are the guideline develop	mont out	man of any barries to it	malomontati	of this	NO			
recommendation?	ment group	aware of any Darners to f	inplementation	Of this	YES			

M18 GRADE Evidence summary

Considered J What is the safety for the mother and fetus, infant, ch	nild, adult	of adminis	tering a re	epeat course	e(s) of antena	tal corticoster	oids to		
women with preterm prelabour rupture of membrane 1. Outcome measures:		Ouglity of evidence					portance of outcome		
Matemal Outcomes	HIGH MOD LOW V.				in making a decision Critical Important				
	mon	MOD	LOW	LOW	Citicai	Important	Importan		
D1 Chorioamnionitis	1				1				
D2 Puerperal sepsis	1				1				
O ₃ Pyrexia after entry to trial				NR		1			
O4 Intrapartum fever requiring antibiotics				NR		1			
O5 Post natal pyrexia	1					1			
O6 Maternal quality of life				NR V.	1		Not		
Infant Outcomes	HIGH	MOD	LOW	LOW	Critical	Important	Importan		
O1 Combined fetal and neonatal death	~				1				
O2 Neonatal death	~				1				
O3 Fetal death		1			1				
O ₄ RDS	4				4				
O5 Composite of serious outcomes for the infant	*				*				
O ₆ Neurosensory disability (composite of impairments) for infant as a child				NR	~				
O7 Survival free of neurosensory disability for the infant as a child				NR	4				
O8 Survival free of metabolic disease for the infant as a child				NR		*			
O9 Neurosensory disability (composite of impairments) for infant as an adult				NR	4				
O_{10} Survival free of neurosensory disability for the infant as an adult				NR	4				
O ₁₁ Survival free of metabolic disease for the infant as an adult				NR		1			
2. Is there is insufficient evidence to make a	recommen	ndation?							
preterm prelabour rupture of membranes. This level Maternal - The evidence for chorioamnionitis is based on Review that reported the proportion of the women recrui pyrexia requiring treatment and puerperal sepsis is based included in the Crowther (2011) Cochrane systematic reviem embranes. There was no evidence for the other outcome quality of life. Infant - The evidence for infant outcomes is based on up (review that reported the proportion of women recruited with 3. What benefit will the proposed intervention	four trials in ted with pr on one trial iew that rep les of pyrex to 6 trials in with preterr	nvolving 33 eterm prela involving 9 ported a pro ia after trial avolving 440 n prelabour	32 women bour ruptu 082 women portion of entry, intra 06 infants in	included in re of membra and four transformed for women recr apartum feve ncluded in tl	the Crowther ranes. Similarly ials involving uited with pre er requiring ar ne Crowther (2	(2011) Cochran y, the evidence f 2599 women re term prelabour tibiotics, and m	for postnatal spectively, rupture of aternal		
Evidence statement Quality of evidence					evidence				
<i>Maternal</i> - There is no evidence of increased risk of ch puerperal sepsis following exposure to a repeat course of the women recruited had preterm prelabour rupture of m <i>Infant</i> - There is evidence of a significant reduction in res course of antenatal corticosteroids compared with no re- had preterm prelabour rupture of membranes at trial entr	of antenatal embranes. piratory dis peat exposi	corticoster stress syndr	oid in trials	s where a pr	roportion of d to a repeat	Not apj			
Judging the benefits in context The evidence is based on well conducted randomised concourse of antenatal corticosteroids, and reported the propopulations included women from Canada, Australia and 4. What harm might the proposed intervention	trolled trial ortion of w New Zeala	vomen with ind, The Ur	preterm, p	relabour rup	oture of memb				
Evidence statement						Quality of ev	ridence		
Evidence statement Maternal - There was no evidence of harm to the mother in terms of increased risk of maternal infection outcomes, where reported. Quality of evidence Infant - There was no evidence of harm to the infant. There was no difference in risk of mortality, or composite Not applicable									

Judging the harms in context			.,	11	
The evidence is direct evidence from randomised co membranes. There was no evidence of increased risk					
5. What is the likely balance between ge		ii, of mercased fisk of mo	itanty for the filla		
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. Overall quality of evidence					
<i>Infant</i> - There is clear benefit for the infant of signilincreased risk of mortality, when exposed to repeat rupture of membranes.	ed risk of respiratory distress syndrome, with no				
Judging the balance of benefits and harms in co Maternal - Repeat antenatal corticosteroids in the pre- Infant - Repeat antenatal corticosteroids in the preser impact of the benefit of reduced risk of respiratory of	esence of preterm pre nce of preterm prelab	our rupture of membrane			
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				
Harms probably outweigh benefits	Consider against/ r	Consider against/make no recommendation			
Benefits clearly don't outweigh harms	D 1 -				
Harms clearly outweigh benefits	Recommend again	st		STRONG	
6. Is the intervention/action implement	table in the New Ze	aland context?		I	
Summary statement Antenatal corticosteroids are already widely in use in	n New Zealand and A				
Yes		Recommend/conside	<u>r</u>		
Not known		Consider economic eval	evaluation		
No		Recommend/consider a	igainst		
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 (<i>number of studies</i> , level of evidence and risk of bias in the in	cluded sti	ıdies)			
Four trials included in the Roberts CPG version 2015 systematic	А	One or more Level I studies with a low risk of bias, or several			
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	В	Level II studies with a low risk of bias One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias			
subsequently diagnosed with chorioamnionitis. Women with chorioamnionitis were not eligible for 14 of the 26 trials included in	С	One or two Level III studies with a low risk of bias or Level I or II studies with moderate risk of bias			
the CPG 2015 version, and no details were provided for the remaining eight trials.	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 af	plicable')				
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,	А	All studies consistent			
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	В	Most studies consistent and inconsistency can be explained			
corticosteroid. There was no difference in risk of postnatal pyrexia. Infant Results were consistent that infants of women with	С	Some inconsistency, reflecting genuine uncertainty around question			
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	D	Evidence is not consistent			
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.		Not applicable (one study only)			
3. Clinical impact (indicate if the study results varied according to some unkno intervention could not be determined)	wn factor	(not simply study quality or sample size) and thus the clinical impact of the			
Maternal The benefit of reductions in risk of perinatal and neonatal death, and respiratory distress syndrome probably outweigh the increased	А	Very large			
risk of maternal infection.		Substantial			
Infant Significant reductions in absolute risk of perinatal death and neonatal death, and significant reduction in absolute risk of	С	Moderate			
respiratory distress syndrome, were seen in favour of a single course of antenatal corticosteroids compared with no antenatal corticosteroids in.	D	Slight / Restricted			
4. Generalisability (how well does the body of evidence match the population and	ıd clinical	settings being targeted by the guideline?)			
Evidence from a variety of healthcare settings. Studies conducted in	А	Evidence directly generalisable to target population			
USA, France, Australia, and The Netherlands.	В	Evidence directly generalisable to target population with some caveats			
	С	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 / Austra	lian healt				
Corticosteroids are readily available in Australia and New Zealand and their use is feasible.	А	Evidence directly applicable to New Zealand / Australian healthcare context			
	В	Evidence applicable to New Zealand / Australian healthcare context with few caveats			
	С	Evidence probably applicable to New Zealand / Australian healthcare context with some caveats			
Other for the second	D	Evidence not applicable to New Zealand / Australian healthcare context			
Other factors (indicate here any other factors that you took into account when a upgrade the recommendation)	ssessing th	e eruaence vase (for example, issues that might cause the group to downgrade or			

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						
		ta from trials that reported they included a prop form a clinical recommendation	ortion of	women with chorioamnionitis. This				
	ON (What recom	mendation(s) does the guideline development group draw		OVERALL GRADE OF RECOMMENDATION				
Use a single course of antenatal corticosteroids for women with chorioamnionitis at risk				Body of evidence can be trusted to guide practice				
of preterm birth.				Body of evidence can be trusted to guide practice in most situations				
Do not delay birth in women with chorioamnionitis to administer a single course of antenatal corticosteroids.			С	Body of evidence provides some support for recommendations(s) but care should be taken in its application				
Where appropriate, mo when antenatal corticos		ith chorioamnionitis for signs of puerperal sepsis een given.	D	Body of evidence is weak and recommendation must be applied with caution				
			PP	Practice Points				
IMPLEMENTATIO information about this. The	N OF RECON	keep a note of specific issues that arise when each recommenda MMENDATION (Please indicate yes or no to the followi ' be used to develop the implementation plan for the guidelines,	ng questions)	s. Where the answer is yes, please provide explanator				
Will this recommendati	ion result in cha	inges in usual care?		YES NO				
Are there any resource implications associated with implementing this recommendation?				ES O				
Will the implementation organised?	n of this recom	mendation require changes in the way care is current	tly YI	ES <u>O</u>				
Are the guideline development group aware of any barriers to implementation of this recommendation?				YES NO				

M19 GRADE Evidence summary

Considered What is the safety for the mother and fetus, infant, c		•			of antonatal	continentareid	e to women	
what is the safety for the mother and fetus, infant, c with chorioamnionitis at risk of preterm birth?	hiid, adult	of adminis	tering a su	ngie course	e of antenata	l corticosteroid	s to women	
1. Outcome measures:		Quality o	f evidence			Importance of outcome in making a decision		
Maternal Outcomes	HIGH	HIGH MOD LOW V.		V. LOW	Critical	Important	Not Important	
O1 Chorioamnionitis	4				1			
O2 Puerperal sepsis					~			
O ₃ Pyrexia after entry to trial				NR				
O4 Intrapartum fever requiring antibiotics				NR				
O5 Post natal pyrexia		*						
O6 Maternal quality of life				NR	1			
Infant Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Importan	
O1 Combined fetal and neonatal death		1			1			
O2 Neonatal death		*			1			
O3 Fetal death			*		4			
O4 RDS		1			4			
O5 Composite of serious outcomes for the infant				NR	4			
O ₆ Neurosensory disability (composite of impairments) for infant as a child				NR	1			
O7 Survival free of neurosensory disability for the infant as a child				NR	1			
O8 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	1			
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	recommen	ndation?	1	1	<u> </u>	1	I	
chorioamnionitis. This level of evidence cannot be <i>Maternal</i> - The evidence for chorioamnionitis as an outco 2015 systematic review for a single course of antenatal co trial entry. The evidence for puerperal sepsis is based on trial involving 118 women, included in the Roberts CPG are reported for other maternal infectious morbidity outce <i>Infant</i> - The evidence for infant mortality is based on trial antenatal corticosteroids that recruited and reported a pri reported on fetal death and perinatal death, three trials in reported on respiratory distress syndrome following expiration 3. What benefit will the proposed interventio	me is based orticosteroic two trials in version 201 comes or ma s included in oportion of volving 362 osure to a si	on four tria ls, which re volving 214 5 systemati aternal quali n the Rober women wit t infants rep ngle course	als, involvin ported recru & women, at c review for ity of life. tts CPG ver h chorioam ported on ne	g 356 woma uiting a prop ad the evide r a single co sion 2015 s mionitis at t conatal deat	portion of wor nce for postn urse of antena ystematic revi- rial entry. One h, and three to	men with choric atal pyrexia is ba atal corticosteroi ew for a single c e trial involving	pamnionitis a used on one ids. No data pourse of 139 infants	
Evidence statement	,					Quality of	evidence	
Maternal - The evidence suggests no difference in chor		· .						
women who received a single course of antenatal corti trial entry.		1				Not apj	plicable	
<i>Infant</i> - Significant reductions in the risk of perinatal and antenatal corticosteroids, compared with no exposure proportion of women with chorioamnionitis at trial e between exposure to a single course of antenatal co proportion of women with chorioamnionitis at trial entry	e, were see ntry. There rticosteroid	n in trials was no di	that repor fference in	ted the inc the risk of	lusion of a fetal death			
Judging the benefits in context The evidence is based on up to four randomised controll of antenatal corticosteroids, from a variety of healthcare	settings suc	h as the Un				atic review for a	single cours	
What harm might the proposed intervention	on/action	do:						

Judging the harms in context Maternal - The evidence is from two trials included th Infant - There is no evidence of harm to the infant, and	¥			2	
syndrome. 5. What is the likely balance between go	0		,	1 2	
Evidence statement Overall Maternal - While there was no difference in risk of chorioamnionitis or postnatal pyrexia requiring treatment quality of evidence following a single course of antenatal corticosteroids in women with chorioamnionitis at trial entry, the evidence Not applicable Infant - The evidence suggests substantial benefit for the infant in terms of significant reductions in risk of Period perinatal and neonatal death, and respiratory distress syndrome. Overall					
Judging the balance of benefits and harms in co Maternal - There is evidence of increased risk of puer in trials that recruited and reported on women with a facilities for monitoring and treating infection, the in There is no evidence for harm to the mother from in Infant - There are significant health benefits for the in syndrome.	peral sepsis in the me chorioamnionitis at tr npact of this harm is nereased risk of other	rial entry. However, in a c low, particularly in view c r infection outcomes.	linical healthcare s of the substantial h	etting where there are ealth benefits for the infant.	
Benefits clearly outweigh harms	Recommend	Recommend			
Benefits probably outweigh harms	CONDITIONAL				
Not known Make a recommendation for research (see 8 below)			<u>WEAK</u>		
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	0			511(61(6	
6. Is the intervention/action implement	able in the New Ze	ealand context?			
Summary statement Antenatal corticosteroids are already widely in use in	New Zealand and A	ustralia			
Yes		Recommend/conside	<u>er</u>		
Not known		Consider economic eval	luation		
No		Recommend/consider a	against		
7. Final 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				JAL	
antenatal corticosteroids have been given.	nomus for signs of p	uciperal sepsis when			
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?							
		l of evidence and risk of bias in the in	ncluded st	tudies)			
		Crowther (2011) Cochrane h chorioamnionitis at time of	А			el I studies with a low risk of bias, or several ith a low risk of bias	
trial entry. The remaining	two trials did	l not provide information on s were included in their trials.	В	One or	One or two Level II studies with a low risk of bias, or SR Level III studies with a low risk of bias		
Therefore no randomised controlled trial data was available.			С	II studi	One or two Level III studies with a low risk of bias or Le II studies with moderate risk of bias		
			D	Level I bias	V studies o	or Level I to III studies/SRs with a high risk of	
2. Consistency (if only one	e study was ava	ilable, rank this component as 'not a	pplicable')			
N/A			А		lies consist		
			В			sistent and inconsistency can be explained	
			С	Some is questio		cy, reflecting genuine uncertainty around	
			D		ce is not co		
		1 1 1	NA			ne study only)	
3. Clinical impact (indica intervention could not be deter		esults varied according to some unking	own factor	r (not simpl	y study qual	ity or sample size) and thus the clinical impact of the	
N/A			A	Very la			
			B	Substan			
			C D	Moder:	ate ' Restricted	1	
4. Generalisability (how well does the body of evidence match the population and clinical settings being targeted by the guideline?)							
N/A		555	А	-		generalisable to target population	
			В	Eviden	ce directly	generalisable to target population with some	
			С	Eviden	caveats Evidence not directly generalisable to target population but could		
				be sens Eviden	ibly applie ce not dire	d ectly generalisable to target population and hard	
			D			sensible to apply	
			alian heal			of health services / delivery of care and cultural factors?)	
Corticosteroids are readily and their use is feasible.	y available in	Australia and New Zealand	А	healthc	are contex		
			В	Evidence applicable to New Zealand / Australian healthcare context with few caveats			
			С	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 her upgrade the recommendation)	re any other fact	ors that you took into account when a	assessing i	the evidence	base (for ex	ample, issues that might cause the group to downgrade or	
					., ,		
account)	ENI MAII	XIX (summarise the development gro	up s synti	vesis of the	evidence rela	ting to the key question, taking all the above factors into	
Component	Rating	Description					
1. Evidence base	NA	Not applicable					
2. Consistency	NA	Not applicable					
 Clinical Impact Generalisability 	NA NA	Not applicable Not applicable					
5. Applicability	NA	Not applicable					
Evidence statement	1 1 1	rvot applicable					
					steroids in	women with chorioamnionitis.	
RECOMMENDATION <i>draw from this evidence?</i> Use	· ·	mendation(s) does the guideline devel ts where possible)	opment gr	roup	OVER	ALL GRADE OF RECOMMENDATION	
~		woman with chorioamnionitis a	t risk of		A	Body of evidence can be trusted to guide	
preterm birth.					В	practice Body of evidence can be trusted to guide	
	men with cho	rioamnionitis to administer rep	eat antei	natal	D	practice in most situations Body of evidence provides some support for	
corticosteroids.		.,			С	recommendations(s) but care should be taken in its application	
Use repeat antenatal corti discretion of the attending		women with chorioamnionitis	at the			Body of evidence is weak and	
					D	recommendation must be applied with caution	
			-				

Where appropriate, monitor women with chorioamnionitis for signs of puerperal sepsis when antenatal corticosteroids have been given	РР	Practice Points
UNRESOLVED ISSUES (If needed, keep a note of specific issues that arise when each recomment		
IMPLEMENTATION OF RECOMMENDATION (Please indicate yes or no to the fold		ions. Where the answer is yes, please provide explanatory
information about this. This information will be used to develop the implementation plan for the guideli	ines)	
Will this recommendation result in changes in usual care?		YES
		NO
Are there any resource implications associated with implementing this recommendation	15	YES
		NO
Will the implementation of this recommendation require changes in the way care is curr	ently	YES
organised?		NO
Are the guideline development group aware of any barriers to implementation of this		YES
recommendation?		NO

M20 GRADE Evidence summary

What is the safety for the mother and fetus, infant,	Judgement	of adminis	tering a re	peat course	e(s) of anten	atal corticoster	oids to	
 Outcome measures: 			f evidence	-	Imp	oortance of outcome		
laternal Outcomes	HIGH MO			V. LOW	In Critical	Important Important		
D ₁ Chorioamnionitis				NR	1		Importan	
D ₂ Puerperal sepsis				NR	· ·			
D ₃ Pyrexia after entry to trial				NR	•			
04 Intrapartum fever requiring antibiotics				NR		4		
05 Post natal pyrexia				NR		4		
D6 Maternal quality of life				NR	1	,		
nfant Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Importan	
D1 Combined fetal and neonatal death				NR	1			
D2 Neonatal death				NR				
D ₃ Fetal death				NR				
D4 RDS				NR	4			
D5 Composite of serious outcomes or the infant				NR	1			
06 Neurosensory disability (composite of impairments) or infant as a child				NR	4			
07 Survival free of neurosensory disability for the afant as a child				NR	4			
D ₈ Survival free of metabolic disease for the infant as a hild				NR		*		
D ₉ Neurosensory disability (composite of impairments) or infant as an adult				NR	4			
D10 Survival free of neurosensory disability for the afant as an adult				NR	4			
D ₁₁ Survival free of metabolic disease for the infant as n adult				NR		1		
2. Is there is insufficient evidence to make	a recommen	ndation?						
 horioamnionitis. This level of evidence cannot be <i>laternal</i> - No maternal infectious morbidity data were rehere women with chorioamnionitis were recruited. We itals in the Crowther (2011) Cochrane systematic review <i>afant</i> - No infant primary outcome data were reported it women with chorioamnionitis were recruited. Women we crowther (2011) Cochrane systematic review. 3. What benefit will the proposed intervent 	eported in th omen with ch v. n the randon vith chorioan	e randomise norioamnion nised contro nnionitis at	ed controlle nitis at the t olled trials o	ed trials of re time of trial of repeat cou	entry were executed anten	cluded from eig	ht of the ten ids where	
Evidence statement						Quality of	evidence	
<i>Maternal</i> - No relevant data for maternal primary outco- netuded in the Crowther (2011) Cochrane systematic ntry. Women with chorioamnionitis at the time of tria crowther (2011) Cochrane systematic review. <i>ufant</i> - No relevant data for infant primary outcome netuded in the Crowther (2011) Cochrane systematic ntry. Women with chorioamnionitis at the time of tria crowther (2011) Cochrane systematic review.	review that r l entry were es were repo review that r	ecruited wo excluded fr orted in the ecruited wo	omen with om the rem two rando omen with	chorioamnic naining eight omised con chorioamnic	onitis at trial trials in the trolled trials onitis at trial	Not apj		
udging the benefits in context						1		
J/A								
4. What harm might the proposed interven	tion/action	do?						
Evidence statement <i>Iaternal</i> - No relevant data for maternal primary outco- cluded in the Crowther (2011) Cochrane systematic ntry. Women with chorioamnionitis at the time of tria crowther (2011) Cochrane systematic review.	review that r	ecruited wo	omen with	chorioamnio	onitis at trial	Quality of Not app		

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. Judging the balance of benefits and harms in context				Quality of evidence Not applicable
N/A				
Benefits clearly outweigh harms	Recommend			STRONG
Benefits probably outweigh harms	Consider			CONDITIONAL
Not known	Make a recommen	dation for research (see 8	below)	WEAK
Benefits probably don't outweigh harms	Consider against/r	naka no recommendation		CONDITIONAL
Harms probably outweigh benefits	Consider against/1	nake no recommendation	L	CONDITIONAL
Benefits clearly don't outweigh harms	Recommend against			STRONG
Harms clearly outweigh benefits	SINONG			
6. Is the intervention/action implementable in the New Zealand context?				
Summary statement Antenatal corticosteroids are already widely in use ir	n New Zealand and A	ustralia.		
Yes		Recommend/conside	<u>er</u>	
Not known		Consider economic eva	luation	
No		Recommend/consider	against	
7. Final recommendation				
Repeat antenatal corticosteroids for a woman with chorioamnionitis at risk of preterm birth. Strength of recommendation Please select level Do not delay birth in women with chorioamnionitis to administer repeat antenatal corticosteroids. STRONG CONDITIONAL WEAK (Practice Points) 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. 8. Recommendations for research				IAL
 Randomised trials are needed to investigate if antenatal corticosteroids 7 days previously and 			women at risk of 1	preterm birth who had

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 adwith antepartum haemorrhage at risk of preterm birth?	ministe	ring a single course of antenatal corticosteroids to women				
1. Evidence base (number of studies, level of evidence and risk of bias in the in	icluded si	tudies)				
Six of the 26 trials included in the Roberts CPG version 2015 systematic review for a single course of antenatal corticosteroids		One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias				
reported including a small proportion of women with an antepartum haemorrhage in their trials.	В	One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias				
	С	One or two Level III studies with a low risk of bias or Level I or II studies with moderate risk of bias				
		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 ap	pplicable)				
Maternal The evidence for chorioamnionitis appears consistent with the	А	All studies consistent				
overall treatment effect with no difference seen in the risk.	В	Most studies consistent and inconsistency can be explained				
Infant Evidence for perimetal death, fatal death, permetal death, and	С	Some inconsistency, reflecting genuine uncertainty around question				
Evidence for perinatal death, fetal death, neonatal death, and respiratory distress syndrome appears to be consistent with the	D	Evidence is not consistent				
overall treatment effect with no difference seen in the risk.	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.	А	Very large				
	В	Substantial				
	С	Moderate				
	D	Slight / Restricted				
4. Generalisability (how well does the body of evidence match the population and	nd clinica	l settings being targeted by the guideline?)				
Evidence from a variety of healthcare settings. Studies conducted in USA, France, Australia, and The Netherlands.	А	Evidence directly generalisable to target population				
	В	Evidence directly generalisable to target population with some caveats				
	С	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 / Austra	lian heal					
Corticosteroids are readily available in Australia and New Zealand and their use is feasible.	А	Evidence directly applicable to New Zealand / Australian healthcare context				
	В	Evidence applicable to New Zealand / Australian healthcare context with few caveats				
	С	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 a upgrade the recommendation)	ussessing i	the evidence base (for example, issues that might cause the group to downgrade or				

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 from this evidence? Use action			OVERALL GRADE OF RECOMMENDATION				
Use a single course of ant	enatal cortic	Α	Body of evidence can be trusted to guide practice				
haemorrhage at risk of pr		В	Body of evidence can be trusted to guide practice in most situations				
Where appropriate, monit haemorrhage when anten		С	Body of evidence provides some support for recommendations(s) but care should be taken in its application				
				Body of evidence is weak and recommendation must be applied with caution			
		PP	Practice Points				
	12	keep a note of specific issues that arise when each recommendat	2				
information about this. This i	nformation wil	l be used to develop the implementation plan for the guidelines)					
Will this recommendation result in changes in usual care?				YES			
		N	NO				
Are there any resource im	plications as	Y	YES				
		N	NO				
Will the implementation of this recommendation require changes in the way care is currently				YES			
organised?			NO				
	oment group aware of any barriers to implementation of this			YES			
recommendation?			N	<u>NO</u>			

M21 GRADE Evidence summary

Considered What is the safety for the mother and fetus, infant, cl		Ũ			of antenata	l corticosteroid	ls to women
with antepartum haemorrhage at risk of preterm birt		01 44111110	tering a on	ingre course			
1. Outcome measures:	Quality of evidence				Importance of outcome in making a decision		
Maternal Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O1 Chorioamnionitis	-				~		
O2 Puerperal sepsis					*		
O ₃ Pyrexia after entry to trial		4				4	
O4 Intrapartum fever requiring antibiotics				NR		4	
O ₅ Post natal pyrexia				NR		4	
O ₆ Maternal quality of life				NR	1	•	
Infant Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O1 Combined fetal and neonatal death		1			~		
O2 Neonatal death					*		
O₃ Fetal death			~		~		
O4 RDS		*			*		
O ₅ Composite of serious outcomes for the infant				NR	*		
O ₆ Neurosensory disability (composite of impairments) for infant as a child				NR	*		
O7 Survival free of neurosensory disability for the infant as a child				NR	*		
Os Survival free of metabolic disease for the infant as a child				NR		1	
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		4	
2. Is there is insufficient evidence to make a	recommen	ndation?		•			·
Evidence statement - Evidence is based on a subset antepartum haemorrhage. This level of evidence can <i>Maternal</i> - Evidence for maternal outcomes is based on si review for a single course of antenatal corticosteroids tha their trials. Four trials involving 442 women reported on women, and the evidence for pyrexia after trial entry requ other measures of maternal infection or maternal quality <i>Infant</i> - Evidence for infant outcomes is based on random single course of antenatal corticosteroids that recruited an Fetal death and perinatal death is based on five trials invo	nnot be use x randomis t recruited a chorioamni uiring treatm of life. nised contro nd reported olving 800 ir	ed to form ed controlle and reporter onitis, evide nent is base on the prop of ants, and	a clinical r ed trials inc d on the pre ence for pue d on one tri included in t	ecomment luded in the oportion of erperal seps ial involving he Roberts (women with	lation Roberts CPC women with is is based on 118 women. CPG version	G version 2015 s antepartum haei four trials invol No data were re 2015 systematic naemorrhage in	ystematic morrhage in ving 403 eported for review for a their trials.
involving 870 infants reported data on respiratory distres3. What benefit will the proposed intervention							
Evidence statement	, uction i	iuve.					fevidence

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 Not applicable 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. 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. What harm might the proposed intervention/action do? 4. Quality of evidence Evidence statement 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 Not applicable 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.

Infant - There was no evidence of any harm to the inf								
Judging the harms in context <i>Maternal</i> - 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. <i>Infant</i> - There is no evidence of harm to the infant.								
5. What is the likely balance between good and harm?								
Evidence statement <i>Maternal</i> - The evidence from trials that recruited haemorrhage at trial entry suggests an increased risk single course of antenatal corticosteroids compared to <i>Infant</i> - There are significant health benefits for the perinatal death and risk of respiratory distress syndre	Overall quality of evidence 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 recomme	endation for research (se	<u>WEAK</u>					
Benefits probably don't outweigh harms	Consider against/	nake no recommendation		CONDITIONAL				
Harms probably outweigh benefits	Consider against/1	make no recommendation	CONDITIONAL					
Benefits clearly don't outweigh harms	Recommend again	et	STRONG					
Harms clearly outweigh benefits	0			SIRONG				
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.								
Yinchata concoscioles are aready widely in use in Yes	Thew Zealand and T	Recommend/consider						
Not known		Consider economic evaluation						
No		Recommend/consider against						
7. Final recommendation								
Use a single course of antenatal corticosteroids for w risk of preterm birth. Where appropriate, monitor for signs of puerperal so	Strength of red STRONG CONDITION WEAK (Practi							
haemorrhage when antenatal corticosteroids have been given. 8. Recommendations for research								
o. Accommendations 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 antepartum haemorrhag			niniste	ring repeat antenatal corticosteroids to women with		
1. Evidence base (number	of studies, lev	el of evidence and risk of bias in the in	cluded st	udies)		
	proportion	Crowther, 2011 review of women with an antepartum	А	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias		
haemorrhage in their trials			В	One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias		
			С	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 ava	uilable, rank this component as 'not ap	plicable')		
Maternal The evidence for chorioamnionitis, postnatal pyrexia and puerperal sepsis appears to be consistent with the overall treatment effect with				All studies consistent		
	isk between	those women treated with	В	Most studies consistent and inconsistency can be explained		
Infant Evidence for perinatal dea	.th, fetal dea	th, neonatal death, respiratory	С	Some inconsistency, reflecting genuine uncertainty around question		
distress syndrome, severe a of serious infant outcomes treatment effect observed	s appears co		D	Evidence is not consistent		
corticosteroids compared	with no repo	eat exposure.	NA	Not applicable (one study only)		
3. Clinical impact (indicat intervention could not be determ		results varied according to some unkno	wn factor	r (not simply study quality or sample size) and thus the clinical impact of the		
The proportion of women and infants in trials that reported including women with an antepartum haemorrhage are too small to				Very large		
make inferences about ber interpreted with caution.	rences about benefits and harms, and the data should be		В	Substantial		
			С	Moderate		
			D	Slight / Restricted		
			ıd clinica	l settings being targeted by the guideline?)		
Evidence from a variety of Canada, Australia and New		settings. Studies conducted in he United States, and a	А	Evidence directly generalisable to target population		
multicentre trial involving	20 countries	S.	В	Evidence directly generalisable to target population with some caveats		
			С	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		
	-		lian heal	theare context in terms of health services / delivery of care and cultural factors?)		
Corticosteroids are readily and their use is feasible.	available in	Australia and New Zealand	А	Evidence directly applicable to New Zealand / Australian healthcare context		
			В	Evidence applicable to New Zealand / Australian healthcare context with few caveats		
			С	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 upgrade the recommendation)	any other fac	tors that you took into account when a	ssessing i	the evidence base (for example, issues that might cause the group to downgrade or		
		ata from trials that reported th ce cannot be used to form a cl		uded a proportion of women with an antepartum ecommendation		
EVIDENCE STATEMI account)	ENT MAT	RIX (summarise the development grou	up's synti	besis of the evidence relating to the key question, taking all the above factors into		
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	Not applicable					
5. Applicability	NA	Not applicable	Not applicable					
Evidence statement								
RECOMMENDATIO from this evidence? Use action		mmendation(s) does the guideline development group draw here possible)		OVERALL GRADE OF RECOMMENDATION				
		woman with an antepartum haemorrhage at risk of	А	Body of evidence can be trusted to guide practice				
preterm birth.				Body of evidence can be trusted to guide practice in most situations				
Where appropriate, monitor for signs of puerperal sepsis in women with an antepartum haemorrhage when antenatal corticosteroids have been given.			С	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				
			РР	Practice Points				
IMPLEMENTATION	I OF RECO	keep a note of specific issues that arise when each recommendation MMENDATION (Please indicate yes or no to the following Il be used to develop the implementation plan for the guidelines)	5	1 0 17				
Will this recommendation	n result in ch							
	in result in en	anges in usual care?	Y	ES				
		anges in usual care?	YI N					
Are there any resource in		anges in usual care? ssociated with implementing this recommendation?		0				
Are there any resource in			N	Q ES				
Will the implementation	nplications as			0 ES Q				
	nplications as	ssociated with implementing this recommendation?		Q ES Q ES				
Will the implementation organised?	nplications as of this recorr	ssociated with implementing this recommendation?		0 ES 0 ES 0				

M22 GRADE Evidence summary

Considered	Judgement	t - Strength	of recom	mendation			
What is the safety for the mother, fetus, infant, child with antepartum haemorrhage at risk of preterm birt		dministeri	ng a repea	t course(s)	of antenatal	corticosteroids	to women
1. Outcome measures:		Quality o	f evidence		Importance of outcome in making a decision		
Matemal Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O1 Chorioamnionitis	*				1		
O ₂ Puerperal sepsis	1				1		
O ₃ Pyrexia after entry to trial				NR		4	
O4 Intrapartum fever requiring antibiotics				NR		4	
O5 Post natal pyrexia		-				1	
O6 Maternal quality of life				NR	1		
Infant Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O1 Combined fetal and neonatal death		1			1		
O2 Neonatal death		1			1		
O3 Fetal death			*		1		
O4 RDS		-			1		
O ₅ Composite of serious outcomes for the infant		4			4		
O ₆ Neurosensory disability (composite of impairments) for infant as a child				NR	1		
O7 Survival free of neurosensory disability for the infant as a child				NR	4		
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	1		
O ₁₀ Survival free of neurosensory disability for the infant as an adult				NR	1		
O ₁₁ Survival free of metabolic disease for the infant as an adult				NR		*	
2. Is there is insufficient evidence to make a	recommer	ndation?					
Evidence statement - Evidence is based on a subset antepartum haemorrhage. This level of evidence can						tion of women	with an
<i>Maternal</i> - The evidence for maternal outcomes is based of and reported a proportion of women who had an antepar corticosteroids with those who did not. Five trials involve on postnatal pyrexia requiring treatment, and three trials in measures of maternal infection or maternal quality of life <i>Infant</i> - The evidence for infant outcomes is based on the reported a proportion of women who had an antepartum	rtum haemo ing 3776 wo involving 23 trials includ	orrhage, and omen report 357 women led in the C	compared red on chor reported of rowther (20	those who l ioamnionitis n puerperal 011) Cochra	had received a s, one trial inv sepsis. No da ne systematic	a repeat course of olving 982 worn ta was reported review that recr	of antenatal ten reported for other uited 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	Not applicable
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.	
Judging the benefits in context	
The evidence is based on trials included in the Crowther (2011) Cochrane systematic review that recruited and report	red a proportion of women
with antepartum haemorrhage. They are conducted trials involving women exposed to repeat antenatal corticosteroic	ls (or placebo) after
remaining at risk of imminent preterm birth following an initial single course of antenatal corticosteroids. The popula	ations were drawn from a
variety of healthcare settings including Canada, Australia and New Zealand, the United States, as well as a multicentry	e trial involving 20 countries.
4. What harm might the proposed intervention/action do?	
Endern statement	Or ality of anidam as
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 <i>Infant</i> - There was no evidence of health harms for th in trials that recruited and reported a proportion of y	he infant following ex	posure to repeat antenatal		Not applicable	
Judging the harms in context Direct evidence from trials conducted in women exp following an initial single course suggests no health h	harms for the mother		emaining at immin	nent risk of preterm birth	
5. What is the likely balance between go	ood and harm?				
Evidence statement <i>Maternal</i> - There are no clear direct health benefits for exposure to repeat antenatal corticosteroids. There of <i>Infant</i> - There is evidence for substantial benefit for t respiratory distress syndrome and composite serious	loes not appear to be the infant in terms of outcome, with no in	any increased risk of infect significant reductions in r	ction.	Overall quality of evidence Not applicable	
Judging the balance of benefits and harms in co Maternal - It is unlikely that women with antepartum corticosteroids. The impact of any potential harm we infection. Infant - It is likely that exposure to repeat antenatal co The impact of reduced risk of respiratory distress sym- preterm infants.	haemorrhage would ould be low in health orticosteroids for infa	care settings with facilities ants of mothers with an an	for monitoring sintepartum haemon	igns and timely treatment of rhage is highly beneficial.	
Benefits clearly outweigh harms	Recommend			STRONG	
Benefits probably outweigh harms	Consider			CONDITIONAL	
Not known	Make a recomme	endation for research (se	<u>e 8 below)</u>	<u>WEAK</u>	
Benefits probably don't outweigh harms	Consider against/1	CONDITIONAL			
Harms probably outweigh benefits	Gonsteler against/	nake no recommendation		CONDITION	
Benefits clearly don't outweigh harms	Recommend again	st		STRONG	
Harms clearly outweigh benefits	Recommence again	St.		511(61(6	
6. Is the intervention/action implement	able in the New Ze	ealand context?			
Summary statement Consider evidence of cost effectiveness, financial (cost and value Antenatal corticosteroids are already widely in use in		*			
Yes		Recommend/consider	[
Not known		Consider economic eval	uation		
No		Recommend/consider a	gainst		
7. Final recommendation					
Repeat antenatal corticosteroids for a woman with an antepartum haemorrhage at risk of preterm birth. Strength of recommendation Where appropriate, monitor for signs of puerperal sepsis in women with an antepartum haemorrhage when antenatal corticosteroids have been given. STRONG 8. Recommendations for research					

M23 Women with a multiple pregnancy at risk of preterm birth – Single course of antenatal corticosteroids

M23 NHMRC Evidence summary

Γ

				istering a single course of antenatal corticosteroids to women isk factor(s) for preterm birth?
1. Evidence base (number	• of studies, lev	el of evidence and risk of bias in the in	cluded st	udies)
review for a single course	of antenatal		А	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias
including a small proportion with an additional risk of i		n with a multiple pregnancy eterm birth.	В	One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias
			С	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 ava	ailable, rank this component as 'not ap	plicable')
Maternal The evidence for chorioan intrapartum or postnatal r		vrexia after trial entry, ring treatment was consistent	А	All studies consistent
with the overall treatment between those treated with	effect with	no difference seen in the risk corticosteroids and those with	В	Most studies consistent and inconsistency can be explained
no treatment. Infant			С	Some inconsistency, reflecting genuine uncertainty around question
	me, modera	te/severe respiratory distress	D	Evidence is not consistent
difference seen in the risk corticosteroids and those	between the with no exp	osure.	NA	Not applicable (one study only)
3. Clinical impact (indicat intervention could not be determ		results varied according to some unkno	wn factor	r (not simply study quality or sample size) and thus the clinical impact of the
The proportion of women including women with an	n and infants antepartum	haemorrhage are too small to	А	Very large
make inferences about ber interpreted with caution.	nefits and ha	arms. The data should be	В	Substantial
			С	Moderate
			D	Slight / Restricted
4. Generalisability (how n	vell does the bo	ndy of evidence match the population an	ıd clinica	l settings being targeted by the guideline?)
		settings. Studies conducted in JK, Finland, New Zealand and	А	Evidence directly generalisable to target population
The Netherlands	,	_ , ,	В	Evidence directly generalisable to target population with some caveats
			С	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
			lian heal	theare context in terms of health services / delivery of care and cultural factors?)
Corticosteroids are readily and their use is feasible.	available in	Australia and New Zealand	А	Evidence directly applicable to New Zealand / Australian healthcare context
			В	Evidence applicable to New Zealand / Australian healthcare context with few caveats
			С	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 upgrade the recommendation)	e any other fac	tors that you took into account when a	ssessing i	he evidence base (for example, issues that might cause the group to downgrade or
		ata from trials that reported th ence cannot be used to form a		uded a proportion of women with a multiple pregnancy at risk al recommendation
EVIDENCE STATEM	ENT MAT	RIX (summarise the development grou	up's synti	besis of the evidence relating to the key question, taking all the above factors into
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	Not applicable					
5. Applicability	NA	Not applicable						
Evidence statement								
RECOMMENDATION from this evidence? Use action		nmendation(s) does the guideline development group draw ere possible)		OVERALL GRADE OF RECOMMENDATION				
		osteroids for women with a multiple pregnancy	Α	Body of evidence can be trusted to guide practice				
with an additional risk fac	tor(s) for pr	eterm birth.	В	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. Where appropriate, monitor women with a multiple pregnancy at risk of preterm birth for signs of puerperal sepsis when antenatal corticosteroids have been given.			С	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				
			РР	Practice Points				
IMPLEMENTATION	OF RECO	keep a note of specific issues that arise when each recommendate MMENDATION (Please indicate yes or no to the followin	5	1 V 1/				
information about this. This i	nformation wi	ll be used to develop the implementation plan for the guidelines)						
		* * * * 0 ,	YI					
Will this recommendation	result in ch	anges in usual care?	N	<u>0</u>				
Will this recommendation	result in ch	* * * * 0 ,		0 25 25				
Will this recommendation Are there any resource im Will the implementation of	result in ch	anges in usual care?	Iy YI	0 33 0 23 35				
Will this recommendation Are there any resource im Will the implementation or organised?	n result in ch pplications as	anges in usual care?		0 2S 0 2S 0 0				

M23 GRADE Evidence summary

Considered] What is the safety for the mother and fetus, infant, cl	-	-			ofantonatal	corticostaroid	e to women	
 What is the safety for the mother and fetus, infant, ci with a multiple pregnancy (twins and higher order) y Outcome measures: 		ditional ris		for pretern	n birth? Imp	portance of outcome making a decision		
Matemal Outcomes	HIGH	HIGH MOD		V. LOW	Critical	Important	Not Important	
O1 Chorioamnionitis	1				1			
O2 Puerperal sepsis		1						
O3 Pyrexia after entry to trial		1				4		
O4 Intrapartum fever requiring antibiotics		-				4		
O5 Post natal pyrexia	1					· ·		
O6 Maternal quality of life				NR	1			
Infant Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Importan	
O1 Combined fetal and neonatal death		1		20 11	1		Importan	
O2 Neonatal death								
O₃ Fetal death			*		-			
O4 RDS			-		* *			
O ₅ Composite of serious outcomes				NR				
for the infant O ₆ Neurosensory disability (composite of impairments)				NR	*			
for infant as a child O7 Survival free of neurosensory disability for the					1			
infant as a child				NR	1			
O8 Survival free of metabolic disease for the infant as a child				NR		4		
O ₉ Neurosensory disability (composite of impairments) for infant as an adult				NR	1			
O10 Survival free of neurosensory disability for the infant as an adult				NR	1			
O ₁₁ Survival free of metabolic disease for the infant as an adult				NR		*		
2. Is there is insufficient evidence to make a	recommen	ndation?	•					
multiple pregnancy with an additional risk factor(s) is recommendation Maternal - The evidence is based on twelve trials included corticosteroids that recruited and reported a proportion of these Clinical Practice guidelines. Seven trials, involving 1 on pyrexia after trial entry requiring antibiotics, one trial i involving 1105 women reported on postnatal pyrexia requ data were reported for maternal quality of life. Infant - The evidence is based on twelve trials included in corticosteroids that recruited and reported a proportion of perinatal death, twelve trials involving 3290 infants report trials involving 3250 infants reported on respiratory dister 3. What benefit will the proposed intervention	in the Rob of women w 862 womer nvolving 1(uiring treatr the Robert: the Robert: of women w ted on neor ess syndrom	erts CPG v vith a multip n, reported 11 women r nent, and fi s CPG versi vith a multip natal death, ne. No data	ersion 2015 ble pregnan on chorioar eported on ve trials inv on 2015 sy ble pregnan and ten tria	systematic c cy, nine of v nnionitis. Tr intrapartum olving 569 v stematic rev cy. Ten trial ls involving	review for a si which reported wo trials invol a pyrexia requi women report iew for a sing s involving 32 3225 trials rep	ngle course of a l maternal outco ving 219 wome rring treatment. ed on puerperal le course of anto 25 infants repor ported on fetal o	ntenatal mes for n reported Four trials sepsis. No enatal rted on leath. Twelvo	
Evidence statement					-	Quality of	evidence	
Maternal - There was no increase in risk of chorioamni pyrexia requiring treatment between women exposed to exposed in trials that recruited and reported a proportion <i>Infant</i> - There was a significant reduction in the risk of per fetal death in trials that recruited and reported a proporti significant reduction in respiratory distress syndrome, a reported for a composite of serious infant outcomes.	a single cou of women rinatal and on of wom	urse of ante with a mult neonatal de en with a m	natal cortic iple pregna ath, and no ultiple preg	costeroids ar ncy. difference i gnancy. The	nd those not in the risk of re was also a	Not apj	plicable	
Judging the benefits in context The evidence is direct evidence from trials comparing our with those exposed to placebo or not exposed to antenata settings, including Canada, the United Kingdom, South A sizes for infant mortality outcomes, where applicable, are	al corticoste Africa, Tunis substantial	eroids. The sia, the Unit and demor	trials were o ed States, F	conducted in Finland, Nev	n a variety of o v Zealand and	countries and he	althcare	
4. What harm might the proposed intervention	on/action	uo ?					• •	
Evidence statement Maternal - There was an increased risk of puerperal sepsis	among wor	men expose	d to a singl	e course of	antenatal	Quality of ev	idence	

	the infant.				
Judging the harms in context					
The evidence is from trials that recruited and a 5. What is the likely balance between		omen with a multiple pre	gnancy.		
Evidence statement Maternal - There is no increased risk of chorioz evidence suggests an increased risk of puerper Infant - Significant reductions in mortality and	al sepsis.		ough the	Overall quality of evidence Not applicable	
Judging the balance of benefits and harms Exposure to a single course of antenatal cortic and treating signs of possible puerperal sepsis. morbidity outweigh potential low impact harm	costeroids is unlikely to cau . The significant health ben				
Benefits clearly outweigh harms	Recommend			STRONG	
Benefits probably outweigh harms	Consider			CONDITIONAL	
Not known	Make a recomme	endation for research (s	ee 8 below)	WEAK	
Benefits probably don't outweigh harms		1 1.1		CONDUTIONAL	
Harms probably outweigh benefits	Consider against/i	make no recommendation	1	CONDITIONAL	
Benefits clearly don't outweigh harms					
Harms clearly outweigh benefits	Recommend again	ist		STRONG	
6. Is the intervention/action imple	ementable in the New Ze	ealand context?			
Summary statement Antenatal corticosteroids are already widely in	was in New Zeeland and A	anotaolio.			
Yes	use in new Zealand and T	Recommend/conside	er		
Not known		Consider economic evaluation			
No		Recommend/consider against			
7. Final recommendation			-		
Use a single course of antenatal corticosteroid additional risk factor(s) for preterm birth. Where appropriate, estimate the risk of pretern prediction tests including fetal fibronectin and Where appropriate, monitor women with a mu of puerperal sepsis when antenatal corticoster	m birth by considering the assessment of cervical lengultiple pregnancy at risk of	use of adjunct gth.	Strength of a STRONG CONDITIC WEAK (Prac		
			1		

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 multiple pregnancy (twins and higher order) with an additional r		
1. Evidence base (number of studies, level of evidence and risk of bias in the in	cluded si	udies)
Nine of the ten trials in the Crowther, 2011 systematic review reporting maternal and infant primary outcomes for these Clinical	А	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias
Practice Guidelines included a proportion of women in their trials who had a multiple pregnancy with an additional risk of preterm	В	One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias
birth.	С	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 ap	plicable)
Maternal Evidence for chorioamnionitis, postnatal pyrexia requiring treatment and puerperal sepsis is consistent with the overall treatment effect.	А	All studies consistent
There was no difference between those treated with repeat antenatal corticosteroids and those not treated.	В	Most studies consistent and inconsistency can be explained
Infant Evidence for perinatal death, fetal death, neonatal death and severe respiratory distress syndrome the size of the treatment effect was	С	Some inconsistency, reflecting genuine uncertainty around question
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	D	Evidence is not consistent
overall treatment effect, and there was a significant reduction in risk for infants exposed to repeat antenatal corticosteroids compared with those not exposed.	NA	Not applicable (one study only)
3. Clinical impact (indicate if the study results varied according to some unknow intervention could not be determined)	wn factor	r (not simply study quality or sample size) and thus the clinical impact of the
Maternal There does not appear to be an increase in risk of infection for women with multiple pregnancy and an additional risk of preterm	А	Very large
birth following exposure to repeat antenatal corticosteroids.	В	Substantial
Infant Significant benefits for the infants in terms of reduction in risk of respiratory distress syndrome and a composite of serious infant	С	Moderate
outcomes. There is no evidence of harm for infants born of multiple pregnancies exposed to repeat antenatal corticosteroids.	D	Slight / Restricted
4. Generalisability (how well does the body of evidence match the population and	ed clinica	l settings being targeted by the guideline?)
Evidence from a variety of healthcare settings. Studies conducted in USA, France and Australia.	А	Evidence directly generalisable to target population
	В	Evidence directly generalisable to target population with some caveats
	С	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 / Austral	lian heal	theare 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.	А	Evidence directly generalisable to target population
	В	Evidence applicable to New Zealand / Australian healthcare context with few caveats
	С	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 a upgrade the recommendation)	ssessing i	the evidence base (for example, issues that might cause the group to downgrade or
Evidence is based on a subset of data from trials that reported th of preterm birth. This level of evidence cannot be used to form a		

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	applicable					
4. Generalisability	NA	Not applicable						
5. Applicability	NA	Not applicable	Not applicable					
Evidence statement								
RECOMMENDATI from this evidence? Use acc		nmendation(s) does the guideline development group draw ere possible)		OVERALL GRADE OF RECOMMENDATION				
Repeat antenatal corticosteroids for a woman with a multiple pregnancy with an				Body of evidence can be trusted to guide practice				
additional risk factor(s)) for preterm bi	rth	В	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.				Body of evidence provides some support for recommendations(s) but care should be taken in its application				
		with a multiple pregnancy at risk of preterm birth enatal corticosteroids have been given.	D	Body of evidence is weak and recommendation must be applied with caution				
			РР	Practice Point				
IMPLEMENTATIC	ON OF RECO	keep a note of specific issues that arise when each recommenda MMENDATION (Please indicate yes or no to the follow I be used to develop the implementation plan for the guidelines	ing question	1 0 17				
Will this recommendat	ion result in ch	anges in usual care?	Y	ES				
			N	0				
Are there any resource	implications as	sociated with implementing this recommendation?	Y	ES				
			N	0				
	on of this recom	mendation require changes in the way care is curren	tly Y	ES				
organised?			N	<u>10</u>				
Are the guideline deve recommendation?	lopment group	aware of any barriers to implementation of this	Y	ES				

M24 GRADE Evidence summary

Considered]	8	0					•••
What is the safety for the mother and fetus, infant, cl women with a multiple pregnancy (twins and higher							oids to
1. Outcome measures:			f evidence	Importance of outcome in making a decision			
Matemal Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Importan
O1 Chorioamnionitis	4				1		P
D ₂ Puerperal sepsis							
O ₃ Pyrexia after entry to trial	1			NR	1		
						1	
D4 Intrapartum fever requiring antibiotics				NR		1	
O5 Post natal pyrexia		1				1	
O ₆ Maternal quality of life				NR	1		N
Infant Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Importan
D1 Combined fetal and neonatal death	1				1		
O2 Neonatal death	1				1		
O3 Fetal death		1			1		
O4 RDS	1				1		
O5 Composite of serious outcomes for the infant	4				~		
O ₆ Neurosensory disability (composite of impairments) for infant as a child		*					
D ₇ Survival free of neurosensory disability for the nfant as a child				NR	1		
O8 Survival free of metabolic disease for the infant as a child				NR		4	
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		4	
2. Is there is insufficient evidence to make a	recommen	ndation?		I	I	· ·	
multiple pregnancy with an additional risk factor(s) is recommendation Maternal - Evidence for maternal outcomes is based on siz reported a proportion of women with a multiple pregnan corticosteroids or placebo following an initial single cours involving 3091 women reported on puerperal sepsis, and data were reported for pyrexia after trial entry or intrapar Infant - Evidence for infant outcomes is based on nine tria reported a proportion of women with a multiple pregnan corticosteroids or placebo following an initial single cours trials involving 2713 infants reported on neonatal death a infants reported on respiratory distress syndrome, and sev	x trials inclu cy and an a se. All six tr one trial in tum pyrexia ils included cy and an a se. All nine nd seven tr	ided in the dditional ris ials, involvi volving 982 a. in the Crow dditional ris of these tria ials involvir	Crowther (2 sk of preten ng 4261 wo women rep wther (2011 sk of preten als, involvin ng 2755 infa	2011) Cochr m birth, tha men report ported on p) Cochrane m birth, tha g 5554 infar unts reported	ane systematic t were exposed ed on chorioa ostnatal pyrexi systematic rev t were exposed nts, reported of d on fetal deat	c review that rec d to repeat anter mnionitis, five t ia requiring trea riew that recruit d to repeat anter on perinatal deat h. Eight trials in	cruited and natal rials tment. No ed and natal h. Seven nvolving 3200
3. What benefit will the proposed intervention	n/action l	nave?				r	
Evidence statement <i>Maternal</i> - In trials that recruited and reported a proportion risk of imminent preterm birth, there was no difference received repeat antenatal corticosteroids and those with m <i>Infant</i> - In trials that recruited and reported a proportion risk of imminent preterm birth, the risk of respirator outcomes were significantly reduced in favour of repeat of perinatal, fetal or neonatal death in trials that recruit	in measure to repeat and the of women y distress se antenatal co ed and rep	es of mater itenatal cort n with a mu syndrome a orticosteroi	nal infectio icosteroids. ultiple preg ind a comp ds. There v	n between y nancy and a posite of se vas no diffe	women who in additional erious infant rence in risk	Quality of Not app	
pregnancy and an additional risk of imminent preterm bir Judging the benefits in context The evidence is direct evidence from trials conducted in v conducted in a variety of healthcare settings, including Ca multicentre study encompassing 80 centres in 20 countrie outcomes are substantial and demonstrate significant redu 4. What harm might the proposed interventi	women at ri inada, Aust s. Effect siz actions in ri	ralia and No zes for resp isk.	ew Zealand	, the United	States, India a	and Finland, as v	well as a

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
 Quality of evidence

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. <i>Infant</i> - 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 tha	t recruited and repor	ted a proportion of wome	n with a multiple i	pregnancy and imminent risk	
of preterm birth following an initial single course of			in which a multiple j	pregnancy and miniment flox	
5. What is the likely balance between go	ood and harm?				
maternal infection in terms of chorioamnionitis, pos <i>Infant</i> - There are significant benefits for the infant is syndrome, and a composite of serious infant outcom	<i>Maternal</i> - 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. <i>Infant</i> - There are significant benefits for the infant in terms of substantial reductions in risk of respiratory distress				
Judging the balance of benefits and harms in co Whilst there are no direct health benefits for the mo significant health benefits for the infant in terms of a impact benefits, outweighing potential lower impact	ther, exposure to rep reduced risk of respir				
Benefits clearly outweigh harms	Recommend			STRONG	
Benefits probably outweigh harms	Consider			CONDITIONAL	
Not known	Make a recommendation for research (see 8 below)			<u>WEAK</u>	
Benefits probably don't outweigh harms				CONDITIONAL	
Harms probably outweigh benefits	Consider against/make no recommendation			CONDITIONAL	
Benefits clearly don't outweigh harms	Recommend against			STRONG	
Harms clearly outweigh benefits	0				
6. Is the intervention/action implement	able in the New Ze	aland context?			
Summary statement					
Antenatal corticosteroids are already widely in use in Yes	New Zealand and A	Recommend/conside	۰r		
Not known		Consider economic evaluation			
No		Recommend/consider :	against		
7. Final recommendation					
Repeat antenatal corticosteroids for a woman with a multiple pregnancy with an additional risk factor(s) for preterm birthPlease select levelWhere appropriate, estimate the risk of preterm birth by considering the use of adjunct prediction tests including fetal fibronectin and assessment of cervical length.STRONG CONDITION WEAK (Practice)					
	Where appropriate, monitor women with a multiple pregnancy at risk of preterm birth for signs of puerperal sepsis when antenatal corticosteroids have been given. 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:						
				nistering a single course of antenatal corticosteroids to women ot at additional risk for preterm birth)?		
1. Evidence base (number	of studies, lev	el of evidence and risk of bias in the in	cluded si	tudies)		
There was no randomised prophylactic use of antena		rial evidence for the eroids in women with multiple	А	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias		
pregnancy with no additional risk of preterm birth.			В	One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias		
				One or two Level III studies with a low risk of bias or Level I or II studies with 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 ava	iilable, rank this component as 'not aț	plicable)		
Not applicable			А	All studies consistent		
			В	Most studies consistent and inconsistency can be explained		
			С	Some inconsistency, reflecting genuine uncertainty around question		
			D	Evidence is not consistent		
			NA	Not applicable (one study only)		
intervention could not be determ		results varied according to some unkno	wn facto	r (not simply study quality or sample size) and thus the clinical impact of the		
Not applicable			А	Very large		
			В	Substantial		
			С	Moderate		
			D	Slight / Restricted		
	vell does the bo	dy of evidence match the population an	ıd clinica	l settings being targeted by the guideline?)		
Not applicable			А	Evidence directly generalisable to target population		
			В	Evidence directly generalisable to target population with some caveats		
			С	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 bod	y of evidence n	elevant to the New Zealand / Austra	lian heal	theare context in terms of health services / delivery of care and cultural factors?)		
Corticosteroids are readily and their use is feasible.	available in	Australia and New Zealand	А	Evidence directly applicable to New Zealand / Australian healthcare context		
			В	Evidence applicable to New Zealand / Australian healthcare context with few caveats		
			С	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 upgrade the recommendation)	e any other fac	tors that you took into account when a	ssessing i	the evidence base (for example, issues that might cause the group to downgrade or		
No randomised controlled	l trial evider	ce identified				
EVIDENCE STATEMI account)	ENT MAT	RIX (summarise the development grou	up's synt	besis of the evidence relating to the key question, taking all the above factors into		
Component	Rating	Description				
1. Evidence base	NA	Not applicable				

2. Consistency	NA	Not applicable								
3. Clinical Impact	NA	Not applicable	Not applicable							
4. Generalisability	NA	Not applicable								
5. Applicability	NA	Not applicable								
Evidence statement										
No randomised control additional risk of preter		nce for the prophylactic use of antenatal corticostero	ids in won	nen with multiple pregnancy and no						
RECOMMENDATIO from this evidence? Use acti		mmendation(s) does the guideline development group draw here possible)		OVERALL GRADE OF RECOMMENDATION						
5		1 /	Α	Body of evidence can be trusted to guide practice						
		al corticosteroids in women with a multiple ntified risk of preterm birth.	В	Body of evidence can be trusted to guide practice in most situations						
			С	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						
			РР	Practice Point						
UNRESOLVED ISSU	J ES (If needed,	keep a note of specific issues that arise when each recommenda	ution is form	ulated and that require follow up)						
		MMENDATION (Please indicate yes or no to the follow Il be used to develop the implementation plan for the guidelines		s. Where the answer is yes, please provide explanatory						
Will this recommendati	on result in ch	anges in usual care?	Y	YES						
			N	<u>0</u>						
Are there any resource	implications a	ssociated with implementing this recommendation?	Y	ES						
			N	0						
	n of this recon	nmendation require changes in the way care is curren	tly Y	ES						
organised?			N	0						
Are the guideline development group aware of any barriers to implementation of this				YES						
Are the guideline develor recommendation?	opinent group	aware of any barriers to imperioritation of this		NO						

M25 GRADE Evidence summary

with a multiple pregnancy (twins and higher order)					preterm birt	h)?	s to women				
1. Outcome measures:		Quality o		Importance of outcome in making a decision							
Maternal Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important				
O1 Chorioamnionitis				NR	1						
O2 Puerperal sepsis				NR	*						
O ₃ Pyrexia after entry to trial				NR		~					
O4 Intrapartum fever requiring antibiotics				NR		1					
O5 Post natal pyrexia				NR		1					
O6 Maternal quality of life				NR	1						
Infant Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Importan				
O1 Combined fetal and neonatal death				NR	4		-				
O2 Neonatal death				NR	~						
O3 Fetal death				NR	4						
O4 RDS				NR	4						
O5 Composite of serious outcomes for the infant				NR	4						
O ₆ Neurosensory disability (composite of impairments) for infant as a child				NR	4						
O7 Survival free of neurosensory disability for the infant as a child				NR	*						
O8 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	4						
O ₁₀ Survival free of neurosensory disability for the infant as an adult				NR	1						
O ₁₁ Survival free of metabolic disease for the infant as an adult				NR		1					
2. Is there is insufficient evidence to make	a recommer	ndation?			L						
 Evidence statement Maternal - No evidence was identified for maternal prim prophylactic antenatal corticosteroids where there is no Infant - No evidence was available from randomised con 3. What benefit will the proposed intervent 	additional ris trolled trials	sk of immin									
Evidence statement						Quality of	evidence				
Maternal - No evidence was available on maternal outcon Infant - No randomised controlled trial evidence.	nes.					NOT REPORTED					
Judging the benefits in context						ITOT KE	OKILD				
Not applicable 4. What harm might the proposed intervent	tion/action	do?									
Evidence statement	,					Quality of ev	idence				
Maternal - No evidence was available on maternal outcom	nes.					NOT REPORTED					
<i>Infant</i> - No randomised controlled trial evidence. Judging the harms in context						NOT RE	PORTED				
Not applicable 5. What is the likely balance between good	and harm?										
Evidence statement	and nami.					Ove	*all				
Maternal - No evidence was available on maternal outcom	nes.					quality of					
Infant - No randomised controlled trial evidence.						NOT REI	PORTED				
Judging the balance of benefits and harms in conte Not applicable	xt										
appneusie	ecommend					STRONG					
Benefits clearly outweigh harms R	· · ·										
	Consider										
Benefits probably outweigh harms		nmendatio	on for resea	arch (see 8	below)	CONDITION WEAK	NAL				
Benefits probably outweigh harms		nmendatio	on for resea	arch (see 8	below)		NAL				

Benefits clearly don't outweigh harms	Peacemmend accient			STRONG	
Harms clearly outweigh benefits	Recommend again	St.		SIRONG	
6. Is the intervention/action implementable in the New Zealand context?					
Summary statement Antenatal corticosteroids are already widely in use in	New Zealand and A	ustralia.			
Yes	Recommend/consider				
Not known	Consider economic evaluation				
No	Recommend/consider against				
7. Final 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.			rength of rec FRONG ONDITION EAK (Practi		
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

				nistering repeat course(s) of antenatal corticosteroids to ally (not at additional risk for preterm birth)?
1. Evidence base (numbe	r of studies, lei	vel of evidence and risk of bias in the	included s	tudies)
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 B C	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias One or two Level III studies with a low risk of bias or Level I or	
			D	II studies with moderate risk of bias Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency (if only on	e study was ave	ailable, rank this component as 'not a	applicable)
N/A			А	All studies consistent
			В	Most studies consistent and inconsistency can be explained
			С	Some inconsistency, reflecting genuine uncertainty around question
			D	Evidence is not consistent
			NA	Not applicable (one study only)
3. Clinical impact (indica intervention could not be deter		results varied according to some unkn	own facto	r (not simply study quality or sample size) and thus the clinical impact of the
N/A			А	Very large
			В	Substantial
		С	Moderate	
			D	Slight / Restricted
	well does the be	ody of evidence match the population of	and clinica	il settings being targeted by the guideline?)
N/A			А	Evidence directly generalisable to target population
			В	Evidence directly generalisable to target population with some caveats
			С	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
	dy of evidence r	elevant to the New Zealand / Austr	alian hea	lthcare context in terms of health services / delivery of care and cultural factors?)
N/A			А	Evidence directly applicable to New Zealand / Australian healthcare context
			В	Evidence applicable to New Zealand / Australian healthcare context with few caveats Evidence probably applicable to New Zealand / Australian
			С	healthcare context with some caveats
			D	Evidence not applicable to New Zealand / Australian healthcare context
upgrade the recommendation)			assessing .	the evidence base (for example, issues that might cause the group to downgrade or
No randomised controlle	d trial data w	vere available		
EVIDENCE STATEM	ENT MAT	' RIX (summarise the development gr	oup's synt	hesis of the evidence relating to the key question, taking all the above factors into
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 from this evidence? Use action		mendation(s) does the guideline developm ere possible)	uent group draw		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.				Α	Body of evidence can be trusted to guide practice			
				В	Body of evidence can be trusted to guide practice in most situations			
					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			
				РР	Practice Point			
UNRESOLVED ISSUE	E S (If needed, .	keep a note of specific issues that arise wh	hen each recommendati	ion is formi	ulated and that require follow up)			
		MMENDATION (Please indicate you be used to develop the implementation p		ng questions	s. Where the answer is yes, please provide explanatory			
Will this recommendation	result in cha	anges in usual care?		YI				
		· · · · · · · · · · · · · · · · · · ·		N				
Are there any resource implications associated with implementing this recommendation?			YI					
Will the implementation of	of this recom	mendation require changes in the	way care is current					
organised?				N				
Are the guideline develop	ment group	aware of any barriers to implement	ation of this	YI				
recommendation?				N	NO			

M26 GRADE Evidence summary

Considered	Judgement	t - Strength	of recom	nendation					
What is the safety for the mother and fetus, infant, cl women with a multiple pregnancy (twins and higher							oids to		
1. Outcome measures:	easures: Quality of evidence					Importance of outcome in making a decision			
Maternal Outcomes	HIGH	GH MOD	LOW	V. LOW	Critical	Important	Not Important		
O1 Chorioamnionitis				NR	*				
O ₂ Puerperal sepsis				NR	*				
O ₃ Pyrexia after entry to trial				NR		4			
O4 Intrapartum fever requiring antibiotics				NR		4			
O5 Post natal pyrexia				NR		4			
O6 Maternal quality of life				NR	4				
Infant Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important		
O1 Combined fetal and neonatal death				NR	*				
O2 Neonatal death				NR	4				
O ₃ Fetal death				NR	4				
O4 RDS				NR	4				
O ₅ Composite of serious outcomes for the infant				NR	*				
O ₆ Neurosensory disability (composite of impairments) for infant as a child				NR	4				
O7 Survival free of neurosensory disability for the				NR	4				
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	4				
O ₁₀ Survival free of neurosensory disability for the infant as an adult				NR	1				
O11 Survival free of metabolic disease for the infant as				NR		4			
an adult 2. Is there is insufficient evidence to make a	recommen	ndation?	l		L				
Evidence statement									
Maternal No evidence was identified for maternal primary outcom	es of these	Clinical Pra	ctice Guide	lines for the	use of a sing	le course of pro	ohvlactic		
antenatal corticosteroids where there is no additional risk									
Infant									
No evidence was available from randomised controlled to 3. What benefit will the proposed intervention		nave?							
Evidence statement	,, ucuon i					Quality of	evidence		
Maternal - No evidence was available on maternal outcom	ies.								
Infant - No randomised controlled trial evidence. NOT REPORTED Judging the benefits in context Image: Controlled trial evidence in the second secon						PORIED			
Not applicable. 4. What harm might the proposed intervention	on laction	do?							
Evidence statement	on/ action	uo:				Quality of ev	ridence		
Maternal - No evidence was available on maternal outcomes.									
Infant - No randomised controlled trial evidence.							PORTED		
Judging the harms in context									
Not applicable. 5. What is the likely balance between good a	und harm?								
Evidence statement						Ove	rall		
Maternal - No evidence was available on maternal outcom Infant - No randomised controlled trial evidence.	ies.					quality of	evidence		
*						NOT RE	PORTED		
Judging the balance of benefits and harms in contex Not applicable.	t								
	commend					STRONG			
	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	Consider against/1	nake no recommendation		CONDITIONAL	
Benefits clearly don't outweigh harms	D				
Harms clearly outweigh benefits	Recommend again	st		STRONG	
6. Is the intervention/action implement	able in the New Ze	ealand context?			
Summary statement Antenatal corticosteroids are already widely in use in	New Zealand and A	ustralia.			
Yes	Recommend/consider				
Not known	Consider economic evaluation				
No Recommend/consid			r against		
7. Final recommendation					
			Strength of re-	commendation	
Do not use repeat antenatal corticosteroids in wome no other identified risk of preterm birth.	STRONG CONDITION <u>WEAK (Pract</u>				
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 with diabetes mellitus or gestational diabetes at risk of preterm b		istering a single course of antenatal corticosteroids to women
1. Evidence base (number of studies, level of evidence and risk of bias in the in	cluded st	udies)
Maternal Five trials included in the Roberts CPG version 2015 systematic review for a single course of antenatal corticosteroids reported the	А	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias
inclusion of a very small proportion of women with diabetes in pregnancy. Two of these trials reported on maternal outcomes.	В	One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias
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.		One or two Level III studies with a low risk of bias or Level I or II studies with moderate risk of bias
		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 at	plicable')
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	А	All studies consistent
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 \geq 72 hours following administration of antenatal corticosteroids.		Most studies consistent and inconsistency can be explained
		Some inconsistency, reflecting genuine uncertainty around question
Infant There were statistically significant reductions in risk of perinatal death, neonatal death, respiratory distress syndrome and	D	Evidence is not consistent
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.		Not applicable (one study only)
3. Clinical impact (indicate if the study results varied according to some unkno intervention could not be determined)	wn factor	r (not simply study quality or sample size) and thus the clinical impact of the
Maternal	А	Very large
No increased risk of maternal infection. Some evidence of increased	В	Substantial
maternal blood glucose in women with severe pre-eclampsia following a single course of antenatal corticosteroids.	С	Moderate
Infant	D	Slight / Restricted
Significant reductions in mortality and respiratory distress syndrome.	. 1 . 1::.	I water have a second of the star weight time?)
4. Generalisability (how well does the body of evidence match the population an Evidence from a variety of healthcare settings. Studies conducted	ia ciinica	i seitings being targetea by the guidetine?)
Brazil, Canada, and USA.	А	Evidence directly generalisable to target population
	В	Evidence directly generalisable to target population with some caveats
	С	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 / Austra	lian heal	
Corticosteroids are readily available in Australia and New Zealand and their use is feasible.	А	Evidence directly applicable to New Zealand / Australian healthcare context
	В	Evidence applicable to New Zealand / Australian healthcare context with few caveats
	С	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 a upgrade the recommendation)	ssessing i	the evidence base (for example, issues that might cause the group to downgrade or

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						
Use a single course of antenatal corticosteroids for women with diabetes in pregnancy or	Α	Body of evidence can be trusted to guide practice					
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.		Body of evidence can be trusted to guide practice in most situations					
		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					
	РР	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 information about this. This information will be used to develop the implementation plan for the guidelines)	g question:	s. Where the answer is yes, please provide explanatory					
Will this recommendation result in changes in usual care?	YES						
	N	<u>0</u>					
Are there any resource implications associated with implementing this recommendation?	YI	YES					
	<u>NO</u>						
Will the implementation of this recommendation require changes in the way care is currently	y YI	ES					
organised?	N	<u>0</u>					
Are the guideline development group aware of any barriers to implementation of this	YI	ES					
recommendation?	N	0					

M27 GRADE Evidence summary

Considered		-					
What is the safety for the mother and fetus, infant, c with diabetes mellitus or gestational diabetes at risk			tering a si	ngle course	e of antenata	l corticosteroid	s to women
1. Outcome measures:		Quality o	f evidence			ortance of out making a deci	
Matemal Outcomes	HIGH	MOD	MOD LOW		Critical	Important	Not Importar
O1 Chorioamnionitis	1				1		
O2 Puerperal sepsis					4		
D ₃ Pyrexia after entry to trial		4				~	
O4 Intrapartum fever requiring antibiotics		*					
O ₅ Post natal pyrexia	4	•				· ·	
O ₆ Maternal quality of life	*			NR		*	
Infant Outcomes	HIGH	MOD	LOW	V. LOW	✓ Critical	Important	Not Importar
O1 Combined fetal and neonatal death					4		
D2 Neonatal death		-			1		
O3 Fetal death			1		4		
O4 RDS		1			· ·		
O5 Composite of serious outcomes for the infant				NR	· ·		
O ₆ Neurosensory disability (composite of impairments) for infant as a child				NR	~		
O7 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 nfant 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	recommen	ndation?	•			•	
Evidence statement - Evidence is based on a subset diabetes in pregnancy. This level of evidence canno Maternal - Evidence for maternal primary outcomes is ba course of antenatal corticosteroids that recruited and rep for pyrexia after trial entry and puerperal sepsis is based of pyrexia requiring treatment, and postnatal pyrexia requiring maternal quality of life. Infant - The evidence for infant primary outcomes is based course of antenatal corticosteroids that recruited and rep trials, involving 489 infants reported on perinatal and fet involving 783 infants reported on respiratory distress syr	the used t sed on trials orted on a p on two trials ng treatmer of on trials in orted on a p al death, and	o form a cl included in proportion o s, involving at is based o ncluded in t proportion o d four trials	inical reco the Rober of women v 336 women n one trial the Roberts of women v involving 7	mmendati ts CPG vers vith diabete n, and evide involving 21 CPG versio vith diabete '83 infants r	on sion 2015 syste s mellitus or g nce for chorio 18 women. No on 2015 syster s mellitus or g reported on ne	ematic review fo estational diabet amnionitis, intr o data were repo natic review for estational diabet conatal death. Fo	or a single res. Evidence apartum rted for a single res. Three
3. What benefit will the proposed intervention	on/action l	nave?	*	*			
Evidence statement						Quality of	fevidence
Maternal - One trial reporting maternal outcomes in wom			~				
exposure to single course of antenatal corticosteroids fo						Not app	plicable

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. 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. What harm might the proposed intervention/action do? 4. Evidence statement Quality of evidence Maternal - One trial recruited and reported that 18% of participants had gestational diabetes and reported a Not applicable 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.

Judging the harms in context						
Evidence for increased maternal blood glucose follow						
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 go						
Evidence statement Overall 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. Quality of evidence						
Infant - Significant reductions in mortality and respira			teroius.	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	efits probably outweigh harms Consider					
<u>Not known</u>	Make a recomme	endation for research (se	e 8 below)	<u>WEAK</u>		
Benefits probably don't outweigh harms	Consider against/r	make no recommendation		CONDITIONAL		
Harms probably outweigh benefits	Consider against/make no recommendation			CONDITIONAL		
Benefits clearly don't outweigh harms	Recommend again	et		STRONG		
Harms clearly outweigh benefits	0			511(6)(6)		
6. Is the intervention/action implement	able in the New Ze	ealand context?				
Summary statement Antenatal corticosteroids are already widely in use in	New Zealand and A	ustralia.				
Yes		Recommend/conside	<u>r</u>			
Not known		Consider economic eval	uation			
No		Recommend/consider a	gainst			
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.						
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 diabetes mellitus or gestational diabetes at risk of preterm birth?		istering repeat antenatal corticosteroids to women with			
1. Evidence base (number of studies, level of evidence and risk of bias in the in	icluded st	udies)			
Maternal Four of the ten trials included in the Crowther (2011) systematic	А	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias			
review reported including a small proportion of women with diabetes in pregnancy and report on maternal outcomes.	В	One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias			
Infant Four trials included in the Crowther (2011) systematic review	С	One or two Level III studies with a low risk of bias or Level I or II studies with moderate risk of bias			
reported included in the crowner (2011) systemate review reported including a small proportion of women with diabetes in pregnancy and report on infant outcomes.	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 ap	plicable')			
Maternal The treatment effects for chorioamnionitis and puerperal sepsis were similar to the overall treatment effect and no significant	А	All studies consistent			
difference was seen between the treatment groups.		Most studies consistent and inconsistency can be explained			
Infant For perinatal, fetal and neonatal death, respiratory distress	С	Some inconsistency, reflecting genuine uncertainty around question			
syndrome, severe respiratory distress syndrome and a composite of serious infant outcomes the treatment effect was similar to the		Evidence is not consistent			
overall treatment effect with no statistically significant differences seen between those exposed to repeat antenatal corticosteroids and those not exposed.	NA	Not applicable (one study only)			
3. Clinical impact (indicate if the study results varied according to some unkno intervention could not be determined)	wn factor	r (not simply study quality or sample size) and thus the clinical impact of the			
Maternal No evidence of increased risk of infection following treatment with repeat antenatal corticosteroids.	А	Very large			
Infant	В	Substantial			
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	С	Moderate			
statistically significant differences between groups from trials that reported including a proportion of women with diabetes in pregnancy.	D	Slight / Restricted			
4. Generalisability (how well does the body of evidence match the population and	nd clinica	l 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	А	Evidence directly generalisable to target population			
countries.	В	Evidence directly generalisable to target population with some caveats			
	С	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 / Austra	lian heal	theare 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.	А	Evidence directly applicable to New Zealand / Australian healthcare context			
	В	Evidence applicable to New Zealand / Australian healthcare context with few caveats			
	С	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 a upgrade the recommendation)	ssessing i	the evidence base (for example, issues that might cause the group to downgrade or			
Evidence is based on a subset of data from trials that reported th level of evidence cannot be used to form a clinical recommendat		uded a proportion of women with diabetes in pregnancy. This			

EVIDENCE STATEMENT MATRIX (summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account)

Rating	Description
NA	Not applicable
	NA NA NA NA

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 (W hat 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	Α	Body of evidence can be trusted to guide practice					
diabetes at risk of preterm birth.	В	Body of evidence can be trusted to guide practice in most situations					
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.	С	Body of evidence provides some support for recommendations(s) but care should be taken in its application					
Where appropriate, monitor women with diabetes in pregnancy or gestational diabetes for signs of puerperal sepsis when antenatal corticosteroids have been given.	D	Body of evidence is weak and recommendation must be applied with caution					
Where appropriate, estimate the risk of preterm birth by considering the use of adjunct prediction tests including fetal fibronectin and assessment of cervical length.	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	YES
organised?	<u>NO</u>
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	t - Strength	of recom	mendation			
What is the safety for the mother and fetus, infant, cl women with diabetes mellitus or gestational diabete			0	peat course			
1. Outcome measures:					portance of outcome making a decision		
Matemal Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O1 Chorioamnionitis	1				1		
O2 Puerperal sepsis	1				*		
O ₃ Pyrexia after entry to trial				NR		1	
O4 Intrapartum fever requiring antibiotics				NR			
O5 Post natal pyrexia				NR		4	
O6 Maternal quality of life				NR	4		
Infant Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O1 Combined fetal and neonatal death	-				1		
O2 Neonatal death	1				*		
O3 Fetal death		1			1		
O4 RDS	1						
O5 Composite of serious outcomes							
for the infant O ₆ Neurosensory disability (composite of impairments) for infant as a child				NR	+		
O7 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	1		
O_{10} Survival free of neurosensory disability for the infant as an adult				NR	4		
O ₁₁ Survival free of metabolic disease for the infant as				NR			
an adult 2. Is there is insufficient evidence to make a	*0.0000000	adation?		NK		4	
diabetes in pregnancy. This level of evidence canno Maternal - Evidence for maternal primary outcomes is bas and reported a proportion of women with diabetes in pre involving 2102 women reported on puerperal sepsis. No Infant - Evidence for infant primary outcomes is based on reported a proportion of women with diabetes in pregnat 438 infants reported on neonatal death and fetal death. T involving 2304 infants reported on a composite of seriou	ed on trials gnancy. Or data were ru trials inclu- ncy. Three t wo trials inv	included ir ne trial invo eported for ded in the (rrials involv volving 438	the Crowt lving 1853 v the other p Crowther (2 ing 2742 inf	her (2011) (women repo primary outc 2011) Cochr: fants reporte	Cochrane syste orted on chori omes. ane systematic ed on perinata	oamnionitis, and review that rec l death, two tria	l two trials ruited and ls involving
3. What benefit will the proposed intervention							
Evidence statement <i>Maternal</i> - 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. <i>Infant</i> - 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.							f evidence plicable
Judging the benefits in context The evidence is direct evidence from trials conducted in v imminent risk of preterm birth following an initial single systematic review. Evidence for outcomes of these Clinic reported on the proportion of women with diabetes in pr States and Finland, and a multicentre trial involving 80 cc 4. What harm might the proposed interventi	course of a al Practice (regnancy. T entres in 20	ntenatal con Guidelines he populati countries.	ticosteroids s based on	s that were i the trials inc	ncluded in the cluded in the 1	e Crowther (201 review that recru	1) Cochrane uited and
	motherin	ormo of i		of infortion		Quality of ev	idence
Evidence statement <i>Maternal</i> -There do not appear to be health harms for the mother in terms of increased risk of infection.							
<i>Infant</i> - There do not appear to be health harms for the in Judging the harms in context			reased fisk	or intection		Not app	olicable

diabetes or type 2 diabetes were unable to be deterr	nined, if any.			
5. What is the likely balance between g	ood and harm?			
 Evidence statement Maternal - There does not appear to be an increased risk of elevated maternal blood glucose le Infant - There do not appear to be any health harm for the infant. Judging the balance of benefits and harms in configuration of the significant benefits to the infant in the significant benefits to the significan	vels following antenat as for the infant. Ove ontext erms of reduced morta	al corticosteroids in non- rall evidence indicates sig lity and respiratory morbi	diabetic women. nificant benefits idity, the presence	
pregnancy is not a reason to withhold antenatal cor maternal hyperglycaemia.	ticosteroids where the	ere is a risk of preterm bir	th and facilities exi	st to monitor and manage
Benefits clearly outweigh harms	Recommend			STRONG
Benefits probably outweigh harms	Consider			CONDITIONAL
Not known	Make a recomme	endation for research (se	ee 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 6. Is the intervention/action implement	Recommend against			
Summary statement Antenatal corticosteroids are already widely in use in Yes			<u>er</u>	
Not known		Consider economic eva	luation	
No		Recommend/consider a	against	
7. Final 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				commendation NAL l <u>ice points)</u>
where appropriate, monitor wonten with diabetes r of puerperal sepsis when antenatal corticosteroids h Where appropriate, estimate the risk of preterm bir prediction tests including fetal fibronectin and asses 8. Recommendations for research	have been given.	use of adjunct		
Any future randomised trials of repeat antenaIdentify the best management of women with		1	0	colerance.

M29 Women with systemic infection at trial entry at risk of preterm birth – Single course of antenatal corticosteroids

M29 NHMRC Evidence summary

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		nd fetus, infant, child, adult of y at risk of preterm birth?	admin	istering a single course of antenatal corticosteroids to women
1. Evidence base (number	r of studies, lev	el of evidence and risk of bias in the in	cluded si	tudies)
systematic review for a sir	ngle course c	Roberts CPG version 2015 of antenatal corticosteroids	А	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias
excluded women with sys remaining 18 did not state		on at trial entry and the tion of women included in	В	One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias
	nfection at tr	ial entry. Consequently there is	С	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	e study was ava	uilable, rank this component as 'not ap	plicable)
N/A			А	All studies consistent
			В	Most studies consistent and inconsistency can be explained
			С	Some inconsistency, reflecting genuine uncertainty around question
			D	Evidence is not consistent
			NA	Not applicable (one study only)
3. Clinical impact (indica intervention could not be detern		results varied according to some unkno.	wn factor	r (not simply study quality or sample size) and thus the clinical impact of the
N/A			А	Very large
			В	Substantial
			С	Moderate
			D	Slight / Restricted
	well does the bo	ody of evidence match the population an	d clinica	l settings being targeted by the guideline?)
N/A			А	Evidence directly generalisable to target population
			В	Evidence directly generalisable to target population with some caveats
			С	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
	dy of evidence n	elevant to the New Zealand / Austra	lian heal	theare context in terms of health services / delivery of care and cultural factors?)
N/A			А	Evidence directly applicable to New Zealand / Australian healthcare context
			В	Evidence applicable to New Zealand / Australian healthcare context with few caveats
			С	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 upgrade the recommendation)	e any other fac	tors that you took into account when a	ssessing i	the evidence base (for example, issues that might cause the group to downgrade or
There was no RCT evider	nce identified	1		
EVIDENCE STATEM	ENT MAT	RIX (summarise the development grou	up's synt.	hesis of the evidence relating to the key question, taking all the above factors into
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 at trial entry.	l t r ial evider	nce was available for the use of a single course of ante	natal cor	cicosteroids in women with systemic infection				
RECOMMENDATION from this evidence? Use action		mmendation(s) does the guideline development group draw here possible)		OVERALL GRADE OF RECOMMENDATION				
Use a single course of ante		Α	Body of evidence can be trusted to guide practice					
risk of preterm birth.		В	Body of evidence can be trusted to guide practice in most situations					
Do not delay birth in women with a systemic infection to administer a single course antenatal corticosteroids if at risk of preterm birth.				Body of evidence provides some support for recommendations(s) but care should be taken in its application				
				Body of evidence is weak and recommendation must be applied with caution				
			PP	Practice Points				
UNRESOLVED ISSUE	E S (If needed,	keep a note of specific issues that arise when each recommendat	tion is form	ulated and that require follow up)				
		PMMENDATION (Please indicate yes or no to the following and the used to develop the implementation plan for the guidelines)		s. Where the answer is yes, please provide explanatory				
Will this recommendation	result in ch	anges in usual care?	Y.	ES				
			N	<u>0</u>				
Are there any resource im	plications a	ssociated with implementing this recommendation?		ES				
			<u>N</u>					
Will the implementation of this recommendation require changes in the way care is currently			-	ES				
organised?			<u>N</u>					
Are the guideline develops recommendation?	ment group	aware of any barriers to implementation of this		ES				
recommendation?		<u>N</u>	<u>NO</u>					

M29 GRADE Evidence summary

Considered J	udgement	- Strength	of recom	nendation				
What is the safety for the mother and fetus, infant, ch with systemic infection at trial entry at risk of pretern		of adminis	tering a si	ngle course				
1. Outcome measures:						portance of outcome making a decision		
Maternal Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important	
O1 Chorioamnionitis				NR	1			
O2 Puerperal sepsis				NR	1			
O ₃ Pyrexia after entry to trial				NR		1		
O4 Intrapartum fever requiring antibiotics				NR		*		
O5 Post natal pyrexia				NR		1		
O6 Maternal quality of life				NR	1			
Infant Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important	
O1 Combined fetal and neonatal death				NR	1			
O2 Neonatal death				NR	4			
O3 Fetal death				NR	*			
O4 RDS				NR	4			
O ₅ Composite of serious outcomes for the infant				NR	4			
O ₆ Neurosensory disability (composite of impairments) for infant as a child O ₇ Survival free of neurosensory disability for the				NR	1			
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	4			
O10 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		4		
2. Is there is insufficient evidence to make a	recommer	ndation?		I			1	
 Maternal - The Roberts CPG version 2015 systematic reviews known infection at trial entry. There is no randomised conclinical Practice Guidelines for the use of a single course who were at risk of preterm birth. Infant - No randomised controlled trial evidence is current following exposure to a single course of antenatal corticomere at risk of preterm birth. 3. What benefit will the proposed intervention 	ntrolled tria of antenata tly reported steroids wh	l evidence of l corticoste for the infa ere the mot	currently re roids in wo	ported for the men with a location outcomes f	ne maternal p known systen or these Clini	rimary outcome nic infection at tr cal Practice Guid	s for theses rial entry and delines	
Evidence statement						Quality of	evidence	
Maternal - Not applicable. Infant - Not applicable.							NOT REPORTED	
							UNILD	
Judging the benefits in context Not applicable.		1.5						
Judging the benefits in context Not applicable. 4. What harm might the proposed intervention	on/action	do?				Quality of av		
Judging the benefits in context Not applicable. 4. What harm might the proposed intervention Evidence statement Maternal - Not applicable.	on/action	do?				Quality of ev	idence	
Judging the benefits in context Not applicable. 4. What harm might the proposed intervention Evidence statement Maternal - Not applicable. Infant - Not applicable. Judging the harms in context Maternal - Not applicable.	on/action	do?				Quality of ev NOT REI	idence	
Judging the benefits in context Not applicable. 4. What harm might the proposed intervention Evidence statement Maternal - Not applicable. Infant - Not applicable. Judging the harms in context Maternal - Not applicable.		do?					idence	
Judging the benefits in context Not applicable. 4. What harm might the proposed intervention Evidence statement Maternal - Not applicable. Infant - Not applicable. Judging the harms in context Maternal - Not applicable. Infant - Not applicable. Infant - Not applicable. S. What is the likely balance between good a Evidence statement Maternal - Not applicable.		do?					idence PORTED	
Judging the benefits in context Not applicable. 4. What harm might the proposed intervention Evidence statement Maternal - Not applicable. Infant - Not applicable. Judging the harms in context Maternal - Not applicable. Infant - Not applicable. S. What is the likely balance between good a Evidence statement Maternal - Not applicable. Infant - Not applicable. Infant - Not applicable. Judging the balance of benefits and harms in context	nd harm?	do?				NOT REI	idence PORTED rall evidence	
Judging the benefits in context Not applicable. 4. What harm might the proposed intervention Evidence statement Maternal - Not applicable. Infant - Not applicable. Judging the harms in context Maternal - Not applicable. Infant - Not applicable. S. What is the likely balance between good a Evidence statement Maternal - Not applicable. Infant - Not applicable. Judging the balance of benefits and harms in context Not applicable.	nd harm?	do?				NOT REI	idence PORTED rall evidence	

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				STRONG		
Harms clearly outweigh benefits	Recommend again	St		SIRONG		
6. Is the intervention/action implementable in the New Zealand context?						
Summary statement Antenatal corticosteroids are already widely in use in	New Zealand and A	ustralia.				
Yes Recommend/consi			der			
Not known Consider economic ev			evaluation			
No Recommend/consider against			igainst			
7. Final 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. Strength of recommendation Please select level STRONG CONDITIONAL WEAK (Practice Points)						
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 mothe systemic infection at trial entry		of admii	nistering repeat antenatal corticosteroids to women with				
1. Evidence base (number of studies	, level of evidence and risk of bias in the a	included s	tudies)				
Women with active tuberculosis or human immunodeficiency virus were not eligible for two trials in the Crowther (2011) systematic			One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias				
review. There was insufficient deta ascertain if women with a known s		В	One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias				
As such, no data was available on n		С	One or two Level III studies with a low risk of bias or Level I or				
			II studies with moderate risk of bias Level IV studies or Level I to III studies/SRs with a high risk of				
		D Level i v studies of Level i to in studies/ siks with a high lisk of bias					
2. Consistency (if only one study was	available, rank this component as 'not a	applicable)				
N/A			All studies consistent				
			Most studies consistent and inconsistency can be explained				
		С	Some inconsistency, reflecting genuine uncertainty around question				
		D	Evidence is not consistent				
		NA	Not applicable (one study only)				
3. Clinical impact (indicate if the statistic intervention could not be determined)	udy results varied according to some unkn	own facto	r (not simply study quality or sample size) and thus the clinical impact of the				
N/A			Very large				
		В	Substantial				
		С	Moderate				
		D	Slight / Restricted				
4. Generalisability (how well does the	e body of evidence match the population a	and clinica	al settings being targeted by the guideline?)				
N/A		А	Evidence directly generalisable to target population				
			Evidence directly generalisable to target population with some caveats				
			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 eviden	ce relevant to the New Zealand / Austr	alian hea	lthcare context in terms of health services / delivery of care and cultural factors?)				
N/A		А	Evidence directly applicable to New Zealand / Australian healthcare context				
		В	Evidence applicable to New Zealand / Australian healthcare context with few caveats				
		С	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 upgrade the recommendation)	factors that you took into account when	assessing	the evidence base (for example, issues that might cause the group to downgrade or				
No randomised controlled trial evi	dence identified						
EVIDENCE STATEMENT M account)	ATRIX (summarise the development gr	oup's syni	thesis of the evidence relating to the key question, taking all the above factors into				
Component Ratin	g Description						
1. Evidence base NA	Not applicable						
2. Consistency NA							
	Not applicable						
3. Clinical Impact NA	Not applicable Not applicable						
3. Clinical Impact NA 4. Generalisability NA							

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)		OVERALL GRADE OF RECOMMENDATION			
Repeat antenatal corticosteroids for women with a systemic infection at risk of preterm	Α	Body of evidence can be trusted to guide practice			
irth.		Body of evidence can be trusted to guide practice in most situations			
Do not delay birth in women with a systemic infection to administer repeat antenatal corticosteroids if at risk of preterm birth.	С	Body of evidence provides some support for recommendations(s) but care should be taken in its application			
Where appropriate, monitor women with systemic infection at risk of preterm birth for signs of puerperal sepsis when antenatal corticosteroids have been given		Body of evidence is weak and recommendation must be applied with caution			
	РР	Practice Points			
UNRESOLVED ISSUES (If needed, keep a note of specific issues that arise when each recommendation	ion is form	ulated and that require follow up)			
IMPLEMENTATION OF RECOMMENDATION (Please indicate yes or no to the followin information about this. This information will be used to develop the implementation plan for the guidelines)	ıg question.	s. Where the answer is yes, please provide explanatory			
Will this recommendation result in changes in usual care?	Y	YES			
	N	NO			
Are there any resource implications associated with implementing this recommendation?	YI	YES			
		<u>N0</u>			
Will the implementation of this recommendation require changes in the way care is currently	y YI	YES			
organised?	N	NO			
Are the guideline development group aware of any barriers to implementation of this	YI	ES			
recommendation?	N	NO			

M30 GRADE Evidence summary

Considered] What is the safety for the mother and fetus, infant, cl	6	0			(s) of anton	atal corticester	oids to
women with systemic infection at trial entry at risk o			tering a re	peat course			
1. Outcome measures:	Quality of evidence				nportance of outcome n making a decision		
Matemal Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O1 Chorioamnionitis				NR	*		
O ₂ Puerperal sepsis				NR	4		
O ₃ Pyrexia after entry to trial				NR	•	~	
O4 Intrapartum fever requiring antibiotics				NR			
O ₅ Post natal pyrexia				NR		✓	
O ₆ Maternal quality of life				NR		✓	
Infant Outcomes	HIGH	MOD	LOW	V.	✓ Critical	Important	Not
	mon	MOD	LOW	LOW	Cilicai	Important	Important
O1 Combined fetal and neonatal death				NR	1		
O2 Neonatal death				NR	1		
O ₃ Fetal death				NR	4		
O4 RDS				NR	1		
O ₅ Composite of serious outcomes for the infant				NR	4		
O6 Neurosensory disability (composite of impairments)				NR	4		
for infant as a child O7 Survival free of neurosensory disability for the					•		
infant as a child				NR	4		
O ₈ Survival free of metabolic disease for the infant as a child				NR		1	
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	4		
O11 Survival free of metabolic disease for the infant as				NR			
an adult 2. Is there is insufficient evidence to make a	recommen	ndation?	<u> </u>			1	
Evidence statement <i>Maternal</i> - The Crowther (2011) systematic review did not controlled trial evidence currently reported for the matern course of antenatal corticosteroids in women with a know <i>Infant</i> - No randomised controlled trial evidence is curren following exposure to a repeat course of antenatal corticos who were at risk of preterm birth.	nal primary vn systemic tly reported osteroids wh	outcomes f infection a l for the infi here the mo	or theses C t trial entry ant primary	linical Pract and who we outcomes f	ice Guideline ere at risk of p or these Clini	s for the use of a preterm birth. cal Practice Gui	a repeat delines
3. What benefit will the proposed intervention	on/action l	nave?					
Evidence statement Maternal - Not applicable.						Quality of evidence	
Infant - Not applicable.						NOT RE	PORTED
Judging the benefits in context Not applicable.							
4. What harm might the proposed intervention	on/action	do?					
Evidence statement						Quality of evidence	
Maternal - Not applicable. Infant - Not applicable						NOT REPORTED	
11						•	
<i>Infant</i> - Not applicable Judging the harms in context <i>Maternal</i> - Not applicable.							
<i>Infant</i> - Not applicable Judging the harms in context <i>Maternal</i> - Not applicable. <i>Infant</i> - Not applicable	and harm?						
<i>Infant</i> - Not applicable Judging the harms in context <i>Maternal</i> - Not applicable. <i>Infant</i> - Not applicable 5. What is the likely balance between good a	and harm?					Ove	rall
Infant - Not applicable Judging the harms in context Maternal - Not applicable. Infant - Not applicable 5. What is the likely balance between good a Evidence statement Maternal - Not applicable.	nd harm?					Ove quality of	
<i>Infant</i> - Not applicable Judging the harms in context <i>Maternal</i> - Not applicable. <i>Infant</i> - Not applicable	nd harm?						evidence
Infant - Not applicable Judging the harms in context Maternal - Not applicable. Infant - Not applicable 5. What is the likely balance between good a Evidence statement Maternal - Not applicable. Infant - Not applicable. Infant - Not applicable. Infant - Not applicable. Judging the balance of benefits and harms in context						quality of	evidence
Infant - Not applicable Judging the harms in context Maternal - Not applicable. Infant - Not applicable 5. What is the likely balance between good a Evidence statement Maternal - Not applicable. Infant - Not applicable. Infant - Not applicable. Judging the balance of benefits and harms in contex Not applicable.						quality of	evidence

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 implement	table in the New Ze	ealand context?			
Summary statement Antenatal corticosteroids are already widely in use im	New Zealand and A				
Yes	Recommend/cons		ler		
Not known	Consider economic evalu		luation		
No	Recommend/consider a		against		
7. Final recommendation					
Repeat antenatal corticosteroids for women with a s Do not delay birth in women with a systemic infecti corticosteroids if at risk of preterm birth. Where appropriate, monitor women with systemic in puerperal sepsis when antenatal corticosteroids have	Strength of recommendation Please select level STRONG CONDITIONAL WEAK (Practice Point)				
8. Recommendations for research					
 In future randomised trials of repeat antenatal at risk of preterm birth. 	corticosteroids there	is a need to assess the im	pact, if any, on wo	men with systemic infection	

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, leve	el of evidence and risk of bias in the in	cluded si	udies)
		pertension were included in a	А	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias
small proportion of wome Roberts CPG version 2015 antenatal corticosteroids.		he trials included in the review for a single course of	В	One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias
Infant				One or two Level III studies with a low risk of bias or Level I or II studies with moderate risk of bias
Ten trials included in the F review for a single course of	of antenatal		D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency (if only one	study was ava	ilable, rank this component as 'not af	plicable')
Maternal Treatment effects for chor puerperal sepsis were simil			А	All studies consistent
there was no difference be	etween group	os. Intrapartum pyrexia and effects opposite to the overall	В	Most studies consistent and inconsistency can be explained
effect, with no difference l			С	Some inconsistency, reflecting genuine uncertainty around question
Infant There was a significant red respiratory distress syndro			D	Evidence is not consistent
distress syndrome. There v perinatal death.			NA	Not applicable (one study only)
3. Clinical impact (indicat intervention could not be determ		results varied according to some unkno	wn factor	r (not simply study quality or sample size) and thus the clinical impact of the
Maternal No evidence of increased a	risk of mater	mal infection.	А	Very large
Infant				Substantial
Significant reductions in the respiratory distress syndrometers	ne infant outcomes neonatal death and me.		С	Moderate
			D	Slight / Restricted
4. Generalisability (how w	vell does the bo	dy of evidence match the population an	ıd clinica	l settings being targeted by the guideline?)
Evidence from a variety of Brazil, USA, Tunisia, UK,		settings. Studies conducted in d New Zealand.	А	Evidence directly generalisable to target population
, , , ,	,		В	Evidence directly generalisable to target population with some caveats
			С	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	y of evidence re	elevant to the New Zealand / Austra	lian heal	theare context in terms of health services / delivery of care and cultural factors?)
Corticosteroids are readily and their use is feasible.	available in	Australia and New Zealand	А	Evidence directly applicable to New Zealand / Australian healthcare context
			В	Evidence applicable to New Zealand / Australian healthcare context with few caveats
			С	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 upgrade the recommendation)	any other fact	tors that you took into account when a	ssessing i	the evidence base (for example, issues that might cause the group to downgrade or
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 STATEMI account)	ENT MAT	RIX (summarise the development grou	up's synt.	besis of the evidence relating to the key question, taking all the above factors into
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	•	•						
RECOMMENDATI from this evidence? Use act.		mmendation(s) does the guideline development group draw		OVERALL GRADE OF RECOMMENDATION				
, ,		costeroids for women with pregnancy associated	Α	Body of evidence can be trusted to guide practice				
hypertension at risk of preterm birth.				Body of evidence can be trusted to guide practice in most situations				
			С	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				
			РР	Practice Points				
IMPLEMENTATIO information about this. The	N OF RECC	keep a note of specific issues that arise when each recommendation MMENDATION (Please indicate yes or no to the follow Il be used to develop the implementation plan for the guidelines	ing question	1 v 1/				
Will this recommendation	ion result in ch	anges in usual care?	Y	ES O				
Are there any resource implications associated with implementing this recommendation?				YES				
Will the implementation of this recommendation require changes in the way care is curren				<u>O</u> ES				
		1 0 ,	·					
organised?			<u>N</u>	<u>U</u>				
0	opment group	aware of any barriers to implementation of this		ES				

M31 GRADE Evidence summary

with pregnancy associated hypertension / pre-eclam 1. Outcome measures:	psia at risi		f evidence			ortance of out		
Matemal Outcomes	HICH MOD LOW V. Critical				in : Critical	n making a decision Important Importa		
O ₁ Chorioamnionitis	_	mob	Low	LOW		Important	Importan	
O ₂ Puerperal sepsis	1				1			
* *		1			√			
O ₃ Pyrexia after entry to trial		1				1		
O4 Intrapartum fever requiring antibiotics		1				1		
O5 Post natal pyrexia	1					1		
O ₆ Maternal quality of life				NR V.	1		Not	
Infant Outcomes	HIGH	MOD	LOW	LOW	Critical	Important	Importan	
O1 Combined fetal and neonatal death		1			1			
O2 Neonatal death		*			4			
O₃ Fetal death			~		4			
O4 RDS		~			4			
O ₅ Composite of serious outcomes				NR				
for the infant O ₆ Neurosensory disability (composite of impairments)					4			
for infant as a child				NR	1			
O7 Survival free of neurosensory disability for the infant as a child				NR	4			
O ₈ Survival free of metabolic disease for the infant as a				NR		4		
child O ₂ Neurosensory disability (composite of impairments)						*		
for infant as an adult				NR	1			
O10 Survival free of neurosensory disability for the infant as an adult				NR	4			
O ₁₁ Survival free of metabolic disease for the infant as				NR		4		
an adult 2. Is there is insufficient evidence to make a	recommer	dation?				•		
pregnancy associated hypertension. This level of evi Maternal - The Roberts CPG version 2015 systematic revi women with pregnancy associated hypertension at risk of (2006) that recruited and reported a proportion of womer not eligible for five trials, and the remaining twelve trials a recruitment. Infant - The Roberts CPG version 2015 systematic review of women with pregnancy induced hypertension at risk o in the Roberts (2006) review that recruited and reported a 3. What benefit will the proposed intervention	ew for a sin preterm bi n in their tri did not spec for a single f preterm b a proportion	gle course of rth. These ial with pre- cify if wom e course of irth. These n of womer	of antenatal Clinical Pra gnancy asso en with pre antenatal co Clinical Pra	l corticostere actice Guide pciated hyper gnancy asso prticosteroid actice Guide	bids reported o lines analysed rtension. Won ciated hyperte s reported dat lines analysed	data from two to ten trials includ nen with pre-ecl nsion were eligi a from two trial data from ten to	ed in Robert ampsia were ble for s for infants rials included	
Evidence statement						Quality of	evidence	
<i>Maternal</i> - 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. <i>Infant</i> - 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.								
Judging the benefits in context The evidence is direct evidence from trials that recruited a compared outcomes in women and infants exposed to an healthcare settings, including Brazil, United Kingdom, Ur and demonstrate significant reductions in risk. 4. What harm might the proposed intervention	and reporte tenatal cort nited States,	ed on a prop ricosteroids , Finland an	oortion of w with those	vomen with unexposed.	The trials wer	e conducted in	a variety of	
Evidence statement						Quality of ev	idence	
Maternal - There was no evidence of harm to the mother.								
Infant - There was no evidence of harm to the infant.						Not and	hicable	

5. What is the likely balance between good and harm?					
Evidence statement <i>Maternal</i> - There does not appear to be an increased risk to the mother. <i>Infant</i> - There are significant benefits for the infant in terms of reduced risk of neonatal mortality and respiratory				Overall quality of evidence	
distress syndrome. Judging the balance of benefits and harms in co	ntovt			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 recomme	endation for research (se	ee 8 below)	<u>WEAK</u>	
Benefits probably don't outweigh harms	Consider against/r	nake no recommendation		CONDITIONAL	
Harms probably outweigh benefits	Consider against/1	nake no recommendation		CONDITIONAL	
Benefits clearly don't outweigh harms				STRONG	
Harms clearly outweigh benefits	Recommend again	st		SIROING	
6. Is the intervention/action implement	able in the New Ze	aland context?			
Summary statement Antenatal corticosteroids are already widely in use in	New Zealand and A	ustralia.			
Yes		Recommend/conside	<u>r</u>		
Not known		Consider economic evaluation			
No		Recommend/consider against			
7. Final recommendation					
Strength of recommendation Please select level					
Use a single course of antenatal corticosteroids for women with pregnancy associated hypertension at risk of preterm birth. STRONG CONDITIONAL WEAK (Practice points)					
8. Recommendations for research	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 in	icluded si	tudies)
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	А	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias
chorioannionitis, one provided data on postnatal pyrexia, and three provided data on puerperal sepsis.		One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias
Infant Seven trials included in the Crowther (2011) systematic review reported including a proportion of women with pregnancy associated hypoteneica. Six trials provided data on accimptal death	С	One or two Level III studies with a low risk of bias or Level I or II studies with moderate risk of bias
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.	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 ap	pplicable')
Maternal Treatment effects for chorioamnionitis, postnatal pyrexia and puerperal sepsis were similar to the overall treatment effect. There	А	All studies consistent
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	В	Most studies consistent and inconsistency can be explained
pregnancy associated hypertension. Infant	С	Some inconsistency, reflecting genuine uncertainty around question
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	D	Evidence is not consistent
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.		Not applicable (one study only)
3. Clinical impact (indicate if the study results varied according to some unkno intervention could not be determined)	own factor	r (not simply study quality or sample size) and thus the clinical impact of the
Maternal	А	Very large
No evidence of increased risk of infection for the mother.	В	Substantial
Infant Significant reductions in risk of respiratory distress syndrome and a	C B	Moderate
composite of serious infant outcomes. No increased risk of mortality.	D	Slight / Restricted
4. Generalisability (how well does the body of evidence match the population and		о́
Evidence from a variety of healthcare settings. Studies conducted in	r	
Australia and New Zealand, USA, Finland and a multicentre trial	А	Evidence directly generalisable to target population Evidence directly generalisable to target population with some
incorporating 80 centres in 20 countries.	В	caveats
	С	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 / Austra	lian heal	theare 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.	А	Evidence directly applicable to New Zealand / Australian healthcare context
	В	Evidence applicable to New Zealand / Australian healthcare context with few caveats
	С	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 a upgrade the recommendation)	ussessing i	the evidence base (for example, issues that might cause the group to downgrade or

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 STATE	MENT MAT	'RIX (summarise the development group's synthesis of the evide	ence rela	ting to the key question, taking all the above factors into					
Component	Rating	Description	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									
RECOMMENDATIO from this evidence? Use acti	ON (What recon	mmendation(s) does the guideline development group draw here possible)		OVERALL GRADE OF RECOMMENDATION					
		woman with pregnancy associated hypertension at	Α	Body of evidence can be trusted to guide practice					
risk of preterm birth.		, , , , , , , , , , , , , , , , , , ,	В	Body of evidence can be trusted to guide practice in most situations					
			С	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					
			РР						
IMPLEMENTATIO	N OF RECO	keep a note of specific issues that arise when each recommendati MMENDATION (Please indicate yes or no to the followin Il be used to develop the implementation plan for the guidelines)	, i						
Will this recommendati	on result in ch	anges in usual care?	_	YES					
				<u>NO</u>					
Are there any resource	implications as	ssociated with implementing this recommendation?		YES					
			<u>NO</u>						
	n of this recorr	nmendation require changes in the way care is currentl	ly	YES					
organised?				<u>NO</u>					
	opment group	aware of any barriers to implementation of this		YES					
recommendation?				NO					

M32 GRADE Evidence summary

Considered J	8	0					
What is the safety for the mother and fetus, infant, ch women with pregnancy associated hypertension / pr				-			
1. Outcome measures:					portance of outcome n making a decision		
Maternal Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Importan
O1 Chorioamnionitis	1				1		
O2 Puerperal sepsis	1				1		
O ₃ Pyrexia after entry to trial				NR		*	
O4 Intrapartum fever requiring antibiotics				NR			
O5 Post natal pyrexia		1				*	
O6 Maternal quality of life				NR	1		
Infant Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Importan
O1 Combined fetal and neonatal death	4				1		-
O2 Neonatal death				l	-		
O3 Fetal death		1			*		1
O4 RDS	1	,			*		
O ₅ Composite of serious outcomes							
for the infant O ₆ Neurosensory disability (composite of impairments)	4				1		
for infant as a child				NR	1		
O7 Survival free of neurosensory disability for the infant as a child				NR	4		
O8 Survival free of metabolic disease for the infant as a				NR			
child O ₂ Neurosensory disability (composite of impairments)						*	
for infant as an adult				NR	1		
O ₁₀ Survival free of neurosensory disability for the infant as an adult				NR	4		
O ₁₁ Survival free of metabolic disease for the infant as an adult				NR			
2. Is there is insufficient evidence to make a	recommen	ndation?					
 Evidence statement - Evidence is based on a subset of pregnancy associated hypertension. This level of evidence is based on the pregnancy associated hypertension. This level of evidence is a subset of the pregnancy induced hypertension at risk of preterm birth. Infant - These Clinical Practice Guidelines analysed trials the hypertension at risk of preterm birth. 3. What benefit will the proposed intervention 	dence can report spec trials that hat recruite	not be use cific data fo recruited an d and repor	d to form a r women w id reported	a clinical re ith pregnand the inclusio	commendati cy associated l n of a propor	on hypertension at tion of women y	risk of with
Evidence statement						Quality of	evidence
<i>Maternal</i> - 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. <i>Infant</i> - 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.						plicable	
Judging the benefits in context The evidence is from randomised controlled trials conduc corticosteroids, and which reported including a proportio treatment effect. 4. What harm might the proposed intervention	n of wome	n with preg					
Evidence statement Quality of evidence							
Maternal - There was no difference in risk between repeat exposure for chorioamnionitis, postnatal pyrexia requiring reported a proportion of women with pregnancy associate <i>Infant</i> - There was no difference in risk between repeat exp exposure for perinatal, neonatal or fetal death among infa hypertension from trials that recruited and reported a pro hypertension at risk of preterm birth. There was a signific and a composite of serious infant outcomes in infants bon following exposure to repeat antenatal corticosteroids.	treatment ed hyperter posure to a nts born to portion of ant reduction	or puerpers asion at risk ntenatal cor mothers w women with on in the ris	al sepsis in of preterm ticosteroids ith pregnancy k of respira	trials that re birth s and no rep ney associated y associated atory distres	cruited and beat d s syndrome	Not apj	plicable

antenatal corticosteroids for the women with pregna	incy associated hyper	tension, or their infants.				
5. What is the likely balance between go	ood and harm?					
Evidence statement Overall 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. Quality of evidence 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 recomme	endation for research (se	ee 8 below)	WEAK		
Benefits probably don't outweigh harms	Consider against/1	make no recommendation		CONDITIONAL		
Harms probably outweigh benefits	Consider against,			CONDITION		
Benefits clearly don't outweigh harms	Recommend again			STRONG		
Harms clearly outweigh benefits	Recommend again	151		5110110		
6. Is the intervention/action implement	able in the New Ze	ealand context?				
Summary statement Antenatal corticosteroids are already widely in use in	New Zealand and A					
Yes		Recommend/consider				
Not known		Consider economic evaluation				
No		Recommend/consider against				
7. Final recommendation						
Repeat antenatal corticosteroids for a woman with pregnancy associated hypertension at risk of preterm birth. Strength of recomment Please select level STRONG CONDITIONAL WEAK (Practice point)				JAL		
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 One or more Level I studies with a low risk of bias, or several Three of the 26 trials in the Roberts CPG version 2015 systematic А Level II studies with a low risk of bias review for a single course of antenatal corticosteroids reported including a very small proportion of women in their trial with a fetus One or two Level II studies with a low risk of bias or SR/several with intrauterine growth restriction. Two of these trials report on В Level III studies with a low risk of bias chorioamnionitis and puerperal sepsis. One or two Level III studies with a low risk of bias or Level I or C Infant II studies with moderate risk of bias 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 Level IV studies or Level I to III studies/SRs with a high risk of restriction. One trial reported on perinatal death, one trial reported D on fetal death, three trials reported on neonatal death and respiratory distress syndrome 2. Consistency (if only one study was available, rank this component as 'not applicable') Maternal All studies consistent А 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 В Most studies consistent and inconsistency can be explained the confidence intervals were wide and overlapped the overall treatment effect that was not significant. Some inconsistency, reflecting genuine uncertainty around С question Infant Perinatal and fetal death had treatment effects in the opposite D Evidence is not consistent 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 NA Not applicable (one study only) respiratory distress syndrome. 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 А Very large No evidence of increased risk of maternal infection. в Substantial Infant No evidence of increased risk of mortality. С 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 Evidence directly generalisable to target population USA, and Brazil. Evidence directly generalisable to target population with some в caveats Evidence not directly generalisable to target population but could С be sensibly applied Evidence not directly generalisable to target population and hard D 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 Evidence directly applicable to New Zealand / Australian А and their use is feasible. healthcare context Evidence applicable to New Zealand / Australian healthcare в context with few caveats Evidence probably applicable to New Zealand / Australian С

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)

D

context

healthcare context with some caveats

Evidence not applicable to New Zealand / Australian healthcare

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 STATE	EMENT MAT	RIX (summarise the development group's synthesis of the evide	ence relati	ng to the key question, taking all the above factors into				
Component	Rating	Description	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								
RECOMMENDATI from this evidence? Use act		nmendation(s) does the guideline development group draw ere possible)		OVERALL GRADE OF RECOMMENDATION				
Use a single course of a	antenatal cortic	osteroids for women with a fetus with intrauterine	Α	Body of evidence can be trusted to guide practice				
growth restriction at ris	sk of preterm b	irth.	В	Body of evidence can be trusted to guide practice in most situations				
		with intrauterine fetal growth restriction for signs of osteroids have been given.	С	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				
			РР	Practice Points				
IMPLEMENTATIO	ON OF RECO	keep a note of specific issues that arise when each recommendat. MMENDATION (Please indicate yes or no to the followin l be used to develop the implementation plan for the guidelines)	ng questio	x v x/				
Will this recommendat	ion result in ch	anges in usual care?	Y	/ES				
A				<u>10</u>				
Are there any resource	implications as	sociated with implementing this recommendation?		TES NO				
Will the implementatio	on of this recom	mendation require changes in the way care is current		YES				
organised?			·	<u>10</u>				
	lopment group	aware of any barriers to implementation of this		/ES				
recommendation?		N	<u>N0</u>					

M33 GRADE Evidence summary

Clinical question: What is the safety for the mother and fetus, infant, cl with a fetus with intrauterine growth restriction at ris			tering a si	ngle course	e of antenatal	corticosteroid	s to women	
1. Outcome measures:	Unality of evidence					mportance of outcome in making a decision		
Matemal Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Importan	
O1 Chorioamnionitis	1				4			
O2 Puerperal sepsis		1			4			
D ₃ Pyrexia after entry to trial				NR		4		
D4 Intrapartum fever requiring antibiotics				NR		4		
D5 Post natal pyrexia				NR		4		
D6 Maternal quality of life				NR	4			
Infant Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Importan	
D ₁ Combined fetal and neonatal death		1			4			
D2 Neonatal death					4			
D3 Fetal death			1		4			
O4 RDS		-			4			
O5 Composite of serious outcomes for the infant				NR	4			
O ₆ Neurosensory disability (composite of impairments) for infant as a child				NR	1			
O7 Survival free of neurosensory disability for the nfant as a child				NR	1			
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	1			
O10 Survival free of neurosensory disability for the infant as an adult				NR	1			
O ₁₁ Survival free of metabolic disease for the infant as				NR		1		
2. Is there is insufficient evidence to make a	recommen	ndation?		•		· ·	•	
 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. What benefit will the proposed intervention/action have? 								
Evidence statement Meternal There do not encour do by any direct health he	nofit- f 1					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						plicable		
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	on/action	do?						
Evidence statement Quality of evide Maternal - There is no evidence of harm to the mother. Image: Comparison of the mother is no evidence of harm to the mother.						idence		
Infant - There is no evidence of harm to the infant.						Not app	olicable	
<i>Maternal</i> - The evidence is from trials that recruited and re compared exposure to a single course of antenatal cortice <i>Infant</i> - One trial included in the Roberts CPG version 20	osteroids wi	th no expos	sure.			-		

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 go	ood and harm?					
and respiratory distress syndrome. In trials that recru intrauterine growth restriction there was no evidence	cates significant benefit to the infant in terms of reduced risk of mortality,		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 recomme	endation for research (se	ee 8 below)	<u>WEAK</u>		
Benefits probably don't outweigh harms	Consider against/r	nake no recommendation		CONDITIONAL		
Harms probably outweigh benefits	Consider against/make no recommendation			CONDITIONAL		
Benefits clearly don't outweigh harms	Recommend against			STRONG		
Harms clearly outweigh benefits	0			511(61(6		
6. Is the intervention/action implement	table in the New Ze	aland context?				
Summary statement Antenatal corticosteroids are already widely in use in	n New Zealand and A	ustralia				
Yes		Recommend/conside	<u>r</u>			
Not known		Consider economic evaluation				
No		Recommend/consider a	igainst			
7. Final recommendation						
			Strength of re Please select level	commendation		
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.						
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 in	icluded st	udies)
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	А	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias
chorioamnionitis and puerperal sepsis, and one trial reported on postnatal pyrexia.		One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias
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	С	One or two Level III studies with a low risk of bias or Level I or II studies with moderate risk of bias
death, composite of serious infant outcomes and birthweight. Four trials reported on fetal death, neonatal death and respiratory distress syndrome.	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 ap	pplicable',)
Maternal The evidence was consistent that there was no difference in risk of maternal infection for women with a fetus with intrauterine growth	А	All studies consistent
restriction treated with antenatal corticosteroids compared to those not treated.	В	Most studies consistent and inconsistency can be explained
Infant The evidence was consistent for significant reduction in risk of respiratory distress syndrome and composite of serious infant	С	Some inconsistency, reflecting genuine uncertainty around question
outcomes for infants with intrauterine growth restriction exposed to repeat antenatal corticosteroids compared with no repeat exposure.	D	Evidence is not consistent
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.		Not applicable (one study only)
3. Clinical impact (indicate if the study results varied according to some unknow	own factor	r (not simply study quality or sample size) and thus the clinical impact of the
intervention could not be determined) Maternal	А	X7 1
There is no evidence of increased risk of infection for the mother		Very large
with a fetus with intrauterine growth restriction.	В	Substantial
Infant There are significant benefits for the infant in terms of reduced risk	С	Moderate
of respiratory distress and a composite of serious infant outcomes. The clinical significance of reduced birthweight is unclear.	D	Slight / Restricted
4. Generalisability (how well does the body of evidence match the population and	nd clinica	l 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	А	Evidence directly generalisable to target population
incorporating 80 centres in 20 countries.	В	Evidence directly generalisable to target population with some caveats
	С	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 / Austra	lian heal	theare 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.	А	Evidence directly applicable to New Zealand / Australian healthcare context
	В	Evidence applicable to New Zealand / Australian healthcare context with few caveats
	С	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 a upgrade the recommendation)	ssessing t	the evidence base (for example, issues that might cause the group to downgrade or

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 STATE	EMENT MAT	RIX (summarise the development group's synthesis of the ev	idence relat	ing to the key question, taking all the above factors into			
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							
RECOMMENDATI from this evidence? Use act		nmendation(s) does the guideline development group draw ere possible)		OVERALL GRADE OF RECOMMENDATION			
Repeat antenatal cortic restriction at risk of pr		woman with a fetus with intrauterine growth	A	Body of evidence can be trusted to guide practice			
			В	Body of evidence can be trusted to guide practice in most situations			
			С	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			
			РР	Practice Points			
UNRESOLVED ISS	UES (If needed,	keep a note of specific issues that arise when each recommend	lation is for	mulated and that require follow up)			
		MMENDATION (Please indicate yes or no to the follow I be used to develop the implementation plan for the guideline		ons. Where the answer is yes, please provide explanatory			
Will this recommendat	tion result in ch	anges in usual care?		YES			
			-	NO			
Are there any resource	implications as	sociated with implementing this recommendation?		YES NO			
Will the implementation	on of this recorr	mendation require changes in the way care is curren		YES			
organised?		1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0		NO			
	lopment group	aware of any barriers to implementation of this		YES			
recommendation?			1	NO			

M34 GRADE Evidence summary

Considered]	-							
What is the safety for the mother and fetus, infant, cl women with a fetus with intrauterine growth restricti				peat course	e(s) of antena	tal corticoster	oids to	
1. Outcome measures:	Quality of evidence					portance of outcome making a decision		
Matemal Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Importan	
O1 Chorioamnionitis	1				1		I • • • •	
O ₂ Puerperal sepsis								
O ₃ Pyrexia after entry to trial	•			NR	•	×		
O4 Intrapartum fever requiring antibiotics				NR		*		
O5 Post natal pyrexia	,							
O ₆ Maternal quality of life	1			NR		*		
Infant Outcomes	HIGH	MOD	LOW	v.	✓ Critical	Important	Not	
O1 Combined fetal and neonatal death				LOW		-	Importan	
O2 Neonatal death		1			1			
O ₂ Fetal death		1			1			
			1		1			
O4 RDS O5 Composite of serious outcomes		1			1			
for the infant		1			1			
O ₆ Neurosensory disability (composite of impairments) for infant as a child				NR	1			
O7 Survival free of neurosensory disability for the				NR	,			
infant as a child Os Survival free of metabolic disease for the infant as a					*			
				NR		4		
O ₉ Neurosensory disability (composite of impairments) for infant as an adult				NR	1			
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 2. Is there is insufficient evidence to make a		1		NR		1		
with intrauterine growth restriction. This level of evi Maternal - The Crowther (2011) systematic review did not preterm birth. Analyses was conducted for the purpose o systematic review that recruited and reported including a Infant - The Crowther (2011) systematic review did not pr the purpose of these Clinical Practice Guidelines on the f including a proportion of women with a fetus with intrau	present da f these Clin proportion resent data f ive trials in terine grow	ta for wome ical Practice of women for infants v cluded in th th restriction	en with a fe e Guideline with a fetus vith intraute e Crowther	etus with intr s on the five s with intrau erine growth	rauterine grow e trials include terine growth n restriction. A	th restriction at d in the Crowth restriction. 	er (2011) nducted for	
3. What benefit will the proposed intervention	on/action l	nave?						
Evidence statement <i>Maternal</i> - There do not appear to be any direct health b	enefits for	the mother	. In line wi	ith the over	all treatment	Quality of	evidence	
effect, no differences between repeat antenatal corticoste for chorioamnionitis, postnatal pyrexia requiring treatmer <i>Infant</i> - In line with the overall treatment effect, no diffe between infants exposed to repeat antenatal cortico corticosteroids in trials that recruited and reported a pro- restriction. Significant reductions were seen for respirat- outcomes for infants exposed to repeat antenatal corticos and reported a proportion of women with a fetus with im-	eroids and in nt or puerpo- erence were osteroids a oportion of ory distress steroids con	no repeat an eral sepsis. e seen for p nd those women wi syndrome npared with	erinatal con erinatal, ne not expose th a fetus v and a corr no exposu	rticosteroids conatal or fe ed to repe with intraute pposite of se	were found tal mortality at antenatal erine growth erious infant	Not apj	plicable	
Judging the benefits in context The evidence is direct evidence from trials conducted in v antenatal corticosteroid, and that recruited and reported t populations were drawn from health care settings in Cana	women who he proport: ada, Austral	o remained ion of wom ia and New	at risk of pr en with a fe	etus with int	rauterine grov	with restriction. S	Study	
centres in 20 countries.4. What harm might the proposed intervention	on/action	uu:						
	on/action	u0:				Quality of ev	idence	
4. What harm might the proposed intervention	for the mot	her.				Quality of ev Not ap		

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 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 recomme	endation for research (se	ee 8 below)	<u>WEAK</u>	
Benefits probably don't outweigh harms	Consider against/r	nake no recommendation		CONDITIONAL	
Harms probably outweigh benefits	Consider against/1	nake no recommendation		CONDITIONAL	
Benefits clearly don't outweigh harms	Deserved	-		STRONG	
Harms clearly outweigh benefits	Recommend again	st		SIRONG	
6. Is the intervention/action implement	able in the New Ze	aland context?			
Summary statement Antenatal corticosteroids are already widely in use in	New Zealand and A	ustralia.			
Yes		Recommend/consider			
Not known		Consider economic evaluation			
No		Recommend/consider a	against		
7. Final recommendation					
Repeat antenatal corticosteroids for a woman with a fetus with intrauterine growth restriction at risk of preterm birth. Strength of recommendation Please select level 8. Recommendations for research WEAK (Practice point)					

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 One or more Level I studies with a low risk of bias, or several А course of antenatal corticosteroids in women with ultrasound Level II studies with a low risk of bias evidence of a short cervix at risk of preterm birth. One or two Level II studies with a low risk of bias, or SR/several В Level III studies with a low risk of bias One or two Level III studies with a low risk of bias or Level I or С II studies with moderate risk of bias Level IV studies or Level I to III studies/SRs with a high risk of D bias 2. Consistency (if only one study was available, rank this component as 'not applicable') Not applicable All studies consistent В Most studies consistent and inconsistency can be explained Some inconsistency, reflecting genuine uncertainty around С question D Evidence is not consistent Not applicable (one study only) NA 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 А Very large В Substantial С 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 Evidence directly generalisable to target population А Evidence directly generalisable to target population with some В caveats Evidence not directly generalisable to target population but could C be sensibly applied Evidence not directly generalisable to target population and hard D 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 Evidence directly applicable to New Zealand / Australian А and their use is feasible. healthcare context Evidence applicable to New Zealand / Australian healthcare В context with few caveats Evidence probably applicable to New Zealand / Australian C healthcare context with some caveats Evidence not applicable to New Zealand / Australian healthcare D 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) Rating Component 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)		OVERALL GRADE OF RECOMMENDATION			
Use a single course of antenatal corticosteroids for a woman presenting with symptoms	A	Body of evidence can be trusted to guide practice			
of preterm labour and with ultrasound evidence of cervical shortening (<15mm) and at risk of preterm birth.	В	Body of evidence can be trusted to guide practice in most situations			
Repeat antenatal corticosteroids for a woman presenting with symptoms of preterm labour with ultrasound evidence of cervical shortening (<15mm) at risk of preterm birth.	С	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			
	РР	Practice Point			
UNRESOLVED ISSUES (If needed, keep a note of specific issues that arise when each recommendate	ion is form	nulated and that require follow up)			
IMPLEMENTATION OF RECOMMENDATION (Please indicate yes or no to the followin information about this. This information will be used to develop the implementation plan for the guidelines)	ng question	ns. Where the answer is yes, please provide explanatory			
Will this recommendation result in changes in usual care?	Y	ES			
	N	<u>10</u>			
Are there any resource implications associated with implementing this recommendation?	Y	YES			

Will the implementation of this recommendation require changes in the way care is currently organised?

Are the guideline development group aware of any barriers to implementation of this recommendation?

<u>N0</u>

YES NO

YES

M35 GRADE Evidence summary

	Judgement	-				· · · · · · · · · · · · · · · · · · ·	
What is the safety for the mother and fetus, infant, cl women with ultrasound evidence of cervical shorten					-		
1. Outcome measures:	Quality of evidence				Importance of outcome in making a decision		
Maternal Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O1 Chorioamnionitis				NR	4		
O2 Puerperal sepsis				NR	4		
O ₃ Pyrexia after entry to trial				NR		4	
O4 Intrapartum fever requiring antibiotics				NR		4	
O5 Post natal pyrexia				NR		1	
O ₆ Maternal quality of life				NR	1		
Infant Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Importan
O1 Combined fetal and neonatal death				NR	4		
O2 Neonatal death				NR	1		
O3 Fetal death				NR	4		
O4 RDS				NR	1		
O ₅ Composite of serious outcomes for the infant				NR	*		
O ₆ Neurosensory disability (composite of impairments) for infant as a child				NR	1		
O7 Survival free of neurosensory disability for the infant as a child O8 Survival free of metabolic disease for the infant as a				NR	4		
child				NR		4	
O9 Neurosensory disability (composite of impairments) for infant as an adult				NR	4		
O ₁₀ Survival free of neurosensory disability for the infant as an adult				NR	4		
O ₁₁ Survival free of metabolic disease for the infant as an adult				NR		1	
2. Is there is insufficient evidence to make a	recommer	ndation?	I	I	<u> </u>	I	I
Evidence statement Maternal - There was no randomised controlled trial data to repeat antenatal corticosteroids. Infant - There was no randomised controlled trial data for course or repeat antenatal corticosteroids. 3. What benefit will the proposed intervention Evidence statement Reader or the providence of the second of the secon	infants bor on/action H	n to mothe nave? rse or repea	rs with a sh	ortened cer	vix at risk of p ids reported	Quality of	a single
in Chapters 4 to 8, there is unlikely to be health benefits t	o the moth		e is likely to	be significa	ni benenito	Not re	ported
in Chapters 4 to 8, there is unlikely to be health benefits t to the infant.	the moun		e is likely to	be significa	in benefits	Not re	ported
in Chapters 4 to 8, there is unlikely to be health benefits t to the infant. Judging the benefits in context			e is likely to	be significa		Not rej	ported
 in Chapters 4 to 8, there is unlikely to be health benefits to the infant. Judging the benefits in context Not applicable. 4. What harm might the proposed interventi Evidence statement	on/action	do?	-			Quality of	
 in Chapters 4 to 8, there is unlikely to be health benefits to to the infant. Judging the benefits in context Not applicable. What harm might the proposed interventi Evidence statement Based on overall treatment effects of a single course or rethere is no evidence of harm to the mother or infant and 	on/action	do? atal corticos	teroids deta				evidence
 in Chapters 4 to 8, there is unlikely to be health benefits to to the infant. Judging the benefits in context Not applicable. What harm might the proposed interventi Evidence statement Based on overall treatment effects of a single course or rethere is no evidence of harm to the mother or infant and Judging the harms in context 	on/action	do? atal corticos	teroids deta			Quality of	evidence
 in Chapters 4 to 8, there is unlikely to be health benefits to to the infant. Judging the benefits in context Not applicable. What harm might the proposed interventi Evidence statement Based on overall treatment effects of a single course or rethere is no evidence of harm to the mother or infant and Judging the harms in context 	on/action epeat antena significant 1	do? atal corticos	teroids deta			Quality of	evidence
 in Chapters 4 to 8, there is unlikely to be health benefits to to the infant. Judging the benefits in context Not applicable. What harm might the proposed interventi Evidence statement Based on overall treatment effects of a single course or red there is no evidence of harm to the mother or infant and Judging the harms in context Not applicable. What is the likely balance between good a Evidence statement Based on overall treatment effects of a single course or red there is no evidence of harm to the mother or infant and Judging the harms in context Not applicable. 	on/action epeat antena significant i and harm? epeat antena	do? ttal corticos benefits to ttal corticos	teroids detz the infant. teroids detz	hiled in Chap	oters 4 to 8,	Quality of	evidence ported
 in Chapters 4 to 8, there is unlikely to be health benefits to to the infant. Judging the benefits in context Not applicable. What harm might the proposed interventi Evidence statement Based on overall treatment effects of a single course or rethere is no evidence of harm to the mother or infant and Judging the harms in context Not applicable. What is the likely balance between good a Evidence statement Based on overall treatment effects of a single course or rethere is no evidence of harm to the mother or infant and Judging the harms in context Not applicable. What is the likely balance between good a Evidence statement Based on overall treatment effects of a single course or rethere is no evidence of harm to the mother or infant and 	on/action epeat antena significant and harm? epeat antena significant	do? ttal corticos benefits to ttal corticos	teroids detz the infant. teroids detz	hiled in Chap	oters 4 to 8,	Quality of Not re Ove	evidence ported rall evidence
Judging the benefits in context Not applicable. 4. What harm might the proposed interventi Evidence statement Based on overall treatment effects of a single course or re there is no evidence of harm to the mother or infant and Judging the harms in context Not applicable. 5. What is the likely balance between good a Evidence statement Based on overall treatment effects of a single course or re there is no evidence of harm to the mother or infant and Judging the balance of barm to the mother or infant and Judging the balance of barm to the mother or infant and Judging the balance of barm to the mother or infant and Judging the balance of barefits and harms in context Not applicable.	on/action epeat antena significant and harm? epeat antena significant	do? ttal corticos benefits to ttal corticos	teroids detz the infant. teroids detz	hiled in Chap	oters 4 to 8,	Quality of Not re Quality of	evidence ported rall evidence

Not known	Make a recomme	endation for research (se	e 8 below)	WEAK		
Benefits probably don't outweigh harms	Consider against/	nake no recommendation		CONDITIONAL		
Harms probably outweigh benefits		CONDITIONAL				
Benefits clearly don't outweigh harms	Descention description			STRONG		
Harms clearly outweigh benefits	Recommend again	st		STRONG		
6. Is the intervention/action implement	able in the New Ze	ealand 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 a	r against			
7. Final recommendation						
			Strength of re	commendation		
Use a single course of antenatal corticosteroids for a preterm labour and with ultrasound evidence of cerv preterm birth. Repeat antenatal corticosteroids for a woman presen ultrasound evidence of cervical shortening (<15mm)	STRONG CONDITION WEAK (Practi					
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 th women having undergo			f admir	istering a single course or repeat antenatal corticosteroids to				
1. Evidence base (number	• of studies, leve	el of evidence and risk of bias in the i	ncluded si	tudies)				
		rial evidence that addressed the presence of a positive or	А	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias				
negative fetal fibronectin		X X	В	One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias				
			С	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			А	All studies consistent				
			В	Most studies consistent and inconsistency can be explained				
			С	Some inconsistency, reflecting genuine uncertainty around question				
			D	Evidence is not consistent				
			NA	Not applicable (one study only)				
3. Clinical impact (indical intervention could not be determ		results varied according to some unkno	own factor	r (not simply study quality or sample size) and thus the clinical impact of the				
Not applicable			А	Very large				
			В	Substantial				
			C	Moderate				
			D	Slight / Restricted				
4. Generalisability (how n Not applicable	vell does the bo	dy of evidence match the population a		I settings being targeted by the guideline?)				
Not applicable			A	Evidence directly generalisable to target population Evidence directly generalisable to target population with some				
			В	caveats				
			С	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 bog	ly of evidence re	elevant to the New Zealand / Austra	alian heal	theare context in terms of health services / delivery of care and cultural factors?)				
Corticosteroids are readily and their use is feasible.	v available in	Australia and New Zealand	А	Evidence directly applicable to New Zealand / Australian healthcare context				
			В	Evidence applicable to New Zealand / Australian healthcare context with few caveats				
			С	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 upgrade the recommendation)	e any other faci	ors that you took into account when a	assessing i	the evidence base (for example, issues that might cause the group to downgrade or				
EVIDENCE STATEM	ENT MAT	RIX (summarise the development gro	oup's synt.	besis of the evidence relating to the key question, taking all the above factors into				
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 Evidence statement	NA	Not applicable						
There was no randomised	controlled t	rial evidence that addressed the	use of a	intenatal corticosteroids in the presence of a positive or negative				
fetal fibronectin test.								

OVERALL GRADE OF RECOMMENDATION			
Body of evidence can be trusted to guide practice			
Body of evidence can be trusted to guide practice in most situations			
Body of evidence provides some support for recommendations(s) but care should be taken in its application			
Body of evidence is weak and recommendation must be applied with caution			
Practice Points			
ted and that require follow up)			
ł			

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
	<u>N0</u>
Are there any resource implications associated with implementing this recommendation?	YES
	<u>NO</u>
Will the implementation of this recommendation require changes in the way care is currently	YES
organised?	NO
Are the guideline development group aware of any barriers to implementation of this	YES
recommendation?	<u>NO</u>

M36 GRADE Evidence summary

	hild ad-1	of admini	torina'	nala 20	0	tonatal and	storeids t-	
What is the safety for the mother and fetus, infant, c women having undergone fetal fibronectin testing?	hiid, adult			ngie course	-	oortance of out		
1. Outcome measures:	Quality of evidence					in making a decision		
Matemal Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Importan	
O1 Chorioamnionitis				NR	1			
O2 Puerperal sepsis				NR	1			
O ₃ Pyrexia after entry to trial				NR		1		
O4 Intrapartum fever requiring antibiotics				NR		1		
O5 Post natal pyrexia				NR		1		
O6 Maternal quality of life				NR	4			
Infant Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Importan	
O1 Combined fetal and neonatal death				NR	4		-	
O2 Neonatal death				NR	~			
O3 Fetal death				NR	*			
O4 RDS				NR	1			
O5 Composite of serious outcomes for the infant				NR	4			
O_6 Neurosensory disability (composite of impairments) for infant as a child				NR	1			
O7 Survival free of neurosensory disability for the				NR	4			
infant as a child O8 Survival free of metabolic disease for the infant as a child				NR	•	4		
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		4		
2. Is there is insufficient evidence to make a	recommer	ndation?	I	J	I			
 Evidence statement Maternal - There was no randomised controlled trial evided positive or negative fetal fibronectin test. Infant - There was no randomised controlled trial evidence or negative fetal fibronectin test. 3. What benefit will the proposed intervention 	e that addre	ssed the us	1			*		
						Quality of evidence		
Evidence statement		Not applicable					evidence	
Not applicable Judging the benefits in context Not applicable						Not re		
Not applicable Judging the benefits in context	on/action	do?						
Not applicable Judging the benefits in context Not applicable	on/action	do?					ported	
Not applicable Judging the benefits in context Not applicable 4. What harm might the proposed interventi Evidence statement Not applicable	on/action	do?				Not re	ported Cevidence	
Not applicable Judging the benefits in context Not applicable 4. What harm might the proposed interventi Evidence statement Not applicable Judging the harms in context Not applicable		do?				Not re Quality of	ported Cevidence	
Not applicable Judging the benefits in context Not applicable 4. What harm might the proposed interventi Evidence statement Not applicable Judging the harms in context Not applicable 5. What is the likely balance between good a		do?				Not re Quality of Not re	revidence	
Not applicable Judging the benefits in context Not applicable 4. What harm might the proposed interventi Evidence statement Not applicable 5. What is the likely balance between good a Evidence statement		do?				Not re Quality of	evidence ported rall	
Not applicable Judging the benefits in context Not applicable 4. What harm might the proposed interventi Evidence statement Not applicable Judging the harms in context Not applicable 5. What is the likely balance between good a Evidence statement Not applicable Judging the balance of benefits and harms in context	and harm?	do?				Quality of Not re	evidence rall evidence	
Not applicable Judging the benefits in context Not applicable 4. What harm might the proposed interventi Evidence statement Not applicable Judging the harms in context Not applicable 5. What is the likely balance between good a Evidence statement Not applicable Judging the balance of benefits and harms in context Not applicable	and harm?	do?				Quality of Not re Quality of Not re	evidence rall evidence	
Not applicable Judging the benefits in context Not applicable 4. What harm might the proposed interventi Evidence statement Not applicable Judging the harms in context Not applicable 5. What is the likely balance between good a Evidence statement Not applicable Judging the balance of benefits and harms in context Not applicable Benefits clearly outweigh harms	and harm? .t ecommend	do?				Quality of Not re Quality of Ove quality of Not re	rall ported	
Not applicable Judging the benefits in context Not applicable 4. What harm might the proposed interventi Evidence statement Not applicable Judging the harms in context Not applicable 5. What is the likely balance between good a Evidence statement Not applicable Judging the balance of benefits and harms in context Not applicable Benefits clearly outweigh harms Re Benefits probably outweigh harms	and harm? tt ecommend onsider			arch (see 8		Quality of Not re Quality of Not re	rall ported	

Harms probably outweigh benefits					
Benefits clearly don't outweigh harms	- Recommend again	st		STRONG	
Harms clearly outweigh benefits	Recommenci agam	st.	STRONG		
6. Is the intervention/action implement	table in the New Ze	aland context?			
Summary statement Antenatal corticosteroids are already widely in use im	n New Zealand and A	ustralia.			
Yes	Recommend/conside	<u>r</u>			
Not known	Consider economic evaluation				
No	Recommend/consider against				
7. Final 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. 8. Recommendations for research			Strength of re Please select level STRONG CONDITION <u>WEAK</u> (Pract		

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, lev	el of evidence and risk of bias in the in	icluded si	udies)			
		nce was reported for the use of roids for a variety of maternal	А	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias			
conditions where preterm	birth may b	e medically indicated.	В	One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias			
			С	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 ava	uilable, rank this component as 'not ap	pplicable?)			
Not applicable			А	All studies consistent			
		В	Most studies consistent and inconsistency can be explained				
			С	Some inconsistency, reflecting genuine uncertainty around question			
			D	Evidence is not consistent			
			NA	Not applicable (one study only)			
3. Clinical impact (indicat intervention could not be detern		results varied according to some unkno	own factor	r (not simply study quality or sample size) and thus the clinical impact of the			
Not applicable			А	Very large			
			В	Substantial			
			С	C Moderate			
			D	Slight / Restricted			
4. Generalisability (how m	vell does the bo	ody of evidence match the population a	nd clinica	l settings being targeted by the guideline?)			
Not applicable			А	Evidence directly generalisable to target population			
			В	Evidence directly generalisable to target population with some caveats			
			С	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			
			lian heal	theare context in terms of health services / delivery of care and cultural factors?)			
Corticosteroids are readily and their use is feasible.	available in	Australia and New Zealand	А	Evidence directly applicable to New Zealand / Australian healthcare context			
			В	Evidence applicable to New Zealand / Australian healthcare context with few caveats			
			С	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 upgrade the recommendation)	e any other fac	tors that you took into account when a	ussessing i	the evidence base (for example, issues that might cause the group to downgrade or			
No randomised trial evide	nce identifie	ed					
EVIDENCE STATEM	ENT MAT	RIX (summarise the development gro	up's synt.	besis of the evidence relating to the key question, taking all the above factors into			
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 from this evidence? Use action		nmendation(s) does the guideline development group draw ere possible)		OVERALL GRADE OF RECOMMENDATION					
			A	Body of evidence can be trusted to guide practice					
Use a single course of ante for preterm birth.	enatal cortic	osteroids for women with other medical indications	В	Body of evidence can be trusted to guide practice in most situations					
Do not delay birth to adm indicated.	inister anter	С	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						
		РР	Practice Points						
UNRESOLVED ISSUE	S (If needed,	keep a note of specific issues that arise when each recommendation	on is form	ulated and that require follow up)					
		MMENDATION (Please indicate yes or no to the following Il be used to develop the implementation plan for the guidelines)	g question	s. Where the answer is yes, please provide explanatory					
Will this recommendation	result in ch	anges in usual care?	Y	YES					
			N	0					
Are there any resource im-	plications as	sociated with implementing this recommendation?	Y	ES					
		N	0						
Will the implementation o	f this recorr	y Y	YES						
organised?		N	NO						
Are the guideline develop	nent group	Y	YES						
recommendation?		N	<u>NO</u>						

M37 GRADE Evidence summary

Considered	Judgement	t - Strength	of recom	nendation					
What is the safety for the mother and fetus, infant, of for whom preterm birth is medically indicated?	hild, adult	of adminis	tering a si	ngle course	e of antenata	corticosteroid	s to women		
1. Outcome measures:				portance of outcome making a decision					
Matemal Outcomes	HIGH MOD LOW V. LOW Critical				Important	Not Important			
O1 Chorioamnionitis				NR	*				
O2 Puerperal sepsis				NR					
O ₃ Pyrexia after entry to trial				NR		*			
O4 Intrapartum fever requiring antibiotics				NR					
O5 Post natal pyrexia				NR					
O6 Maternal quality of life				NR	4				
Infant Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Importan		
O1 Combined fetal and neonatal death				NR	1		Importan		
O2 Neonatal death				NR					
O3 Fetal death	1			NR	*		1		
O4 RDS	1			NR	*				
O5 Composite of serious outcomes				NR					
for the infant O ₆ Neurosensory disability (composite of impairments)					4				
for infant as a child				NR	1				
O_7 Survival free of neurosensory disability for the infant as a child				NR	1				
Os Survival free of metabolic disease for the infant as a child				NR		4			
O_9 Neurosensory disability (composite of impairments) for infant as an adult				NR	1				
O10 Survival free of neurosensory disability for the				NR	1				
infant as an adult O ₁₁ Survival free of metabolic disease for the infant as				NR	•				
an adult 2. Is there is insufficient evidence to make a	recommen	ndation?		INK		*			
Evidence statement									
No randomised controlled trial evidence was reported th							preterm		
birth may be medically indicated such as maternal cardia 3. What benefit will the proposed interventi			ia, renal dis	ease, cancer	or cholestasis				
Evidence statement						Quality of	evidence		
Based on the overall treatment effect, it is likely there corticosteroids, with no health harms for the mother. He				1		Not reported			
in cases where preterm birth is medically indicated have						THOLIC	ponea		
further research is required. Judging the benefits in context									
Not applicable	• / .•	1.5							
4. What harm might the proposed intervent	ion/action	do:					• 1		
Evidence statement Not applicable							Quality of evidence		
Judging the harms in context Not reported									
Not applicable									
5. What is the likely balance between good	and harm?								
Evidence statement Not applicable							Overall quality of evidence		
						Not re	ported		
Judging the balance of benefits and harms in contex Not applicable	ct 🗌								
	ecommend					STRONG			
Benefits probably outweigh harms C	onsider					CONDITION	NAL		
	lake a recor	nmendatio	on for resea	arch (see 8	below)	WEAK			
Not known Make a recommendation for research (see 8 below) Benefits probably don't outweigh harms Consider against/make no recommendation							NAL		

Harms probably outweigh benefits						
Benefits clearly don't outweigh harms				STRONG		
Harms clearly outweigh benefits	Recommend again	st		STRONG		
6. Is the intervention/action implement	able in the New Ze	aland context?				
Summary statement Antenatal corticosteroids are already widely in use in	New Zealand and A	ustralia.				
Yes		Recommend/conside	r			
Not known	Consider economic evaluation					
No		Recommend/consider against				
7. Final 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. 8. Recommendations for research Strength of recommendation STRONG CONDITIONAL WEAK (Practice Point) Strength of recommendation						
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, lev	el of evidence and risk of bias in the in	ncluded si	udies)			
No randomised controlled trial evidence was reported for the use of repeat antenatal corticosteroids for a variety of maternal conditions			А	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias			
where preterm birth may l			В	One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias			
			С	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 ava	uilable, rank this component as 'not ap	pplicable')			
Not applicable			А	All studies consistent			
			В	Most studies consistent and inconsistency can be explained			
			С	Some inconsistency, reflecting genuine uncertainty around question			
			D	Evidence is not consistent			
			NA	Not applicable (one study only)			
intervention could not be detern		results varied according to some unkno	own factor	r (not simply study quality or sample size) and thus the clinical impact of the			
Not applicable			А	Very large			
			В	Substantial			
			С	Moderate			
			D	Slight / Restricted			
4. Generalisability (how n	vell does the bo	dy of evidence match the population a	nd clinica	l settings being targeted by the guideline?)			
Not applicable			А	Evidence directly generalisable to target population			
			В	Evidence directly generalisable to target population with some caveats			
			С	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 bod	ly of evidence re	elevant to the New Zealand / Austra	alian heal	theare context in terms of health services / delivery of care and cultural factors?)			
Corticosteroids are readily and their use is feasible.	available in	Australia and New Zealand	А	Evidence directly applicable to New Zealand / Australian healthcare context			
			В	Evidence applicable to New Zealand / Australian healthcare context with few caveats			
			С	Evidence probably applicable to New Zealand / Australian			
				healthcare context with some caveats Evidence not applicable to New Zealand / Australian healthcare			
	e any other fac	tors that you took into account when a	D ussessing i	context the evidence base (for example, issues that might cause the group to downgrade or			
upgrade the recommendation) Not randomised evidence	identified						
EVIDENCE STATEM	ENT MAT	RIX (summarise the development gro	up's synt.	besis of the evidence relating to the key question, taking all the above factors into			
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 cortic preterm birth may be medically indicated.	osteroids	for a variety of maternal conditions where
RECOMMENDATION (W hat 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 other medical indications for preterm	Α	Body of evidence can be trusted to guide practice
birth.	В	Body of evidence can be trusted to guide practice in most situations
	С	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
	РР	Practice Point
UNRESOLVED ISSUES (If needed, keep a note of specific issues that arise when each recommendat	tion is form.	ulated 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
	<u>NO</u>
Are there any resource implications associated with implementing this recommendation?	YES
	<u>NO</u>
Will the implementation of this recommendation require changes in the way care is currently	YES
organised?	<u>N0</u>
Are the guideline development group aware of any barriers to implementation of this	YES
recommendation?	<u>N0</u>

M38 GRADE Evidence summary

Considered	Judgement	t - Strength	of recom	nendation				
What is the safety for the mother and fetus, infant, c women for whom preterm birth is medically indicate		of adminis	tering a re	peat course	.,			
1. Outcome measures:				portance of outcome making a decision				
Matemal Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Importan	
O1 Chorioamnionitis				NR	1			
O ₂ Puerperal sepsis				NR	1			
O ₃ Pyrexia after entry to trial				NR		1		
O4 Intrapartum fever requiring antibiotics				NR		1		
O5 Post natal pyrexia				NR		1		
O6 Maternal quality of life				NR	1			
Infant Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Importan	
O1 Combined fetal and neonatal death				NR	1		I · · · ·	
O2 Neonatal death				NR				
O₃ Fetal death				NR				
O4 RDS				NR				
O ₅ Composite of serious outcomes for the infant				NR	1			
O ₆ Neurosensory disability (composite of impairments) for infant as a child				NR	4			
O_7 Survival free of neurosensory disability for the infant as a child				NR	4			
O ₈ Survival free of metabolic disease for the infant as a child				NR		4		
O ₉ Neurosensory disability (composite of impairments) for infant as an adult				NR	1			
O ₁₀ Survival free of neurosensory disability for the infant as an adult				NR	4			
O ₁₁ Survival free of metabolic disease for the infant as an adult				NR		+		
2. Is there is insufficient evidence to make a	recommen	ndation?	I				•	
Evidence statement (No randomised controlled trial evidence was reported th preterm birth may be medically indicated such as matern	al cardiac di	sease, chroi					where	
3. What benefit will the proposed intervention	on/action l	nave?				1		
Based on the overall treatment effect, it is likely there would be benefit to the infant of exposure to antenatal							evidence	
Not applicable 4. What harm might the proposed intervent	ion /action	doð						
4. what harm hight the proposed intervent.	ion, action					Quality of evidence		
Not applicable								
Judging the harms in context	Not re	ported						
Not applicable 5. What is the likely balance between good and a second se	and harm?							
Evidence statement Not applicable		Ove quality of						
Not reported								
Judging the balance of benefits and harms in contex Not applicable	xt					1.0010		
	ecommend					STRONG		
Benefits probably outweigh harms Co	onsider					CONDITIONAL		
Not known M	lake a recor	nmendatio	on for resea	arch (see 8	below)	WEAK		
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				STRONG	
Harms clearly outweigh benefits	Recommend again	st		SIROING	
6. Is the intervention/action implement	able in the New Ze	ealand context?			
Summary statement Antenatal corticosteroids are already widely in use in	New Zealand and A	ustralia.			
Yes		Recommend/conside	<u>r</u>		
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

				and adult of administering a single course or repeat antenatal is or gestational diabetes at term?		
		el of evidence and risk of bias in the a				
There were no data from randomised trials identified for maternal or neonatal outcomes associated with the use of a single course of			А	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias		
antenatal corticosteroids i diabetes at term.	n women wi	th diabetes or gestational	В	One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias		
			С	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	e study was ava	ulable, rank this component as 'not c	applicable')		
Not applicable			А	All studies consistent		
			В	Most studies consistent and inconsistency can be explained		
			С	Some inconsistency, reflecting genuine uncertainty around question		
			D	Evidence is not consistent		
			NA	Not applicable (one study only)		
intervention could not be determ	te if the study : mined)	results varied according to some unkn	nown factor	r (not simply study quality or sample size) and thus the clinical impact of the		
Not applicable			А	Very large		
			В	Substantial		
				Moderate		
			D	Slight / Restricted		
4. Generalisability (how n	vell does the bo	dy of evidence match the population d	and clinica	l settings being targeted by the guideline?)		
Not applicable			А	Evidence directly generalisable to target population		
			В	Evidence directly generalisable to target population with some caveats		
			С	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		
			alian heal	theare context in terms of health services / delivery of care and cultural factors?)		
Corticosteroids are readily and their use is feasible.	v available in	Australia and New Zealand	А	Evidence directly applicable to New Zealand / Australian healthcare context		
			В	Evidence applicable to New Zealand / Australian healthcare context with few caveats		
			С	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 upgrade the recommendation)	e any other faci	tors that you took into account when	assessing 1	the evidence base (for example, issues that might cause the group to downgrade or		
EVIDENCE STATEM	ENT MAT	RIX (summarise the development gr	oup's synti	besis of the evidence relating to the key question, taking all the above factors into		
Component	Rating	Description				
1. Evidence base	N/A					
2. Consistency	N/A					
3. Clinical Impact	N/A					
 Generalisability Applicability 	N/A N/A					
o. approading	- 1/ /1					

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 (W hat 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	Α	Body of evidence can be trusted to guide practice						
corticosteroids at term (≥37 weeks' gestation) for women with diabetes in pregnancy.		Body of evidence can be trusted to guide practice in most situations						
Use antenatal corticosteroids 48 hours prior to caesarean birth planned beyond 34 weeks' and 6 days gestation if there is known fetal lung immaturity.	С	Body of evidence provides some support for recommendations(s) but care should be taken in its application						
Monitor maternal blood glucose concentrations and treat if elevated.	D	Body of evidence is weak and recommendation must be applied with caution						
	РР	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
	<u>NO</u>
Will the implementation of this recommendation require changes in the way care is currently	YES
organised?	<u>NO</u>
Are the guideline development group aware of any barriers to implementation of this	YES
recommendation?	NO

M39 GRADE Evidence summary

Considered		-						
What are the maternal and fetus, infant, child, adult corticosteroids for fetal lung maturation to women w						repeat antenat	al	
1. Outcome measures:				Imp	nportance of outcome in making a decision			
Maternal Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Importan	
O1 Chorioamnionitis				NR	4			
O2 Puerperal sepsis				NR	1			
O ₃ Pyrexia after entry to trial				NR		+		
O4 Intrapartum fever requiring antibiotics				NR				
O5 Post natal pyrexia				NR		4		
O ₆ Maternal quality of life				NR	4			
Infant Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Importan	
O1 Combined fetal and neonatal death				NR	4			
O2 Neonatal death				NR	4			
O3 Fetal death				NR	4			
O4 RDS				NR	4			
O ₅ Composite of serious outcomes for the infant				NR	4			
O ₆ Neurosensory disability (composite of impairments) for infant as a child				NR	1			
O7 Survival free of neurosensory disability for the infant as a child				NR	4			
O ₈ Survival free of metabolic disease for the infant as a child				NR		1		
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	1			
O ₁₁ Survival free of metabolic disease for the infant as an adult				NR		*		
2. Is there is insufficient evidence to make a	recommen	ndation?		1		1	1	
Evidence statement (For example, low volume or inconsisten No evidence was identified for maternal or neonatal out				ntenatal cort	icosteroids in	women with dia	abetes or	
gestational diabetes at term. 3. What benefit will the proposed intervention	/ 1	2						
1 1		laver				0 11		
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					0			
Not applicable.								
Not applicable. 4. What harm might the proposed intervent	ion/action	do?						
 What harm might the proposed intervent Evidence statement 	ion/action	do?				Quality of ev		
 What harm might the proposed intervent Evidence statement Not applicable. 	ion/action	do?				Quality of ev Not re		
 What harm might the proposed intervent Evidence statement Not applicable. Judging the harms in context Not applicable. 		do?						
 What harm might the proposed intervent Evidence statement Not applicable. Judging the harms in context Not applicable. What is the likely balance between good and applicable. 		do?				Not re	ported	
 4. What harm might the proposed intervent Evidence statement Not applicable. Judging the harms in context Not applicable. 5. What is the likely balance between good and g		do?					rall	
4. What harm might the proposed intervent Evidence statement Not applicable. Judging the harms in context Not applicable. 5. What is the likely balance between good a Evidence statement Not applicable. Judging the balance of benefits and harms in context	and harm?	do?				Not re	rall evidence	
 What harm might the proposed intervent Evidence statement Not applicable. Judging the harms in context S. What is the likely balance between good = Evidence statement Not applicable. Judging the balance of benefits and harms in context 	and harm?	do?				Not re Ove quality of Not re	rall evidence	
4. What harm might the proposed intervent Evidence statement Not applicable. 5. What is the likely balance between good a Evidence statement Not applicable. Judging the balance of benefits and harms in context Not applicable. Benefits clearly outweigh harms Reference Referen	and harm? ct	do?				Not re Quality of Not re STRONG	rall evidence ported	
4. What harm might the proposed intervent Evidence statement Not applicable. Judging the harms in context Not applicable. 5. What is the likely balance between good a Evidence statement Not applicable. Judging the balance of benefits and harms in context Not applicable. Benefits clearly outweigh harms Re Benefits probably outweigh harms Co	and harm?		on for rese	arch (see 8	below)	Not re Ove quality of Not re	rall evidence ported	

Harms probably outweigh benefits								
Benefits clearly don't outweigh harms	Recommend against			STRONG				
Harms clearly outweigh benefits	Recommenci agam	si		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	Rec		Recommend/consider against					
7. Final recommendation								
			Strength of re-	commendation				
There is insufficient evidence currently to make a rec at term (≥37 weeks' gestation) for women with diabu Use antenatal corticosteroids 48 hours prior to caesa days gestation if there is known fetal lung immaturity	STRONG CONDITION WEAK (Pract							
Monitor maternal blood glucose concentrations and treat if elevated.								
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
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rigule 1. Siligi	le course or a	ntena	ar cortic	Uster	nus -	respiratory uns	aress syndrome
	Antenatal corticost	eroids	No corticost	eroids		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
5.1.1 Moderate/sever	re 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 Subtotal (95% CI)	6	27 417	14	34 425	8.3% 54.5%	0.54 [0.24, 1.22] 0.60 [0.38, 0.95]	
Total events	81		145				
Heterogeneity: Tau ² =	0.19; Chi [≥] = 15.69, df	= 5 (P =	0.008); I ^z = 689	%			
Test for overall effect:							
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 Subtotal (95% CI)	1	27 418	0	35 426	1.2% 45.5%	3.86 [0.16, 91.12] 0.86 [0.64, 1.17]	
Total events	58		65				
Heterogeneity: Tau ² =	0.04; Chi ² = 6.76, df =	5 (P = 0	24); I ² = 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: Tau ² = Test for overall effect: Test for subgroup diff	Z = 2.06 (P = 0.04)					a	0.01 0.1 1 10 100 antenatal corticosteroids no corticosteroids

Figure 2: Repeat antenatal corticosteroids - respiratory distress syndrome

	Repeat corticos	teroids	No repeat corticost	eroids		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
7.1.1 Severe respira	tory 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: Tau ² =			< 0.00001); I ² = 91%				
Test for overall effect	Z = 1.23 (P = 0.22)						
7.1.2 Moderate/Mild	respiratory distres	s					
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: Tau ² =	= 0.13; Chi ² = 10.74	, df = 4 (P	= 0.03); I ^z = 63%				
Test for overall effect	Z = 0.16 (P = 0.87)	I.					
Total (95% CI)		1263		1259	100.0%	0.86 [0.64, 1.16]	•
Total events	363		424				
Heterogeneity: Tau ² =	= 0.13; Chi ² = 46.58	, df = 9 (P	< 0.00001); I ² = 81%				
Test for overall effect	Z = 0.99 (P = 0.32)						0.01 0.1 1 10 100 Repeat corticosteroids No repeat corticosteroids
Test for subgroup dif	ferences: Chi ² = 1.1	4. df = 1 ((P = 0.28), I ² = 12.6%				Repear conicosteroius INO repear conicosteroids

Figure 3: Subgroup analysis: Chorioamnionitis by of type of antenatal corticosteroid administered

	Antenatal corticos	steroid	No corticos	teroid		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI
1.2.1 Betamethason	e						
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: Chi ² =	5.06, df = 8 (P = 0.7)	5); I⁼ = 0%					
Test for overall effect	Z = 2.01 (P = 0.04)						
1.2.2 Dexamethasor	ie						
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: Chi ² =	1.35, df = 3 (P = 0.7)	2); I ^z = 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: Chi ² =		.52): I ^z = 0					L
Test for overall effect							0.01 0.1 i 10 100
Test for subaroup dif		df = 1 (P)	= 0.02) I ² =	82.2%			Antenatal corticosteroid No corticosteroid
				/0			

	Antenatal corticos	eroids	No corticoste	roids		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.3.1 Betamethason	e						
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				
	= 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 Dexamethason	le						
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: Tau ² =	= 0.19; Chi ² = 4.84, df =	= 3 (P = 0.	18); I 2 = 38%				
Test for overall effect:	Z = 1.52 (P = 0.13)						
Total (95% CI)		496		507	100.0%	1.35 [0.81, 2.25]	•
Fotal events	57		44				
Heterogeneity: Tau ² =	= 0.19; Chi ² = 10.97, di	í = 7 (P = 0	0.14); I ² = 36%				
Test for overall effect:							0.01 0.1 1 10 10 Antenatal corticosteroid No corticosteroid
	ferences: Chi² = 0.99.	df = 1 (P =	= 0.32) I ² = 0%				Anternatal controusteroid INO controusteroid

Figure 4: Subgroup analysis: Puerperal sepsis by type of antenatal corticosteroid administered

Figure 5: Subgroup analysis: Pyrexia after trial entry by type of antenatal corticosteroid administered

	Antenatal corticos	teroid	No corticos	teroid		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
1.4.1 Betamethasone	е						
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 Subtotal (95% Cl)	4	50 182	6	51 181	21.7% 64.2%	0.68 [0.20, 2.27] 0.68 [0.37, 1.25]	
Total events	16		24				
Heterogeneity: Tau ² = Test for overall effect: 1.4.2 Dexamethason	Z = 1.24 (P = 0.21)	= 2 (P =	0.61); I² = 0%				
Taeusch 1979 Subtotal (95% CI)	21	52 52	13	66 66	35.8% 35.8%	2.05 [1.14, 3.69] 2.05 [1.14, 3.69]	
Total events Heterogeneity: Not ap Test for overall effect:			13				
Total (95% CI)		234		247	100.0%	0.95 [0.43, 2.06]	-
Total events Heterogeneity: Tau ² = Test for overall effect: Test for subgroup diff	Z = 0.14 (P = 0.89)						0.01 0.1 1 10 100 Antenatal corticosteroid No corticosteroid

Figure 6: Subgroup analysis: Postnatal pyrexia by type of antenatal corticosteroid administered

				-		
Antenatal cortioc	steroid	No corticos	teroid		Risk Ratio	Risk Ratio
Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
;						
9	110	13	108	24.2%	0.68 [0.30, 1.52]	
2	59	2	59	3.7%	1.00 [0.15, 6.87]	
5	50	3	51	5.5%	1.70 [0.43, 6.74]	
	219		218	33.4%	0.88 [0.46, 1.68]	
16		18				
1.29, df = 2 (P = 0.5	3); I² = 0%					
Z = 0.38 (P = 0.70)						
e						
27	342	29	340	53.7%	0.93 [0.56, 1.53]	
7	102	7	102	12.9%	1.00 [0.36, 2.75]	
	444		442	66.6%	0.94 [0.60, 1.47]	•
34		36				
0.02, df = 1 (P = 0.8	9); I ^z = 0%					
Z = 0.27 (P = 0.79)						
	663		660	100.0%	0.92 [0.64, 1.33]	•
50		54				
1.34, df = 4 (P = 0.8	5); I ^z = 0%					
Z = 0.44 (P = 0.66)						0.01 0.1 1 10 10 Antenatal corticosteroid No corticosteroid
erences: Chi ^z = 0.03	2 df = 1 (P	- 0.00\ 12-	0.04			Anternatal controusteroid INO controusteroid
	Events 9 2 5 16 1.29, df = 2 (P = 0.5 Z = 0.38 (P = 0.70) e 27 7 34 0.02, df = 1 (P = 0.8 Z = 0.27 (P = 0.79) 50 1.34, df = 4 (P = 0.8 Z = 0.44 (P = 0.66)	$\begin{array}{c} 9 & 110\\ 2 & 59\\ 5 & 50\\ 219\\ 16\\ 1.29, df = 2 \ (P = 0.53); \ I^2 = 0\%\\ Z = 0.38 \ (P = 0.70)\\ e\\ 27 & 342\\ 7 & 102\\ 444\\ 0.02, df = 1 \ (P = 0.89); \ I^2 = 0\%\\ Z = 0.27 \ (P = 0.79)\\ 663\\ 50\\ 1.34, df = 4 \ (P = 0.85); \ I^2 = 0\%\\ Z = 0.44 \ (P = 0.66)\\ \end{array}$	Events Total Events 9 110 13 2 59 2 5 60 3 219 18 129 1.29, df = 2 (P = 0.53); P = 0% 18 2.27 342 29 7 102 7 444 36 0.02, df = 1 (P = 0.89); P = 0% Z = 0.27 (P = 0.79) 663 54 50 54 54 1.34, df = 4 (P = 0.85); P = 0% 54 54	Events Total Events Total 9 110 13 108 2 59 2 59 5 50 3 51 219 218 16 18 1.29, df = 2 (P = 0.53); P = 0% Z 9 340 7 102 7 102 444 442 36 0.02, df = 1 (P = 0.89); P = 0% Z = 0.27 (P = 0.79) 663 660 50 54 54	Events Total Events Total Weight 9 110 13 108 24.2% 2 59 3.7% 5 50 3 51 5.5% 2 59 3.7% 5 50 3 51 5.5% 2 10 218 3.4% 16 18 1.29, df = 2 (P = 0.53); P = 0% Z 9 340 53.7% 7 102 7 102 12.9% 444 36 34 36 0.02, df = 1 (P = 0.89); P = 0% 54 54 2 50 54 54 1.34, df = 4 (P = 0.85); P = 0% 54 54	$\begin{tabular}{ c c c c c c c } \hline Events & Total Veight M-H, Fixed, 95\% CI \\ \hline 9 & 110 & 13 & 108 & 24.2\% & 0.68 [0.30, 1.52] \\ 2 & 59 & 2 & 59 & 3.7\% & 1.00 [0.15, 6.87] \\ 5 & 50 & 3 & 51 & 5.5\% & 1.70 [0.43, 6.74] \\ 219 & 218 & 33.4\% & 0.88 [0.46, 1.68] \\ 1.29, df = 2 (P = 0.53); P = 0\% \\ Z = 0.38 (P = 0.70) \\ \hline 9 & & & & & & & & & & & & & \\ 27 & 342 & 29 & 340 & 53.7\% & 0.93 [0.56, 1.53] \\ 7 & 102 & 7 & 102 & 12.9\% & 1.00 [0.36, 2.75] \\ 444 & 442 & 66.6\% & 0.94 [0.60, 1.47] \\ 34 & 36 \\ 0.02, df = 1 (P = 0.89); P = 0\% \\ Z = 0.27 (P = 0.79) \\ \hline 663 & 660 & 100.0\% & 0.92 [0.64, 1.33] \\ 50 & 54 \\ 1.34, df = 4 (P = 0.85); P = 0\% \\ Z = 0.44 (P = 0.66) \\ \hline \end{tabular}$

	Antenatal corticos	teroids	No corticoste	roids		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.6.1 Betamethasone	e						
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]	\bullet
Total events	174		225				
Heterogeneity: Tau ^z =	0.04; Chi ² = 9.90, df:	= 7 (P = 0.	19); I² = 29%				
Test for overall effect:	Z = 2.38 (P = 0.02)						
1.6.2 Dexamethason	e						
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: Tau ² =	0.12; Chi ² = 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: Tau ² =	0.05; Chi ² = 19.21, d	f = 12 (P =	0.08); I ² = 38%	6			
Test for overall effect:							0.01 0.1 1 10 100 Antenatal corticosteroid No corticosteroid
Test for subgroup diff	erences: Chi ² = 0.00,	df = 1 (P =	= 0.98), I ^z = 0%				Antenatal conicosteroid INO conicosteroid

Figure 7: Subgroup analysis: Perinatal death by type of antenatal corticosteroid administered

Figure 8: Subgroup analysis: Neonatal death by type of antenatal corticosteroid administered

	Antenatal corticost	eroids	No corticoste	roids		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
1.7.1 Betamethason	e						
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				
	: 14.90, df = 14 (P = 0.3 : Z = 3.97 (P < 0.0001)	39); I² = 69	6				
1.7.2 Dexamethason							
		005			10.10	4 00 10 07 4 00	
Collaborative 1981	34 4	365	32	364	10.4%	1.06 [0.67, 1.68]	
Dexiprom 1999	4	105 91	8	101 88	2.6% 2.0%	0.48 [0.15, 1.55]	
Kari 1994 Qublan 2001	4 19	70	6 39	65	13.1%	0.64 [0.19, 2.21]	
Silver 1996	7	54	39	42	2.9%	0.45 [0.29, 0.70]	
Taeusch 1979	8	54	10	4∠ 69	2.9%	0.68 [0.27, 1.73]	
Subtotal (95% CI)	0	739	10	729	33.9%	0.72 [0.55, 0.94]	
Total events	76		103				
Heterogeneity: Chi ² =	8.29, df = 5 (P = 0.14)	; I ² = 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: Chi ² =	22.98, df = 20 (P = 0.2	29); I ^z = 13	1%				0.01 0.1 1 10 100
Test for overall effect	Z = 4.64 (P < 0.00001)					Antenatal corticosteroid No corticosteroid
	ferences: Chi ² = 0.21,		0.65), I ² = 0%				Antenatal controusteroru - No controusteroru

Figure 9: Subgroup analysis: Fetal death by type of antenatal corticosteroid administered

-				-			
	Antenatal corticos	teroids	No corticoste	roids		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
1.8.1 Betamethason	e						
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		6.26 [0.33, 118.64]	
Subtotal (95% CI)		1107		1100	69.0%	1.01 [0.73, 1.39]	◆
Total events	68		68				
Heterogeneity: Chi ² =	7.13, df = 6 (P = 0.31); I [≥] = 16%					
Test for overall effect	: Z = 0.05 (P = 0.96)						
1.8.2 Dexamethason	ie						
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: Chi ² =	= 1.67, df = 4 (P = 0.80); I ² = 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: Chi ² =	8.85, df = 11 (P = 0.6	4); I ² = 0%					
	Z = 0.15 (P = 0.88)						0.01 0.1 1 10 1
							Antenatal corticosteroid No corticosteroid

Figure 10: Subgroup analysis: Respiratory distress syndrome by type of antenatal corticosteroid administered Antenatal corticosteroids No corticosteroids Risk Ratio Risk Ratio

	Antenatal corticos	teroids	No corticost	eroids		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	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 Heterogeneity: Tau² = I Test for overall effect: 2			343 0.12); I² = 299	х			
1.9.2 Dexamethasone	•						
Collaborative 1981	46						
	40	361	65	359	7.4%	0.70 [0.50, 1.00]	
Dexiprom 1999	40 32	361 102	65 27	359 100	7.4% 6.4%	0.70 (0.50, 1.00) 1.16 (0.75, 1.79)	
Dexiprom 1999 Kari 1994							
	32	102	27	100	6.4%	1.16 [0.75, 1.79]	
Kari 1994	32 34	102 91 70 54	27 46	100 90	6.4% 7.6%	1.16 [0.75, 1.79] 0.73 [0.52, 1.02]	
Kari 1994 Qublan 2001 Silver 1996 Taeusch 1979	32 34 14	102 91 70 54 54	27 46 24	100 90 65 42 69	6.4% 7.6% 5.0% 9.3% 3.1%	1.16 (0.75, 1.79) 0.73 (0.52, 1.02) 0.54 (0.31, 0.95) 0.98 (0.81, 1.20) 0.64 (0.28, 1.47)	
Kari 1994 Qublan 2001 Silver 1996	32 34 14 43	102 91 70 54	27 46 24 34	100 90 65 42	6.4% 7.6% 5.0% 9.3%	1.16 [0.75, 1.79] 0.73 [0.52, 1.02] 0.54 [0.31, 0.95] 0.98 [0.81, 1.20]	
Kari 1994 Qublan 2001 Silver 1996 Taeusch 1979	32 34 14 43	102 91 70 54 54	27 46 24 34	100 90 65 42 69	6.4% 7.6% 5.0% 9.3% 3.1%	1.16 (0.75, 1.79) 0.73 (0.52, 1.02) 0.54 (0.31, 0.95) 0.98 (0.81, 1.20) 0.64 (0.28, 1.47)	
Kari 1994 Qublan 2001 Silver 1996 Taeusch 1979 Subtotal (95% CI)	32 34 14 43 7 176 0.04; Chi≇ = 10.08, c	102 91 70 54 54 732	27 46 24 34 14 210	100 90 65 42 69 725	6.4% 7.6% 5.0% 9.3% 3.1%	1.16 (0.75, 1.79) 0.73 (0.52, 1.02) 0.54 (0.31, 0.95) 0.98 (0.81, 1.20) 0.64 (0.28, 1.47)	
Kari 1994 Qublan 2001 Silver 1996 Taeusch 1979 Subtotal (95% CI) Total events Heterogeneity: Tau ² = I	32 34 14 43 7 176 0.04; Chi≇ = 10.08, c	102 91 70 54 54 732	27 46 24 34 14 210	100 90 65 42 69 725	6.4% 7.6% 5.0% 9.3% 3.1%	1.16 (0.75, 1.79) 0.73 (0.52, 1.02) 0.54 (0.31, 0.95) 0.98 (0.81, 1.20) 0.64 (0.28, 1.47)	
Kari 1994 Qublan 2001 Silver 1996 Taeusch 1979 Subtotal (95% CI) Total events Heterogeneity: Tau ² = I Test for overall effect: 2	32 34 14 43 7 176 0.04; Chi≇ = 10.08, c	102 91 70 54 732 If = 5 (P = 0	27 46 24 34 14 210	100 90 65 42 69 725	6.4% 7.6% 5.0% 9.3% 3.1% 38.8%	1.16 [0.75, 1.79] 0.73 [0.52, 1.02] 0.54 [0.31, 0.95] 0.98 [0.81, 1.20] 0.64 [0.28, 1.47] 0.81 [0.65, 1.02]	
Kari 1994 Qublan 2001 Silver 1996 Taeusch 1979 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: 2 Total (95% CI) Total events	32 34 14 43 7 176 0.04; Chi [≠] = 10.08, c Z = 1.80 (P = 0.07) 368	102 91 70 54 732 If = 5 (P = 0 2298	27 46 24 34 14 210 0.07); * = 50% 553	100 90 65 42 69 725 2274	6.4% 7.6% 5.0% 9.3% 3.1% 38.8%	1.16 [0.75, 1.79] 0.73 [0.52, 1.02] 0.54 [0.31, 0.95] 0.98 [0.81, 1.20] 0.64 [0.28, 1.47] 0.81 [0.65, 1.02]	
Kari 1994 Qublan 2001 Silver 1996 Taeusch 1979 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: 2 Total (95% CI)	32 34 14 43 7 176 0.04; Chi ^z = 10.08, c Z = 1.80 (P = 0.07) 368 0.07; Chi ^z = 47.47, c	102 91 70 54 732 If = 5 (P = 0 2298 If = 23 (P =	27 46 24 34 14 210 0.07); * = 50% 553	100 90 65 42 69 725 2274	6.4% 7.6% 5.0% 9.3% 3.1% 38.8%	1.16 [0.75, 1.79] 0.73 [0.52, 1.02] 0.54 [0.31, 0.95] 0.98 [0.81, 1.20] 0.64 [0.28, 1.47] 0.81 [0.65, 1.02]	0.01 0.1 10 1 Antenatal corticosteroid No corticosteroid

Figure 11 Subgroup analysis: intraventricular haemorrhage by type of antenatal corticosteroid administered

	Antenatal cortico	steroids	No corticost	eroids		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI
1.10.1 Betamethaso	ne						
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				
Test for overall effect		0					
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	.0	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: Tau ² :	= 0.60; Chi ² = 10.72,	df = 3 (P = 0	0.01); I² = 72%				
Heterogeneity: Tau² = Test for overall effect		df = 3 (P = 0	0.01); I² = 72%				
		df = 3 (P = 0 1445	0.01); I² = 72%		100.0%	0.54 [0.39, 0.74]	•
Test for overall effect			0.01); I² = 72% 155		100.0%	0.54 [0.39, 0.74]	•
Test for overall effect Total (95% CI)	: Z = 1.49 (P = 0.14) 88	1445	155	1427	100.0%	0.54 [0.39, 0.74]	★
Test for overall effect Total (95% CI) Total events	: Z = 1.49 (P = 0.14) 88 = 0.09; Chi ² = 16.25,	1445 df= 11 (P =	155	1427	100.0%	0.54 [0.39, 0.74]	O.01 O.1 Antenatal corticosteroids No corticosteroids

Figure 12: Subgroup analysis – Chorioamnionitis betamethasone regimens

8	P	<i>j</i> ===					8
	etametha		No corticos			Risk Ratio	Risk Ratio
	vents	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
1.11.1 12mg immediatel	y						
Subtotal (95% CI)		0		0		Not estimable	
Total events	0		0				
Heterogeneity: Not applic	able						
Test for overall effect: Not	applicab	le					
1.11.2 12mg in 12 hours							
Subtotal (95% CI)		0		0		Not estimable	
Total events	0		0				
Heterogeneity: Not applic	able						
Test for overall effect: Not	applicab	le					
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 applic	able						
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: Chi ² = 3.9	1, 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 applic	able						
Test for overall effect: Not	applicab	le					
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 applic							
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	304	70	500	1001070	011 0 [0140] 0100]	▼
Heterogeneity: Chi ² = 5.0		P = 0.76					
Test for overall effect: Z =			, i = 0.0				0.01 0.1 1 10 100
Test for subgroup differen			df = 2/P = 0	67) 18-1	196		Betamethasone No corticosteroid
rescion subgroup differen	ices. cm	- 1.13,	$a_1 = 2 (r = 0)$	57.1 = 1	5.00		

Figure 13: Subgroup analysis Chorioamnionitis dexamethasone regimen

Study or Subgroup	Dexametha Events	Total	No corticost Events		Weight	Risk Ratio M-H, Fixed, 95% Cl	Risk Ratio M-H, Fixed, 95% Cl
1.12.1 20mg in 36 hou		. o tui	Lionto	Total	inoight	in the thread of the thread	
Bilver 1996 Subtotal (95% CI)	13	39 39	12	36 36	39.7% 39.7%	1.00 [0.53, 1.90] 1.00 [0.53, 1.90]	
Fotal events Heterogeneity: Not app	13 olicable		12				
Test for overall effect: 2		1.00)					
1.12.2 24mg in 24 hou	Irs						
Dexiprom 1999 Subtotal (95% CI)	11	102 102	8	102 102	25.4% 25.4%	1.38 [0.58, 3.28] 1.38 [0.58, 3.28]	-
Total events Heterogeneity: Not app Test for overall effect: 2		: 0.47)	8				
1.12.3 24mg in 36 hou	Irs						
<ari 1994<="" td=""><td>13</td><td>77</td><td>8</td><td>80</td><td>25.0%</td><td>1.69 [0.74, 3.85]</td><td>--</td></ari>	13	77	8	80	25.0%	1.69 [0.74, 3.85]	- -
Qublan 2001 Subtotal (95% CI)	6	72 149	3	67 147	9.9% <mark>34.8%</mark>	1.86 [0.48, 7.15] 1.74 [0.86, 3.51]	
Total events Heterogeneity: Chi² = (Test for overall effect: 2			11); I² = 0%				
1.12.4 24mg in 40 hou Subtotal (95% Cl)	irs	0		0		Not estimable	
Total events Heterogeneity: Not app Test for overall effect: 1		_	0	Ū		not osumable	
Total (95% CI)		290		285	100.0%	1.35 [0.89, 2.05]	•
Total events	43		31				
Heterogeneity: Chi ² = 1); I² = 0%				0.01 0.1 1 10 1
Test for overall effect: 2			df = 2 (P = 0.5				Dexamethasone No corticosteroid

Figure 14: Subgrou	in analysis	Puerperal se	psis betametha	sone regimen
I Igaie I ii caogio	p analyono	r aciperar oc	poio setuinetina	oone regimen

	Betametha	isone	No corticos	teroid		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
.13.1 12mg immedia	tely						
Subtotal (95% CI)		0		0		Not estimable	
otal events	0		0				
leterogeneity: Not app	licable						
est for overall effect: N	lot applicat	ole					
.13.2 12mg in 12 hou	rs						
Subtotal (95% CI)		0		0		Not estimable	
otal events	0		0				
leterogeneity: Not app	licable						
est for overall effect: N	lot applicat	ole					
.13.3 24mg in 12 hou	rs						
ubtotal (95% CI)		0		0		Not estimable	
otal events	0		0				
leterogeneity: Not app	licable						
est for overall effect: N	lot applicat	ole					
.13.4 24mg in 24 hou	rs						
morim 1999	9	110	13	108	57.8%	0.68 [0.30, 1.52]	
arite 1992	10	33	5	38	20.5%	2.30 [0.88, 6.06]	
ewis 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]	•
otal events	21		22				
Heterogeneity: Chi² = 4 Test for overall effect: 2); I² = 54%				
.13.5 24mg in 36 hou	rs or more						
ubtotal (95% CI)		0		0		Not estimable	
otal events	0		0				
leterogeneity: Not app	licable						
est for overall effect: N	lot applicat	ole					
.13.6 28mg in 24 hou	rs						
Schutte 1980	1	50	1	51	4.4%	1.02 [0.07, 15.86]	
ubtotal (95% CI)		50		51	4.4%	1.02 [0.07, 15.86]	
otal events	1		1				
eterogeneity: Not app							
est for overall effect: 2	C = 0.01 (P =	= 0.99)					
otal (95% CI)		231		236	100.0%	1.00 [0.58, 1.72]	+
otal events	22		23				
leterogeneity: Chi² = 4); I² = 31%				
est for overall effect: 2	(= 0.01 (P =	: 0.99)					Betamethasone No corticosteroid
		7 0 00	df = 1 (P = 0.	0.00	201		Detainethasone into contcosteroid

Figure 15: Subgroup analysis Puerperal sepsis dexamethasone regimen

	Dexametha	asone	No corticos	teroid		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.14.1 20mg in 36 ho	urs						
Silver 1996 Subtotal (95% Cl)	11	39 39	5	36 36	29.3% 29.3%	2.03 [0.78, 5.28] 2.03 [0.78, 5.28]	-
Total events	11		5				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z=1.45 (P=	0.15)					
1.14.2 24mg in 24 ho	urs						
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 ap	plicable						
Test for overall effect:	Z=0.92 (P=	0.36)					
1.14.3 24mg in 36 ho	urs						
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 ap	plicable						
Test for overall effect:	Z = 1.88 (P =	0.06)					
1.14.4 24mg in 40 ho	urs						
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 ap	plicable						
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: Tau ² =	0.19; Chi ² =	4.84, df=	= 3 (P = 0.18)	² = 38%	5		
Test for overall effect:	Z = 1.52 (P =	0.13)					Dexamethasone No corticosteroid
Fest for subaroup diff	erences: Chi	² = 4.84,	df = 3 (P = 0.1)	18), I ² = 3	38.0%		Boxametrasone No concosterolu

Figure 16: Subgroup analysis Neonatal death – Betamethasone regimens

	Betametha Events	sone Total	No corticoste		Mainht	Risk Ratio	Risk Ratio
tudy or Subgroup .15.1 12mg immediat		Total	Events	Total	weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Subtotal (95% CI)	eiy	0		0		Not estimable	
otal events	0	0	0	0		Notestimable	
leterogeneity: Not appl	-		0				
est for overall effect: N		lo					
estion overall effect. 14	orapplicad	ile.					
.15.2 12mg in 12 hour	s						
Subtotal (95% CI)		0		0		Not estimable	
otal events	0		0				
leterogeneity: Not app	licable						
est for overall effect: N	ot applicab	le					
45.2.24mg in 42 hour							
.15.3 24mg in 12 hour		20	c .	20	2.00	4 00 10 00 0 501	
.opez 1989	6	20	6	20	3.0%	1.00 [0.39, 2.58]	
Jelson 1985	1	22	1	22	0.5%	1.00 [0.07, 15.00]	
arsons 1988 Subtotal (95% CI)	0	23 65	1	22 64	0.8% 4.3%	0.32 [0.01, 7.45] 0.88 [0.37, 2.07]	
	7	00	8	04	-+.J70	0.00 [0.07, 2.07]	
'otal events łeterogeneity: Chi² = 0.		$P = 0.70^{\circ}$					
est for overall effect: Z			, 1 = 0.20				
.15.4 24mg in 24 hour			~~				_
morim 1999	14	100	28	100	14.2%	0.50 [0.28, 0.89]	
Nock 1977	1	57	5	53	2.6%	0.19 [0.02, 1.54]	
ekih 2002	9	63	21	68	10.3%	0.46 [0.23, 0.93]	
erite 1992	9	33	11	40	5.1%	0.99 [0.47, 2.10]	
ewis 1996.	1	38	1	39	0.5%	1.03 [0.07, 15.82]	
iggins 1972	61	554	72	567	36.2%	0.87 [0.63, 1.19]	
forales 1989	7	87 163	8	78	4.3%	0.78 [0.30, 2.06]	
orto 2011 Subtotal (95% CI)	U	163 1095	2	157 1102	1.3% 74.4%	0.19 [0.01, 3.98] 0.71 [0.56, 0.90]	`
otal events	102	1055	148	1102	/ 4.4 /0	0.71[0.50, 0.50]	•
leterogeneity: Chi ² = 7.		n = 0.20					
est for overall effect: Z			1,1 = 0.36				
.15.5 24mg in 36 hour					0.40	0.07 10.00 0.00	
oran 1980	4	80	11	60	6.4%	0.27 [0.09, 0.81]	
amsu 1989 Subtotal (95% CI)	14	130 210	17	132 192	8.6% 15.0%	0.84 [0.43, 1.63] 0.60 [0.34, 1.03]	
otal events	18	210	28	192	15.0%	0.00 [0.04, 1.05]	
otal events leterogeneity: Chi² = 2.		P = 0.00					
est for overall effect: Z			,1 = 00 %				
	-						
.15.6 28mg in 24 hour		_		_			
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]	
otal events	3		12				
leterogeneity: Not appl							
est for overall effect: Z	= 2.35 (P =	0.02)					
otal (95% CI)		1432		1416	100.0%	0.67 [0.55, 0.82]	◆
otal events	130		196				-
leterogeneity: Chi ² = 1		3 (P = 0.)					
est for overall effect: Z							0.01 0.1 1 10 Betamethasone No corticosteroid

Figure 17: Subgroup analysis Neonatal death – dexamethasone regimens

0	0 1	2					0
	Dexameth		No corticoste			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.16.1 20mg in 36 h							
Collaborative 1981	34	365	32	364	27.6%	1.06 [0.67, 1.68]	
Bilver 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: Tau ²	= 0.00; Chi ² =	0.70, df:	= 1 (P = 0.40); i	²=0%			
Test for overall effec	t: Z = 0.14 (P =	: 0.89)					
1.16.2 24mg in 24 h	ours						
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 a	pplicable						
Test for overall effec	t: Z = 1.23 (P =	0.22)					
1.16.3 24mg in 36 h	ours						
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)	15	161	38	153	37.1%	0.47 [0.31, 0.71]	
Total events	23		45		0		•
Heterogeneity: Tau ²		0.20 df:		= 0%			
Test for overall effec				- 0 /0			
		,					
1.16.4 24mg in 40 h							
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 a							
Test for overall effec	t: Z = 0.05 (P =	= 0.96)					
Total (95% CI)		739		729	100.0%	0.70 [0.47, 1.03]	•
Total events	76		103				
Heterogeneity: Tau ²	= 0.09; Chi ² =	8.29, df=	= 5 (P = 0.14); i	² = 40%			
			· · · · · · · · · · · · · · · · · · ·				0.01 0.1 1 10 10
Test for overall effec	t: Z = 1.82 (P =	: 0.07)					Dexamethasone No corticosteroid

		n • .		-	D1	•
Figure 18: Subgroup	n analysis	Respirator	v distress s	vndrome -	– Ketamethasone	reormens
I Iguit 10. Oubgiou	J allary 010	iteophator.	y anoticou o	ynuionne	Detainetinaoone	, regimento

Study on Subarour	Betametha		No corticos		Mojakt	Risk Ratio	Risk Ratio
Study or Subgroup 1.17.1 12mg immedia	Events	Total	Events	rotar	weight	M-H, Random, 95% CI	M-H, Random, 95% CI
alci 2010	2	50	8	50	1.7%	0.25 [0.06, 1.12]	
Salci 2010 Subtotal (95% Cl)	2	50 50	8	50 50	1.7%	0.25 [0.06, 1.12] 0.25 [0.06, 1.12]	
otal events	2	50	8	50	1.1 /0	0.25 [0.00, 1.12]	
Heterogeneity: Not app			0				
est for overall effect: 2		- 0.07)					
corror overall check 2		- 0.017					
1.17.2 12mg in 12 hou	rs						
Subtotal (95% CI)		0		0		Not estimable	
Total events	0		0				
Heterogeneity: Not app	licable						
est for overall effect: N		ole					
1.17.3 24mg in 12 hou	rs						
opez 1989	9	20	10	20	6.9%	0.90 [0.47, 1.73]	
Velson 1985	10	20	11	20	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)	5	65		64	16.1%	0.91 [0.59, 1.40]	+
otal events	22		24				
Heterogeneity: Tau ² = I		0.01, df:); I ^z = 0%			
est for overall effect: 2							
.17.4 24mg in 24 hou	rs						
morim 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]	
arlan 1991	1	11	4	13	1.0%	0.30 [0.04, 2.27]	
ekih 2002	3	63	19	68	2.7%	0.17 [0.05, 0.55]	
∋arite 1992	21	33	28	40	14.4%	0.91 [0.65, 1.26]	-
_ewis 1996	7	38	17	39	5.6%	0.42 [0.20, 0.90]	
iggins 1972	53	542	89	550	14.7%	0.60 [0.44, 0.83]	
Aorales 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]	
Feramo 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]	•
Fotal events	141		257				
Heterogeneity: Tau ² = I				6); I ² = 44	%		
'est for overall effect: 2	2= 4.12 (P <	< 0.0001)					
.17.5 24mg in 36 hou							
oran 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]	
Fotal events	11		26				
leterogeneity: Tau ² = I			= 1 (P = 0.58); I² = 0%			
est for overall effect: 2	2 = 2.77 (P =	= U.006)					
.17.6 28mg in 24 hou							
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]	-
Fotal events			17				
Heterogeneity: Not app Test for overall effect: 2		= 0.14)					
				450.5	400.00	0.50.50.40.0.703	
fotal (95% CI)		1519		1504	100.0%	0.59 [0.48, 0.73]	▼
			332				
Total events	187						
	0.05; Chi ^z =		f= 16 (P = 0.	10); I ² = 3	2%		

Figure 19: Subgroup analysis Respiratory distress syndrome - Dexamethasone regimens

	Dexametha	asone	No corticost	eroids		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
1.18.1 20mg in 36 ho							
Collaborative 1981	46	361	65	359	19.3%	0.70 [0.50, 1.00]	1
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]	-
Fotal events	89		99				
Heterogeneity: Tau ² =			= 1 (P = 0.04);	I ² = 77%			
Fest for overall effect:	Z = 0.77 (P =	0.44)					
1.18.2 24mg in 24 ho	urs						
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]	•
Fotal events	32		27				
Heterogeneity: Not ap							
Fest for overall effect:	Z = 0.68 (P =	0.50)					
1.18.3 24mg in 36 ho	urs						
<ari 1994<="" td=""><td>34</td><td>91</td><td>46</td><td>90</td><td>20.1%</td><td>0.73 [0.52, 1.02]</td><td></td></ari>	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]	•
Fotal events	48		70				
Heterogeneity: Tau² = Fest for overall effect: .			= 1 (P = 0.37);	I ² = 0%			
1.18.4 24mg in 40 ho	urs						
Faeusch 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]	
Fotal events	7		14				
Heterogeneity: Not ap	plicable						
Fest for overall effect:	Z = 1.05 (P =	0.29)					
Fotal (95% CI)		732		725	100.0%	0.81 [0.65, 1.02]	•
Fotal events	176		210				-
Heterogeneity: Tau ² =	0.04; Chi ² =	10.08, df	= 5 (P = 0.07)); I [≥] = 509	6		
est for overall effect:			,				0.01 0.1 1 10 10 Dexamethasone No corticosteroid
Fest for subaroup diffe			df = 3 (P = 0.2)	1) 17 = 31	3.8%		Devametriasone INO controosteroid

Figure 20: Subgroup analysis Repeat antenatal corticosteroids - Chorioamnionitis

0	0	-	•	1				
		Repeat c	ourse	Single co	ourse		Risk Ratio	Risk Ratio
Study or Subgrou	ip	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
1.19.1 12mg com		ed immedi	ately (no	o repeat d	oses)			
Subtotal (95% CI)			0		0		Not estimable	
Total events		0		0				
Heterogeneity: No								
Test for overall eff	fect: N	lot applica	able					
1.19.2 11.4 mg co	omple	eted imme	ediately	(repeat do	ses allo	owed)		
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: No								
Test for overall eff	fect: 2	C = 0.38 (P	= 0.70)					
1.19.3 24mg in 24	4 hou	rs (no rep	eat dos	es)				
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: No								
Test for overall eff	fect: Z	C = 0.86 (P	= 0.39)					
1.19.4 24mg in 24	4 hou	rs (repea	t 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: Ch				$(1); I^{2} = 0.98$,			
Test for overall eff	ect. 2	2 = 1.60 (P	= 0.11)					
Total (95% CI)			2152		2109	100.0%	1.16 [0.92, 1.46]	◆
		140		118				
Heterogeneity: Ch				i9); I* = 0%	,			0.01 0.1 1 10 10
Total events Heterogeneity: Ch Test for overall eff Test for subgroup	fect: Z	(P	= 0.22)					0.01 0.1 1 10 10 Repeat course Single course

Figure 21: Subgroup analysis Repeat antenatal corticosteroids - Puerperal sepsis

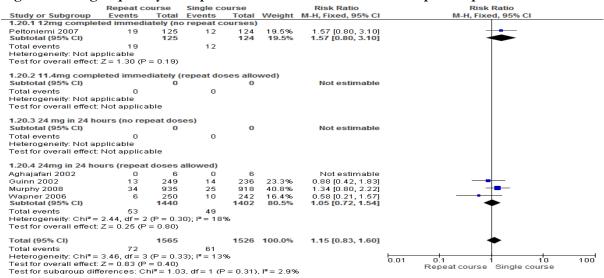


Figure 22: Subgroup analysis Repeat antenatal corticosteroids - Neonatal death

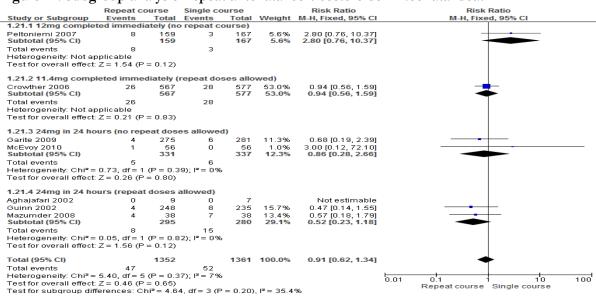


Figure 23: Subgroup analysis Repeat antenatal corticosteroids - Respiratory distress syndrome

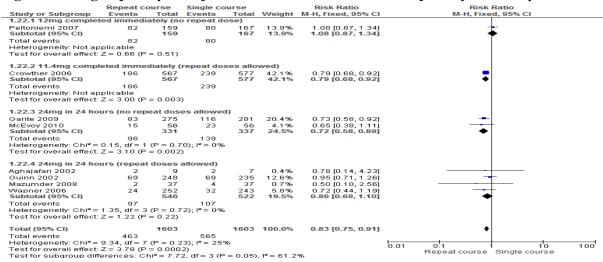
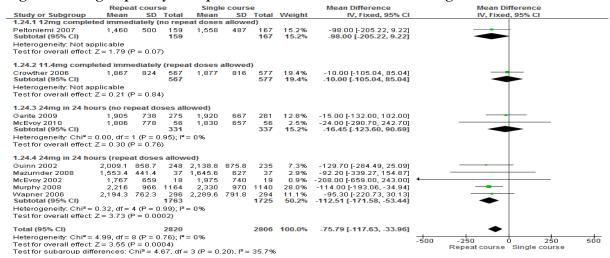


Figure 24: Subgroup analysis Repeat antenatal corticosteroids - Composite of serious infant outcomes

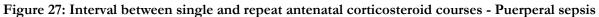
	Repeat c		Single co			Risk Ratio	Risk Ratio
Study or Subgroup	Events		Events			M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
1.23.1 12mg comple	eted immedi		o repeat d		owed)		
Subtotal (95% CI)		0		0		Not estimable	
Total events	0		0				
Heterogeneity: Not a							
Test for overall effect	t: Not applica	able					
1.23.2 11.4mg com	pleted imme	diately (repeat do	ses allo	wed)		
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 a							
Test for overall effect	t: Z = 2.35 (P	= 0.02)					
1.23.3 24mg in 24 h	ours (no rep	eat dos	es allowe	d)			
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 a	pplicable						
Test for overall effect	t: Z = 2.58 (P	= 0.010)				
1.23.4 24mg in 24 h	ours (repeat	t doses a	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 :			2); I ² = 15	%			
Test for overall effect	t: Z = 1.00 (P	= 0.32)					
Total (95% CI)		2561		2533	100.0%	0.84 [0.75, 0.94]	•
Total events	438		519				
Heterogeneity: Chi⁼ :	= 7.24, df = 6	i (P = 0.3	0); $I^2 = 1.7$	%			
Test for overall effect	t: Z = 3.06 (P	= 0.002)				Repeat course Single course
Test for subaroup di					17 00 0	or.	Repearcourse Single Course

Figure 25: Subgroup analysis Repeat antenatal corticosteroids Birthweight



8			8	1			
	Repeat c	ourse	Single cou	rse		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
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]	I - ≠ -
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: Chi ² =	0.68, df = 2	? (P = 0.7	'1); 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 = 0.3	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: Chi ² =	2.27, df = 4	(P = 0.6	i9); I² = 0%				
Test for overall effect:	Z=1.24 (P	= 0.22)					Repeat course Single course
Test for subgroup dif	ferences: C	hi ² = 0.8	1. df = 1 (P =	= 0.37)	, I² = 0%		Repeatedurse Ongre course

Figure 26: Interval between single and repeat antenatal corticosteroid courses - Chorioamnionitis



0			0	-	-		1
	Repeat co	ourse	Single co	ourse		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	I M-H, Fixed, 95% CI
1.26.1 Between 7 to	14 days						
Aghajafari 2002	0	6	0	6		Not estimable	9
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: Chi ² =	= 2.93, df = 2	(P = 0.2)	23); I ^z = 32 ^o	%			
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]	1 🔶
Total events	34		25				
Heterogeneity: Not a	pplicable						
Test for overall effect	:: Z = 1.11 (P	= 0.26)					
Total (95% CI)		1565		1526	100.0%	1.15 [0.83, 1.60]	1 🔶
Total events	72		61				
Heterogeneity: Chi ² =	= 3.46, df = 3	(P = 0.3)	83); F = 13 ⁴	%			
Test for overall effect	: Z = 0.83 (P	= 0.40)					0.01 0.1 1 10 100 Repeat course Single course
Test for subgroup dif	fferences: Cl	hi² = 0.6	0, df = 1 (P	² = 0.44)	, I² = 0%		Repear course - Olligie course

Figure 28: Interval between single and repeat antenatal corticosteroid courses - Perinatal death

0			0		-		
	Repeat co	ourse	Single co	ourse		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	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: Chi ² =	8.56, df = 5	i (P = 0.1	3); I ² = 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: Chi ² =	0.85, df = 2	(P = 0.6)	65); I² = 0%	5			
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: Chi ^z =	9.50. df = 8	(P = 0.3)	30): I ^z = 16	%			
Test for overall effect:							
Test for subgroup dif				^o = 0.81)	, I ≈ = 0%		Repeat course Single course

0			0						
	Repeat co	ourse	Single co	urse		Risk Ratio		Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H, Fixed, 95% Cl	
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 Subtotal (95% CI)	0	38 871	1	38 869	33.2% 77.8%	0.33 [0.01, 7.93] 0.71 [0.14, 3.57]			
Total events	2		3						
Heterogeneity: Chi ² =	0.33, df = 2	(P = 0.8)	35); I ² = 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	56 345	0	56 344	22.26	Not estimable			
Subtotal (95% CI)	4	343		J44	22.2%	1.00 [0.06, 15.86]			
Total events) In the set of		1						
Heterogeneity: Not a Test for overall effect	•	= 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 = 0.9)	95); I² = 0%				0.01		100
Test for overall effect	: Z = 0.36 (P	= 0.72)					0.01	Repeat course Single course	100
Test for subgroup dif	ferences: Ch	ni = 0.0	4. df = 1 (P	= 0.83)	, I² = 0%			Repeat course Olligie course	

Figure 29: Interval between single and repeat antenatal corticosteroid courses - Fetal death

Figure 30: Interval between single and repeat antenatal corticosteroid courses - Neonatal death

-			-	-			
	Repeat co	ourse	Single co	urse		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
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 Subtotal (95% Cl)	8	159 1021	3	167 1024	5.6% 87.7%	2.80 [0.76, 10.37] 0.92 [0.61, 1.38]	
Total events	42		46				
Heterogeneity: Chi ² =	4.66. df = 3	(P = 0.2)	(0): I ₹ = 369	%			
Test for overall effect		-					
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: Chi ² =	0.73, df = 1	(P = 0.3)	9); I ^z = 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: Chi ² =	5.40, df = 5	(P = 0.3	(7); I ^z = 7%				0.01 0.1 1 10 10
Test for overall effect	Z = 0.46 (P	= 0.65)					Repeat course Single course
Test for subgroup dif	ferences: C	hi² = 0.0	1. df = 1 (P	= 0.91)	, I² = 0%		Repear course Single course

Figure 31: Interval between single and repeat antenatal corticosteroid courses - Respiratory

distress syndrome

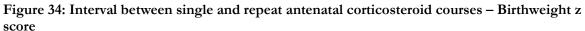
	Repeat co	ourse	Single co	urse		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI
1.30.1 Between 7 to 1	4 days						
Aghajafari 2002	2	9	2	7	0.4%	0.78 [0.14, 4.23]	
Crowther 2006	186	567	239	577	42.1%	0.79 [0.68, 0.92]	=
Guinn 2002	69	248	69	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				
Test for overall effect: ; 1.30.2 >/= 14 days Garite 2009	Z = 2.60 (P 83	= 0.009) 116	281	20.4%	0.73 [0.58, 0.92]	
McEvoy 2010 Subtotal (95% CI)	15	56 331	23	56 337	4.1% 24.5%	0.65 [0.38, 1.11] 0.72 [0.58, 0.89]	•
Total events Heterogeneity: Chi ^a = 1 Test for overall effect: 2				I			
Total (95% CI)		1603		1603	100.0%	0.83 [0.75, 0.91]	•
Total events Heterogeneity: Chi ² = 9 Test for overall effect: 3 Test for subgroup diffe	Z = 3.78 (P	= 0.000	2)				0.01 0.1 10 10 Repeat course Single course

Figure 32: Interval between single and repeat antenatal corticosteroid courses - Composite of serious infant outcomes

	Repeat co	ourse	Single co	urse		Risk Ratio	Risk Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl			
1.31.1 Between 7 to 1	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: Chi ² =	Heterogeneity: Chi# = 1.79, df = 4 (P = 0.77); I# = 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: Chi ² =	4.17, df = 1	(P = 0.0	l4); l² = 769	%						
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: Chi ² =	7.24, df = 6	(P = 0.3)	(0); I ² = 179	%						
Test for overall effect:	Z = 3.06 (P	= 0.002)				Repeat course Single course			
Test for subgroup diff	erences: C	hi² = 1.7	5. df = 1 (P	= 0.19)	. I² = 42.8	%	Repeat course Shight Course			

Figure 33: Interval between single and repeat antenatal corticosteroid courses - Birthweight

	Repea	at cours	se	Singl	e cours	е		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.32.1 Between 7 to 1	4 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]	
/Vapner 2006 Subtotal (95% CI)	2,194.3	762.3	296 1325	2,289.6	791.8	294 1329	11.1% 56.8%	-95.30 [-220.73, 30.13] -72.88 [-128.42, -17.35]	•
Test for overall effect: . 1.32.2 >/= 14 days	Z = 2.57 (I	P = 0.01)						
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 Subtotal (95% CI)	2,216	966	1164 1495	2,330	970	1140 1477	28.0% 43.2%	-114.00 [-193.06, -34.94] -79.61 [-143.23, -16.00]	
Heterogeneity: Chi² = Test for overall effect: .				= 3%					
Fotal (95% CI) Heterogeneity: Chi ^z =	4.99, df=	8 (P = 0	2820	= 0%		2806	100.0%	-75.79 [-117.63, -33.96]	-500 -250 0 250 500



Repeat cour	e Single course	Mean Difference	Mean Difference
or Subgroup Mean SD	Fotal Mean SD Total	Weight IV, Fixed, 95% CI	IV, Fixed, 95% CI
/= 7 and up to 14 days			
er 2006 -0.4 1.05 al (95% CI)	567 -0.27 1.14 577 567 577		
geneity: Not applicable			
r overall effect: Z = 2.01 (P = 0.	4)		
>/= 14 days			
2010 -0.14 0.86 al (95% CI)	56 -0.14 0.98 56 56 56		-
geneity: Not applicable			
overall effect: Z = 0.00 (P = 1.	0)		
95% CI)	623 633	100.0% -0.11 [-0.23, 0.00]	◆
geneity: Chi² = 0.49, df = 1 (P = ′ overall effect: Z = 1.88 (P = 0. ′ subgroup differences: Chi² =	-1 -0.5 0 0.5 1 Repeat course Single course		
geneity: Not applicable roverall effect: Z = 0.00 (P = 1. 15% CI) geneity: Chi ² = 0.49, df = 1 (P = roverall effect: Z = 1.88 (P = 0.	0) 623 633 0.48); I ² = 0% 6)	100.0% -0.11 [-0.23, 0.00]	

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