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14.11 Women wit

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

Clinical recommendation	Strength of recommendation	Chapter

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

Clinical recommendations	Strength of recommendation

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

With additional risk factor(s) for preterm birth

Clinical recommendations	Strength of recommendation		Chapter
	NHMRC	GRADE	
Use a single course of antenatal corticosteroids for women with a			

Summary of research recommendations

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

m birth

	Chapter(s)

- body size and body composition,
- neurosensory impairments,
- respiratory function.

Health outcomes:

- cardiovascular disease,

Use of antenatal corticosteroids for fetal lung maturation prior to elective

Glossary of terms

Periventricular leucomalacia	A form of brain injury characterised by the death of white matter near the cerebral ventricles in the newborn due to damage and softening of the brain tissue.
Placebo	

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 [illegible]

Summary of the development process

Clinical Practice Guidelines Panel

A multidisciplinary expert advisory Clinical Practice Guidelines Panel was established to oversee the development of these antenatal corticosteroid Clinical Practice Guidelines (Appendix A). The purpose of the Clinical Practice Guidelines Panel was to prepare evidence based guidelines on the best practice for clinical care in the use of antenatal corticosteroids for improving fetal,

Primary f

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

Other infant morbidity outcomes for these Clinical Practice Guidelines:

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

- Blood pressure
- Age at puberty

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Summary of timeline

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

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 percB0cBl(o)11lc 0 T b W-anpa5(Na)4rTJ-m oipe

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 adm0.6(1)0.6(4(ta)4.8(l)1.7(c)5(or)-3(ti)1.820 Tc.9(e)0.9(s)3.3(s)-7.5(s)-(-)Tj0.001[(g)1.3(e)3(n)]TJ0

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

Risk of bias for

- 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, Morrence < 161 >>BDC 4.37 0 T0[(T)-0.6( )]TJEJ0 T149 >>B1ekihns,

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

Author (Year)	Random sequence generation	Allocation concealment	Blinding of participants / personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Amorim (1999)							

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

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

- 2 x 12 mg (Celestone® Soluspan®), 24 hours apart. Repeat course every 14 days until 33

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 2009Garhl200,.003 6.065 0

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

Author, Year	Country	Pre-intervention treatment for both intervention and control group	Intervention if at risk of preterm birth after first course	Control	Outcomes reported			
					Maternal	Neonatal	Child	Adul

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

Author (Year)	Random sequence generation	Allocation concealment	

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 ac ref1i1T2i5f)3orte (f)36(f)36t(t)1(.1(ri1T2i51T2i5)162(e)0E*

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,

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

				Outcomes reported			
Author/year	Country	Betamethasone (number of women/infants)	Dexamethasone or other comparison (number of women/infants)	Maternal	Neonatal	Child	Adult
Chen (2005)	Taiwan	Betamethasone 2 x 12 mg 24 hourly (brand not specified) (n=81 infants)^	Dexamethasone 4x 6 mg (brand not specified) 12 hourly (n=76 infants)^	X	√	X	X

Dane

4. ‘C*orticosteroids 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 ‘C*orticosteroids 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

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

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

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

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

Maternal primary outcomes for these Clinical Practice Guidelines:

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

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

Table 8: Maternal infection in women treate with at21.3(e)4.5(e)0.6(n)7.5(t)-3.3(tTc 0 Tw (8)Tj--3.)TjET*01 Tc 4

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 ga-2.5(e)27(e)1(61tMCID 9 >>BDC q0 0 595.31.h(1)0.6(8)R8(t)-27298)R8(t)-27.5(o8(h)-3.3.9(r9h1tMCI27-5(i)10.(t)-(i(20

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?

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

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

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

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

Infant secondary outcomes for these Clinical Practice Guidelines:

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

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

- a significantly reduced need for respiratory support (27%) nsign banly sign banly

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

Outcome	Risk ratio (RR), Mean difference (MD) (95% Confidence Interval)	Number of trials	Trials contributing data	Number of infants
Need for respiratory support	RR 0.73 (0.59 to 0.92)	7	Amorim 1999; Balci 2010; Block 1977; Dexiprom 1999; Garite 1992; P	

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; 9(a)2.3ia riae-or6 reW D1.6(;)0.6(9(aJ-0

Infant as an adult primary outcomes for the Clinical Practice Guidelines:
None of the 26 trials included in the 2226

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

Outcome in adulthood	Risk ratio (RR)/ mean difference (MD) (95% Confidence Interval)	Number of trials	Trials

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

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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, pyr t t tauisuraasrt.9(pa)2.9(t)-2.554.21 a

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 (Da5 Tc 0.c 0 T8]TJ0 T 0 Td[b0

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.

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

Outcome	Risk ratio RR (95% Confidence Interval)	Number of trials	Trials contributing data	Number of women
Chorioamnionitis	RR 1.16 (0.92 to 1.46)	6	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Murphy 2008; Wapner 2006	4261
Puerperal sepsis	RR 1.15 (0.83 to 1.60)			

Chapter 7

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

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

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

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 t o

 he13[(he13[(he1l)-5o)-o42(h-35(-gxpT

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

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

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

Outcome at primary hospital discharge	Mean difference (MD) (95% Confidence Interval)	Number of trials	Trials contributing data	Number of infants
Mean measurements at hospital discharge				

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

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

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

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

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

Table 19: Secondary early childhood

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 (200

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 associs(s)9(s( )]99o2(0)11.1s(s( )]99o2(0)11.1svri/5-0.002 Tc 0.1

For the infant as an adult

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

See Appendix M2 – Evidence

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,

Table 20:

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

Outcome	Betamethasone		Dexamethasone	
	Risk ratio (RR) (95% Confidence Interval)	Trials contributing data	Risk ratio (RR) (95% Confidence Interval)	Trials contributing data
Perinatal death	RR 0.72 (0.55 to 0.94); 8 trials, n=2207 infants	Amorim 1999; Block, 1977; Doran, 1980; Gamsu, 1989; Garite, 1992; Liggins, 1972; Parsons, 1988; Schutte, 1980	RR 0.72 (0.46 to 1.11); 5 trials, n=1420 infants	Collaborative, 1981; Dexiprom, 1999; Kari, 1994; Qublan, 2001; Taeusch, 1979
Subgroup interaction test	Chi^2=0.00, p=0.98, I^2=0%; 13 trials, n=3627 infants			
Fetal death	RR 1.01 (0.73 to 1.39); 8 trials, n=2207 infants	Amorim 1999; Block, 1977; Doran, 1980; Gamsu, 1989; Garite, 1992; Liggins, 1972; Parsons, 1988; Schutte, 1980	RR 0.92 (0.56 to 1.50); 5 trials, n=1420 infants	Collaborative, 1981; Dexiprom, 1999; Kari, 1994; Qublan, 2001; Taeusch, 1979
Subgroup interaction test	Chi^2=0.1, p=0.15, I^2=0%; 13 trials, n=3627 infants			
Neonatal death	RR 0.67 (0.54 to 0.82); 15 trials, n=2940 infants	Amorim 1999; Block, 1977; Doran, 1980; Fekih, 2002; Gamsu, 1989; Garite, 1992; Goodner, 1979; Lewis, 1996; Liggins, 1972; Lopez, 1989; Morales, 1989,		

Respiratory distress syndrome -

Head to head comparisons of betamethasone and dexamethasone -

For respiratory distress no difference

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

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

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

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

There was a significant subgroup interaction test for:

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

For the infant as a child

Direct comparison of betamethasone and dexamethasone -

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

Single course of antenatal corticosteroids -

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

See Appendix M3 – Evidence Summary (Page 319)

Do benefits or harms in the mother, fetus, infant, child or adult vary by whether betamoo os19.

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

See Appendix M4 –Evidence Summary (Page 323)

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

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

Practice point:
• If betamethasone is not available use dexamethasone.

Research recommendation:
• A randomised trial of dexamethasone as the repeat corticosteroid is required.

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

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

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):

significant for puerperal sepsis (Chi^2=0.00, p=0.99, I^2=0%) (Appendix N - Figure 14). This can be interpreted as indicating that these betamethasone regimens did not differentially influence the risk of puerperal sepsis.

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

For dexamethasone no difference w293 T4 Tw 39dn( )03 Tc 0.003 Tw.7(f)5(ia)2(ial1T9200)0.6(%)-4.1()1 TD 11 >>BDC /TT

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

Total dose dexamethasone	Time to complete course	Chorioamnionitis	Puerperal sepsis

Table 28: Primary infant outcomes for different

(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).

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.

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 (i0.7(j)-13p0(n)-Tso6 6(o)-0.(j)-1o.2b.7(d)-10(p)an hoC Q66.36

Total dose of betamethasone ≤12 mg

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

Total dose of betamethasone 24 mg

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

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

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

Total dose of betamethasone	Time to complete course	Chorioamnionitis		Puerperal sepsis	
		Risk ratio RR (95% Confidence Interval)	Trials contributing data	Risk ratio RR (95% Confidence Interval)	Trials contributing data
≤12 mg betamethasone					
12 mg	Immediate (no repeat doses)	NR		1.57 (0.80 to 3.10), 1 trial, n= 249 women	Peltoniemi 2007
11.4 mg	ef199.32 3BT				

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

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

Primary infant outcomes for these Clinical Practice Guidelines:

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

Betamethasone:

- ≤12 mg completed immediately
- 24 mg completed in 24 hours 301 Tc -0.001 Tw -4.3296 Td293 Td(()n=-0.001 Tc 0.001 Tw [(c74 0 Td( )0.6(4)0

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

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

Total d

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

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, Guinneat e.8(r)a30(tu)4e9(t

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

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

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

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

Total dose of betamethasone	Time to complete course	Mean difference MD (95% Confidence Interval)
		Birthweight
≤12 mg betamethasone		
12 mg	Immediate (no repeat courses)	-98 g (-205. 22 to 9.22); 1 trial, n=326 infants
11.4 mg^	Immediate (repeat courses allowed)	-10 g (-105.04 to 85.04); 1 trial, n=1144 infants
24 mg betamethasone		
24 mg	24 hours (no repeat doses)	-16.45 g (-123.60 to 90.69); 2 trials, n=668 infants
24 mg		

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

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

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

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 bi

See Appendix M6

- 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 - I

Respiratory distress syndrome

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

Outcome	Risk ratio (RR) (95%Confidence Interval)	Number of trials	

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

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

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

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

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

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

For the mother

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

For the infant

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

The benefits for reduced risk of respiratory distress syndrome are observed where the infant had been exposed to antenatal corticosteroids for <48 hours and between one and up to seven days before birth

Evidence indicates that:

- for reduction in the risk of death, the optimal time prior to birth to administer a single course of

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*

What is the optimal timing between a first course of antenatal corticosteroids and initiating a [redacted]

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

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

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

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

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

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

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).

(274 0 Td9(r)-5(y53( )-10.8(N)-1(a)-3(e)-0.9(n)-5.5(e)-0.9(d)-7.1(i)-1.1(c)-0.1(t)-2.6(i)-0.8(n)-5.7(e)-0.9(d)-7.1(i)-1.1(c)-0.1(t)-2.6(i)-0.8(n)-5.7(e)-0.9(d)-7.1(i)-1.1(c)-0.1(t)-2.6(i)-0.8(n)-5.7(e)-0.9(d)-7.1(i)-1.1(c)-0.1(t)-2.6(i)-0.8(n)-5.7(e)-0.9(d)-7.1(i)-1.1(c)-0.1(t)-2.6(i)-0.8(w)1tv)045h)2.9352<004ii)2

respiratory distress syndrome and

Chapter 12: Gestational age for administration of antenatal corticosteroids

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 diOver w27.6(.4( )9(r)-3Tc 0.)10.8(s)-3.5(e6-2.3(n)-3.83(l)1.7(( )]TJ)4.9(r)-12.6(s)7.3(n)-(k)2.6(c

Gestational age ≥34 weeks' and 0 days
No trials that recruited and randomised women with a gestation at trial entry ≥34 weeks' and 0 days reported on maternal infection outcomes (chorioamnionitis, puerperal sepsis, pyrexia after trial entry, intrapartum pyrexia or postnatal pyrexia requiring treatment with antibiotics).

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

Primary infant outcomes for these Clinical Practice Guidelines:

Fetal, neonatal or later death -

Perinatal death - Overall there was a significant reduction in the risk for perinatal death for infants who had been exposed to a single course of antenatal corticosteroids compared with no exposure (RR 0.77, 95%CI 0.67 to 0.89; 13 trials, n=3627 infants).

- *Gestational age ≤34 weeks' and 6 days* - There was a significant reduction in the risk of perinatal death for infants exposed to a single course of antenatal corticosteroids compared with no exposure when gestational age at trial entry was ≤34 weeks' and 6 days (RR 0.57, 95%CI 0.45 to 0.73; 7 trials, n=1020 infants).
- *Gestational age ≥34weeks' and 0 days* - No trials that recruited and randomised women with a gestation at trial entry ≥34 weeks' and 0 days reported on perinatal death

Fetal death - Overall no difference was seen in the risk for fetal death between infants who had been exposed to antenatal corticosteroids and those with no exposure (RR 0.98, 95%CI 0.73 to 1.30; 13 trials, n=3627 infants).

- *Gestational age ≤34 weeks' and 6 days* - No difference was seen in the risk for fetal death between infants exposed to a single course of antenatal corticosteroids compared with no exposure when gestational age at trial entry was ≤34 weeks' and 6 days (RR 1.02, 95%CI 0.54 to 1.94; 7 trials, n=1020 infants).
- *Gestational age ≥34weeks' and 0 days* - No trials that recruited and randomised women with a gestation at trial entry ≥34 weeks' and 0 days reported on fetal death

Neonatal death - Overall there was a significant reduction in the risk for neonatal death for infants who had been exposed to a single course of antenatal corticosteroids compared with no exposure (RR 0.68, 95%CI 0.58 to 0.80; 21 trials, n=4408 infants).

- *Gestational age* ≤34 weeks' and 6 days - There was a significant reduction in the risk for neonatal death for infants exposed to a single course of antenatal corticosteroids compared with no exposure when gestational age at trial entry was ≤34 weeks' and 6 days (RR 0.53, 95%CI 0.42 to 0.68; 13 trials, n=1583 infants).
- *Gestational age ≥34 weeks' and 0 days* - No difference was seen in the risk for neonatal death between infants exposed to a single course of antenatal corticosteroids and those with no exposure when gestational age at trial entry was ≥34 weeks' and 0 days (RR 0.19, 95%CI 0.01 to 3.98; 1 trial, n=320 infants). The event rates in this single trial (Porto 2011) are very low with only 2 deaths reported in the non-exposed group and no deaths in the antenatal corticosteroid group. There is also evidence of imprecision with wide confidence intervals.

Respiratory distress syndrome -
Overall there was a significant reduction in the risk of respiratory distress syndrome for infants exposed to a single course of antenatal corticosteroids compared with those with no exposure (RR 0.65, 95%CI 0.58 to 0.73; 25 trials, n=4590 infants).

- *Gestational age ≤34 weeks' and 6 days* - There was a significant reduction in the risk of respiratory

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 (e)3(a)2.8(t 29j0.0li49(t)8. 0 Td[(t)2)0.645.3(st.9(ir)-43(s)5 4s9(,)0.6n in)9(.0.0l

See Appendix M10 - Evidence Summary (Page 348)

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

Practice Points:

- Use a single course of antenatal corticosteroids in women of 34 weeks' and 6 days or less gestation if birth is expected within the next seven days.
- If considering use of antenatal corticosteroids prior to 24 weeks' gestation, there should be careful consideration of benefit and risks with parental consultation.

At what gestational ages is a repeat dose(s) of antenatal corticosteroids effective?

For the purpose of these Clinical Practice Guidelines gestational age at trial entry was categorised into the following subgroups for analysis:

≤31

- *≤32 weeks' and 6 days* - No difference was seen in the risk for puerperal sepsis between women who were treated with repeat antenatal corticosteroids and those with no repeat treatment when the gestational age at trial entry was ≤32 weeks' and 6 days (RR 1.17, 95%CI 0.77 to 1.77; 2 trials, n=2338 women).
- *≤33 weeks' and 6 days* - No difference was seen in the risk for puerperal sepsis between women who were treated with repeat antenatal corticosteroids and those with no repeat treatment when the gestational age at trial entry was ≤33 weeks' and 6 days (RR 1.57, 95%CI 0.80 to 3.10; 1 trial, n=249 women) (Table 38).

Postnatal pyrexia requiring treatment - Overall no difference was seen in the risk for postnatal pyrexia between women who had been treated with repeat antenatal corticosteroids and those with no repeat corticosteroid treatment (RR 0.92, 95%CI 0.64 to 1.33; 5 trials, n=1323 women).

- One trial (Crowther 2006) that randomised women at ≤31 weeks' and 6 days gestation found no difference in postnatal pyrexia requiring treatment between women who had received repeat antenatal corticosteroids and those with no repeat treatment (RR 0.87, 95%CI 0.55 to 1.38; 1 trial, n=972 women).

Other maternal infection outcomes - There were no data for other maternal infection outcomes including pyrexia after trial entry or intrapartum pyrexia requiring treatment.

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

Outcome Gestational age at trial entry (weeks $^{+days}$)	Risk Ratio (RR) (95% Confidence Interval)	Trials contributing data	Number of women
Chorioamnionitis			
$\leq 31^{+6}$	1.11 (0.76 to 1.62), 3 trials	Aghajafari 2002; Crowther 2006; Wapner 2007	1486
$\leq 32^{+6}$	1.19 (0.89 to 1.59), 3 trials	Garite 2009; Guinn 2001; Murphy 2008	2775
$\leq 33^{+6}$	Not reported	Not reported	Not reported
Puerperal sepsis			
$\leq 31^{+6}$	0.58 (0.21 to 1.57), 2 trials	Aghajafari 2002; Wapner 2007	504
$\leq 32^{+6}$	1.17 (0.77 to 1.77), 2 trials	Garite 2009; Murphy 2008	2338
$\leq 33^{+6}$	1.57 (0.80 to 3.10), 1 trial	Peltoniemi 2007	249

$Source: Crowther (2011); *Meta-analysis conducted for these Clinical Practice Guidelines.

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

Primary infant outcomes for these Clinical Practice Guidelines:

Fetal, neonatal or later death -

Perinatal death - Overall there was no difference in the risk of perinatal death for infants exposed to repeat antenatal corticosteroids compared with infants with no exposure (RR 0.94, 95%CI 0.71 to 1.23; 9 trials, n=5554 infants).

- *≤31weeks' and 6 days* - No difference was seen in the risk for perinatal death between infants who were exposed to repeat antenatal corticosteroids and those with no repeat exposure when the gestational age at trial entry was ≤31 weeks' and 6 days (RR 0.87, 95%CI 0.54 to 1.39; 3 trials, n=1657 infants).

- *≤32 weeks' and 6 days* - No difference was seen in the risk for perinatal death between infants who were exposed to repeat antenatal corticosteroids and those with no repeat exposure when the gestational age at trial entry was ≤32 weeks' and 6 days (RR 0.87, 95%CI 0.62 to 1.24; 4 trials, n=3459 infants).
- *≤33 weeks' and 6 days* - No difference was seen in the risk for perinatal death between infants who were exposed to repeat antenatal corticosteroids and those with no repeat exposure when the gestational age at trial entry was ≤33 weeks' and 6 days (RR 2.83, 95%CI 0.84 to 9.49; 2 trials, n=438 infants) (

- *≤31 weeks' and 6 days* - A composite of serious infant outcomes was significantly reduced for infants who had been exposed to repeat antenatal corticosteroids compared with those with no repeat exposure when the gestational age at trial entry was ≤31 weeks' and 6 days (RR 0.78, 95%CI 0.64 to 0.95; 3 trials, n=1655 infants).
- *≤32 weeks' and 6 days* - No difference was seen in the risk for a composite of serious infant outcomes between infants who were exposed to repeat antenatal corticosteroids compared with those with no repeat exposure when the gestational age at trial entry was ≤32 weeks' and 6 days (RR 0.83, 95%CI 0.67 to 1.03; 4 trials, n=3439 infants).
- *≤33 weeks' and 6 days* - No data were reported for a composite of serious infant outcomes in the trials included in the Crowther (2011) systematic review when the gestational age at trial entry was ≤33 weeks' and 6 days (Table 39).

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

Birthweight - Overall birthweight was significantly reduced following repeat antenatal corticosteroids compared with no repeat exposure (MD-75.79 grams, 95%CI -117.63 to -33.96; 9 trials, n=5626 infants) (Crowther 2006, Garite 2009, Guinn 2001, Mazumder 2008, McEvoy 2002, McEvoy 2010, Murphy 2008, Peltoniemi 2007, Wapner 2006).

- *≤31 weeks' and 6 days* - No difference was see in birthweight when the gestational age at trial entry was ≤31 weeks' and 6 days (MD -41.11 grams, 95%CI -116.86 to 34.64; 2 trials, n= 1734 infants).
- *≤32 weeks' and 6 days* - There was a significant reduction in birthweight seen when the gestational age at trial entry was ≤32 weeks' and 6 days (MD -90.19 grams, 95%CI -148.79 to -31.58; 4 trials, n=3417 infants).
- *≤33 weeks' and 6 days* - No difference was seen in birthweight when the gestational age at trial entry was ≤33 weeks' and 6 days (-93.29 grams, 95%CI -190.43 to 3.86; 3 trials, n=475 infants).

Birthweight z score - Overall no difference was seen in birthweight z scores reported in two trials (MD -0.11, 95%CI -0.23 to 0.00; 2 trials, n=1256 infants) (Crowther 2006, McEvoy 2010).

- *≤31 weeks' and 6 days* - There was a borderline significant reduction in birthweight z score reported in a single trial (Crowther, 2006) (MD -0.13, 95%CI -0.26 to -0.00; 1 trial, n=1144 infants).
- *≤33 weeks' and 6 days* - No significant difference was seen in birthweight z scores in a single trial (McEvoy 2010) (MD 0.00, 95%CI -0.34 to 0.34; 1 trial, n=112 infants).

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

Neurosensory disability -

≤31 weeks' and 6 days - No difference was seen in survival free of neurosensory disability at early childhood follow-up from the Crowther (2006) trial when the gestational age at trial entry was ≤31 weeks' and 6 days (RR 1.04, 95% CI 0.99 to 1.10; 1 trial, n=1060 children) (Crowther 2007). No difference was seen in survival free of disability when the gestational age at trial entry was ≤31 weeks' and 6 days (RR 1.02, 95%CI 0.92 to 1.12; 1 trial, n=1060 children).

≤32 weeks' and 6 days - No difference was seen in survival free of disability at early childhood follow-up from the Murphy (2008) trial when the gestational age at trial entry was ≤32 weeks' and 6 days (RR 1.01, 95%CI 0.97 to 1.04; 1 trial, n=2095 children) (Asztalos 2010).

≤33 weeks' and 6 days - No difference was seen in survival free of neurosensory disability at early childhood follow-up from the Peltoniemi (2007) trial when the gestational age at trial entry was ≤33 weeks' and 6 days (RR 0.98, 95% CI 0.95 to 1.01; 1 trial, n=257 children) (Peltoniemi 2009).

Survival free of metabolic disease - No randomised controlled trials included in the Crowther CPG version 2015 systematic review reported data for survival free of metabolic disease at early childhood follow-up (Appendix I).

Summary of evidence for the timing of repeat antenatal corticosteroids.

For the mother

No differences were seen in the risks of maternal infection outcomes including chorioamnionitis, puerperal sepsis and postnatal pyrexia requiring treatment with antibiotics following treatment with repeat antenatal corticosteroids compared with no repeat treatment when the gestational age at trial entry was ≤31 weeks' and 6 days, ≤32 weeks' and 6 days or ≤33 weeks' and 6 days.

For the infant

No differences were seen in the risks of infant mortality (perinatal, fetal, neonatal) between exposure to repeat antenatal corticosteroids compared with no repeat exposure when the gestational age at trial entry was ≤31 weeks' and 6 days, ≤32 weeks' and 6 days or ≤33 weeks' and 6 days.

Respiratory distress syndrome was significantly reduced following repeat antenatal corticosteroids compared with no repeat exposure when gestational age at trial entry was ≤31 weeks' and 6 days and ≤32 weeks' and 6 days. There was no difference in the risk for respiratory distress syndrome when the gestational age at trial entry was ≤33 weeks' and 6 days between infants exposed to repeat antenatal corticosteroids and those with no repeat antenatal corticosteroids.

A composite of serious infant outcomes was significantly reduced following exposure to repeat antenatal corticosteroids compared with no repeat exposure when the gestational age at trial entry was ≤31 weeks' and 6 days but there was no difference when the gestational age at trial entry was ≤32 weeks' and 6 days compared with no repeat exposure. No data were reported when the gestational age at trial entry was ≤33 weeks' and 6 days.

There was no significant difference in birthweight when gestational age at trial entry was ≤31 weeks' and 6 days or ≤33 weeks' and 6 days between infants exposed to repeat antenatal corticosteroids and those with no repeat exposure. Birthweight was significantly reduced when gestational age at trial entry was ≤ 32 weeks' and 6 days. The clinical importance of the reduction in birthweight is unclear.

Overall there was no difference in birthweight z scores between infants exposed to repeat ant3.8(n)-3.9(a)( )10.9(tho)-3.9(e)

Chapter 13: Use of antenatal corticosteroids for women planning an elective caesarean section at term

What are the benefits and harms 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

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.

See Appendix M12 – Evidence

Chapter 14: Use of antenatal corticosteroids for women with specific risk factors for preterm birth

What is the safety for the mother, fetus, infant, child, adult of administering a single course or a repeat course(s) of antenatal corticosteroids to women with the following risk factors for preterm birth:

a) women with a history of previous preterm birth
b) women in preterm labour
c) women with preterm prelabour rupture of membranes
d) women with chorioamnionitis
e) women with an antepartum haemorrhage
f) women with a multiple pregnancy (twins and higher order)
g) women with diabetes mellitus or gestational diabetes
h) women with systemic infection (eg tuberculosis/sepsis)
i) women with pregnancy associated hypertension or pre-eclampsia
j) women with intrauterine growth restriction/fetal compromise
k) women with ultrasound evidence of cervical shortening/funnelling
l) women with results of a fetal fibronectin (FFN) test
m) women where preterm birth is medically indicated?

To find evidence to address these clinical questions on the use of antenatal corticosteroids for women with specific risk factors for preterm birth we reviewed the eligibility criteria for trials included in the Roberts CPG version 2015 systematic review for use of a single course of antenatal corticosteroids (Table 40 and Appendix J) and the Crowther CPG version 2015 systematic review for repeat antenatal corticosteroids (Table 41 and Appendix K). Whether women with specific risk factors for preterm birth were eligible for recruitment in the individual trials is tabulated and the proportion of the total study participants this represented (Table 40, Table 41).

These specific groups of women were selected as there was uncertainty about the use of antenatal corticosteroids.

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

Author (Year)	

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

Author (Year)	Women with history of previous preterm birth		Women in preterm labour		Preterm prelabour rupture of membranes at trial entry		Women with chorioamnionitis		Women with antepartum haemorrhage		Women with multiple pregnancies (twins and higher order)	
	Eligible	% reported	Eligible	% reported	Eligible	% reported	Eligible	% reported	Eligible	% reported	Eligible	% reported
Aghajafari (2002)	Yes	-	Yes	25	Yes	34	No	0	Yes	17	Yes	34
Crowther (2006)	Yes	15	Yes	27	Yes	34	No	0	Yes	29	Yes	16
Garite (2009)	NS	-	Yes	31	No	0	No	0	Yes	4	Yes	32 twins^
Guinn (2002)		NS										

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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

Table 42: Comparison of the overall effect estimate for use of a single course of antenatal corticosteroids with trials that reported including a proportion of women with a history of a previous preterm birth – Maternal primary outcomes*

Primary outcome	Single course of antenatal corticosteroid*			Trials known to include women with a history of a previous preterm birth^				
	Trials contributing data	Number of women	Overall risk ratio (RR) (95% Confidence Interval)	Trials contributing data	Number of women	Risk ratio (RR) (95% Confidence Interval)	Actual proportion detailed in trials	Actual number of mothers
Chorioamnionitis	Amorim 1999; Carlan 1991;							

Table 43: Comparison of the overall effect estimate for use of a single course of antenatal corticosteroids with trials reported including a proportion of women with a history of a previous preterm birth – Infant primary outcomes*

Primary outcome	Single course of antenatal corticosteroid*			Trials known to have included women with a history of a previous preterm birth^				
	Trials contributing data	Number of infants	Overall risk ratio (RR) (95%Confidence Interval)	Trials contributing data	Number of infants	Risk ratio (RR) (95%Confidence Interval)	Actual proportion detailed in trials	Actual number of infants
Perinatal death	Amorim 1999; Block 1977; Collaborative 1981; Dexiprom 1999; Doran 1980; Gamsu 1989; Garite 1992; Kari 1994; Liggins 1972; Parsons 1988; Qublan 2001; Schutte 1980; Taeusch 1979							

See Appendix M13 – Evidence Summary (Page 360)

What is the safety for the mother, fetus, infant, child, adult of administering a single course of antenatal corticosteroids to women with a history of previous preterm birth?

Practice points

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

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).

-

Table 45: Comparison of the overall effect estimate for use of repeat antenatal corticosteroids with trials that reported including a proportion of women with a history of a previous preterm birth – Infant primary outcomes

Primary outcome	Repeat course of antenatal corticosteroid*			Trials known to have included women with a history of a previous preterm birth^				
	Trials contributing data	Number of infants	Overall risk ratio (RR) (95% Confidence Interval)	Trials contributing data	Number of infants	Risk ratio (RR) (95% Confidence Interval)	Actual proportion detailed in trials	Actual number of infants
Perinatal death	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Mazumder 2008; McEvoy 2010; Murphy 2008; Peltoniemi 2007;							

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 repea003 . Tat antenan roropon

See

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 Goodner

Table 46: Comparison of the overall effect estimate for use of a single course of antenatal corticosteroids with trials that reported including a proportion of women in preterm labour – Maternal primary outcomes

Primary outcome	Single course of antenatal corticosteroid*			Trials known to have included women in preterm labour^			[redacted]
	Trials contributing data	Number of women	Risk ratio (RR) (95%Confidence Interval)	Trials contributing data	Number of women	Risk ratio (RR) (95%Confidence Interval)	

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).

Table 47: Comparison of the overall effect estimate for use of a single course of antenatal corticosteroids with trials that reported including a proportion of women in preterm labour – Infant primary outcomes

Primary outcome	Single course of antenatal corticosteroid*			Trials known to have included women in preterm labour^	
	Trials contributing data	Number of infants	Risk ratio (RR) (95% Confidence Interval)	Trials contributing data	Number of

See Appendix M15 – Evidence Summary (Page 368)

What is the safety for the mother, fetus, infant, child, adult of administering a single course of antenatal corticosteroids to women in preterm labour?

Practice Points:

What is the safety for the mother of administering repeat dose(s) of antenatal corticosteroids to women in preterm labour?

What is the safety for the fetus, infant, child, adult of administering repeat antenatal corticosteroids to women in preterm labour?

Repeat dose(s) of antenatal corticosteroids

Nine of the 10 trials in the '*Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes'* (Crowther 2011) reported that a proportion of the women included were in preterm labour (Table 41):

- Aghajafari (2002) 25%
- Crowther (2006) 27%
- Garite (2009) 31%
- Guinn (2002) 54%
- Mazumder (2008) (proportion not reported)
- McEvoy (2002) 30%
- McEvoy (2010) 76%
- Murphy (2008) 84%
- Wapner (2006) 67%.

Peltoniemi (2007) did not provide details as to whether women in preterm labour were eligible for inclusion. An inclusion criterion for recruitment into each of the trials was that the woman had already received a single course of antenatal corticosteroids seven or more days prior and there was a risk of preterm birth. Preterm labour was considered to be a risk factor for preterm birth (Appendix K). No additional trials were identified for the Crowther CPG version 2015 systematic review.

In the summary of the evidence we report the overall treatment effects from all trials with available data, for the primary outcomes of these Clinical Practice Guidelines, for repeat antenatal corticosteroids. We then report on the subset of nine trials that specifically reported that a proportion of the women recruited into their trial were in spontaneous *preterm labour*.

Maternal primary outcomes for these Clinical Practice Guidelines:

Maternal infection -

Chorioamnionitis - Overall no difference was seen in the risk for chorioamnionitis between women who had received repeat antenatal corticosteroids and those with no repeat treatment (RR 1.16, 95%CI 0.92 to 1.46; 6 trials, n=4261 women). All six trials reported that they had included women in preterm labour (range 25% to 84%) (Aghajafari 2002, Crowther 2006, Garite 2009, Guinn 2001, Murphy 2008, Wapner 2006) (Table 48).

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

- Four trials reported they included a proportion of women in preterm labour (range 25% to 84%) and provided data for puerperal sepsis (Aghajafari 2002, Guinn 2001, Murphy 2008, Wapner 2006). The size of the treatment effect was similar to the overall effect and there was no significant difference between groups (RR 1.05, 95%CI 0.72 to 1.54; 4 trials, n=2842 women) (Table 48).

Postnatal pyrexia - Overall no difference was seen in the risk for postnatal pyrexia requiring treatment with antibiotics between women who had received repeat antenatal corticosteroids and those with no repeat treatment in one trial

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 fetT6i8.174 04- 0lssni8.1n pdirite der344( )10.9(f)-2.1(o5(e)3si4s5

Table 49

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 an

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

Maternal primary outcomes for these Clinical Practice GuiT Guine :

Table 50: Comparison of the overall effect estimate for use of a single course of antenatal corticosteroids with trials that reported including a

Infant primary outcomes for these Clinical *Practice Guidelines:*

Respiratory distress syndrome - Overall there was a significant reduction in the risk of respiratory distress syndrome for infants that been exposed to a single course of antenatal corticosteroids compared with no exposure (RR 0.65, 95%CI 0.58 to 0.73; 25 trials, n=4590 infants).

- Sixteen trials reported they included a proportion of women with preterm prelabour rupture of membranes at trial entry (23% to 100% where reported) and provided data for respiratory distress syndrome (Block 1977, Cararach 1991, Carlan 1991, Collaborative 1981, Dexiprom 1999, Doran 1980, Lewis 1996, Liggins 1972, Lopez 1989, Morales 1989, Nelson 1985, Parsons 1988, Porto 2011, Qublan 2001, Schutte 1980, Silver 1996). The size of the treatment effect was similar to the overall effect and was also statistically significant (RR 0.68, 95%CI 0.60 to 0.78; 16 trials, n=3348 infants).
- Seven trials reported they included only women with preterm prelabour rupture of membranes at trial entry and provided data for respiratory distress syndrome (Cararach 1991, Carlan 1991, Dexiprom 1999, Lopez 1989, Morales 1989, Nelson 1985, Parsons 1988). The size of the treatment effect was similar to the overall effect and there was no significant difference between groups, probably due to fewer infants (RR 0.80, 95%CI 0.57 to 1.14; 7 trials, n=538) (Table 51).

Composite of serious infant outcomes - This outcome was not reported in any of the trials of a single course of antenatal corticosteroids.

Table 51: Comparison of the overall effect estimate for use of a single course of antenatal corticosteroids with trials that reported including a proportion of women with preterm prelabour rupture of membranes at trial entry – Infant primary outcomes

Primary outcome	Single course of antenatal corticosteroid*			Trials known to have included women with preterm prelabour rupture of membranes at trial entry^				
	Trials contributing data	Number of infants	Risk ratio (RR) (95% Confidence Interval)	Trials contributing data	Number of infants	Risk ratio (RR) (95% Confidence Interval)	Actual proportion detailed in trials	Actual number of infants
Perinatal death	Amorim 1999; Block 1977; Collaborative 1981; Dexiprom 1999; Doran 1980; Gamsu 1989; Garite 1992; Kari 1994; Liggins 1972; Parsons 1988; Qublan 2001; Schutte 1980; Taeusch 1979	3627	RR 0.77 (0.67 to 0.89), 13 trials	Block 1977; Collaborative 1981; Dexiprom 1999; Doran 1980; Liggins 1972;				

	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

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 880.0..xter

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)

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, 9

Respiratory distress syndrome -

Table 52: Comparison of the overall effect estimate for use of repeat antenatal corticosteroids with trials that reported including a proportion of women with preterm prelabour rupture of membranes at trial entry – Maternal primary outcomes

	Repeat course of antenatal corticosteroid*			Trials known to have included women with preterm prelabour rupture of membranes at trial entry^
Primary outcome	Trials contributing data	Number of women	Risk ratio (RR)	

Table 53: Comparison of the overall effect estimate for use of repeat antenatal corticosteroids with trials that reported including a proportion of women with preterm prelabour rupture of membranes at trial entry – Infant primary outcomes

	Repeat course of antenatal corticosteroid*	Trials known to have included women with preterm prelabour rupture of membranes at trial entry^
Primary outcome	Trials contributing data	

Table 54: C[illegible]on of the overall effect estimate for use of a single course of antenatal corticosteroids with trials that reported incl[illegible] proportion of women with chorioamnionitis at trial entry – Maternal primary outcomes

Primary outcome	[illegible]urse of antenatal corticosteroid*			Trials known to have included women with chorioamnionitis at trial entry^			
	[illegible]ntributing	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
Puerperal sepsis	[illegible]999; [illegible] 1999; [illegible]92; Lewis						

Table 55: Comparison of the overall effect estimate for use of a single course of antenatal corticosteroids with trials that reported including a proportion of women with chorioamnionitis at trial entry – Infant primary outcomes

	Single course of antenatal corticosteroid*			Trials known to have included women with chorioamnionitis at trial entry^			
Primary outcome	Trials contributing data	Number of infants	Risk ratio (RR) (95% Confidence Interval)	Trials contributing data	Number of infants	Risk ratio (RR) (95% Confidence Interval)	Actual (I)-12. proportion detailed in

Evidence summary for use of a single course of antenatal corticosteroids for women with chorioamnionitis

Four of 26 trials included in the Roberts CPG version 2015 systematic review reported they included a proportion of women who had chorioamnionitis at trial entry. The proportion of women included with chorioamnionitis ranged from 2% to 33% for the trials of a single course of antenatal corticosteroids, where reported.

For the mother

Overall, where reported in 26 trials, no differences were seen between women treated with a single course of antenatal corticosteroids and women with no corticosteroids in the risk for pyrexia after trial entry, intrapartum pyrexia, postnatal pyrexia or puerperal sepsis.

Four trials reported including a proportion of women with chorioamnionitis at trial entry.

- For postnatal pyrexia, the size of the treatment effect was similar to the overall effect and there was no difference between groups;
- For puerperal sepsis the direction of the treatment effect was similar to the overall effect and was statistically significant. However the confidence intervals overlap with the overall effect which was not statistically significant.

No data were reported for pyrexia after trial entry, intrapartum pyrexia or maternal quality of life in these four trials.

For the infant

Overall, where reported in 26 trials, there was a significant reduction in the risks for perinatal death, neonatal death and respiratory distress syndrome. No difference was seen in the risk for fetal death between infants exposed to a single course of antenatal corticosteroids and infants with no exposure.

Four trials reported including a proportion of women with chorioamnionitis at trial entry and the data are consistent with the overall treatment effect.

- For perinatal death, neonatal death and respiratory distress syndrome the size of the treatment effect was similar to the overall effect and the difference was statistically significant for infants exposed to a single course of antenatal corticosteroids compared with no exposure.
- For fetal death, the size of the treatment effect was similar to the overall effect and there was no difference between groups.

Evidence is based on a subset of data from trials that reported they included a proportion of women with chorioamnionitis at trial entry. This level of evidence cannot be used to form a clinical recommendation.

See Appendix M19

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*

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(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 withe.9(omt 0 Tw 0 Tw(c)2.9(lud)-)-4.5(e)0.99eBTw [((i)

- 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

Table 56: Comparison of the overall effect estimat

Table 57: Comparison of the overall effect estimate for use of a single course of antenatal corticosteroids with trials that reported including a proportion of women with antepartum haemorrhage at risk of preterm birth – Infant primary outcomes

Primary outcome	Single course of antenatal corticosteroids			Trials known to have included a proportion of women with antepartum haemorrhage
	Trials contributing data	Number of infants	Risk ratio (RR) (95% Confidence	

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 -

2009, McEvoy 2010, Wapner 2006). The treatment effect was similar to the overall effect and was statistically significant (RR 0.76, 95%CI 0.68 to 0.86; 5 trials, n=2323 infants) (Table 59).

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

- Five trials reported they included a proportion of women with an antepartum haemorrhage (4% to 29%) and provided data for a composite of serious infant outcomes (Aghajafari 2002, Crowther 2006, Garite 2009, Murphy 2008, Wapner 2006). The treatment effect was similar to the overall effect and was statistically significant (RR 0.85, 95%CI 0.76 to 0.96; 5 trials, n=4517 infants) (Table 59).

Table 58: Comparison of the overall effect estimate for use of repeat antenatal corticosteroids with trials that reported including a proportion of women with antepartum haemorrhage at risk of preterm birth –

Table 59: Comparison of the overall effect estimate for use of repeat antenatal corticosteroids with trials that reported including a proportion of women with antepartum haemorrhage at risk of preterm birth – Infant primary outcomes

Primary outcome 5(r)-8.(	Repeat antenatal corticosteroids* s	Trials known to have included a proportion of women with antepartum haemorrhage^

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

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%

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- 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

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

- Eleven trials reported they included a proportion of women with a multiple pregnancy (2% to 20%, where reported) and provided data for fetal death (Block 1977, Collaborative 1981, Dexiprom 1999, Doran 1980, Gamsu 1989, Garite 1992, Kari 1994, Liggins 1972, Schutte 1980, Taeusch 1979). The size of the treatment effect was similar to the overall effect and there was no significant difference between groups (RR 0.95, 95%CI 0.70 to 1.29; 10 trials, n=3225 infants) (Table 61).

Neonatal death - Overall there was a significant reduction in the risk for neonatal death for infants who were exposed to a single course of antenatal corticosteroids compared with no exposure (RR 0.68, 95%CI 0.58 to 0.80; 21 trials, n=4408 infants).

- Twelve trials reported they included a proportion of women with a multiple pregnancy (2% to 23%, where reported) and provided data for neonatal death (Block 1977, Collaborative 1981, Dexiprom 1999, Doran 1980, Fekih 2002, Gamsu 1989, Garite 1992, Kari 1994, Liggins 1972, Schutte 1980, Silver 1996, Taeusch 1979). The size of the treatment effect was similar to the overall effect and was statistically significant (RR 0.75, 95%CI 0.62 to 0.91; 12 trials, n=3290 infants) (Table 61).

Respiratory distress syndrome - Overall there was a significant reduction in the risk for respiratory distress syndrome for infants who were exposed to a single course of antenatal corticosteroids compared with no exposure (RR 0.65, 95%CI 0.58 to 0.73; 25 trials, n=4590 infants).

- Twelve trials reported they included a proportion of women with a multiple pregnancy (2% to 23%, where reported) and provided data for respiratory distress syndrome (Block 1977, Collaborative 1981, Dexiprom 1999, Doran 1980, Fekih 2002, Gamsu 1989, Garite 1992, Kari 1994, Liggins 1972, Schutte 1980, Silver 1996, Taeusch 1979). The size of the treatment effect was similar to the overall effect and was statistically significant (RR 0.69, 95%CI 0.61 to 0.79; 12 trials, n=3250 infants) (Table 61).

Composite of serious infant outcomes - This outcome was not reported in any of the trials of a single course of antenatal corticosteroids included in the Roberts CPG version 2015 systematic review.

Table 60: Comparison of the overall effect estimate for use of a single course of antenatal corticosteroids with trials that reported including a proportion of women with a multiple pregnancy at risk of preterm birth – Maternal primary outcomes

Primary outcome	Single course of antenatal corticosteroids			Trials known to have included a proportion of women with a multiple pregnancy at risk of preterm birth				
	Trials contributing data	Number of women	Risk ratio (RR) (95% Confidence Interval)	Trials contributing data	Number of women	Risk ratio (RR) (95% Confidence Interval)	Actual proportion detailed in trials	Actual number of women
Chorioamnionitis	Amorim 1999; Carlan 1991; Dexiprom 1999; Fekih 2002; Garite 1992; Kari 1994; Lewis 1996; Liggins 1972; Lopez 1989; Morales 1989; Qublan 2001; Schutte 1980; Silver 1996	2525						

Table 61

Table 62: Comparison of the overall effect estimate for use of repeat antenatal corticosteroids with trials that reported including a proportion of women with multiple pregnancy at risk of preterm birth – Maternal primary outcomes

Primary outcome	Repeat course of antenatal corticosteroids and trials known to have included a proportion of women with a multiple pregnancy at risk of preterm birth*		
	Trials contributing data	Number of women	

Evidence summary for the use of repeat antenatal corticosteroids for women with a multiple pregnancy at risk of imminent preterm birth

Nine of 10 trials in the Crowther (2011) systematic review reported including a proportion of women in their trials who had a multiple pregnancy at risk of preterm birth (range 7% to 34% where reported).

For the mother

Overall, where reported in 10 trials, no differences were seen between women treated with repeat antenatal corticosteroids and women with no repeat corticosteroids in the risk for chorioamnionitis, postnatal pyrexia or puerperal sepsis.

Nine trials reported including a proportion of women with a multiple pregnancy at risk of preterm birth. The evidence is consistent with the overall treatment effect:

- For chorioamnionitis, postnatal pyrexia and puerperal sepsis, the size of the treatment effect was the same or similar to the overall effect and there was no difference between groups.

No data were reported for pyrexia after trial entry, intrapartum pyrexia or maternal quality of life from these seven trials.

For the infant

Overall, where reported in 10 trials, there was a significant reduction in the risks for respiratory distress syndrome and a composite of serious infant outcomes. No differences were seen in the risks for perinatal death, fetal death and neonatal death between infants exposed to a repeat antenatal corticosteroids and infants with no repeat exposure.

Nine trials reported including a proportion of women with a multiple pregnancy at risk of preterm birth. The evidence is consistent with the overall treatment effect:

- For respiratory distress syndrome and a composite of serious infant outcomes the size of the treatment effect was similar to the overall effect and there was a significant reduction in risk for infants exposed to a repeat antenatal corticosteroids compared with no repeat exposure;
- For perinatal death, fetal death and neonatal death the size of the treatment effect was similar to the overall effect and there was no difference between groups.

Evidence is based on a subset of data from trials that reported they included a proportion of women with a multiple pregnancy at risk of preterm birth. This level of evidence cannot be used to form a clinical recommendation.

See Appendix M24 – Evidence Summary (Page 404)

What is the safety for the mother and fetus, infant, child, adult of administering repeat antenatal corticosteroids to women with a multiple pregnancy (twins and higher order) with an additional risk factor(s) for preterm birth?

What is the safety for the mother and fetus, infant, child, adult of administering a single course or a repeat course(s) of antenatal corticosteroids to women with a multiple pregnancy (twins and higher order) prophylactically (with no additional risk factor(s) for preterm birth)?

Repeat antenatal corticosteroids

Maternal primary outcomes for these Clinical Practice Guidelines:

There was no randomised controlled trial evidence reported for maternal primary outcomes for these Clinical Practice Guidelines for the use of prophylactic antenatal corticosteroids in women with a multiple pregnancy with no additional risk of preterm birth. These women were not eligible for inclusion in the randomised trials included in the Crowther (2011) systematic review (Appendix K).

Infant primary outcomes for these Clinical Practice Guidelines:

There was no randomised controlled trial evidence reported for infant primary outcomes for these Clinical Practice Guidelines for the use of prophylactic antenatal corticosteroids in women with a multiple pregnancy with no additional risk of preterm birth. These women were not eligible for inclusion in the randomised trials included in the Crowther (2011) systematic review (Appendix K).

Evidence summary for the use of repeat prophylactic antenatal corticosteroids for women with a multiple pregnancy with no additional risk of preterm birth

There was no randomised controlled trial evidence for prophylactic antenatal corticosteroids in women with a multiple pregnancy with no additional risk of preterm birth.

There is an absence of both short and long term neonatal and childhood follow-up data reported for exposure prophylactic use of antenatal corticosteroids in a multiple pregnancy where there is no additional risk of preterm birth.

See Appendix M26 – Evidence Summary (Page 412)

What is the safety for the mother and fetus, infant, child, adult of administering a single course or a repeat course(s) of antenatal corticosteroids to women with a multiple pregnancy (twins and higher order) prophylactically (with no additional risk factor(s) for preterm birth)?

Practice Point:

- Do not use repeat antenatal corticosteroids in women with a multiple pregnancy where there is no other identified risk ofi9(r)-7/39.7(t)d.4(o)p.7(ti)1.8T2 8 resis (

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).

- 6

- 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 tovr.5(e)11.84mfec4eed3.8(t)-4.5(h)-3.9r52 Tc 0.012 6..8((e)-5(o)-1.9-33.1.n8

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* *347Ts291.68i e661(10 436 426C24687.(s) 10081 4398)566986(W31308

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Table 65

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

See Appendix M27 - Evidence Summary (Page 416)

What is the safety for the mother, fetus, infant, child,

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

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=(()83.6(,)06.4(0)0.Wmp18-0.001 Tc 0.001 Tw 0 -1.28s.-1.9(0.61c5(.)0..9

Table 66: Comparison of the overall effect estimate for use of repeat antenatal corticosteroids with trials that rep0.9(o).9(r)-98na

Table 67: Comparison of the overall effect estimate for us

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

See Appendix M28 – Evidence Summary (Page 420)

What is the safety for the mother, fetus, infant, child,

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?

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%.

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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

Table 68: Comparison of the overall effect estimate for use of a single course of antenatal corticosteroids with trials that reported including a proportion of women with hypertension – Maternal primary outcomes*

Primary outcome	Single course of antenatal corticosteroids			Trials known to have included a proportion of women with pregnancy associated hypertension^				
	Trials contributing data	Number of women	Risk ratio (RR) (95% Confidence Interval)	Trials contributing data	Number of women	Risk ratio (RR) (95% Confidence Interval)	Actual proportion detailed in trials	Actual number of women
Chorioamnionitis	Amorim 1999; Carlan 1991; Dexiprom 1999; Fekih 2002; Garite 1992; Kari 1994; Lewis 1996; Liggins 1972; Lopez 1989; Morales 1989; Qublan 2001; Schutte 1980; Silver 1996	2525	RR 0.90 (0.69 to 1.17), 13 trials	Amorim 1999; Fekih 2002; Garite 1992; Kari 1994; Liggins 1972; Silver 1996	1775	RR 0.98 (0.70 to 1.38) 6 trials, n=1775 women	Amorim 1999; Fekih 2002; Garite 1992; Kari 1994; Liggins 1972; Silver 1996	377
Puerperal sepsis	Amorim 1999; Dexiprom 1999; Garite 1992; Lewis 1996; Qublan 2001; Schutte 1980; Silver 1996; Taeusch 1979	1003	RR 1.35 (0.93 to 1.95), 8 trials	Amorim 1999; Garite 1992; Silver 1996	364	RR 1.31 (0.80 to 2.17) 3 trials, n=364 women	Amorim 1999; Garite 1992; Silver 1996	229
Pyrexia after trial								

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*

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

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

Postnatal pyrexia -

similar to the overall effect and the difference was statistically significant (RR 0.84, 95%CI 0.76 to 0.92; 5 trials, n=2663 infants) (Table 71).

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

- Four trials reported that they included a proportion of women with pregnancy associated hypertension (6% to 14%, where reported) and provided data for a composite of serious infant outcomes (Crowther 2006, Garite 2009, Guinn 2001, Murphy 2008). The size of the treatment effect was similar to the overall effect and there was a significant difference between groups (RR 0.85, 95%CI 0.76 to 0.95; 4 trials, n=4508 infants) (Table 71).

Table 70: Comparison of the overall effect estimate for use of repeat antenatal corticosteroids with trials that reported including a proportion of women with hypertension – Maternal primary outcomes*

Primary outcome	Repeat course of antenatal corticosteroids			Trials known to have included a proportion of women with pregnancy associated hypertension^				
	Trials contributing data	Number of women	Risk ratio (RR) (95% Confidence Interval)	Trials contributing data	Number of women	Risk ratio (RR) (95% Confidence Interval)	Actual proportion detailed in trials	Actual number of women

Table 71: Comparison of the overall effect estimate for use of repeat antenatal corticosteroids with trials that reported including a proportion of women with hypertension – Infant primary outcomes*

Primary outcome	Repeat course of antenatal corticosteroids			Trials known to have included a proportion of women with pregnancy associated hypertension^				
	Trials contributing data	Number of infants	Risk ratio (RR) (95% Confidence Interval)	Trials contributing data	Number of infants	Risk ratio (RR) (95% Confidence Interval)	Actual proportion detailed in trials	Actual number of infants
Perinatal death	Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2001; Mazumder 2008; McEvoy 2010; Murphy 2008; Peltoniemi 2007; Wapner 2006	5554	RR 0.94 (0.71 to 1.23), 9 trials	Crowther 2006; Garite 2009; Guinn 2001; McEvoy 2010; Murphy 2008; Peltoniemi 2007	4967	RR 1.01 (0.75 to 1.34), 6 trials, n=4967 infants	Crowther 2006; Garite 2009; McEvoy 2010; Murphy 2008; Peltoniemi 2007	496
Fetal death	Aghajafari 2002; C.7(f)0.7(a)-0							

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.

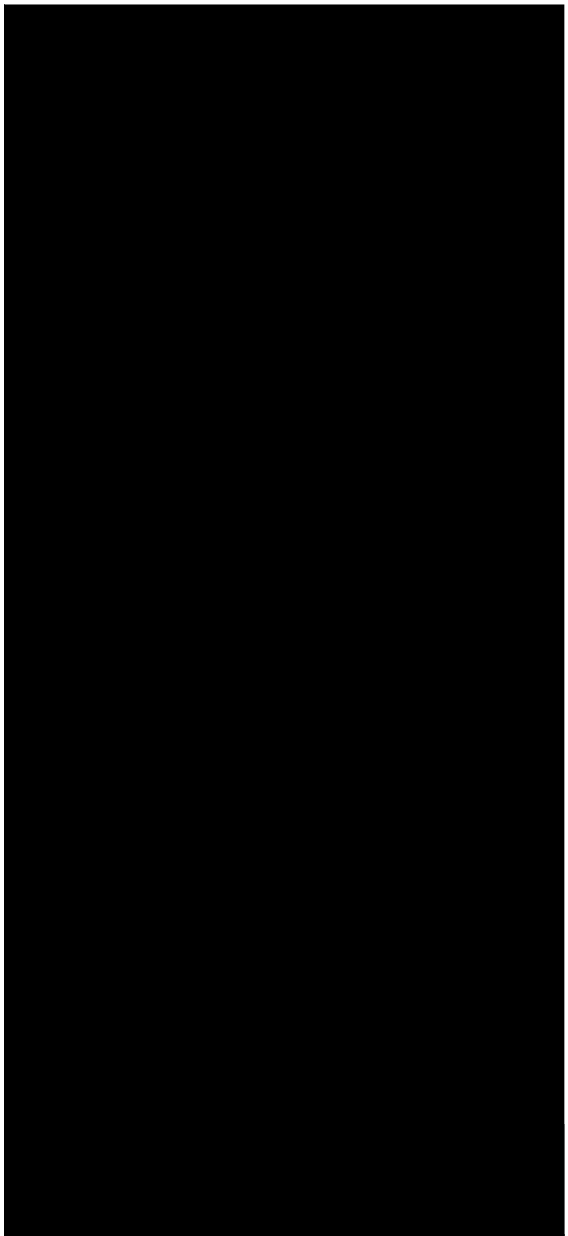
For the mother

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 siz s, in8Tw [(t)6.4(r2.3(a)0.9(2.2(a)0.8(r)-6.9(t)-u.6(i)-2.2(m7-6.91(o)-p)7(y)1(r)-



14.10 Women with a fetus with intrauterine growth restriction at risk of preterm birth

What is the safety for the mother of administering a single course of antenatal corticosteroids to women with a fetus with intrauterine growth restriction at risk of preterm birth?

What is the safety for the fetus, infant, child, adult of administering a single course of antenatal corticosteroids to women with a fetus with intrauterine growth restriction at risk of preterm birth?

Single course of antenatal corticosteroids

Three of 26 trials in the Roberts CPG version 2015 systematic review reported that they included a very small proportion of women in their trial with a fetus with intrauterine growth restriction at risk of preterm birth (Table 40):

- Garite (1992) 6%
- Porto (2011) 1%
- Silver (1996) 9%

Of the remaining 23 trials, women with a fetus with intrauterine growth restriction were not eligible for two trials (Balci 2010, Schutte 1980). Twenty-one trials did not provide details of whether women with intrauterine growth restriction were eligible for and included in their trials (Appendix J).

In the summary of the evidence we report the overall treatmscn390.84 481.8 48. 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 restrictitco a2-e(a)21 scn-0Tjppor 01 scnD 27(2-e(a*

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 difT4DCa[illegible]

Table 72: Comparison of the overall effect estimate for use of a single course of antenatal corticosteroids with trials that reported including a proportion of women with a fetus with intrauterine growth restriction– Maternal primary outcomes*

Primary outcome	Single course of antenatal corticosteroids	Trials known to have included a proportion of women with a fetus with intrauterine growth

Table 73 Comparison of the overall effect estimate for use of a single course of antenatal corticosteroids with trials that reported including a

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

What is the safety for the mother of administering

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 di

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=.125.0es1(a)2.8(n)9(t)-s

Table 75: Comparison of the overall effect estimate for use of repeat antenatal corticosteroids with trials that reported including a proportion of women with a fetus with intrauterine growth restriction – Infant primary outcomes*

Primary outcome	Repeat antenatal corticosteroids			Trials known to have included a proportion of women with a fetus with intrauterine growth restriction			
	Trials contributing data	Number of infants	Risk ratio (RR) (95% Confidence Interval)	Trials contributing data	Number of infants	Risk ratio (RR) (95% Confidence Interval)	

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*.

labour and

Evidence summary for the use of antenatal corticosteroids following a fetal fibronectin test in women at risk of preterm birth

There was no randomised controlled trial evidence that addressed the use of antenatal corticosteroids in the presence of a positive or negative fetal fibronectin test.

The fetal fibronectin test has a very high negative predicative value and therefore women with a negative test are unlikely to be at imminent risk of preterm birth.

See Appendix M36 – Evidence Summary (Page 452)

What is the safety for the mother, fetus/infant/child/adult of administering a single course or a repeat dose(s) of antenatal corticosteroids to women having undergone fetal fibronectin testing?

Practice Points:
• Use a single course of antenatal corticosteroids for a woman presenting with symptoms of preterm labour with a positive fetal fibronectin test and at risk of preterm birth.

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 to2.5(p)11(os)-3.5(u)12.7(r)-4imB e cou72.3(s)-7.5(e)0 of

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 .7(u)1.9(ng)3.3(d)1(e)5(v)2.6(e)5(l)1.7(opme)5(nt w)5(i)1.7(a)0.813-(ng)3.37(n)-3

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 i

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

Summary for cost-effectiveness of antenatal corticosteroids

Single course of antenatal corticosteroids

The costs of administering a single, complete course of antenatal betamethasone or

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;
- forda4be (o)11(ns)]T7(0 Tc

The key stakeholders

- *Women who are at risk of preterm birth and their family:*

Table 78: Stages of change for implementation of the ‘Antenatal corticosteroids given to women prior to birth to improve fetal, child and adult health’ clinical practice guidelines.

Methods / Stages of change

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Tw 2*0 -18.88s-4.1(e)-8.7(C)-3..6o /M-57 /b / 9(a)1(yA)-1uSt 0M-5tg01.1(c2.3(nta)-18.7.l01(/ 1989;)8(/4061:)3.147037.313 0 Td(-)T(

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Mushkat Y, Ascher-

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Appendix B: Health Outcomes for these Clinical Practice Guidelines

Health service use outcomes for these Clinical Practice Guidelines

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

*primary outcomes for these Guidelines

Appendix C: Clinical Practice Guidelines Process and Methods

Evidence tables

Evidence was summarised in risk of bias or evidence tables depending on the level of evidence.

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:

484)

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

Appendix E: Single course of antenatal corticosteroids - Fetal, Neonatal and Infant Outcomes (Roberts CPG version 2015)

Outcome	Effect Size	95%CI	P	No of studies	n
Fetal, neonatal or later death	RR 0.77	0.67 to 0.89	0.00035	13	3627
Sub group analysis for fetal & neonatal death:					
Singleton pregnancies	*0.79*	*0.65 to 0.96*	*0.016*	*3*	*1425*
Multiple pregnancies	*0.71*	*0.41 to 1.22*	*0.22*	*2*	*252*
Delivery <28 weeks'	*0.81*	*0.65 to 1.01*	*0.065*	*2*	*129*
Delivery <30 weeks'	*0.86*	*0.70 to 1.05*	*0.14*	*1*	*201*
Delivery <32 weeks'	*0.71*	*0.57 to 0.88*	*0.0018*	*3*	*453*
Delivery <34 weeks'	*0.73*	*0.58 to 0.91*	*0.0063*	*1*	*598*

Dexamethasone	*0.92*	*0.56 to 1.50*	*0.73*	*5*	*1420*
Betamethasone	*1.01*	*0.73 to 1.39*	*0.96*	*8*	*2207*
<26 weeks' at 1st dose	*0.65*	*0.33 to 1.25*	*0.20*	*1*	*49*
Between 26 and <30 weeks'					

Dexamethasone	*1.81*	*0.44 to 7.46*	*0.41*	*3*	*380*
Betamethasone	*0.63*	*0.29 to 1.35*	*0.0025*	*3*	*438*
Courses including weekly repeats	*0.77*	*0.42 to 1.44*	*0.42*	*4*	*534*

Birth length	Not reported				
Birth head circumference	Not reported				

Delivery 24 – 48 hours after 1st

Adult Outcome	Effect Size	95%CI	P	No of studies	n
Diabetes:					
Mean adult glucose (mmol/L) – fasting	MD 0.01	-0.09 to 0.11	0.84	1	432
Mean adult glucose (mmol/L) – 30 minutes following 75g oral GTT					

[redacted]	Mental anxiety	Not reported			

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				

or less/week					
Planned repeat drug exposure was >12 mg/week to 24 mg/week	*0.97*	*0.65 to 1.44*	*0.87*	*4*	*1068*
Necrotising enterocolitis	RR 0.74	0.51 to 1.08	0.12	8	5394
Retinopathy of prematurity	RR 1.02	0.81 to 1.28	0.86		

Use of oxygen supplementation	RR 0.92	0.85 to 0.99	0.025	2	3448

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

Childhood Outcome	Effect Size	95%CI	P	No of studies	n
Total mortality	RR 1.06	0.80 to 1.41	0.66	4	4370
Sub g					

or less/week			

Use of Health Services

Outcome	Effect Size	95%CI	P	No of studies	n
Length of antenatal hospitalisation for the woman	Not reported				

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)

	2000 g if gestational age unknown)	Evidence of antepartum haemorrhage <19 years of age
Doran 1980	Women with PROM, spontaneous preterm labour or planned elective preterm delivery 24 to 34 weeks' gestation	Women with preeclampsia Women for whom steroids are contraindicated on medical grounds.
Fekih 2002	Women in preterm labour 26 to 34 weeks'	Gestational diabetes >4 cm cervical dilatation Fetal abnormalities Contraindication to corticosteroids Delivery elsewhere or after 34 weeks' (post randomisation exclusions)
Gamsu 1989		Contraindication to corticosteroids Contraindications to postponing delivery Diabetes Suspected intrauterine infection
Garite 1992		

Morales 1989	PROM Singleton pregnancy 26 to 34 weeks' gestation	PROM <12 hours before onset of labour Uterine tenderness Foul smelling lochia Fetal tachycardia Allergy to penicillin Congential abnormalities L/S ratio 2 or more Unable to obtain an L/S ratio Dubowitz assigned gestational age different from obstetric assessment by 3 weeks'

Silver 1996	Women at risk of delivery between 24 to 29 weeks'	Infection Maternal or fetal indications for urgent delivery
Taeusch 1979	Women with preterm labour, PROM or with cervical dilatation <5cm at 33 weeks' or less Women with an L/S ratio <2 if >33 weeks' or who had a previous infant with RDS	Indication for immediate delivery Obstetrician objection Pre eclampsia Previously received corticosteroids
Teramo 1980	Women with preterm labour and cervical dilatation <4 cm without progression of labour upon initial observation of up to 12 hours. 28 to 35 weeks' gestation	Pre eclampsia Diabetes

PROM Prelabour rupture of membranes, IUGR intrauterine growth restriction; RDS respiratory distress syndrome

	(Preterm labour was defined as contractions with either cervical change, 2 cm dilatation, 80% effacement).	Infection other than cystitis or cervicitis; Advanced cervical dilatation; Fetal pulmonary maturity.

Romejko-Wolniewicz (2013)	Women with preterm birth <35 weeks' gestation.	Not stated.
Rotmensch 1999	Women with preterm birth at 27 to 34 weeks' gestation; Preterm premature rupture of membranes with no clinical evidence of infection; Pregnancy induced hypertension syndromes; Intrauterine growth restriction; Third trimester bleeding due to placenta praevia.	Not stated.
Senat 1998	Women with preterm labour <34 weeks' gestation.	Uncertain pregnancy history; Clinical infection in women; Vaginal bleeding; Suspicion of premature rupture of membranes.
Subtil 2003	Women at high risk of preterm birth; 27 to 35 weeks' gestation; Singleton pregnancy.	Imminent birth; Multiple pregnancy; Previously participated in the protocol; Received corticosteroid therapy <10 days prior.
Urban 2005	Preterm contractions of the uterus; Preterm premature rupture of membranes; Cervical length less than 20 mm; Placenta praevia before 34 weeks'; Singleton pregnancy.	Fetal major structural malformation or abnormal karyotype.

Appendix M: Evidence summaries

M1 Benefits and harms of a single course of antenatal corticosteroids

M1 NHMRC Evidence Summary

What are the short and long term benefits and harms of a single course of antenatal corticosteroids for the mother and fetus, infant, child adult prior to preterm birth?		
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Maternal The Roberts CPG version 2015 systematic review included 26 randomised controlled trials involving 4469 women and 4853 infants (Level I). Infant The Roberts CPG version 2015 systematic review 26 randomised controlled trials involving 4469 women and 4853 infants (Level I).	A	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias

M1 GRADE Evidence summary

Considered Judgement - Strength of recommendation
What are the short and long term benefits and harms of a single course of antenatal corticosteroids for the mother and fetus, infant, child adult

Judging the harms in context

Maternal - The evidence is from trials conducted in women at risk of preterm birth, exposed or not to antenatal corticosteroids. Some trial protocols allowed for repeat doses of antenatal corticosteroids if women were eligible. There is no indication of increased harm to the mother in terms of risk of infection. Evidence indicates that women exposed to antenatal corticosteroids may be at risk of transient elevated blood glucose concentrations (clinical significance of which is unclear).

Infant - The evidence is based on data from a single trial and relevant caution is required in extrapolation of findings.

5. What is the likely balance between good and harm?

Evidence statement	Overall quality of evidence
Maternal - There does not appear to be an increased risk of infection, although there is potentially increased risk of transient maternal glucose intolerance. Any effects on maternal health are probably outweighed by the significant benefits to the infant (Chapter 4).	HIGH
Infant - There are clear benefits to the infant in terms of survival and reduced risk of respiratory distress syndrome. The evidence for HPA axis suppression is limited in volume. There are no differences in developmental outcomes. The benefits are likely to outweigh the harms.	HIGH

Judging the balance of benefits and harms in context

Maternal - There do not appear to be any direct health benefits for the mother. Evidence indicates an increased risk of maternal glucose intolerance following exposure to antenatal corticosteroids the clinical significance of this in non-diabetic women in unclear and requires further research. This increased risk for the mother is outweighed by the evidence of clear and large benefits for the neonate.

Infant - Benefits clearly outweigh harms

Benefits clearly outweigh harms	Recommend	STRONG
Benefits probably outweigh harms	Consider	CONDITIONAL
Not known	Make a recommendation for research (see 8 below)	WEAK
Benefits probably don't outweigh harms	Consider against/make no recommendation	CONDITIONAL
Harms probably outweigh benefits		

EVIDENCE STATEMENT MATRIX

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 corticos.7(t)15c 8.04 -0 0 8.04 448.68 733.68 Tm[(a)-08rCT

into childhood associated with the exposure to repeat antenatal corticosteroids.		
Judging the harms in context *Maternal* - The evidence is direct evidence from trials conducted in women at risk of preterm birth, exposed to repeat antenatal corticosteroids. *Infant* - The evidence for lack of harm is direct evidence from trials in which the women and infants involved were exposed to a repeat antenatal corticosteroids (or placebo), after remaining at risk of imminent preterm birth following an initial single course.		
5. What is the likely balance between good and harm?		
Evidence statement *Maternal* - There are no clear direct health benefits for the mother exposed to repeat antenatal corticosteroids. There is no evidence of increased risk of infection (risk of pyrexia or sepsis) when compared to women exposed to a single course of antenatal corticosteroids. *Infant* - The benefit of reduction in risk of composite serious outcome and respiratory distress syndrome outweigh any potential harms.		Overall quality of evidence HIGH HIGH
Judging the balance of benefits and harms in context *Maternal* - The potential health harms for the mother are clearly outweighed by the significant benefits to the infant. *Infant* - The benefit of reduction in risk of composite serious outcome and respiratory distress syndrome outweigh any potential harms.		
Benefits clearly outweigh harms	Recommend	STRONG
Benefits probably outweigh harms	Consider	CONDITIONAL
Not known	Make a recommendation for research (see 8 below)	WEAK
Benefits probably don't outweigh harms	Consider against/make no recommendation	CONDITIONAL
Harms probably outweigh benefits		
Benefits clearly don't outweigh harms	Recommend against	STRONG
Harms clearly outweigh benefits		
6.		

M3 Regimen of single antenatal corticosteroids for women at risk of preterm birth

M3 NHMRC Evidence Summary

Do benefits or harms in the mother,

M3 GRADE Evidence Summary

Considered Judgement - Strength of recommendation
Do benefits or harms in the mother, fetus, infant, child, adult vary by whether betamethasone or dexamethasone is administered as a

dexamethasone was identified. There does not appear to be any detrimental effect into early childhood, with no differences seen between those exposed to betamethasone or dexamethasone for a composite of neurosensory disability.	HIGH
Judging the harms in context *Maternal* - The evidence of greater risk of puerperal sepsis in women treated with dexamethasone is based on an indirect comparison due to the lack of data on maternal outcomes from head to head comparison of different types of corticosteroids. *Infant* - Both betamethasone and dexamethasone have demonstrated benefits on neonatal outcomes. A small subgroup followed up at 18 months of age suggests no statistically significant differences in neurosensory disability between those exposed to dexamethasone or betamethasone. There is no evidence to suggest that one is clinically superior to the other.	
5. What is the likely balance between good and harm?	
Evidence statement *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. *Infant* - Both direct and indirect evidence suggest neither is clinically superior to the other. The benefits of the use of both betamethasone and dexamethasone clearly appear to outweigh any potential harms.	Overall quality of evidence HIGH HIGH
Judging the balance of benefits and harms in context *Maternal* - Exposure to a single course of betamethasone is unlikely to cause harm for the mother. The impact	

M4 Regimen of repeat antenatal corticosteroids for women at risk of preterm birth

M4 NHMRC Evidence Summary

Do benefits or harms in the mother, fetus, infant, child or adult vary by whether betamethasone or dexamethasone is administered as the repeat course(s) of antenatal corticosteroids?		
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Maternal The systematic review on repeat courses only included trials that used betamethasone as no trials that used dexamethasone were identified (Crowther 2011). The systematic review on different regimens did not report maternal outcomes (Brownfoot 2013). Infant Two systematic reviews (Brownfoot 2013) (Crowther 2011) (Level I).	A	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Maternal There is no current trial evidence that directly compares betamethasone and dexamethasone as the repeat antenatal corticosteroid. The available evidence compares betamethasone as a repeat course versus a single course, and finds no differences for any of the maternal primary outcomes of the Clinical Practice Guidelines. Infant Currently, no randomised controlled trials have reported on the effects of repeat course(s) of dexamethasone. One systematic review (Brownfoot 2013) found no statistically significant differences between those exposed to betamethasone or dexamethasone for neurosensory disability in a small subgroup followed up at 18 months		

Evidence statement

The available evidence for repeat antenatal corticosteroids has only used betamethasone. Randomised controlled trial evidence for the primary outcomes of these Clinical Practice Guidelines is limited for dexamethasone as the repeat course.

Indicate any dissenting opinions

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

M4 GRADE Evidence Summary

Considered Judgement - Strength of recommendation							
Do benefits or harms in the mother, fetus, infant, child, adult vary by whether betamethasone or dexamethasone is administered as the repeat course(s) of antenatal corticosteroids?							
1. Outcome measures:	Quality of evidence (NR = not reported)				Importance of outcome in making a decision		
Maternal Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important

O_1 Chorioamnionitis

Judging the harms in context

Maternal - The evidence for lack of harm is direct evidence from trials conducted in women at risk of preterm birth, exposed to repeat treatment with antenatal

M5 Dose and interval for a single course of antenatal corticosteroids for women at risk of preterm birth

M5 NHMRC Evidence Summary

What is the most effective dose, number of doses in a course and optimal interval between doses when using a single course of antenatal corticosteroids?
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*

Two systematic reviews updated in the

B Eviden

vidence Summary

Considered Judgement - Strength of recommendation							
ective dose, number of doses in a course and optimal interval between doses when using a single course of oids?							
measures:	Quality of evidence (NR = not reported)				Importance of outcome in making a decision		
	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
to trial				NR			
requiring antibiotics				NR			
				NR			

distress syndrome, with no evidence of increased risk of harms. There is no evidence that increasing the dose improves outcomes for the infant.	MOD

Judging the harms in context

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

Component	Rating	Description
1. Evidence base	A	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias
2. Consistency	B	Most studies consistent and inconsistency can be explained
3. Clinical Impact	B	Substantial
4. Generalisability	A	Evidence directly generalisable to target population
5. Applicability	A	Evidence directly applicable to New Zealand / Australian healthcare context

Evidence statement

Comparative evidence on more than one repeat course of antenatal corticosteroids is limited. There was no increased risk of chorioamnionitis and puerperal sepsis for the mother, or perinatal, neonatal and fetal death, or respiratory distress syndrome among trials that compared one planned repeat course with no repeat courses of antenatal corticosteroids.

Indicate any dissenting opinions

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

EITHER

Use a single repeat dose(s) of 12 mg betamethasone following a single course of antenatal corticosteroid seven or more days prior, where the woman is still at risk of preterm birth within the next seven days.

After this dose, if the woman has not given birth seven or more days and less than 14 days from administration of the previous repeat dose and is still considered to be at risk of preterm birth within the next seven days a further repeat dose(s) of 12 mg betamethasone can be administered.

OR

Use a single repeat course of 24 mg betamethasone in divided doses completed within 24 hours following a single course of antenatal corticosteroids seven or more days prior, where the woman is still at risk of pretr

significant decrease in birthweight, and significantly more infants exposed to four or more courses of antenatal corticosteroids born below the 5th percentile for birthweight.	MODERATE

Judging the harms in context

Maternal - There was no evidence of harm to the mother of one planned repeat course of antenatal corticosteroids.

Infant - There was no evidence of increase in risk of mortality, respiratory distress syndrome or disability at early childhood follow-up following one planned repeat course of antenatal corticosteroids. The evidence of reduction in birthweight following exposure to four or more repeat

M7 Optimal time prior to preterm birth to administer a single course of antenatal corticosteroids

M7 NHMRC Evidence summary

What is the optimal time prior to preterm birth to administer a single course of antenatal corticosteroids?		
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Maternal Roberts CPG version 2015 systematic review for a single course of antenatal corticosteroids (Level 1) included two randomised controlled trials that reported on chorioamnionitis and puerperal sepsis in relation to time interval from administration of first dose to birth. Infant Roberts CPG version 2015 systematic review for a single course of antenatal corticosteroids included nine randomised controlled trials (Level 1), that reported on mortality and respiratory distress syndrome in relation to the time interval from administration of first dose to birth.	A	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Maternal The evidence is consistent that there is no increased risk of chorioamnionitis for those who received antenatal corticosteroids compared with those who did not receive antenatal corticosteroids at any of the time points reported in the Roberts CPG version 2015 systematic review (<24 hours before birth, <48 hours before birth, between one to seven days before birth, ≥7 days before birth). A single trial reported no difference in puerperal sepsis for women giving birth <24 hours from receiving the first dose, no data were reported for other time points for this outcome. Infant The evidence shows a significant reduction in risk of mortality when exposure to antenatal corticosteroids occurs <48 hours before birth compared with no exposure. No further benefit for mortality outcomes are observed after this time point. The risk of respiratory distress syndrome is reduced where the infant had been exposed to antenatal corticosteroids between 1 and up to 7 days prior to birth compared with no exposure. No further benefit of a single course of antenatal corticosteroids was seen for respiratory distress syndrome after 7 days.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is not consistent
	NA	Not applicable (one study only)
3. Clinical impact *(indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Maternal No maternal benefits or harms were associated with the timing of administration. Infant Evidence shows large effect sizes and precise confidence intervals for infant outcomes. The optimal timing of a single course of antenatal corticosteroids appears to be within 7 days of anticipated birth, with significant reductions in mortality and RDS seen at this time.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight / Restricted
4. Generalisability *(how well does the body of evidence match the population and clinical settings being targeted by the guideline?)*		
Evidence is generalizable. All studies included in the Roberts CPG version 2015 systematic review were conducted in women at risk of preterm birth (variously defined by the trial authors), in a variety of countries and healthcare settings.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats

Other factors *(indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*		
EVIDENCE STATEMENT MATRIX *(summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account)*		
Component	Rating	Description
1. Evidence base	A	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias
2. Consistency	A	All studies consistent
3. Clinical Impact	A	Very large
4. Generalisability	A	Evidence directly generalisable to target population
5. Applicability	A	Evidence directly applicable to New Zealand / Australian healthcare context

M7 GRADE Evidence summary

Considered Judgement - Strength of recommendation							
What is the optimal time prior to birth to administer a single course of antenatal corticosteroids?							
1. Outcome measures:	Quality of evidence				Importance of outcome in making a decision		
Maternal Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O_1 Chorioamnionitis							
O_2 Puerperal sepsis							
O_3 Pyrexia after entry to trial				NR			
O_4							

RECOMMENDATION *(What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible)*	OVERALL GRADE OF RECOMMENDATION	
Use repeat antenatal corticosteroids in women at continued risk of preterm birth where the antenatal corticosteroids were given seven or more days prior, when birth is planned or expected within the next seven days, even if birth is likely within 24 hours	A	Body of evidence can be trusted to guide practice
	B	Body of evidence can be trusted to guide practice in most situations
	C	Body of evidence provides some support for recommendations(s) but care should be taken in its application
	D	Body of evidence is weak and recommendation must be applied with

M8 GRADE Evidence summary

Considered Judgement - Strength of recommendation							
What is the optimal time prior to birth to administer a repeat dose(s) of antenatal corticosteroids?							
1. Outcome measures:	Quality of evidence				Importance of outcome in making a decision		
Maternal Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O_1 Chorioamnionitis				NR			
O_2 Puerperal sepsis				NR			
O_3 Pyrexia after entry to trial				NR			
O_4 Intrapartum fever requiring antibiotics				NR			
O_5 Post natal pyrexia				NR			

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Benefits probably don't outweigh harms	Consider against / make no recommendation	CONDITIONAL
Harms probably outweigh benefits		
Benefits clearly don't outweigh harms	Recommend against	STRONG
Harms clearly outweigh benefits		

6. Is the intervention / action implementable in the New Zealand and Australian context?

Summary statement

Antenatal corticosteroids are13ef8(ar)1.6(e)-18 reW6.84 710tidalarySpan <</12 461.64 18 reW nBT-0.003 Tc 0.00 72 680.28 Tm[206(nt)2.3(nt)-9./

M9

4. Generalisability *(how well does the body of evidence match the population and clinical settings being targeted by the guideline?)*

Evidence is generalisable. All studies included in the Crowther (2011) systematic review were conducted in women who remained at risk of preterm birth (variously defined by the trial authors) following an initial course of antenatal corticosteroids, in a variety of countries and healthcare settings.

A Evidence directly]TJ-0.662 23.3(i)t2 by the trial ae[illegible] >>BDC -0.003 Tc 0.00

M9 GRADE Evidence summary

reduced when the interval between single and repeat antenatal corticosteroid was more than 14 days after the single course, with no significant difference in birthweight z scores. The clinical impact of this, if any, is unclear.	HIGH

Judging the harms in context

Maternal - There is no evidence of harm to the mother. There do not appear to be any direct health benefits for the mother.

Infant - The clinical significan

M10 Gestational age for administration of a s

Corticosteroids are readily available in Australia and New Zealand and their use is feasible.	A	Evidence directly applicable to New Zealand / Australian healthcare context
	B	Evidence applicable to New Zealand / Australian healthcare context with few caveats
	C	Evidence probably applicable to New Zealand / Australian healthcare context with some caveats
	D	Evidence not applicable to New Zealand / Australian healthcare context
Other factors *(indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*		
The evidence is based on a subset of data from the trials, true subgroups cannot be explored as the groups selected are not mutally exclusive. Clinical recommendations cannot be made.		
EVIDENCE STATEMENT MATRIX *(summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account)*		

M10 GRADE Evidence summary

Considered Judgement - Strength of recommendation							
At what gestational age is a single course of antenatal corticosteroids effective?							
1. Outcome measures:	Quality of evidence				Importance of outcome in making a decision		
Maternal Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important

O_1 Chorioamnionitis

gestational age at trial entry was ≤33 weeks' and 6 days. A composite of serious infant outcomes was significantly reduced following exposure to repeat antenatal corticosteroids compared with no repeat exposure when the gestational age at trial entry was ≤31 weeks' and 6 days. There was no significant difference between those exposed to repeat antenatal corticosteroids and those not exposed when the gestational age at trial entry was ≤32 weeks' and 6 days for a composite of serious infant outcomes.	

Judging the benefits in context

The evidence is based on well designed and conducted randomised controlled trials conducted in women who remained at risk of preterm birth

M12

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

Component	Rating	Description
1. Evidence base	D	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias
2. Consistency	B	All studies consistent
3. Clinical Impact	C	Moderate
4. Generalisability	D	Evidence directly generalisable to target population with some caveats
5. Applicability	C	Evidence applicable to New Zealand / Australian healthcare context with few caveats

Evidence statement

The evidence for the use of antenatal corticosteroids at term and with elective caesarean section remains unclear with the evidence currently limited to a single trial. There were no cases of perinatal death reported, and no difference in respiratory distress syndrome between infants exposed to antenatal corticosteroids and those with no exposure. There were low event rates and the trial was underpowered to detect differences in this outcome. No maternal data were reported.

Judging the benefits in context

There are benefits for the infant in terms of reduced respiratory distress syndrome and respiratory distress and reduced length of stay in neonatal intensive care. Likely to be reduced costs

4. What harm might the proposed intervention / action do?

Evidence statement

Maternal - No data were reported in the Sotiriadis (2009) systematic review on the maternal primary outcomes for these Clinical Practice Guidelines. The Ahmed (2014) trials did not pre-specify or report on any maternal outcomes.

Infant - School performance data was available from 352 children (37% of original study) followed-up from the Stutchfield (2005) trial. Children who had been exposed to antenatal corticosteroids *in utero* were more likely to be in the lowest achievement group at school compared with children who had not been exposed to antenatal

M13 Women with a previous history of preterm birth – Single course of antenatal corticosteroids

M13 NHMRC Evidence summary

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

Evidence is based on a subset of dat

M13 GRADE Evidence summary

Considered Judgement - Strength of recommendation
What is the safety for the mother and fetus, infant, child, adult of administering a single course of antenatal corticosteroids to women

birth. There was some imprecision in the confidence intervals for puerperal sepsis.

Infant -

M14 Women with a previous history of preterm birth – Repeat antenatal corticosteroids

M14 NHMRC Evidence summary

What is the safety for the mother and fetus, infant, child, adult of administering a repeat course(s) of antenatal corticosteroids to women with a history of previous preterm birth?		
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Maternal No randomised controlled trial evidence was found for the use of prophylactic antenatal corticosteroids for women whose only risk factor for preterm birth in the current pregnancy is a history of previous preterm birth. However, as four trials in the Crowther (2011) Cochrane systematic review included a proportion of women who had a previous history of preterm birth, overall treatment effects were compared with this subgroup of trials. Infant No randomised controlled trial evidence was found for the use of prophylactic antenatal corticosteroids for women whose only risk factor for preterm birth in the current pregnancy is a history of previous preterm birth. However, as four trials in the Crowther (2011) Cochrane systematic review included a proportion of women who had a history of previous preterm birth, overall treatment effects were compared with this subgroup of trials.	A	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias, or SR / several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with moderate risk of bias
	D	Level IV studies or Level I to III studies / SRs with a high risk of bias

M14 GRADE Evidence summary

Considered Judgement - Strength of recommendation

Infant - The beneficial effect of reduced composite serious outcome seen in the overall treatment effect does not exist in the subgroup of trials that reported a proportion of women with a previous preterm birth. However, there is no increase in harms.	

Judging the harms in context

Maternal - The evidence for maternal outcomes is based on four trials, involving up to 3339 women, included in the Crowther (2011) Cochrane systematic review that detailed the proportion of women with a previous preterm birth in their trial. The women had already received a single course of antenatal corticosteroids between 7 and 21 days prior and were at continued risk of pre-

-5.5(r)1.6(s)3.8n6

M15 Women in preterm labour – Single course of antenatal corticosteroids

M15 NHMRC Evidence summary

2. Consistency	NA	Not applicable
3. Clinical Impact	NA	Not applicable

M15 GRADE Evidence summary

Considered Judgement - Strength of recommendation							
What is the safety for the mother and fetus, infant, child, adult of administering a single course of antenatal corticosteroids to women in preterm labour?							
1. Outcome measures:	Quality of evidence				Importance of outcome in making a decision		
Maternal Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O_1 Chorioamnionitis							
O_2 Puerperal sepsis							
O_3 Pyrexia after entry to trial							
O_4 Intrapartum fever requiring antibiotics							
O_5 Post natal pyrexia							
O_6 Maternal quality of life				NR			
Infant Outcomes	HIGH	MOD	LOW	V. LOW	Critical		

corticosteroids in the trials that reported including a proportion of women in spontaneous preterm labour.	
Judging the harms in context *Maternal* - The evidence is based on seven trials involving 1797 women who were in spontaneous preterm labour and received a single course of antenatal corticosteroids (or placebo). *Infant* - The evidence is based on 15 trials involving 3683 infants who were exposed to a single course of antenatal corticosteroids and whose mothers were in spontaneous preterm labour.	
5. What is the likely balance between good and harm?	

Recommend / consider

C o n s i d

R e c o m m

7. Final recommendation

a n t e n a t a l c o

M16 Women in preterm labour – Repeat course of antenatal corticosteroids

M16 NHMRC Evidence summary

What is the safety for the mother and the fetus, infant, child, adult of administering repeat dose(s) of antenatal steroids to women in preterm labour?
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*

Six trials included in the Crowther (2011) Cochrane systematic review reported on maternal outcomes and detailed a proportion of women who were in preterm labour with 49% of women being in spontaneous labour, where reported.

Eight trials included in the Crowther (2011) Cochrane systematic review reported on infant o

Evidence statement
The evidence suggests that even an incomplete course of antenatal corticosteroids may have benefits to the neonate when the mother is in preterm labour.

RECOMMENDATION *(What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible)*	OVERALL GRADE OF RECOMMENDATION	
Repeat antenatal corticosteroids for a woman in preterm labour. Where appropriate, estimate the risk of preterm birth by considering the use of adjunct prediction tests including fetal fibronectin and assessment of cervical length.	A	Body of evidence can be trusted to guide practice
	B	Body of evidence can be trusted to guide practice in most situations
	C	Body of evidence provides some support for recommendations(s) but care should be taken in its application
	D	Body of evidence is weak and recommendation must be applied .6( )1(i)0 0 8.04 457W ns3MCID

M16 GRADE Evidence summary

Considered Judgement - Strength of recommendation							
What is the safety for the mother and fetus, infant, child, adult of administering repeat dose(s) of antenatal corticosteroids to women in preterm labour?							
1. Outcome measures:	Quality of evidence				Importance of outcome in making a decision		
Maternal Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O_1 Chorioamnionitis							

Infant - Evidence is based on eight well conducted trials involving up to 5228 infants, generalizable to the target population and applicable to the New Zealand and Australian health care setting.

5. What is the likely balance between good and harm?

Evidence statement	Overall quality of evidence
Maternal - Following a repeat dose(s) of antenatal corticosteroids there is no evidence of an increased risk for any maternal infection (chorioamnionitis, pyrexia at trial entry, intrapartum pyrexia or postnatal pyrexia requiring treatment, puerperal sepsis). *Infant* - There were no differences between repeat and no repeat antenatal corticosteroids for infant mortality in trials that reported a proportion of women in preterm labour. Respiratory distress syndrome was reduced in women in preterm labour for a repeat dose(s) of antenatal corticosteroids compared with no repeat exposure. There was a significant reduction in a composite of serious infant outcomes following a repeat dose(s) of antenatal corticosteroids compared with no repeat exposure in women in preterm labour.	Not applicable

Judging the balance of benefits and harms in context

Maternal - No evidence of harm or benefit to the mother.

Infant - No evidence of harm for the infant and clear evidence of benefit.

Benefits clearly outweigh harms Recommen

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

M17 GRADE Evidence summary

Considered Judgement - Strength of recommendation							
What is the safety for the mother and fetus, infant, child, adult of administering a single course of antenatal corticosteroids to women with preterm prelabour rupture of membranes (at trial entry) at risk of preterm birth?							
1. Outcome measures:	Quality of evidence				Importance of outcome in making a decision		
Maternal Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O_1 Chorioamnionitis				NR			
O_2 Puerperal sepsis							
O_3 Pyrexia after entry to trial							
O_4 Intrapartum fever requiring antibiotics				NR			
O_5 Post natal pyrexia							

4. What harm might the proposed intervention / action do?

Evidence statement

Maternal -

M18 GRADE Evidence summary

Considered Judgement - Strength of recommendation							
What is the safety for the mother and fetus, infant, child, adult of administering a repeat course(s) of antenatal corticosteroids to women with preterm prelabour rupture of membranes (at trial entry) at risk of preterm birth?							
1. Outcome measures:	Quality of evidence				Importance of outcome in making a decision		
Maternal Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not

Judging the harms in context

The evidence is direct evidence from randomised controlled trials that reported the proportion of women with preterm prelabour rupture of membranes. There was no evidence of increased risk of maternal infection, or increased risk of mortality for the infant.

5. What is the likely balance between good and harm?

Evidence statement	Overall quality of evidence
Maternal - The evidence suggests no increased risk of harm for the mother when treated with repeat antenatal corticosteroids in the presence of preterm prelabour rupture of membranes.	
Infant - There is clear benefit for the infant of significantly reduced risk of respiratory distress syndrome, with no increased risk of mortality, when exposed to repeat antenatal corticosteroids in the presence of preterm prelabour rupture of membranes.	Not applicable

Judging the balance of benefits and harms in context

Maternal - Repeat antenatal corticosteroids in the presence of preterm prelabour rupture of membra

M19 Women with chorioamnionitis at risk of preterm birth – Single course of antenatal corticosteroids

M19 NHMRC Evidence summary

What is the safety for the mother and fetus, infant, child, adult of administering a single course of antenatal corticosteroids to women with chorioamnionitis at risk of preterm birth?		
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Four trials included in the Roberts CPG version 2015 systematic review for a single course of antenatal corticosteroids recruited a proportion of women with chorioamnionitis in their trial (at trial entry), and three of the trials reported on the proportion of women subsequently diagnosed with chorioamnionitis. Women with chorioamnionitis were not eligible for 14 of the 26 trials included in the CPG 2015 version, and no details were provided for the remaining eight trials.	A	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies w

M19 GRADE Evidence summary

Considered Judgement - Strength of recommendation							
What is the safety for the mother and fetus, infant, child, adult of administering a single course of antenatal corticosteroids to women with chorioamnionitis at risk of preterm birth?							
1. Outcome measures:	Quality of evidence				Importance of outcome in making a decision		
Maternal Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O_1 Chorioamnionitis							

O_2 Puerperal sepsis

Where appropriate, monitor women with chorioamnionitis for signs of puerperal sepsis when antenatal corticosteroids have been given..	PP	Practice Points

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

IMPLEMENTATION OF RECOMMENDATION *(Please indicate yes or no to the following questions. Where the answer is yes, please provide explanatory*

Judging the harms in context N/A		
5. What is the likely balance between good and harm?		
Evidence statement *Maternal* - No relevant data for maternal primary outcomes were reported in the two randomised controlled trials included in the Crowther (2011) Cochrane systematic review that recruited women with chorioamnionitis at trial entry. Women with chorioamnionitis at the time of trial entry were excluded from the remaining eight trials in the Crowther (2011) Cochrane systematic review. *Infant* - No relevant data for infant primary outcomes were reported in the two randomised controlled trials included in the Crowther (2011) Cochrane systematic review that recruited women with chorioamnionitis at trial entry. Women with chorioamnionitis at the time of trial entry were excluded from the remaining eight trials in the Crowther (2011) Cochrane systematic review.		Quality of evidence Not applicable
Judging the balance of benefits and harms in context N/A		
Benefits clearly outweigh harms	Recommend	STRONG
Benefits probably outweigh harms	Consider	CONDITIONAL
Not known	07 Tw ef433(38(32 Tc 0 Tw 5.657 0 Tn621.6 94.68 0.48 ref08m2[(u)- 0.48 0f-0.48 ref4336Ws32 Tc EMC f433.3f	

M21 Women with antepartum haemorrhage at risk of preterm birth – Single course of antenatal corticosteroids

M21 NHMRC Evidence summary

What is the safety for the mother, fetus, infant, child, adult of administering a single course of antenatal corticosteroids to women with antepartum haemorrhage at risk of preterm birth?		
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Six of the 26 trials included in the Roberts CPG version 2015 systematic review for a single course of antenatal corticosteroids reported including a small proportion of women with an antepartum haemorrhage in their trials.	A B	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias

M21 GRADE Evidence summary

Considered Judgement - Strength of recommendation			
[redacted]			roids to women
[redacted]	e measures:	Quality of evidence	

Infant - There was no evidence of any harm to the infant.	

Judging the harms in context

Maternal - The evidence for increased risk of pyrexia after trial entry requiring treatment and puerperal sepsis following exposure to a single course

M22 Women with antepartum haemorrhage at risk of preterm birth – Repeat antenatal corticosteroids

M22 NHMRC Evidence summary

What is the safety for the mother, fetus, infant, child, adult of administering repeat antenatal corticosteroids to women with antepartum haemorrhage at risk of preterm birth?		
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Seven of the ten trials included in the Crowther, 2011 review reported including a small proportion of women with an antepartum haemorrhage in their trials.	A	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Maternal The evidence for chorioamnionitis, postnatal pyrexia and puerperal sepsis appears to be consistent with the overall treatment effect with no difference seen in the risk between those women treated with repeat antenatal corticosteroids and those not treated. Infant Evidence for perinatal death, fetal death, neonatal death, respiratory distress syndrome, severe respiratory distress syndrome, composite		

M22 GRADE Evidence summary

Considered Judgement - Strength of recommendation
What is the safety for the moBox ryher, feyus, ifa, chi, auly of administering a reBox3(p)0.8(eBox3(a)2.4(t)0.6(cBox4(o)14.5(u)0.8(r)1.7(

corticosteroids in trials that recruited and reported a proportion of women with antenatal corticosteroids. *Infant* - There was no evidence of health harms for the infant following exposure to repeat antenatal corticosteroids in trials that recruited and reported a proportion of women with antenatal corticosteroids.	Not applicable
Judging the harms in context Direct evidence from trials conducted in women exposed to repeat antenatal corticosteroids after remaining at imminent risk of preterm birth following an initial single course suggests no health harms for the mother or the infant.	

5.

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

M23 NHMRC Evidence summary

What is the safety for the mother and fetus, infant, child, adult of administering a single course of antenatal corticosteroids to women with a multiple pregnancy (twins and higher order) with an additional risk factor(s) for preterm birth?
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*

2. Consistency	NA	Not applicable

3. Clinical Impact

Infant - There was no evidence of any harm to the infant.	

M25 Women with a multiple pregnancy with no risk of preterm birth – Single course of antenatal corticosteroids

M25 NHMRC Evidence summary

Clinical questions: What is the safety for the mother and fetus, infant, child, adult of administering a single course of antenatal corticosteroids to women with a multiple pregnancy (twins and higher order) prophylactically (not at additional risk for preterm birth)?
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)* There was no randomised controlled trial evidence for the prophylactic use of antenatal corticosteroids in women with multiple pregnancy with no additional risk of preterm birth.

2. Consistency	NA	Not applicable
3. Clinical Impact	NA	Not applicable
4. Generalisability	NA	Not applicable
5. Applicability	NA	Not applicable

Evidence statement

M25 GRADE Evidence summary

Considered Judgement - Strength of recommendation							
What is the safety for the mother and fetus, infant, child, adult of administering a single course of antenatal corticosteroids to women with a multiple pregnancy (twins and higher order) prophylactically (not at additional risk for preterm birth)?							
1. Outcome measures:	Quality of evidence				Importance of outcome in making a decision		
Maternal Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O_1 Chorioamnionitis				NR			
O_2 Puerperal sepsis				NR			
O_3							

Benefits clearly don't outweigh harms Harms clearly outweigh benefits	Recommend against	STRONG

6.

M26

4. Generalisability	N/A	
5. Applicability	N/A	
Evidence statement		

Not known	Make a recommendation for research (see 8 below)	WEAK
Benefits probably don't outweigh harms	Consider against/make no recommendation	CONDITIONAL
Harms probably outweigh benefits		
Benefits clearly don't outweigh harms	Recommend against	STRONG
Harms clearly outweigh benefits		
6. Is the intervention/action implementable in the New Zealand context?		

Summary statement

M27 Women with diabetes mellitus or gestational diabetes at risk of preterm birth – Single course of antenatal corticosteroids

M27 NHMRC Evidence summary

What is the safety for the mother and fetus, infant, child, adult of administering a single course of antenatal corticosteroids to women with diabetes mellitus or gestational diabetes at risk of preterm birth?
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*

Maternal
Five trials included in the Roberts CPG version 2015 systematic review for a single course of antenatal corticosteroids reported the inclusion of a very small proportion of women with diabetes mellitus [illegible]

M27 GRADE Evidence summary

Considered Judgement - Strength of recommendation							
What is the safety for the mother and fetus, infant, child, adult of administering a single course of antenatal corticosteroids to women with diabetes mellitus or gestational diabetes at risk of preterm birth?							
1. Outcome measures:	Quality of evidence				Importance of outcome in making a decision		
Maternal Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O_1 Chorioamnionitis							
O_2 Puerperal sepsis							
O_3 Pyrexia after entry to trial							
O_4 Intrapartum fever requiring antibiotics							
O_5 Post natal pyrexia							
O_6 Maternal quality of life				NR			
Infant Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O_1 Combined fetal and neonatal death							
O_2 Neonatal death							
O_3 Fetal death							
O_4 RDS							
O_5 Composite of serious outcomes for the infant				NR			
O_6 Neurosensory di(or)1.Tc 0.007 3b20.ory di(or)1.s57eis							

M28 Women with diabetes mellitus or gestational diabetes at risk of preterm birth – Repeat antenatal corticosteroids

M28 NHMRC Evidence summary

What is the safety for the mother and fetus, infant, child, adult of administering repeat antenatal corticosteroids to women with diabetes mellitus or gestational diabetes at risk of preterm birth?
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*

Maternal
Four of the ten trials included in the Crowther (2011) systematic
review reported including a small proportion of women with
diabetes in pregnancy and 1)1j27(on 5.6 (at)-921( )TjETEMC QBT/P <</MCID 6 >>BDC /TT1 1 Tf-0.003 Tc 0.007 Tw 8)-9.6(0.119 ref/P <</MCID 1 l13w/P <<

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)*

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.

OVERALL GRADE OF RECOMMENDATION	
A	Body of evidence can be trusted to guide practice
B	Body of evidence can be trusted to guide practice in most situations
C	Body of evidence provides some support for recommendations(s) but care should be taken in its application
D	Body of evidence is weak and recommendation must be applied with caution
PP	Practice Point

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

IMPLEMENTATION OF RECOMMENDATION *(Please indicate yes or no to the following questions. Where the answer is yes, please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines)*

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M28 GRADE Evidence summary

Considered Judgement - Strength of recommendation							
What is the safety for the mother and fetus, infant, child, adult of administering a repeat course(s) of antenatal corticosteroids to women with diabetes mellitus or gestational diabetes at risk of preterm birth?							
1. Outcome measures:	Quality of evidence				Importance of outcome in making a decision		
Maternal Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O_1 Chorioamnionitis							
O_2 Puerperal sepsis							
O_3							

diabetes or type 2 diabetes were unable to be determined, if any.

5. What is the likely balance between good and harm?

Evidence statement

Maternal - There does not appear to be an increased risk of maternal infection. Overall evidence indicates an increased risk of elevated maternal blood glucose levels following antenatal corticosteroids in non-diabetic women.
Infant - There do not appear to be any hea

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

M29 NHMRC Evidence summary

4. Generalisability	NA	Not applicable
5. Applicability	NA	Not applicable

Evidence statement

No randomised controlled trial evidence was available for the use of a single course of antenatal corticosteroids in women with systemic infection at trial entry.

RECOMMENDATION *(What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible)*	OVERALL GRADE OF RECOMMENDATION	
Use a single course of antenatal corticosteroids for women with a systemic infection at risk of preterm birth. Do not delay birth in women with a systemic infection to administer a single course antenatal corticosteroids if at risk of preterm birth.	A	Body of evidence can be trusted to guide practice

M29 GRADE Evidence summary

Considered Judgement - Strength of recommendation							
What is the safety for the mother and fetus, infant, child, adult of administering a single course of antenatal corticosteroids to women with systemic infection at trial entry at risk of preterm birth?							
1. Outcome measures:	Quality of evidence				Importance of outcome in making a decision		
Maternal Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O_1 Chorioamnionitis				NR			
O_2 Puerperal sepsis				NR			
O_3 Pyrexia after entry to trial				NR			
O_4 Intrapartum fever requiring antibiotics				NR			
O_5							

Not known	Make a recommendation for research (see 8 below)	WEAK

M30 Women with systemic infection at trial entry at risk of preterm birth – Repeat antenatal corticosteroids

M30 NHMRC Evidence summary

What is the safety for the mother and fetus,

M30 GRADE Evidence summary

Not known	Make a recommendation for research (see 8 below)	WEAK
Benefits probably don't outweigh harms	Consider against/make no recommendation	CONDITIONAL
Harms probably outweigh benefits		
Benefits clearly don't outweigh harms	Recommend against	STRONG
Harms clearly outweigh benefits		

6. Is the intervention/action implementable in the New Zealand context?

Summary statement
Antenatal corticosteroids are already widely in use in New Zealand and Australia.

Yes	Recommend/consider
Not known	Consider economic evaluation
No	Recommend/consider against

7. Final recommendation

Repeat antenatal corticosteroids for women with a systemic infection at risk of preterm birth.

Do not delay birth in women with a systemic infection to administer repeat antenatal corticosteroids if at risk of preterm birth.

Where appropriate, monitor women with systemic infection at risk of preterm birth for signs of puerperal sepsis when antenatal corticosteroids have been given

Strength of recommendation
Please select level

STRONG

1. Evidence base	NA	Not applicable
2. Consistency	NA	Not applicable
3. Clinical Impact	NA	Not applicable
4. Generalisability	NA	Not applicable
5. Applicability	NA	Not applicable
Evidence statement		

RECOMMENDATION *(What recommendation(s) does the guide*

M31 GRADE Evidence summary

Considered Judgement - Strength of recommendation
What is the safety for the mother and fetus, infant, child, adult of administering a single course of antenatal corticosteroid to women with pregnancy associated hypertension / pre-eclampsia at risk of preterm birth?

1. O(n) (Dy -0BDC h5m4 T13n)0.9235e

5. What is the likely balance between good and harm?		
Evidence statement *Maternal* - There does not appear to be an increased risk to the mother. *Infant* - There are significant benefits for the infant in terms of reduced risk of neonatal mortality and respiratory distress syndrome.		Overall quality of evidence Not applicable
Judging the balance of benefits and harms in context Exposure to a single course of antenatal corticosteroids in the presence of pregnancy induced hypertension is unlikely to harm to the mother. The significant health benefits for the infant, in terms of reduced risk of mortality and respiratory distress syndrome outweigh potential low impact harm for the mother.		
Benefits clearly outweigh harms	Recommend	STRONG
Benefits probably outweigh harms	Consider	CONDITIONAL
Not known	Make a recommendation for research (see 8 below)	WEAK
Benefits probably don't outweigh harms	Consider against/make no recommendation	CONDITIONAL
Harms probably outweigh benefits		
Benefits clearly don't outweigh harms	Recommend against	STRONG
Harms clearly outweigh benefits		
6. Is the intervention/action implementable in the New Zealand context?		

Summary statement
Antenatal corticosteroids are already widely in use in New Zealand and Australia.

M32 Women with pregnancy associated hypertension / pre-eclampsia at risk of preterm birth – Repeat antenatal corticosteroids

M32 NHMRC Evidence summary

What is the safety for the mother and fetus, infant, child, adult of administering repeat antenatal corticosteroids to women with pregnancy associated hypertension / pre-eclampsia at risk of preterm birth?		
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Maternal Seven of the ten trials included in the Crowther (2011) systematic review reported including a small proportion of women in their trial with pregnancy associated hypertension. Four of these reported on chorioamnionitis, one provided data on postnatal pyrexia, and three provided data on puerperal sepsis. Infant Seven trials included in the Crowther (2011) systematic review reported including a proportion of women with pregnancy associated hypertension. Six trials provided data on perinatal death, five provided data for fetal death, five for neonatal death and respiratory distress syndrome and four for composite of serious infant outcomes.	A	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias, or SR / several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with moderate risk of bias
	D	Level IV studies or Level I to III studies / SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Maternal Treatment effects for chorioamnionitis, postnatal pyrexia and puerperal sepsis were similar to the overall treatment effect. There was no difference in risk of maternal infection between those exposed to repeat antenatal corticosteroids and those not exposed from trials that reported including a proportion of women with pregnancy associated hypertension. Infant Treatment effect sizes for respiratory distress syndrome and a composite of serious infant outcomes were similar to the overall treatment effects, with a significant reduction in risk for those exposed to repeat antenatal corticosteroids comparted with no repeat exposure. There was no statistically significant difference in risk of perinatal, fetal and neonatal death between groups.	A	All studies consistent

EVIDENCE STATEMENT MATRIX *(summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account)*		
Component	Rating	Description
1. Evidence base	NA	Not applicable
2. Consistency	NA	Not applicable
3. Clinical Impact	NA	Not applicable
4. Generalisability	NA	Not applicable
5. Applicability	NA	Not applicable
Evidence statement		

RECOMMENDATION *(What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible)*	OVERALL GRADE OF RECOMMENDATION
Repeat antenatal corticosteroids for a woman with pregnancy associated hypertension at risk of preterm birth.	A Body of evidence can be trusted to

M32 GRADE Evidence summary

Considered Judgement - Strength of recommendation		
What is the safety for the mother and fetus, infant, child, adult of administering a repeat course(s) of antenatal corticosteroid to women with pregnancy associated hypertension / pre-eclampsia at risk of preterm birth?		
1. Outcome measures:	Quality of evidence	Importance of outcome in making a decision
Maternal Outcomes	HIGH	

antenatal corticosteroids for the women with pregnancy associated hypertension, or their infants.

5. What is the likely balance between good and harm?

Evidence statement

Maternal - There are no direct health benefits for the mother of repeat antenatal corticosteroids. There does not appear to be any increased risk of harm for women with pregnancy associated hypertension exposed to repeat antenatal corticosteroids.

Infant

M33 Women with a fetus with intrauterine growth restriction at risk of preterm birth – Single course of antenatal corticosteroids

M33 NHMRC Evidence summary

What is the safety for the mother and fetus, infant, child, adult of administering a single course of antenatal corticosteroids to women with a fetus with intrauterine growth restriction at risk of preterm birth?
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*

Maternal
Three of the 26 trials in the Roberts CPG version 2015 systematic review for a single course of antenatal corticosteroids reported including a very small proportion of women in their trial with a fetus with intrauterine growth restriction. Two of these trials report on chorioamnionitis and puerperal sepsis.

Infant
Three trials in the Roberts CPG version 2015 systematic review for a single course of antenatal corticosteroids reported inc

M33 GRADE Evidence summary

Considered Judgement - Strength of recommendation
Clinical

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.

M34 Women with a fetus with intrauterine growth restriction at risk of preterm birth – Repeat course of antenatal corticosteroids

EVIDENCE STATEMENT MATRIX *(summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account)*		
Component	Rating	Description
1. Evidence base	NA	Not applicable
2. Consistency	NA	Not applicable
3. Clinical Impact	NA	Not applicable
4. Generalisability	NA	Not applicable
5. Applicability	NA	Not applicable
Evidence statement		

RECOMMENDATION *(What recommendation(s) does the guideline development group draw from this evidence?*

M34 GRADE Evidence summary

antenatal corticosteroids, and that recruited and reported the proportio

cervix at risk of preterm birth.

RECOMMENDATION

M35 GRADE Evidence summary

Considered Judgement - Strength of recommendation							
What is the safety for the mother and fetus, infant, child, adult of administering a single course or repeat antenatal corticosteroids to women with ultrasound evidence of cervical shortening /funnelling at risk of preterm birth?							
1. Outcome measures:	Quality of evidence				Importance of outcome in making a decision		
Maternal Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O_1 Chorioamnionitis				NR			
O_2 Puerperal sepsis				NR			
O_3 Pyrexia after entry to trial				NR			
O_4 Intrapartum fever requiring antibiotics				NR			
O_5 Post natal pyrexia				NR			
O_6 Maternal quality of life				NR			
Infant Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	

Not known	Make a recommendation for research (see 8 below)	WEAK

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 E02 Tw [(F)-2.6(e)3.6(ta)2.8(l)1.1( )10.6(l)1.1at

RECOMMENDATION *(What recommendati*

Harms probably outweigh benefits		
Benefits clearly don't outweigh harms	Recommend against	STRONG
Harms clearly outweigh benefits		

6. Is the intervention/action implementable in the New Zealand context?

Summary statement
Antenatal corticosteroids are already widely in use in New Zealand and Australia.

Yes	Recommend/consider
Not known	Consider economic evaluation
No	Recommend/consider against

7. Final recommendation

Use a single course of antenatal corticosteroids for 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.	Strength of recommendation *Please select level* STRONG CONDITIONAL WEAK (Practice Points)

8.

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

M37 GRADE Evidence summary

Considered Judgement - Strength of recommendation							
What is the safety for the mother and fetus, infant, child, adult of administering a single course of antenatal corticosteroids to women for whom preterm birth is medically indicated?							
1. Outcome measures:	Quality of evidence				Importance of outcome in making a decision		
Maternal Outcomes	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O_1 Chorioamnionitis				NR			
O_2 Puerperal sepsis				NR			
O_3 Pyrexia after entry to trial				NR			

O_4 Intrapartum fever requiring antibiotics

M38 Women for whom preterm birth is medically indicated for other reasons – Repeat antenatal corticosteroids

M38 NHMRC Evidence summary

What is the safety for the mother and fetus, infant, child, adult of administering repeat antenatal corticosteroids to women for whom preterm birth is medically indicated?		
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
No randomised controlled trial evidence was reported for the use of repeat antenatal corticosteroids for a variety of maternal conditions where preterm birth may be medically indicated.	A	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with moderate risk of bias
	D	Level IV studi

Evidence statement

No randomised controlled trial evidence was reported for the use of repeat antenatal corticosteroids for a variety of maternal conditions where preterm birth may be medically indicated.

RECOMMENDATION *(What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible)*	OVERALL GRADE OF RECOMMENDATION
Repeat antenatal corticosteroids for a woman with other medical indications for preterm birth.	

M38 GRADE Evidence summary

Considered Judgement - Strength of recommendation
What is the safety for the mother and fetus, infant, child, adult of administering a repeat course(s) of antenatal corticosteroids to women for whom preterm birth is medically indicated?

Harms probably outweigh benefits		
Benefits clearly don't outweigh harms	Recommend against	STRONG
Harms clearly outweigh benefits		

6. Is the intervention/action implementable in the New Zealand context?

Summary statement
Antenatal corticosteroids are already widely in use in New Zealand and Australia.

Yes	Recommend/consider
Not known	

M39 Use of antenatal corticosteroids for women with diabetes in pregnancy at term – Single course and repeat antenatal corticosteroids

M39 NHMRC evidence summary

What are the benefits and harms for the mother and fetus, infant, child and adult of administering a single course or repeat antenatal corticosteroids for fetal lung maturation to women with diabetes mellitus or gestational diabetes at term?		
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
There were no data from randomised trials identified for maternal or neonatal outcomes associated with the use of a single course of antenatal corticosteroids in women with diabetes or gestational diabetes at term.	A	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Not applicable	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is not consistent
	NA	Not applicable (one study only)

3. Clinical impact *(indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the*

Harms probably outweigh benefits		
Benefits clearly don’t outweigh harms		

Appendix N: Forest plots for meta-analyses

Figure 1: Single course of antenatal corticosteroids - respiratory distress syndrome

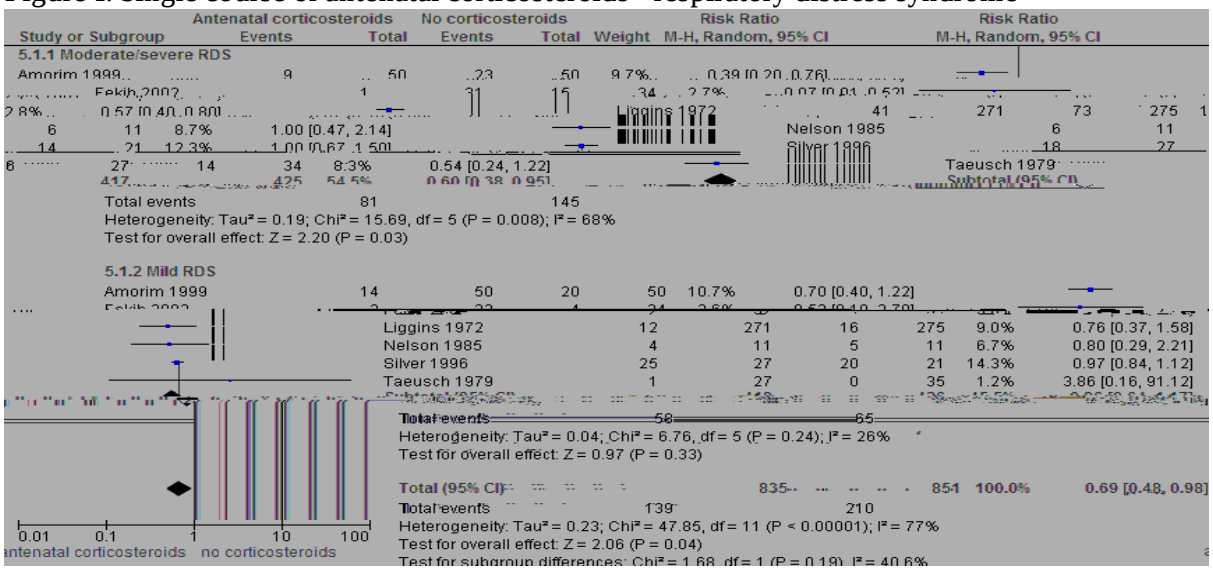

Figure 2: Repeat antenatal corticosteroids – respiratory distress syndrome

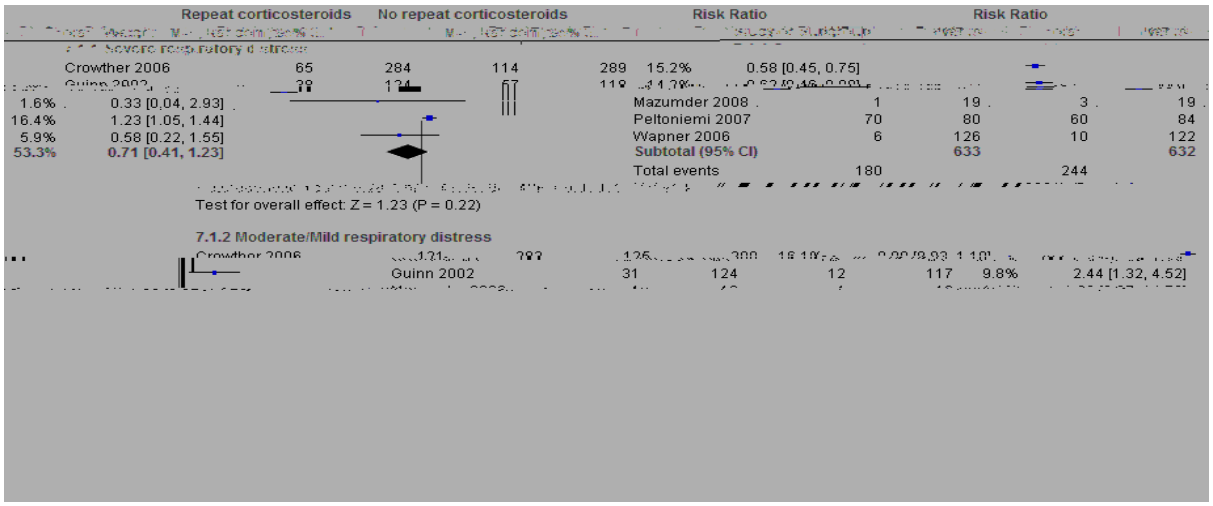

Figure 3: Subgroup analysis: Chorioamnionitis by of type of antenatal corticosteroid administered

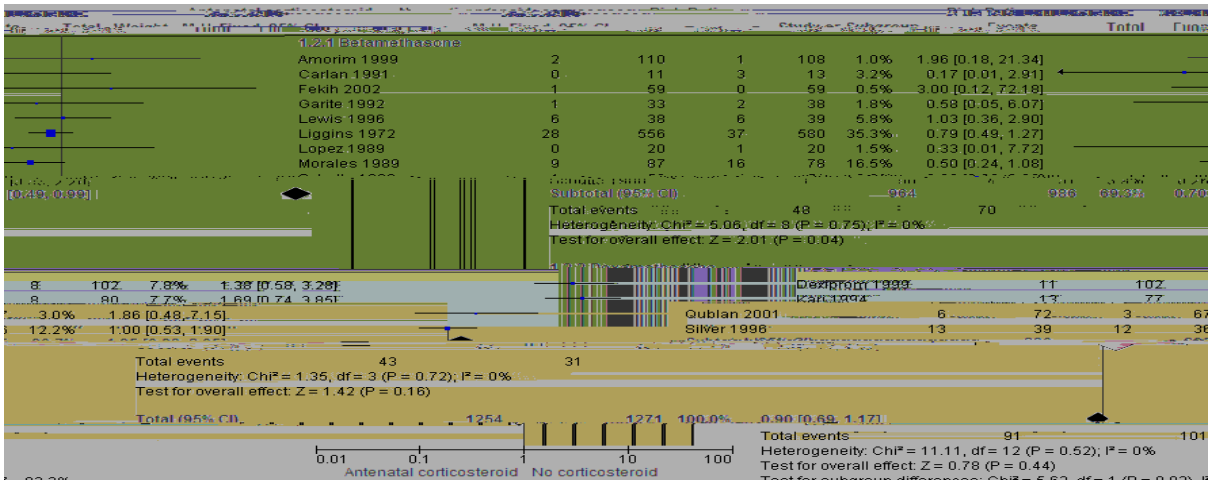

Figure 4: Subgroup analysis: Puerperal sepsis by type of antenatal corticosteroid administered

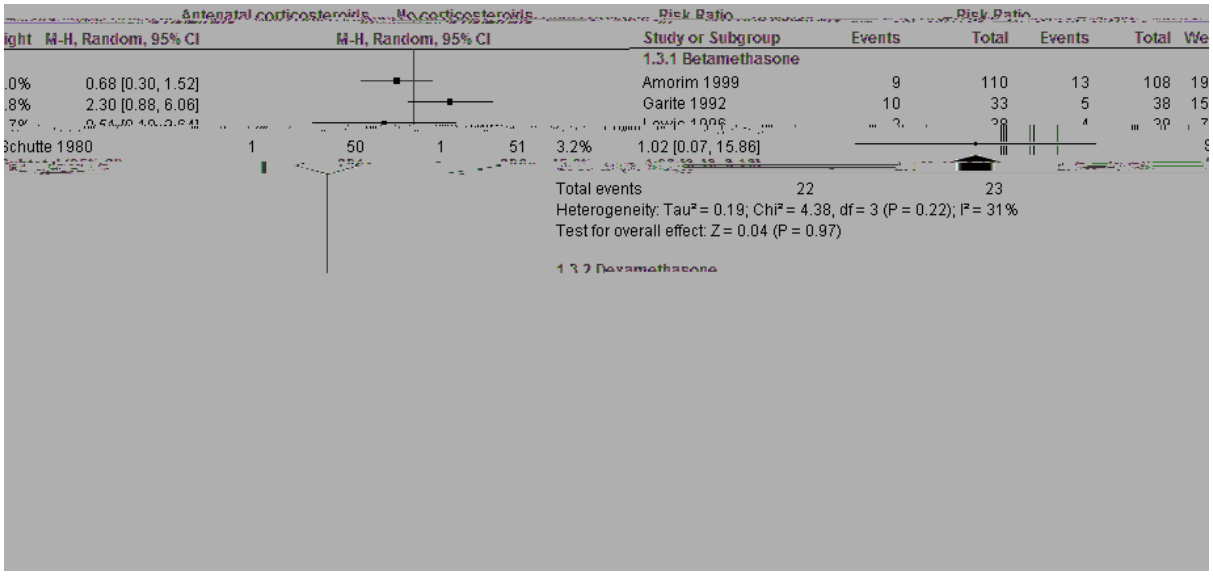

Figure 5: Subgroup analysis: Pyrexia after trial entry by type of antenatal corticosteroid administered

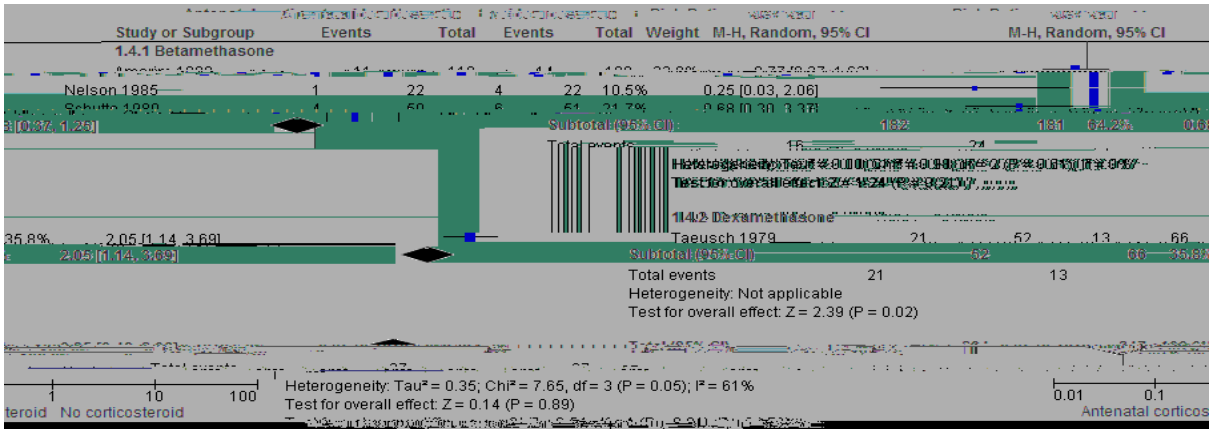

Figure 6: Subgroup analysis: Postnatal pyrexia by type of antenatal corticosteroid administered

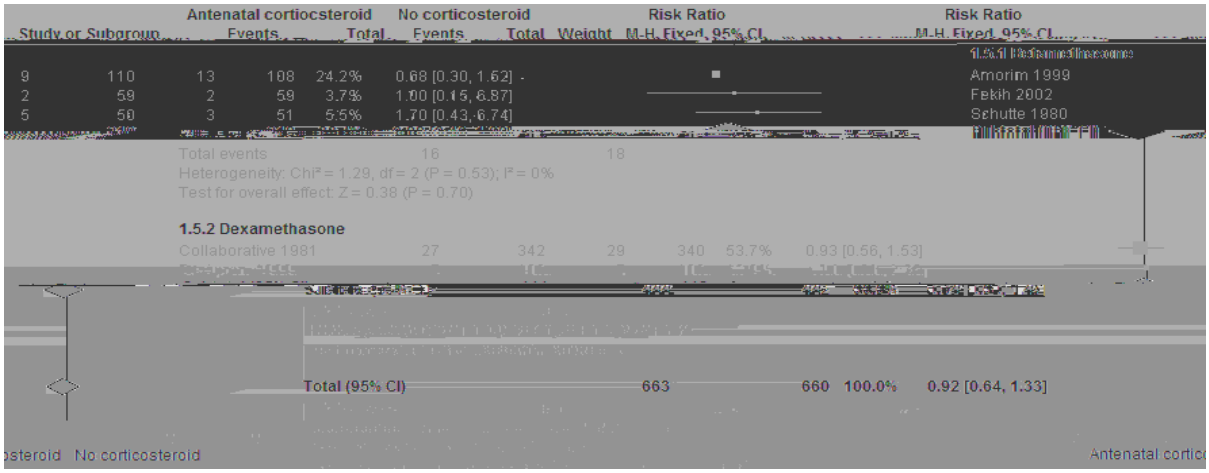

Figure 12: Subgroup analysis – Chorioamnionitis betamethasone regimens

Figure 13

Figure 14: Subgroup analysis Puerperal sepsis betamethasone regimen

Figure 15: Subgroup analysis Puerperal sepsis dexamethasone regimen

Figure 16: Subgroup analysis Neonatal death – Betamethasone regimens

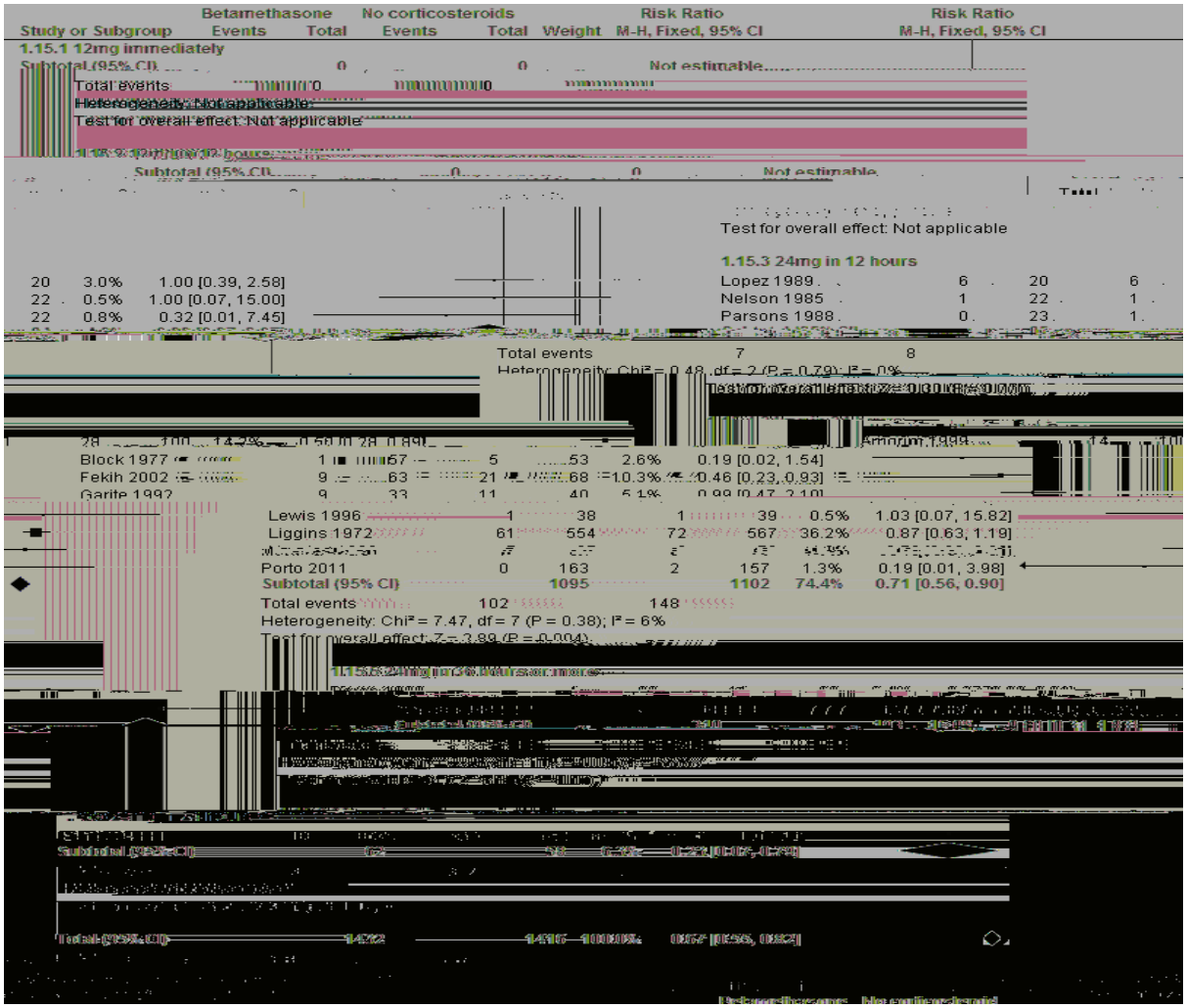

Figure 17: Subgroup analysis Neonatal death – dexamethasone regimens

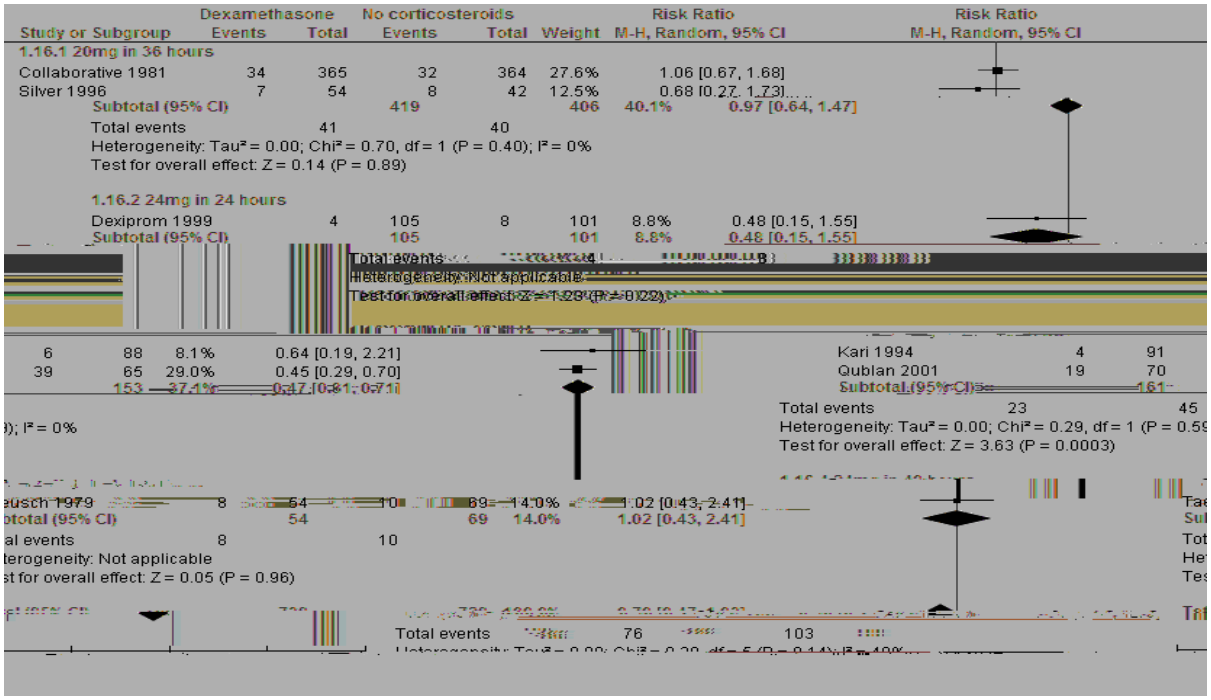

Figure 20: Subgroup analysis Repeat antenatal corticosteroids - Chorioamnionitis

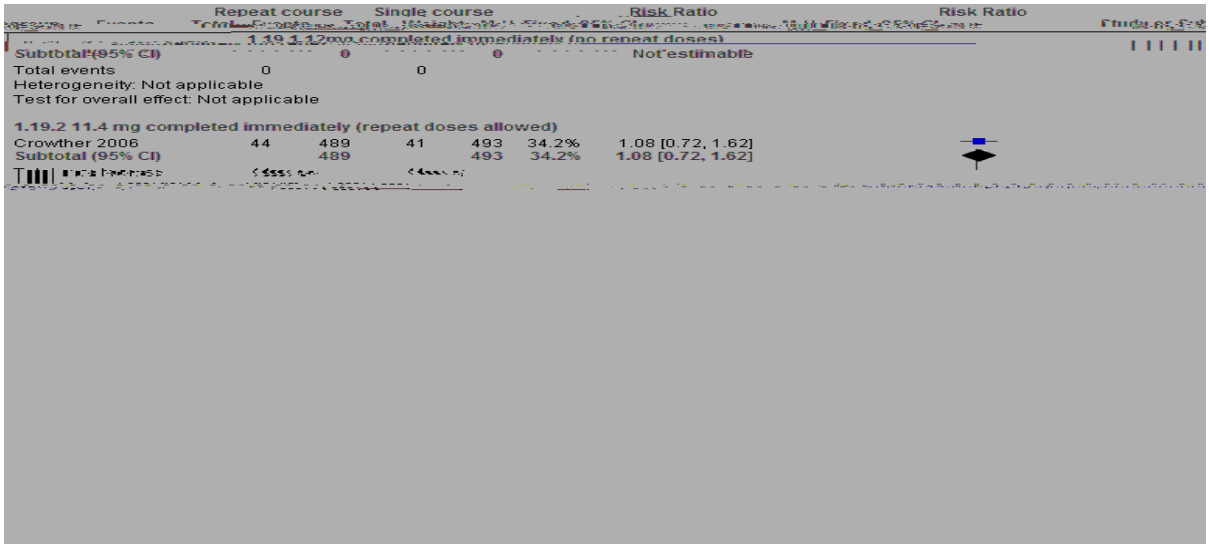

Figure 21: Subgroup analysis Repeat antenatal corticosteroids - Puerperal sepsis

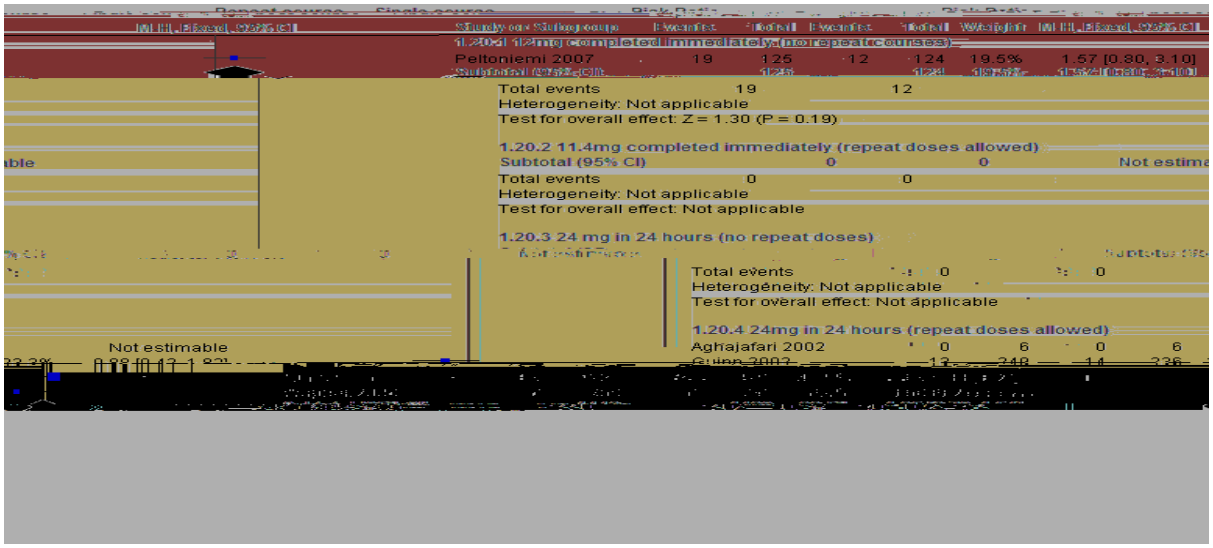

Figure 22: Subgroup analysis Repeat antenatal corticosteroids – Neonatal death

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

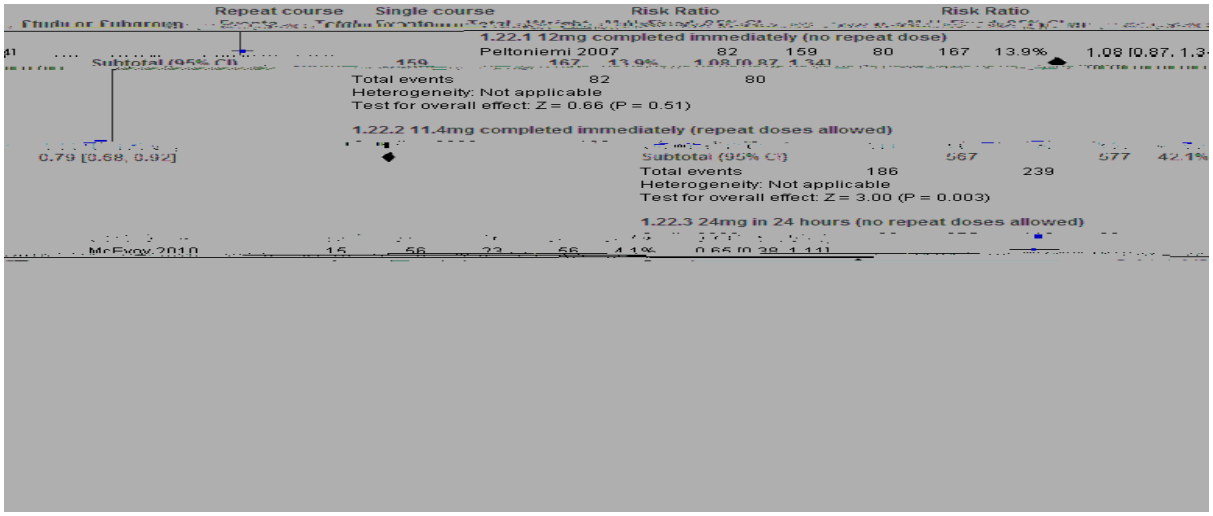

Figure 24: Subgroup analysis Repeat antenatal corticosteroids - Composite of serious infant outcomes

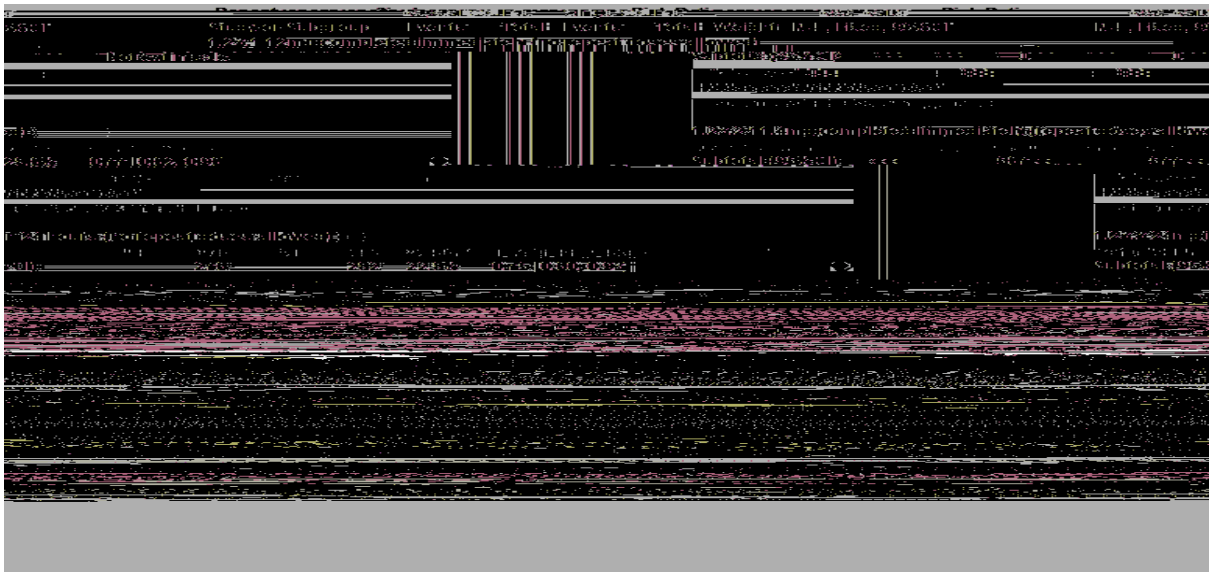

Figure 25: Subgroup analysis Repeat antenatal corticosteroids Birthweight

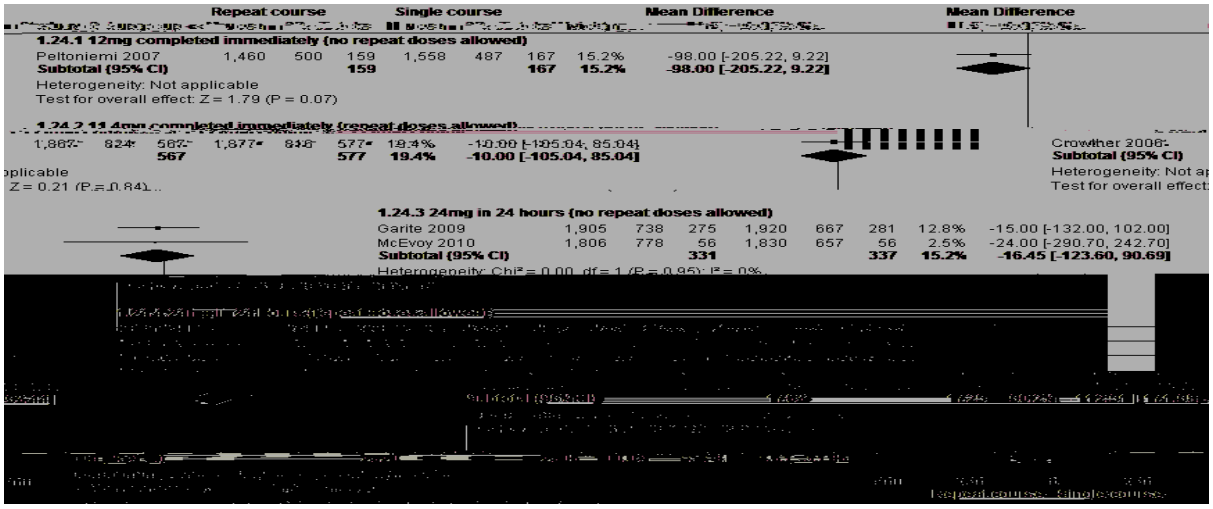

Figure 29

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

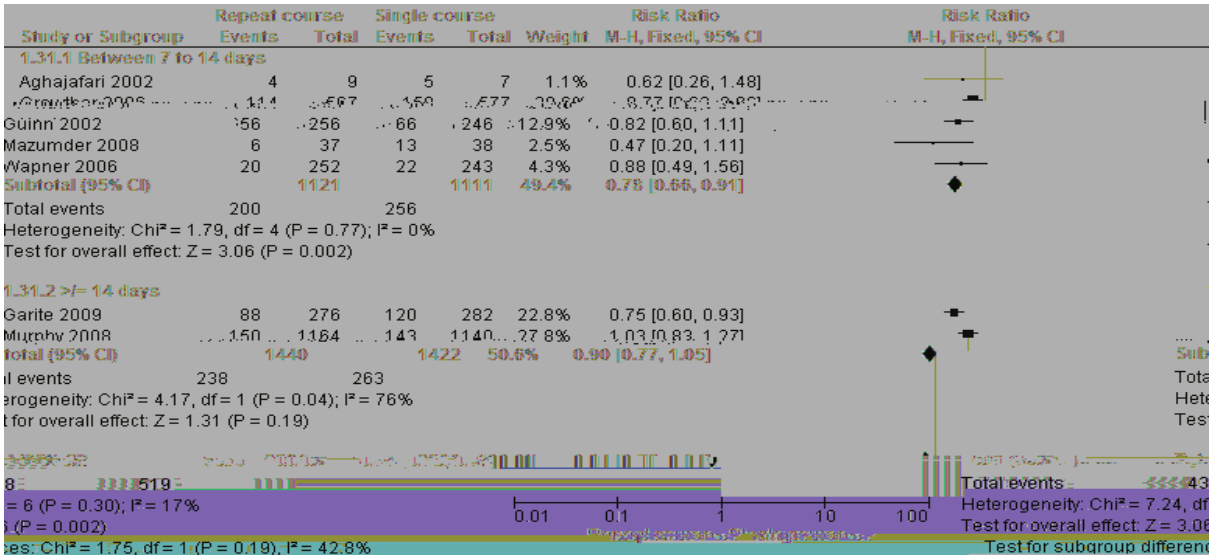

Figure 33: Interval between single and repeat antenatal corticosteroid courses – Birthweight

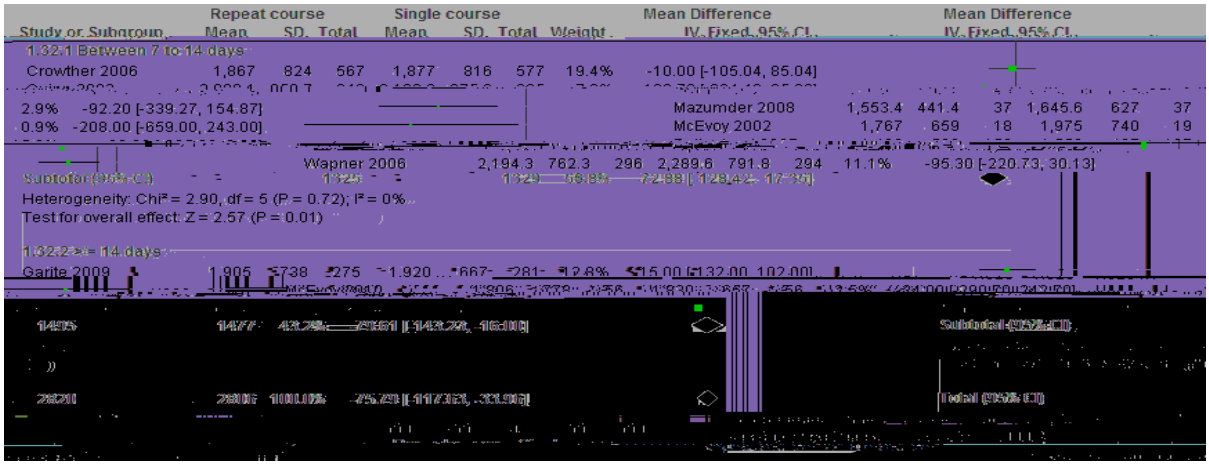

Figure 34: Interval between single and repeat antenatal corticosteroid courses – Birthweight z score