National Institute for Health and Care Excellence

Draft for Consultation

Specialist neonatal respiratory care for babies born preterm

[C] Evidence reviews for managing respiratory disorders

NICE guideline <TBC at publication>

Evidence reviews

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Draft for Consultation

These evidence reviews were developed by the National Guideline Alliance, hosted by the Royal College of Obstetricians and Gynaecologists

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Managing respiratory disorders

This evidence report contains information on 4 reviews relating to managing respiratory disorders.

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Review question 3.4 What is the effectiveness of corticosteroids in preterm babies requiring respiratory support?

Introduction

Lung inflammation is an important risk factor for the development of bronchopulmonary dysplasia (BPD), and preterm babies have immaturity of the hypothalamic-pituitary-adrenal axis, leading to relatively low cortisol levels after the initial surge which follows the stress of birth. This adrenal insufficiency is associated with an amplified immune response which may predispose to inflammation.

Treatment with postnatal corticosteroids with their strong anti-inflammatory properties may therefore decrease or ameliorate BPD. However, it is not known which corticosteroid, if any, is optimal, when it should be given, and at what dose. Corticosteroids can also have significant short and long term adverse effects including an impact on neurodevelopmental outcomes. These risks might outweigh the beneficial effects of corticosteroids in reducing the severity and incidence of BPD.

The aim of this review is to determine the optimal corticosteroid choice, dosing schedule, timing and mode of administration in ameliorating BPD and long-term sequelae.

Summary of the protocol

See Table 1 for a summary of the population, intervention, comparison and outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	Preterm babies requiring respiratory support: **Exclusions:** • Preterm babies with any congenital abnormalities except patent ductus arteriosus • Preterm babies who are ventilated solely due to a specific non-respiratory comorbidity, such as sepsis, necrotising enterocolitis, neurological disorders
Intervention	Corticosteroids: • Intravenous dexamethasone • Intravenous hydrocortisone • Nebulised budesonide
Comparison	• Corticosteroids versus placebo • Corticosteroid A versus corticosteroid B • Lower dose corticosteroid A versus higher dose corticosteroid A • Earlier administration of corticosteroid A versus later administration of corticosteroid A
Outcome	**Critical outcomes:** • Mortality prior to discharge • Bronchopulmonary dysplasia (oxygen dependency at 36 weeks gestation or 28 days of age)

	• Neurodevelopmental outcomes at ≥18 months:
	  ○ Cerebral palsy (CP) (reported as presence or absence of condition, **not** severity of condition)
	  ○ Neurodevelopmental delay (reported as dichotomous outcomes, **not** continuous outcomes such as mean change in score)
	  - Severe (score of >2 SD below normal on validated assessment scales, **or** on Bayleys assessment scale of mental developmental index (MDI) or psychomotor developmental index (PDI) <70 or complete inability to assign score due to CP or severe cognitive delay)
	  - Moderate (score of 1-2 SD below normal on validated assessment scales, **or** on Bayleys assessment scale of MDI or PDI 70-84)
	  ○ Neurosensory impairment (reported as presence or absence of condition, **not** severity of condition)
	  - Severe hearing impairment (for example, deaf)
	  - Severe visual impairment (for example, blind)
	
	Important outcomes:
	• Days on invasive ventilation
	• Gastro-intestinal perforation
	• Hypertension

CP: cerebral palsy; MDI: mental development index; PDI: psychomotor developmental index; RCT: randomised controlled trial; SD: standard deviation

For full details see review protocol in appendix A.

Clinical evidence

The results are presented as an overall population for preterm babies on respiratory support. Additionally by request of the committee analysis was stratified by subgroups according to the timing of corticosteroid administration, whereever there were sufficient numbers of trials to make such subgroup analyses meaningful:

- Early [7 days or younger]
- Moderate [8-20 days of age]
- Late [21 days or older])

In circumstances where it was not feasible or meaningful to group studies into the pre-specified specific sub-groups, the sub-group analyses were adapted to the characteristics of the studies identified using the pre-specified sub-groups as a guide.

Due to the limited evidence on neurodevelopmental outcomes at 18 months or older in preterm babies on respiratory support, studies reporting neurodevelopmental outcomes without specifying the time of assessment were included in the analyses. However, the indirectness of the population was downgraded when assessing the quality and the confidence in the evidence using GRADE, as the committee were concerned that there was uncertainty around the diagnosis of neurodevelopmental outcomes before 18 months of age.

Included studies

Three Cochrane Systematic Reviews (Doyle 2014a; Doyle 2014b; and Onland 2017) were included in this review. Study details, outcomes and risk of bias for the included studies relevant to this review were extracted directly from the Cochrane Systematic Reviews. 31 RCTs were identified (Anttila 2005; Baud 2016; Bloomfield 1998; Bosante 2007; Brozanski 1995; Doyle 2006; Durand 1995; Durand 2002; Garland 1999; Halliday 2001; Jonsson 2000;

Lauterbach 2006; Kari 1993; Kothadia 1999; Kovacs 1998; McEvoy 2004; Odd 2004; Papile 1998; Parikh 2013; Peltoniemi 2005; Rastogi 1996; Romagnoli 1998; Romagnoli 1999; Shinwell 1996; Stark 2001; Soll 1999; Subhedar 1997; Tapia 1998; Walther 2003; Watterberg 1999; Walther 2004). An additional 13 follow-up publications of these RCTs were identified, maintaining the initial randomisations while giving the subsequent long term neurodevelopmental outcomes (Armstrong 2002 [Bloomfield 1998]; Baud 2017 [Baud 2016]; Doyle 2007 [Doyle 2006]; Parikh 2015 [Parikh 2013]; Peltoniemi 2009 [Peltoniemi 2005]; Peltoniemi 2016 [Peltoniemi 2005]; Romagnoli 2002 [Romagnoli 1998]; Shinwell 2000 [Shinwell 1996]; Stark 2014 [Stark 2001]; Vermont Oxford Network Steroid Group 2001 [Soll 1999]; O'Shea 2007 [Kothadia 1999]; Watterberg 2007 [Watterberg 2004]; Wilson 2006 [Halliday 2001].

24 of the included studies compared systemic dexamethasone to placebo (Anttila 2005; Brozanski 1995; Doyle 2006 [Doyle 2007]; Durand 1995; Garland 1999; Kari 1993; Kothadia 1999 [O'Shea 2007]; Kovacs 1998; Lauterbach 2006; Rastogi 1996; Romagnoli 1998 [Romagnoli 2002]; Romagnoli 1999; Shinwell 1996 [Shinwell 2000]; Soll 1999 [Vermont Oxford Network Steroid Group 2001]; Subhedar 1997; Stark 2001 [Stark 2014]; Tapia 1998; Walther 2003).

11 of the included studies compared systemic hydrocortisone to placebo (Baud 2016 [Baud 2017]; Bosante 2007; Parikh 2013 [Parikh 2015]; Peltoniemi 2005 [Peltoniemi 2009 and 2016]; Watterberg 1999; Watterberg 2004 [Watterberg 2007]).

One RCT compared nebulised budesonide to placebo (Jonsson 2000).

Eight of the included studies compared different regimens of systemic dexamethasone (Bloomfield 1998 [Armstrong 2002]; Durand 2002; Halliday 2001 [Wilson 2006]; McEvoy 2004; Odd 2004; Papile 1998). Two RCTs compared lower dose dexamethasone regimens with higher dexamethasone regimens (Durand 2002; McEvoy 2004). Five publications compared earlier dexamethasone initiation against later dexamethasone initiation (Bloomfield 1998 [Armstrong 2002]; Halliday 2001 [Wilson 2006]; Papile 1998). One RCT compared a tailored dexamethasone regimen with a continuous tapered dexamethasone course (Odd 2004).

See the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

Studies not included in this review with reasons for their exclusions are provided in appendix K.

Summary of clinical studies included in the evidence review

Table 2 provides a brief summary of the included studies.

Table 2: Summary of included studies

Study and setting	Population	Intervention/ comparison	Outcomes	Comments
Cochrane Systematic Reviews				
Doyle 2014a	n=1424 Preterm infants with evolving or established CLD, defined as oxygen-dependent,	Late (>7 days) postnatal systemic corticosteroids versus control	Follow-up time: Primarily 28 days to 36 weeks PMA, but up to 2 years for long-term outcomes • Mortality prior to discharge • CLD • Death or CLD – *combined outcome*	

Study and setting	Population	Intervention/ comparison	Outcomes	Comments
	ventilator-dependent, or both, with or without radiographic changes of bronchopulmonary dysplasia.		• Long term outcomes (including blindness, deafness, cerebral palsy and major neurosensory disability) • Failure to extubate • Late rescue with corticosteroids • Need for home oxygen therapy • Complications during primary hospitalisation	
Doyle 2014b	n=3750 Preterm infants with evolving or established CLD, defined as oxygen-dependent, ventilator-dependent, or both, with or without radiographic changes of bronchopulmonary dysplasia.	Early (<8 days) postnatal systemic corticosteroids versus control	Follow-up time: Primarily 28 days to 36 weeks PMA, but up to 2 years for long-term outcomes • Mortality prior to discharge • CLD • Death or CLD - *combined outcome* • Long term outcomes (including blindness, deafness, cerebral palsy and major neurosensory disability) • Failure to extubate • Late rescue with corticosteroids • Need for home oxygen therapy • Complications during primary hospitalisation	
Onland 2017	n=232 Preterm infants at risk for BPD	Two or more different regimens of postnatal systemic corticosteroids	Follow-up time: Primarily 36 weeks PMA, but up to 4 years for long-term outcomes • Death or BPD – *combined outcome* • Mortality prior to discharge • BPD • Failure to extubate • Days of invasive ventilation • Days of supplemental oxygen • Complications during primary hospitalisation • Long term outcomes (including blindness, deafness, cerebral	

Study and setting	Population	Intervention/ comparison	Outcomes	Comments
			palsy and major neurosensory disability at 1-4 years of age)	
RCTs that met the NICE review criteria included in the Cochrane Systematic Reviews				
Doyle 2014a Cochrane Systematic Review				
Brozanski 1995 USA	n=88 Preterm infants < 1501g who were ventilator-dependent at 7 days	Dexamethasone (0.25mg/kg/day 12-hourly for 2 days, repeated every 10 days until 36 weeks' PMA or no longer needs ventilator support or supplemental oxygen) versus placebo **Total cumulative dose:** Dependent on gestational age **Timing of administration**: 7 days of age	• Mortality prior to discharge • BPD at 36 weeks corrected gestational age • BPD at 28 days of age • Hypertension	
Doyle 2006 Australia	n=70 Preterm infants < 28 weeks' gestation or < 1000g birth weight, ventilator-dependent after 7 days	10 day tapering course of dexamethasone versus placebo **Total cumulative dose:** 0.89mg/kg **Timing of administration:** 7 days of age	• Mortality prior to discharge • BPD at 36 weeks corrected gestational age • Gastro-intestinal perforation • Hypertension • Neurodevelopmental outcomes at 18 months of age or older*	Follow-up publications from the same RCT with relevant outcomes for this review: Doyle 2007*
Durand 1995 USA	n=43 Preterm babies, 7 to 14 days old with birth weight 501g to 1500g, gestational age 24 to 32 weeks, needing invasive ventilation with < 30% oxygen	Tapering course of dexamethasone versus placebo **Total cumulative dose:** 2.35mg/kg **Timing of administration:** 7-14 days of age	• Mortality prior to discharge • BPD at 36 weeks corrected gestational age • BPD at 28 days of age • Total days of invasive ventilation • Hypertension • Neurodevelopmental outcomes	

Study and setting	Population	Intervention/ comparison	Outcomes	Comments
Kari 1993 Finland	n=41 Preterm infants 10 days old, weighing < 1500g and with gestational age > 23 weeks, and ventilator-dependent.	Dexamethasone course versus placebo **Total cumulative dose:** 3.5mg/kg **Timing of administration:** 10 days of age	• Mortality prior to discharge • BPD at 28 days of age • Total days of invasive ventilation • Hypertension	
Kothadia 1999 USA	n=118 Preterm infants, < 1501g age 15 to 25 days, ventilator-dependent over 30% oxygen	Tapering course of dexamethasone versus placebo **Total cumulative dose:** 6.7mg/kg **Timing of administration:** 15-25 days of age	• Mortality prior to discharge • BPD at 36 weeks corrected gestational age • Total days of invasive ventilation • Hypertension • Neurodevelopmental outcomes at 18 months of age or older*	Follow-up publications from the same RCT with relevant outcomes for this review: O'Shea 2007*
Kovacs 1998 Canada	n=60 Ventilator-dependent preterm infants of < 30 weeks' gestation and < 1501g birth weight	Dexamethasone course for 3 days followed by nebulised budesonide course for 18 days versus placebo **Total cumulative dose:** 1.5mg/kg dexamethasone + 1.8mg of budesonide **Timing of administration:** 7 days of age	• Mortality prior to discharge • BPD at 36 weeks corrected gestational age • BPD at 28 days of age • Neurodevelopmental outcomes	
Parikh 2013 USA	n=64 Preterm infants with birth weight < 1001g, ventilator-dependent between 10 to 21 days of age with a respiratory index ≥ 2 with	Hydrocortisone course versus placebo **Total cumulative dose**: 17mg/kg **Timing of administration:** 10-21 days of age	• Mortality prior to discharge • BPD at 36 weeks corrected gestational age • Total days of invasive ventilation • Gastro-intestinal perforation • Hypertension	

Study and setting	Population	Intervention/ comparison	Outcomes	Comments
	estimated 75% risk of developing CLD			
Romagnoli 1998 Italy	n=30 Preterm infants, oxygen- and ventilator-dependent on 10th day and at high risk of CLD by authors' own scoring system (90% risk)	Tapering course of dexamethasone versus placebo **Total cumulative dose:** 4.75mg/kg **Timing of administration:** 10 days of age	• Mortality prior to discharge • BPD at 36 weeks corrected gestational age • BPD at 28 days of age • Neurodevelopmental outcomes at 18 months of age or older*	Follow-up publications from the same RCT with relevant outcomes for this review: Romagnoli 2002*
Walther 2003 USA	n=36 Preterm infants of gestation 24 to 32 weeks and birth weight > 599g with respiratory distress syndrome requiring invasive ventilation with > 29% oxygen or respiratory index (MAP x inspired oxygen) > 1.9 and ventilator rate > 16/min on day 7 to 14 after birth	Tapering course of dexamethasone versus placebo **Total cumulative dose:** 1.9mg/kg **Timing of administration:** 7-14 days of age	• Mortality prior to discharge • BPD at 36 weeks corrected gestational age • Neurodevelopmental outcomes	
Anttila 2005 European	n=109 Preterm infants with birthweight 500g to 999g, gestation <32 weeks, need for invasive ventilation and supplemental oxygen by 4 hours of age.	Dexamethasone course versus placebo **Total cumulative dose:** 1mg/kg **Timing of administration:** Before 6 hours of age	• Mortality prior to discharge • BPD at 36 weeks corrected gestational age • Gastro-intestinal perforation	

Study and setting	Population	Intervention/ comparison	Outcomes	Comments
Bosante 2007 Italy	n=50 Preterm infants either <1000g birth weight or <28 weeks gestation, ventilator dependent after 7 days of age and considered to be a candidate for corticosteroids	Tapering course of hydrocortisone versus placebo **Total cumulative dose:** 10.5mg/kg **Timing of administration:** Before 48 hours of age	• Mortality prior to discharge • BPD at 36 weeks corrected gestational age • Total days of invasive ventilation • Gastro-intestinal perforation • Hypertension	
Garland 1999 USA	n=241 Preterm infants weighing between 500g and 1500g, received surfactant, at significant risk for CLD or death using a model to predict at 24 hours	Tapering course of dexamethasone versus placebo **Total cumulative dose:** 1.35mg/kg **Timing of administration:** 24 hours of age	• Mortality prior to discharge • BPD at 36 weeks corrected gestational age • BPD at 28 days of age • Total days of invasive ventilation • Gastro-intestinal perforation • Hypertension • Neurodevelopmental outcomes	
Lauterbach 2006 Poland	n=150 Preterm infants weighing < 1500g who needed oxygen on fourth day of life, regardless of the need for assisted ventilation	Dexamethasone course versus placebo **Total cumulative dose**: 1.5mg/kg **Timing of administration:** 4th day of life	• BPD at 36 weeks corrected gestational age	
Peltoniemi 2005 Finland	n=51 Preterm infants with a birth weight 501g to 1250g, gestation 23 to 29 weeks, needing invasive	Tapering course of hydrocortisone versus placebo **Total cumulative dose:** 11.5mg/kg **Timing of administration:** Before 36 hours of age	• Mortality prior to discharge • BPD at 36 weeks corrected gestational age • Gastro-intestinal perforation • Neurodevelopmental outcomes at 18 months of age or	Follow-up publications from the same RCT with relevant outcomes for this review: Peltoniemi 2009*

Study and setting	Population	Intervention/ comparison	Outcomes	Comments
	ventilation before age of 24 hours		older* (up to 2 years for long-term outcomes)	
Rastogi 1996 USA	n=70 Preterm infants <12 hours old, weighing 700g to 1500g with RDS, confirmed clinically and radiologically, infants needed invasive ventilation >30% O_2 and/or MAP 7cm H_2O a/A <0.25 after surfactant treatment	Tapering course of dexamethasone versus placebo **Total cumulative dose:** 3.03mg/kg **Timing of administration:** <12 hours of age	• Mortality prior to discharge • BPD at 36 weeks corrected gestational age • BPD at 28 days of age • Gastro-intestinal perforation • Hypertension	
Romagnoli 1999 Italy	n=50 Preterm infants <1251g or <33 weeks, oxygen-dependent at 72 hours and at high risk of CLD according to a scoring system predicting 90% risk of CLD	Tapering course of dexamethasone versus placebo **Total cumulative dose:** 2.375mg/kg **Timing of administration:** 72 hours of age	• Mortality prior to discharge • BPD at 36 weeks corrected gestational age • BPD at 28 days of age • Total days of invasive ventilation • Hypertension • Neurodevelopmental outcomes	
Shinwell 1996 Israel	n=248 Preterm infants with birth weight 500g to 2000g, 1-3 days old, requiring invasive ventilation with more than 40% oxygen	Dexamethasone course versus placebo **Total cumulative dose:** 3mg/kg **Timing of administration:** <12 hours of age	• Mortality prior to discharge • BPD at 36 weeks corrected gestational age • BPD at 28 days of age • Total days of invasive ventilation • Hypertension • Neurodevelopmental outcomes at 18 months of age or older*	Follow-up publications from the same RCT with relevant outcomes for this review: Shinwell 2000*
Soll 1999 USA	n=542	Tapering course of dexamethasone versus placebo	• Mortality prior to discharge	Follow-up publications from the same RCT with

Study and setting	Population	Intervention/ comparison	Outcomes	Comments
	Preterm infants weighing 501g to 100g who required assisted ventilation <12 hours, had received surfactant by 12 hours, were physiologically stable and had no life-threatening congenital abnormalities	**Total cumulative dose:** 2.7mg/kg **Timing of administration:** 12 hours of age	• BPD at 36 weeks corrected gestational age • BPD at 28 days of age • Total days of invasive ventilation • Hypertension • Gastro-intestinal perforation	relevant outcomes for this review: Vermont Oxford Network Steroid Group 2001
Stark 2001 USA	n=220 Preterm infants with birth weight 501g to 1000g, invasively ventilated <12 hours. Infants >750g also needed to receive surfactant and have FiO_2 >0.29	Tapering course of dexamethasone versus placebo **Total cumulative dose:** 0.89/kg **Timing of administration:** <24 hours of age	• Mortality prior to discharge • BPD at 36 weeks corrected gestational age • BPD at 28 days of age • Total days of invasive ventilation • Hypertension • Neurodevelopmental outcomes at 18 months of age or older*	Follow-up publications from the same RCT with relevant outcomes for this review: Stark 2014*
Subhedar 1997 UK	n=42 Preterm infants, entry at 96 hours if gestation <32 weeks, invasive ventilation from birth, surfactant treatment and high risk of developing CLD by a score.	Tapering course of dexamethasone versus placebo **Total cumulative dose**: 4.5mg/kg **Timing of administration:** 96 hours of age	• Mortality prior to discharge • BPD at 36 weeks corrected gestational age • Total days of invasive ventilation • Hypertension • Gastro-intestinal perforation • Neurodevelopmental outcomes	
Tapia 1998 Chile	n=113 Preterm infants with birth weight between 700g	Tapering course of dexamethasone versus placebo	• Mortality prior to discharge • BPD at 36 weeks corrected gestational age	

Study and setting	Population	Intervention/ comparison	Outcomes	Comments
	and 1600g, clinical and radiological diagnosis of RDS, needing invasive ventilation at <36 hours of age	**Total cumulative dose:** 2.79mg/kg **Timing of administration:** 36 hours of age	• Total days of invasive ventilation • Hypertension	
Watterberg 1999 USA	n=40 Preterm infants weighing between 500g and 999g who needed invasive ventilation <48 hours of age	Tapering course of hydrocortisone versus placebo **Total cumulative dose:** 10.5mg/kg **Timing of administration:** <48 hours of age	• Mortality prior to discharge • BPD at 36 weeks corrected gestational age • Total days of invasive ventilation • Gastro-intestinal perforation • Neurodevelopmental outcomes	
Watterberg 2004 USA	n=360 Preterm infants 500g to 999g birth weight, needing invasive ventilation and aged 12 to 48 hours	Tapering course of hydrocortisone versus placebo **Total cumulative dose:** 13.5mg/kg **Timing of administration:** 12-48 hours of age	• Mortality prior to discharge • BPD at 36 weeks corrected gestational age • Total days of invasive ventilation • Gastro-intestinal perforation • Neurodevelopmental outcomes at 18 months of age or older*	Follow-up publications from the same RCT with relevant outcomes for this review: Watterberg 2007*
Onland 2017 Cochrane Systematic Review				
Bloomfield 1998 New Zealand	n=40 Preterm infants with a birth weight ≤ 1250g, and ventilated at ≥ 15 cycles/min at 7 days of age.	Pulse course of dexamethasone versus long course of dexamethasone **Total cumulative dose:** Pulse (5.3 mg/kg) versus Long (7.1mg/kg) **Timing of administration:** Pulse (7 days of age) versus long (14 days of age)	• Mortality prior to discharge • BPD at 36 weeks corrected gestational age • BPD at 28 days of age • Hypertension • Neurodevelopmental outcomes at 18 months of age or older	Follow-up publications from the same RCT with relevant outcomes for this review: Armstrong 2002
Durand 2002 USA	n=47 Preterm infants were included when	Moderate dose dexamethasone versus low dose dexamethasone	• Mortality prior to discharge • BPD at 36 weeks corrected gestational age	

Study and setting	Population	Intervention/ comparison	Outcomes	Comments
	having a birth weight between 501 and 1500g, a gestational age between 24 weeks and 32 weeks, postnatal age between 7 and 14 days and at entry on ventilation support	**Total cumulative dose:** moderate dose (2.35mg/kg) versus low dose (1 mg/kg) **Timing of administration:** 7-14 days of age	• Hypertension • Gastro-intestinal perforation • Neurodevelopmental outcomes	
Halliday 2001 Multinational	n=285 Intubated infants < 30 weeks' gestational age, a postnatal age < 72 hours and with an inspired oxygen concentration > 30%. Infants with a gestational age between 30 and 31 weeks could be included if needing inspired oxygen > 50%	Early course of dexamethasone versus moderately early course of dexamethasone **Total cumulative dose:** 2.7mg/kg **Timing of administration:** Early (< 72 hours of age) versus moderate early (> 15 days of age)	• Mortality prior to discharge • BPD at 36 weeks corrected gestational age • BPD at 28 days of age • Gastro-intestinal perforation • Hypertension • Neurodevelopmental outcomes at 18 months of age or older* (up to 7 years of age for long-term outcomes)	Follow-up publications from the same RCT with relevant outcomes for this review: Wilson 2006*
McEvoy 2004 USA	n=62 Preterm infants were included when between 7 and 21 days of postnatal age, with a birth weight of > 501g and < 1500g, a gestational age of > 24 weeks and < 32 weeks. The infants were dependent on ventilation	Moderate dose course of dexamethasone versus low dose course of dexamethasone **Total cumulative dose:** moderate dose (2.35mg/kg) versus low dose (1mg/kg) **Timing of administration:** 7-21 days of age	• Mortality prior to discharge • BPD at 36 weeks corrected gestational age • Total days on invasive ventilation • Gastro-intestinal perforation • Hypertension	

Study and setting	Population	Intervention/ comparison	Outcomes	Comments
	support with 15 cycles per minute or more and oxygen levels of 30% or more at entry			
Odd 2004 New Zealand	n=33 Preterm infants ≤ 1250g, ventilated between postnatal age of 7 days and 28 days for which dexamethasone was indicated	Individual tailored course of dexamethasone versus continuous course of dexamethasone **Total cumulative dose**: individual course (median 3.8mg/kg [2-5.7]) versus continuous course (median 6.5mg/kg [3.8-7.3]) **Timing of administration:** 7 days of age	• Mortality prior to discharge • BPD at 36 weeks corrected gestational age • BPD at 28 days of age • Gastro-intestinal perforation • Hypertension • Total days on invasive ventilation	
Papile 1998 USA	n=371 Ventilator-dependent preterm infants with birth weight 501 to 1500g, at a postnatal age between 13 and 15 days, with a respiratory index of ≥ 2.4	Moderately early course of dexamethasone versus late course of dexamethasone **Total cumulative dose:** 4mg/kg **Timing of administration:** moderately early (14 days of age) versus late (28 days of age)	• Mortality prior to discharge • BPD at 36 weeks corrected gestational age • BPD at 28 days of age • Hypertension	
RCTs and follow-up publications not included in identified systematic reviews				
Baud 2016 France	n=523 Inborn (born in a maternity ward that is at the same site as the NICU) and delivered between 24+0 and 27+6 weeks gestation (randomised	Tapering course of hydrocortisone versus placebo **Total cumulative dose:** 8.5mg/kg **Timing of administration:** Within first 24 hours of age	• Mortality prior to discharge • BPD at 36 weeks corrected gestational age • Gastro-intestinal perforation • Neurodevelopmental outcomes at 18 months of age or older*	Follow-up publications from the same RCT with relevant outcomes for this review: Baud 2017*

Study and setting	Population	Intervention/ comparison	Outcomes	Comments
	within 24 hrs of birth)			
Jonsson 2000 Sweden	n=30 Preterm infants on invasive ventilation on day 6 of life, or if extubated, nCPAP with FiO_2 >0.3	Budesonide (Pulmicort) 500mcg twice daily for 14 days via jet nebulisation versus placebo	• BPD at 36 weeks corrected gestational age • BPD at 28 days of age • Total days on invasive ventilation	
Parikh 2015 USA	See Parikh 2013	See Parikh 2013	• Neurodevelopmental outcomes at 18 months of age or older*	Follow-up publication to Parikh 2013*
Peltoniemi 2016 Finland	See Peltoniemi 2005	See Peltoniemi 2005	• Neurodevelopmental outcomes at 18 months of age or older* • Data up to 5-7 years of age	Follow-up publication to Peltoniemi 2005*

BPD: bronchopulmonary dysplasia; CLD: chronic lung disease; FiO_2: fraction of inspired oxygen; H_2O: water; MAP: mean arterial pressure; nCPAP: nasal continuous positive airway pressure; NICU: neonatal intensive care unit; O_2: oxygen; PMA: post-menstrual age; RDS: respiratory distress syndrome; RCT: randomised controlled trial

See appendix D for clinical evidence tables.

Quality assessment of clinical studies included in the evidence review

See appendix F for full GRADE tables.

Economic evidence

No economic evidence on the cost effectiveness of corticosteroids in preterm babies requiring respiratory support was identified by the literature searches of the economic literature undertaken for this review.

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation.

Clinical evidence statements

Comparison 1. Corticosteroid versus placebo

Comparison 1.1. Dexamethasone versus placebo

Critical outcomes

Mortality prior to discharge

All administration schedules of dexamethasone

- High quality evidence from 17 RCTs (n=2098) showed no clinically significant difference in mortality prior to discharge among preterm babies on respiratory support who received dexamethasone compared to those who received placebo.

Early administration of dexamethasone – 7 days of age or younger

- High quality evidence from 9 RCTs (n=1631) showed no clinically significant difference in mortality prior to discharge among preterm babies on respiratory support who received dexamethasone compared to those who received placebo at 7 days of age or younger.

Later administration of dexamethasone – 8 days of age or older

- Moderate quality evidence from 8 RCTs (n=467) showed no clinically significant difference in mortality prior to discharge among preterm babies on respiratory support who received dexamethasone compared to those who received placebo at 8 days of age or older.

Bronchopulmonary dysplasia at 36 weeks corrected gestational age

All administration schedules of dexamethasone

- Moderate quality evidence from 17 RCTs (n=2166) showed a clinically significant reduction in bronchopulmonary dysplasia at 36 weeks corrected gestational age among preterm babies on respiratory support who received dexamethasone compared to those who received placebo.

Early administration of dexamethasone – 7 days of age or younger

- Moderate quality evidence from 10 RCTs (n=1731) showed a clinically significant reduction in bronchopulmonary dysplasia at 36 weeks corrected gestational age among preterm babies on respiratory support who received dexamethasone compared to those who received placebo at 7 days of age or younger.

Later administration of dexamethasone – 8 days of age or older

- Moderate quality evidence from 7 RCTs (n=435) showed a clinically significant reduction in bronchopulmonary dysplasia at 36 weeks corrected gestational age among preterm babies on respiratory support who received dexamethasone compared to those who received placebo at 8 days of age or older.

Bronchopulmonary dysplasia at 28 days of age

All administration schedules of dexamethasone

- High quality evidence from 11 RCTs (n=1662) showed no clinically significant difference in bronchopulmonary dysplasia at 28 days of age among preterm babies on respiratory support who received dexamethasone compared to those who received placebo.

Early administration of dexamethasone – 7 days of age or younger

- High quality evidence from 6 RCTs (n=1410) showed no clinically significant difference in bronchopulmonary dysplasia at 28 days of age among preterm babies on respiratory support who received dexamethasone compared to those who received placebo at 7 days of age or younger.

Later administration of dexamethasone – 8 days of age or older

- Moderate quality evidence from 5 RCTs (n=252) showed a clinically significant reduction in bronchopulmonary dysplasia at 28 days of age among preterm babies on respiratory support who received dexamethasone compared to those who received placebo at 8 days of age or older.

Neurodevelopmental outcomes at ≥18 months: cerebral palsy

All administration schedules of dexamethasone

- Very low quality evidence from 10 RCTs (n=647) showed no clinically significant increase in cerebral palsy at 18 months of age or older among preterm babies on respiratory support who received dexamethasone compared to those who received placebo.

Early administration of dexamethasone – 7 days of age or younger

- Very low quality evidence from 4 RCTs (n=395) showed no clinically significant increase in cerebral palsy at 18 months of age or older among preterm babies on respiratory support who received dexamethasone compared to those who received placebo at 7 days of age or younger.

Later administration of dexamethasone – 8 days of age or older

- Very low quality evidence from 4 RCTs (n=252) showed no clinically significant difference in cerebral palsy at 18 months of age or older among preterm babies on respiratory support who received dexamethasone compared to those who received placebo at 8 days of age or older.

Neurodevelopmental outcomes at ≥18 months: severe cognitive impairment (Bayley MDI <70 or <-2SD on other validated scales)

All administration schedules of dexamethasone

- Low quality evidence from 3 RCTs (n=198) showed no clinically significant difference in severe cognitive impairment at 18 months of age or older among preterm babies on respiratory support who received dexamethasone compared to those who received placebo.

Early administration of dexamethasone – 7 days of age or younger

- Moderate quality evidence from 1 RCT (n=144) showed no clinically significant difference in severe cognitive impairment at 18 months of age or older among preterm babies on respiratory support who received dexamethasone compared to those who received placebo at 7 days of age or younger.

Later administration of dexamethasone – 8 days of age or older

- Very low quality evidence from 2 RCTs (n=54) showed no clinically significant difference in severe cognitive impairment at 18 months of age or older among preterm babies on respiratory support who received dexamethasone compared to those who received placebo at 8 days of age or older.

Neurodevelopmental outcomes at ≥18 months: severe intellectual impairment (IQ<70 on validated scales)

All administration schedules of dexamethasone

- Low quality evidence from 3 RCTs (n=162) showed no clinically significant difference in severe intellectual impairment at 18 months of age or older among preterm babies on respiratory support who received dexamethasone compared to those who received placebo.

Early administration of dexamethasone – 7 days of age or younger

- Very low quality evidence from 1 RCT (n=30) showed no clinically significant difference in severe intellectual impairment at 18 months of age or older among preterm babies on respiratory support who received dexamethasone compared to those who received placebo at 7 days of age or younger.

Later administration of dexamethasone – 8 days of age or older

- Low quality evidence from 2 RCTs (n=132) showed no clinically significant difference in severe intellectual impairment at 18 months of age or older among preterm babies on

respiratory support who received dexamethasone compared to those who received placebo at 8 days of age or older.

Neurodevelopmental outcomes at ≥18 months: severe psychomotor impairment (Bayley PDI <70 or <-2SD on other validated scales)

Early administration of dexamethasone – 7 days of age or younger

- Low quality evidence from 1 RCT (n=136) showed no clinically significant difference in severe psychomotor impairment at 18 months of age or older among preterm babies on respiratory support who received dexamethasone compared to those who received placebo at 7 days of age or younger.

Neurodevelopmental outcomes at ≥18 months: moderate or severe cognitive impairment (Bayley MDI <85 or <-1SD on other validated scales)

Early administration of dexamethasone – 8 days of age or older

- Low quality evidence from 1 RCT (n=51) showed no clinically significant difference in moderate or severe cognitive impairment at 18 months of age or older among preterm babies on respiratory support who received dexamethasone compared to those who received placebo at 8 days of age or older.

Neurodevelopmental outcomes at ≥18 months: severe deafness

All administration schedules of dexamethasone

- Very low quality evidence from 8 RCTs (n=523) showed no clinically significant difference in severe deafness at 18 months of age or older among preterm babies on respiratory support who received dexamethasone compared to those who received placebo.

Early administration of dexamethasone – 7 days of age or younger

- Very low quality evidence from 4 RCTs (n=377) showed no clinically significant difference in severe deafness at 18 months of age or older among preterm babies on respiratory support who received dexamethasone compared to those who received placebo at 7 days of age or younger.

Later administration of dexamethasone – 8 days of age or older

- Very low quality evidence from 4 RCTs (n=146) showed no clinically significant difference in severe deafness at 18 months of age or older among preterm babies on respiratory support who received dexamethasone compared to those who received placebo at 8 days of age or older.

Neurodevelopmental outcomes at ≥18 months: severe blindness

All administration schedules of dexamethasone

- Very low quality evidence from 9 RCTs (n=539) showed no clinically significant difference in severe blindness at 18 months of age or older among preterm babies on respiratory support who received dexamethasone compared to those who received placebo.

Early administration of dexamethasone – 7 days of age or younger

- Very low quality evidence from 4 RCTs (n=268) showed no clinically significant difference in severe blindness at 18 months of age or older among preterm babies on respiratory support who received dexamethasone compared to those who received placebo at 7 days of age or younger.

Later administration of dexamethasone – 8 days of age or older

- Very low quality evidence from 3 RCTs (n=171) showed no clinically significant difference in severe blindness at 18 months of age or older among preterm babies on respiratory

support who received dexamethasone compared to those who received placebo at 8 days of age or older.

Important outcomes

Days on invasive ventilation

- Evidence from 10 RCTs was available on total days of invasive ventilation, however due to different ways it was reported between studies as means and medians it was not possible to pool these results and thus the results are presented individually.

Early administration of dexamethasone – 7 days of age or younger

- Moderate quality evidence from 1 RCT (n=241) showed no clinically significant difference in total days on invasive ventilation (defined as ventilation) among preterm babies on respiratory support who received dexamethasone compared to those who received placebo at 7 days of age or younger, however there is uncertainty around this estimate
- Moderate quality evidence from 1 RCT (n=50) showed a clinically significant reduction in total days on invasive ventilation (defined as invasive ventilation) among preterm babies on respiratory support who received dexamethasone compared to those who received placebo at 7 days of age or younger
- High quality evidence from 1 RCT (n=248) showed a clinically significant reduction in total days on invasive ventilation among preterm babies on respiratory support who received dexamethasone compared to those who received placebo at 7 days of age or younger
- Moderate quality evidence from 1 RCT (n=42) showed a reduction in the median number of days on invasive ventilation among preterm babies on respiratory support who received dexamethasone compared to those who received placebo at 7 days of age or younger, however there is uncertainty around this estimate
- Moderate quality evidence from 1 RCT (n=109) showed no clinically significant difference in total days on invasive ventilation (defined as ventilation) among preterm babies on respiratory support who received dexamethasone compared to those who received placebo at 7 days of age or younger.
- High quality evidence from 1 RCT (n=542) showed a clinically significant reduction in total days on invasive ventilation (defined as ventilation) among preterm babies on respiratory support who received dexamethasone compared to those who received placebo at 7 days of age or younger.

Later administration of dexamethasone – 8 days of age or older

- Moderate quality evidence from 1 RCT (n=43) showed a clinically significant reduction in total days on invasive ventilation among preterm babies on respiratory support who received dexamethasone compared to those who received placebo at 8 days of age or older, however there is uncertainty around this estimate
- Moderate quality evidence from 1 RCT (n=41) showed no clinically significant difference in total days on invasive ventilation (defined as intermittent positive-pressure ventilation) among preterm babies on respiratory support who received dexamethasone compared to those who received placebo at 8 days of age or older, however there is uncertainty around this estimate
- Moderate quality evidence from 1 RCT (n=118) showed a clinically significant reduction in total days on invasive ventilation (defined as ventilation) among preterm babies on respiratory support who received dexamethasone compared to those who received placebo at 8 days of age or older, however there is uncertainty around this estimate
- Moderate quality evidence 1 RCT (n=36) showed no clinically significant difference in total days on invasive ventilation (defined as ventilation) among preterm babies on respiratory support who received dexamethasone compared to those who received placebo at 8 days of age or older.

Gastrointestinal perforation

All administration schedules of dexamethasone

- Moderate quality evidence from 7 RCTs (n=1290) showed a clinically significant increase in gastro-intestinal perforation among preterm babies on respiratory support who received dexamethasone compared to those who received placebo.

Early administration of dexamethasone – 7 days of age or younger

- Moderate quality evidence from 6 RCTs (n=1220) showed a clinically significant increase in gastro-intestinal perforation among preterm babies on respiratory support who received dexamethasone compared to those who received placebo at 7 days of age or younger.

Later administration of dexamethasone – 8 days of age or older

- Low quality evidence from 1 RCT (n=70) showed no clinically significant increase in gastro-intestinal perforation among preterm babies on respiratory support who received dexamethasone compared to those who received placebo at 8 days of age or older, however there were no events in either arms of the RCT.

Hypertension

All administration schedules of dexamethasone

- High quality evidence from 13 RCTs (n=1822) showed a clinically significant increase in hypertension among preterm babies on respiratory support who received dexamethasone compared to those who received placebo.

Early administration of dexamethasone – 7 days of age or younger

- High quality evidence from 8 RCTs (n=1509) showed a clinically significant increase in hypertension among preterm babies on respiratory support who received dexamethasone compared to those who received placebo at 7 days of age or younger.

Later administration of dexamethasone – 8 days of age or older

- High quality evidence from 5 RCTs (n=313) showed a clinically significant increase in hypertension among preterm babies on respiratory support who received dexamethasone compared to those who received placebo at 8 days of age or older.

Comparison 1.2: Hydrocortisone versus placebo

Critical outcomes

Mortality prior to discharge

All administration schedules of hydrocortisone

- Moderate quality evidence from 7 RCTs (n=1085) showed no clinically significant difference in mortality prior to discharge among preterm babies on respiratory support who received hydrocortisone compared to those who received placebo.

Early administration of hydrocortisone – 7 days of age or younger

- Moderate quality evidence from 5 RCTs (n=1830) showed that there may be a clinically significant reduction in mortality prior to discharge among preterm babies on respiratory support who received hydrocortisone compared to those who received placebo at 7 days of age or younger, however there is uncertainty around the estimate.

Later administration of hydrocortisone – 8 days of age or older

- Low quality evidence from 1 RCT (n=64) showed no clinically significant difference in mortality prior to discharge among preterm babies on respiratory support who received hydrocortisone compared to those who received placebo at 8 days of age or older.

Bronchopulmonary dysplasia at 36 weeks corrected gestational age

All administration schedules of hydrocortisone

- Moderate quality evidence from 6 RCTs (n=1086) showed no clinically significant difference in bronchopulmonary dysplasia at 36 weeks corrected gestational age among preterm babies on respiratory support who received hydrocortisone compared to those who received placebo

Early administration of hydrocortisone – 7 days of age or younger

- Moderate quality evidence from 5 RCTs (n=1022) showed no clinically significant difference in bronchopulmonary dysplasia at 36 weeks corrected gestational age among preterm babies on respiratory support who received hydrocortisone compared to those who received placebo at 7 days of age or younger.

Later administration of hydrocortisone – 8 days of age or older

- Low quality evidence from 1 RCTs (n=64) showed no clinically significant difference in bronchopulmonary dysplasia at 36 weeks corrected gestational age among preterm babies on respiratory support who received hydrocortisone compared to those who received placebo at 8 days of age or older.

Bronchopulmonary dysplasia at 28 days

- No studies reported on this critical outcome

Neurodevelopmental outcomes at ≥18 months: cerebral palsy

All administration schedules of hydrocortisone

- Low quality evidence from 6 RCTs (n=789) showed no clinically significant difference in cerebral palsy at 18 months of age or older among preterm babies on respiratory support who received hydrocortisone compared to those who received placebo.

Early administration of hydrocortisone – 7 days of age or younger

- Low quality evidence from 5 RCTs (n=752) showed no clinically significant difference in cerebral palsy at 18 months of age or older among preterm babies on respiratory support who received hydrocortisone compared to those who received placebo at 7 days of age or younger.

Later administration of hydrocortisone – 8 days of age or older

- Very low quality evidence from 1 RCT (n=37) showed no clinically significant difference in cerebral palsy at 18 months of age or older among preterm babies on respiratory support who received hydrocortisone compared to those who received placebo at 8 days of age or older.

Neurodevelopmental outcomes at ≥18 months: severe cognitive impairment (Bayley Mental Development Index [MDI] <70 or <-2 standard deviations [SD] on other validated scales)

Early administration of hydrocortisone – 7 days of age or younger

- Moderate quality evidence from 2 RCTs (n=297) showed no clinically significant difference in severe cognitive impairment at 18 months of age or older among preterm babies on respiratory support who received hydrocortisone compared to those who received placebo at 7 days of age or younger.

Neurodevelopmental outcomes at ≥18 months; severe intellectual impairment (IQ<70)

Early administration of hydrocortisone – 7 days of age or younger

- Low quality evidence from 1 RCT (n=34) showed no clinically significant difference in severe intellectual impairment at 18 months of age or older among preterm babies on

respiratory support who received hydrocortisone compared to those who received placebo at 7 days of age or younger.

Neurodevelopmental outcomes at ≥18 months: severe psychomotor impairment (Bayley psychomotor development index [PDI] <70 or <-2SD on other validated scales)

Early administration of hydrocortisone – 7 days of age or younger

- Low quality evidence from 1 RCT (n=152) showed no clinically significant difference in severe psychomotor impairment at 18 months of age or older among preterm babies on respiratory support who received hydrocortisone compared to those who received placebo at 7 days of age or younger

Neurodevelopmental outcomes at ≥18 months: moderate or severe cognitive impairment (Bayley MDI <85 or <-1SD on other validated scales)

All administration schedules of hydrocortisone

- Low quality evidence from 2 RCTs (n=340) showed no clinically significant difference in moderate or severe cognitive impairment at 18 months of age or older among preterm babies on respiratory support who received hydrocortisone compared to those who received placebo.

Early administration of hydrocortisone – 7 days of age or younger

- Low quality evidence from 1 RCT (n=304) showed no clinically significant difference in moderate or severe cognitive impairment at 18 months of age or older among preterm babies on respiratory support who received hydrocortisone compared to those who received placebo at 7 days of age or younger.

Later administration of hydrocortisone – 8 days of age or older

- Very low quality evidence from 1 RCT (n=36) showed no clinically significant difference in moderate or severe cognitive impairment at 18 months of age or older among preterm babies on respiratory support who received hydrocortisone compared to those who received placebo at 8 days of age or older

Neurodevelopmental outcomes at ≥18 months: moderate or severe language impairment (Bayley language development index [LDI] <85 or <-1SD on other validated scales)

Later administration of hydrocortisone – 8 days of age or older

- Very low quality evidence from 1 RCT (n=35) showed no clinically significant difference in moderate or severe language impairment at 18 months of age or older among preterm babies on respiratory support who received hydrocortisone compared to those who received placebo at 8 days of age or older

Neurodevelopmental outcomes at ≥18 months: moderate cognitive impairment (Bayley MDI 70-84 or <-1 to -2SD on other validated scales)

Early administration of hydrocortisone – 7 days of age or younger

- Low quality evidence from 1 RCT (n=45) showed no clinically significant difference in moderate cognitive impairment at 18 months of age or older among preterm babies on respiratory support who received hydrocortisone compared to those who received placebo at 7 days of age or younger.

Neurodevelopmental outcomes at ≥18 months: severe deafness

Early administration of hydrocortisone – 7 days of age or younger

- High quality evidence from 2 RCTs (n=397) was available on severe deafness at 18 months of age or older among preterm babies on respiratory support who received

hydrocortisone, however as there were no events in either arms of the RCTs the risk ratios were not estimable.

Neurodevelopmental outcomes at ≥18 months: severe blindness

All administration schedules of hydrocortisone

- High quality evidence from 3 RCTs (n=434) was available on severe blindness at 18 months of age or older among preterm babies on respiratory support who received hydrocortisone, however as there were no events in either arms of the RCTs the risk ratios were not estimable.

Early administration of hydrocortisone – 7 days of age or younger

- High quality evidence from 2 RCTs (n=397) was available on severe blindness at 18 months of age or older among preterm babies on respiratory support who received hydrocortisone, however as there were no events in either arms of the RCTs the risk ratios were not estimable.

Later administration of hydrocortisone – 8 days of age or older

- Moderate quality evidence from 1 RCT (n=37) was available on severe blindness at 18 months of age or older among preterm babies on respiratory support who received hydrocortisone, however as there were no events in either arms of the RCT the risk ratios were not estimable.

Important outcomes

Days on invasive ventilation

- Evidence from 4 RCTs (n=345) was available on total days of invasive ventilation, however due to different ways it was reported between studies as means and medians it was not possible to pool these results and thus the results are presented individually.

Early administration of hydrocortisone – 7 days of age or younger

- Moderate quality evidence from 1 RCT (n=50) showed no clinically significant difference in total days on invasive ventilation (defined as ventilation) among preterm babies on respiratory support who received hydrocortisone compared to those who received placebo at 7 days of age or younger, however there was uncertainty around this estimate
- Moderate quality evidence from 1 RCT (n=34) showed a clinically significant reduction in total days on invasive ventilation among preterm babies on respiratory support who received hydrocortisone compared to those who received placebo at 7 days of age or younger, however there was uncertainty around this estimate
- Moderate quality evidence from 1 RCT (n=197) showed no clinically significant difference in total days on invasive ventilation among preterm babies on respiratory support who received hydrocortisone compared to those who received placebo at 7 days of age or younger, however there was uncertainty around this estimate

Later administration of hydrocortisone – 8 days of age or older

- Moderate quality evidence from 1 RCT (n=64) showed no clinically significant difference in total days on invasive ventilation (defined as nasal continuous positive airway pressure) among preterm babies on respiratory support who received hydrocortisone compared to those who received placebo at 8 days of age or older.

Gastrointestinal perforation

All administration schedules of hydrocortisone

- Moderate quality evidence from 5 RCTs (n=662) showed no clinically significant difference in gastro-intestinal perforation among preterm babies on respiratory support who received hydrocortisone compared to those who received placebo

Early administration of hydrocortisone – 7 days of age or younger

- High quality evidence from 4 RCTs (n=662) showed no clinically significant difference in gastro-intestinal perforation among preterm babies on respiratory support who received hydrocortisone compared to those who received placebo at 7 days of age or younger.

Later administration of hydrocortisone – 8 days of age or older

- Low quality evidence from 1 RCTs (n=34) showed no clinically significant difference in gastro-intestinal perforation among preterm babies on respiratory support who received hydrocortisone compared to those who received placebo at 8 days of age or older.

Hypertension

All administration schedules of hydrocortisone

- Moderate quality evidence from 2 RCTs (n=114) showed no clinically significant difference in hypertension among preterm babies on respiratory support who received hydrocortisone compared to those who received placebo.

Early administration of hydrocortisone – 7 days of age or younger

- Low quality evidence from 1 RCT (n=50) showed no clinically significant difference in hypertension among preterm babies on respiratory support who received hydrocortisone compared to those who received placebo at 7 days of age or younger.

Later administration of hydrocortisone – 8 days of age or older

- Moderate quality evidence from 1 RCT (n=64) showed no clinically significant difference in hypertension among preterm babies on respiratory support who received hydrocortisone compared to those who received placebo at 8 days of age or older.

Comparison 1.3: Budesonide versus placebo

Critical outcomes

Mortality prior to discharge

- No studies reported on this critical outcome

Bronchopulmonary dysplasia at 36 weeks corrected gestational age

- Very low quality evidence from 1 RCT (n=17) showed no clinically significant difference in bronchopulmonary dysplasia at 36 weeks corrected gestational age among preterm babies on respiratory support who received nebulised budesonide compared to those who received placebo.

Bronchopulmonary dysplasia at 28 days of age

- Very low quality evidence from 1 RCT (n=27) showed no clinically significant difference in bronchopulmonary dysplasia at 28 days of age among preterm babies on respiratory support who received nebulised budesonide compared to those who received placebo.

Neurodevelopmental delay at ≥18 months of age or older

- No studies reported on this critical outcome.

Important outcomes

Days on invasive ventilation

- Low quality evidence from 1 RCT (n=27) showed no clinically significant difference in total days on invasive ventilation among preterm babies on respiratory support who received nebulised budesonide compared to those who received placebo, however there was uncertainty around the estimate

Gastrointestinal perforation

- No studies reported on this important outcome.

Hypertension

- No studies reported on this important outcome.

Comparison 2: Corticosteroid A versus corticosteroid B

- No studies reported on this comparison.

Comparison 3: Lower cumulative dose corticosteroid A versus higher cumulative dose corticosteroid A

Comparison 3.1: Lower cumulative dose dexamethasone versus higher cumulative dose dexamethasone

Critical outcomes

Mortality prior to discharge

- Low quality evidence from 2 RCTs (n=109) showed no clinically significant difference in mortality prior to discharge among preterm babies on respiratory support who received lower cumulative dose dexamethasone compared to those who received higher cumulative dose dexamethasone.

Bronchopulmonary dysplasia at 36 weeks corrected gestation

- Low quality evidence from 2 RCTs (n=109) showed no clinically significant difference in bronchopulmonary dysplasia at 36 weeks corrected gestation among preterm babies on respiratory support who received lower cumulative dose dexamethasone compared to those who received higher cumulative dose dexamethasone.

Bronchopulmonary dysplasia at 28 days of age

- No studies reported on this critical outcome.

Neurodevelopmental outcomes at ≥18 months: cerebral palsy

- Very low quality evidence from 1 RCT (n=36) showed no clinically significant difference in cerebral palsy at 18 months of age or older among preterm babies on respiratory support who received lower cumulative dose dexamethasone compared to those who received higher cumulative dose dexamethasone.

Neurodevelopmental outcomes at ≥18 months: severe cognitive impairment (Bayley MDI <70 or <-2SD on other validated scales)

- Very low quality evidence from 1 RCT (n=47) showed no clinically significant difference in severe cognitive impairment at 18 months of age or older among preterm babies on respiratory support who received lower cumulative dose dexamethasone compared to those who received higher cumulative dose dexamethasone.

Neurodevelopmental outcomes at ≥18 months: severe blindness

- Very low quality evidence from 1 RCT (n=47) showed no clinically significant difference in severe blindness at 18 months of age or older among preterm babies on respiratory support who received lower cumulative dose dexamethasone compared to those who received higher cumulative dose dexamethasone.

Important outcomes

Days on invasive ventilation

- Low quality evidence from 1 RCT (n=62) showed no clinically significant difference in total days on invasive ventilation among preterm babies on respiratory support who received lower cumulative dose dexamethasone compared to those who received higher cumulative dose dexamethasone.

Gastrointestinal perforation

- Low quality evidence from 2 RCTs (n=109) showed no clinically significant difference in gastro-intestinal perforation among preterm babies on respiratory support who received lower cumulative dose dexamethasone compared to those who received higher cumulative dose dexamethasone.

Hypertension

- Moderate quality evidence from 2 RCTs (n=109) showed no clinically significant difference in hypertension among preterm babies on respiratory support who received lower cumulative dose dexamethasone compared to those who received higher cumulative dose dexamethasone.

Comparison 3.2: Individual tailored course of dexamethasone versus continuous tapered dexamethasone course

Critical outcomes

Mortality prior to discharge

- Low quality evidence from 1 RCT (n=33) showed no clinically significant difference in mortality prior to discharge among preterm babies on respiratory support who received an individual tailored course of dexamethasone compared to those who received a continuous tapered dexamethasone course.

Bronchopulmonary dysplasia at 36 weeks corrected gestation

- Low quality evidence from 1 RCT (n=33) showed no clinically significant difference in bronchopulmonary dysplasia at 36 weeks corrected gestation among preterm babies on respiratory support who received an individual tailored course of dexamethasone compared to those who received a continuous tapered dexamethasone course.

Bronchopulmonary dysplasia at 28 days of age

- Moderate quality evidence from 1 RCT (n=33) showed no clinically significant difference in bronchopulmonary dysplasia at 28 days of age among preterm babies on respiratory support who received an individual tailored course of dexamethasone compared to those who received a continuous tapered dexamethasone course.

Neurodevelopmental outcomes at ≥18 months

- No studies reported on this critical outcome.

Important outcomes

Total days on invasive ventilation

- Moderate quality evidence from 1 RCT (n=33) showed a clinically significant increase in total days on invasive ventilation among preterm babies on respiratory support who received an individual tailored course of dexamethasone compared to those who received a continuous tapered dexamethasone course.

Gastrointestinal perforation

- Low quality evidence from 1 RCT (n=33) showed no clinically significant difference in gastro-intestinal perforation among preterm babies on respiratory support who received an individual tailored course of dexamethasone compared to those who received a continuous tapered dexamethasone course.

Hypertension

- Low quality evidence from 1 RCT (n=33) showed no clinically significant difference in hypertension among preterm babies on respiratory support who received an individual tailored course of dexamethasone compared to those who received a continuous tapered dexamethasone course.

Comparison 4: Earlier initiation of corticosteroid A versus later initiation of corticosteroid A

Comparison 4.1: Earlier initiation dexamethasone versus later initiation dexamethasone

Critical outcomes

Mortality prior to discharge

All earlier initiation schedules of dexamethasone versus later initiation schedules of dexamethasone

- Low quality evidence from 3 RCTs (n=732) showed no clinically significant difference in mortality prior to discharge among preterm babies on respiratory support who received an earlier initiation schedule of dexamethasone compared to those who received a later initiation schedule of dexamethasone.

Early initiation schedule of dexamethasone versus moderately early initiation schedule of dexamethasone – 7 days of age or younger versus 8-20 days of age

- Moderate quality evidence from 2 RCTs (n=361) showed no clinically significant difference in mortality prior to discharge among preterm babies on respiratory support who received an early initiation schedule of dexamethasone (7 days of age or younger) compared to those who received a moderately early initiation schedule of dexamethasone (8-20 days of age).

Moderately early initiation schedule of dexamethasone versus late initiation schedule of dexamethasone – 8-20 days of age versus 21 days of age or older

- Moderate quality evidence from 1 RCT (n=371) showed no clinically significant difference in mortality prior to discharge among preterm babies on respiratory support who received a moderately early initiation schedule of dexamethasone (8-20 days of age) compared to those who received a late initiation schedule of dexamethasone (21 days of age or older).

Bronchopulmonary dysplasia at 36 weeks corrected gestational age

All earlier initiation schedules of dexamethasone versus later initiation schedules of dexamethasone

- Moderate quality evidence from 3 RCTs (n=732) showed no clinically significant difference in bronchopulmonary dysplasia at 36 weeks corrected gestational age among preterm babies on respiratory support who received an earlier initiation schedule of dexamethasone compared to those who received a later initiation schedule of dexamethasone.

Early initiation schedule of dexamethasone versus moderately early initiation schedule of dexamethasone – 7 days of age or younger versus 8-20 days of age

- Moderate quality evidence from 2 RCTs (n=361) showed that there may be a clinically significant reduction in bronchopulmonary dysplasia at 36 weeks corrected gestation among preterm babies on respiratory support who received an early initiation schedule of dexamethasone (7 days of age or younger) compared to those who received a moderately early initiation schedule of dexamethasone (8-20 days of age), however there is uncertainty around the estimate.

Moderately early initiation schedule of dexamethasone versus late initiation schedule of dexamethasone – 8-20 days of age versus 21 days of age or older

- High quality evidence from 1 RCT (n=371) showed no clinically significant difference in bronchopulmonary dysplasia at 36 weeks corrected gestation among preterm babies on respiratory support who received a moderately early initiation schedule of dexamethasone (8-20 days of age) compared to those who received a late initiation schedule of dexamethasone (21 days of age or older).

Bronchopulmonary dysplasia at 28 days of age

All earlier initiation schedules of dexamethasone versus later initiation schedules of dexamethasone

- Moderate quality evidence from 3 RCTs (n=732) showed no clinically significant difference in bronchopulmonary dysplasia at 36 weeks corrected gestational age among preterm babies on respiratory support who received an earlier initiation schedule of dexamethasone compared to those who received a later initiation schedule of dexamethasone.

Early initiation schedule of dexamethasone versus moderately early initiation schedule of dexamethasone – 7 days of age or younger versus 8-20 days of age

- Moderate quality evidence from 2 RCTs (n=361) showed no clinically significant difference in bronchopulmonary dysplasia at 36 weeks corrected gestation among preterm babies on respiratory support who received an early initiation schedule of dexamethasone (7 days of age or younger) compared to those who received a moderately early initiation schedule of dexamethasone (8-20 days of age).

Moderately early initiation schedule of dexamethasone versus late initiation schedule of dexamethasone – 8-20 days of age versus 21 days of age or older

- High quality evidence from 1 RCT (n=371) showed no clinically significant difference in bronchopulmonary dysplasia at 36 weeks corrected gestation among preterm babies on respiratory support who received a moderately early initiation schedule of dexamethasone (8-20 days of age) compared to those who received a late initiation schedule of dexamethasone (21 days of age or older).

Neurodevelopmental outcomes at ≥18 months: cerebral palsy

Early initiation schedule of dexamethasone versus moderately early initiation schedule of dexamethasone – 7 days of age or younger versus 8-20 days of age

- Low quality evidence from 1 RCT (n=56) showed no clinically significant difference in cerebral palsy at 18 months of age or older among preterm babies on respiratory support who received an early initiation schedule of dexamethasone (7 days of age or younger) compared to those who received a moderately early initiation schedule of dexamethasone (8-20 days of age).

Neurodevelopmental outcomes at ≥18 months: severe cognitive impairment (Bayley MDI <70 or <-2SD on other validated scales)

Early initiation schedule of dexamethasone versus moderately early initiation schedule of dexamethasone – 7 days of age or younger versus 8-20 days of age

- Low quality evidence from 1 RCT (n=61) showed no clinically significant difference in severe cognitive impairment at 18 months of age or older among preterm babies on respiratory support who received an early initiation schedule of dexamethasone (7 days of age or younger) compared to those who received a moderately early initiation schedule of dexamethasone (8-20 days of age).

Neurodevelopmental outcomes at ≥18 months: moderate cognitive impairment (Bayley MDI 70-84 or <-1 to -2SD on other validated scales)

Early initiation schedule of dexamethasone versus moderately early initiation schedule of dexamethasone – 7 days of age or younger versus 8-20 days of age

- Low quality evidence from 1 RCT (n=61) showed no clinically significant difference in moderate cognitive impairment at 18 months of age or older among preterm babies on respiratory support who received an early initiation schedule of dexamethasone (7 days of age or younger) compared to those who received a moderately early initiation schedule of dexamethasone (8-20 days of age).

Neurodevelopmental outcomes at ≥18 months: severe deafness

Early initiation schedule of dexamethasone versus moderately early initiation schedule of dexamethasone – 7 days of age or younger versus 8-20 days of age

- High quality evidence from 1 RCT (n=61) was available on severe deafness at 18 months of age or older among preterm babies on respiratory support who received an early initiation schedule of dexamethasone (7 days of age or younger) compared to those who received a moderately early initiation schedule of dexamethasone (8-20 days of age), however as there were no events in either arms of the RCT the risk ratios were not estimable.

Neurodevelopmental outcomes at ≥18 months: severe blindness at 18 months of age or older

Early initiation schedule of dexamethasone versus moderately early initiation schedule of dexamethasone – 7 days of age or younger versus 8-20 days of age

- High quality evidence from 1 RCT (n=61) was available on severe blindness at 18 months of age or older among preterm babies on respiratory support who received an early initiation schedule of dexamethasone (7 days of age or younger) compared to those who received a moderately early initiation schedule of dexamethasone (8-20 days of age), however as there were no events in either arms of the RCT the risk ratios were not estimable.

Important outcomes

Days on invasive ventilation

- No studies reported on this important outcome

Gastrointestinal perforation

Early initiation schedule of dexamethasone versus moderately early initiation schedule of dexamethasone – 7 days of age or younger versus 8-20 days of age

- Low quality evidence from 1 RCT (n=285) showed no clinically significant difference in gastro-intestinal perforation among preterm babies on respiratory support who received an early initiation schedule of dexamethasone (7 days of age or younger) compared to those who received a moderately early initiation schedule of dexamethasone (8-20 days of age).

Hypertension

All earlier initiation schedules of dexamethasone versus later initiation schedules of dexamethasone

- Low quality evidence from 3 RCTs (n=732) showed no clinically significant difference in hypertension among preterm babies on respiratory support who received an earlier initiation schedule of dexamethasone compared to those who received a later initiation schedule of dexamethasone.

Early initiation schedule of dexamethasone versus moderately early initiation schedule of dexamethasone – 7 days of age or younger versus 8-20 days of age

- Low quality evidence from 2 RCTs (n=361) showed no clinically significant difference in hypertension among preterm babies on respiratory support who received an early initiation schedule of dexamethasone (7 days of age or younger) compared to those who received a moderately early initiation schedule of dexamethasone (8-20 days of age).

Moderately early initiation schedule of dexamethasone versus late initiation schedule of dexamethasone – 8-20 days of age versus 21 days of age or older

- High quality evidence from 1 RCT (n=371) showed no clinically significant difference in hypertension among preterm babies on respiratory support who received a moderately early initiation schedule of dexamethasone (8-20 days of age) compared to those who received a late initiation schedule of dexamethasone (21 days of age or older).

See appendix E for Forest plots.

Economic evidence statements

- No economic evidence on the cost effectiveness of corticosteroids in preterm babies requiring respiratory support was available.

Recommendations

C1.1 For preterm babies who are 8 days or older and still receiving invasive ventilation consider dexamethasone[a] to reduce the risk of BPD. Take into account the risk factors for BPD in Table 19, evidence chapter A, when deciding whether to use dexamethasone.

C1.2 Before starting treatment with dexamethasone, discuss with parents and carers the possible benefits and harms. Topics to discuss include those in Table 3.

C1.3 For preterm babies who are less than 8 days old, be aware that dexamethasone increases the risk of gastrointestinal perforation.

C1.4 Do not use dexamethasone with non-steroidal anti-inflammatory drugs (NSAIDs).

C1.5 Monitor the blood pressure of babies who receive dexamethasone, because of the risk of hypertension.

Table 3: The benefits and harms of dexamethasone in preterm babies 8 days or older

Mortality before discharge	There is no difference in mortality before discharge in babies who receive dexamethasone compared with babies who do not receive dexamethasone.

a Although this use is common in UK clinical practice, at the time of consultation (October 2018), dexamethasone did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

BPD at 36 weeks postmenstrual age	Babies who receive dexamethasone are less likely to develop BPD compared with babies who do not receive dexamethasone. On average, if 100 preterm babies are given dexamethasone, 16 fewer babies will develop BPD compared with 100 preterm babies who do not receive dexamethasone.
Cerebral palsy	There is no difference in the incidence of cerebral palsy in babies who receive dexamethasone compared with babies who do not receive dexamethasone. However, this is uncertain because there is not much good evidence, so the possibility of cerebral palsy occurring should not be excluded.
Other neurodevelopmental outcomes (neurodevelopmental delay and neurosensory impairment)	There is no difference in other neurodevelopmental outcomes in babies who receive dexamethasone compared with babies who do not receive dexamethasone.
Days on invasive ventilation	Babies who receive dexamethasone are likely to have fewer days on invasive ventilation compared with babies who do not receive dexamethasone.
Gastrointestinal perforation	There is no evidence about gastrointestinal perforation in babies who receive dexamethasone compared with babies who do not receive dexamethasone.
Hypertension	Babies who receive dexamethasone are more likely to develop hypertension compared with babies who do not receive dexamethasone. On average, if 100 preterm babies are given dexamethasone, 8 more babies will develop hypertension compared with 100 babies who do not receive dexamethasone.
Abbreviation: BPD, bronchopulmonary dysplasia.	

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Research recommendations

3 What is the comparative efficacy of hydrocortisone compared with dexamethasone for
4 preventing BPD in preterm babies requiring respiratory support?

5 Is nebulised budesonide effective compared to placebo in preventing BPD in preterm babies
6 requiring respiratory support?

Rationale and impact

Why the committee made the recommendations on dexamethasone

9 There was evidence that in babies 8 days or older, dexamethasone reduces the incidence of
10 BPD, but dexamethasone was associated with an increased risk of hypertension. There was
11 some evidence suggesting that dexamethasone reduced the number of days on invasive
12 ventilation.

In babies younger than 8 days, there was evidence that dexamethasone reduces the incidence of BPD but is associated with an increased risk of gastrointestinal perforation.

In babies 8 days or older, there was no evidence that dexamethasone is associated with an increased risk of cerebral palsy or gastrointestinal perforation. However, the committee emphasised that this lack of evidence should not be considered an absence of effect.

There were no clinically important differences in mortality before discharge, or other neurodevelopmental outcomes between babies who received dexamethasone and those who did not.

The committee recommended that dexamethasone be considered for babies 8 days or older, after taking into account risk factors for BPD. This is in line with current practice, which is to use corticosteroids to assist weaning from ventilatory support when a baby is 8 days or older, rather than using corticosteroids as 'prophylaxis' for babies less than 8 days old.

The committee agreed the importance of discussing the risks of gastrointestinal perforation, hypertension and cerebral palsy with parents and carers before starting dexamethasone therapy, because there may be lifelong implications for the baby and their family.

Although the combination of dexamethasone and non-steroidal anti-inflammatory drugs (NSAIDs) was not reviewed, the committee confirmed that they should not be used together because this increases the risk of gastrointestinal bleeding and perforation. The committee agreed that although this risk is widely recognised, it should be reinforced in the guideline to ensure that dexamethasone and NSAIDs are not used together in clinical practice.

Because of the increased risk of hypertension with dexamethasone, the committee recommended that babies' blood pressure should be monitored. There was no evidence about when or for how long to monitor blood pressure, so the committee agreed that this should be decided by the neonatologist responsible for the baby's care.

Evidence did not show any differences between different dosing strategies and so the committee did not make any specific dosing recommendations.

Why the committee didn't make any recommendations on hydrocortisone and nebulised budesonide

Evidence comparing hydrocortisone and placebo was inconclusive so the committee did not make any recommendations. The committee was aware there is an ongoing, large multicentre randomised controlled trial investigating hydrocortisone compared with placebo in preterm babies who need respiratory support, so did not make a research recommendation that would replicate this study. However, they agreed that a comparison of dexamethasone and hydrocortisone could provide useful guidance and so made a research recommendation for this comparison.

There was very little evidence for the use of nebulised budesonide and therefore the committee made a research recommendation.

Impact of the recommendations on practice

Current practice is to use corticosteroids in preterm babies to assist weaning or removal from ventilatory support, but they are not routinely used to prevent BPD in all preterm babies. The choice of dexamethasone or hydrocortisone varies among neonatal units. These recommendations are unlikely to affect how often corticosteroids are used, but they might prompt units who currently use hydrocortisone to consider dexamethasone as an alternative.

The committee's discussion of the evidence

Interpreting the evidence

Note: The results are presented as an overall population for preterm babies on respiratory support and subgroup analyses are included by the timing of corticosteroid administration (early [7 days or younger]; moderate [8-20 days of age]; and late [21 days or older]) where there were sufficient numbers of trials to make such subgroup analyses meaningful.

The outcomes that matter most

The committee agreed that the use of corticosteroids in preterm babies on respiratory support aims to reduce the incidence of BPD and mortality prior to discharge, thus BPD and mortality prior to discharge were both considered critical outcomes for decision making. However, a major concern with the use of early corticosteroids in babies is the possible risk of adverse neurodevelopmental outcomes, which could have a life-long impact on the affected individual and their parents or carers. The committee therefore considered neurodevelopmental outcomes at 18 months corrected gestational age or older as critically important outcomes for decision making. The committee prioritised mortality occurring prior to first discharge as being of primary importance. Neurodevelopmental outcomes were considered second in importance because of their potential lifelong impact and BPD was considered third in importance

In terms of neurodevelopmental outcomes, the committee prioritised cerebral palsy, moderate and/ or severe neurodevelopmental impairment, and severe neurosensory impairment as key categories for decision making.

The total days on invasive ventilation (which may itself increase the risk of BPD) was considered an important outcome. Gastro-intestinal perforation and systemic hypertension, which are both possible adverse events associated with corticosteroid administration, were also considered as important outcomes in decision-making and in considering the balance of benefit and harm.

The quality of the evidence

The evidence in the pairwise comparisons was assessed using the GRADE methodology. The quality of evidence in this review ranged from high to very low. Most of the evidence on outcomes assessed between birth and discharge from the neonatal intensive care unit was of high or moderate quality. The evidence on the long-term neurodevelopmental outcomes was of low or very low quality.

The quality of evidence was most often downgraded because of the uncertainty around the risk estimate, uncertainty around the timeframe of the neurodevelopmental outcome assessment, heterogeneity in the population, and considerable loss to follow-up.

The committee discussed the difficulty that the timing of neurodevelopmental assessments could not always be ascertained to be at 18 months corrected age or older. For pragmatic reasons, considering that neurodevelopmental outcomes were not always available for every RCT, the committee agreed to include studies without a specified timeframe for neurodevelopmental assessment, but but downgraded for indirectness to account for the uncertainty in the outcome in the quality assessment of the evidence. Due to the lack of evidence for neurodevelopmental outcomes, the committee also prioritised making a research recommendation on this topic.

Uncertainty around the risk estimate, in particular with neurodevelopmental outcomes, was generally attributable to the low event rates and small sample sizes of these follow-up studies.

Considerable heterogeneity was observed in the studies assessing the number of days on invasive ventilation, which may be attributed to the subjectivity of the outcome and variation in clinical practice in different settings and countries.Furthermore, approximately half of the

studies did not report the number of days on ventilation as means, but rather as medians. In view of this, studies were not meta-analysed, but rather assessed individually. Imprecision could not be assessed for the outcomes reported as medians, in these cases the quality of the evidence was downgraded by one level.

No evidence was found on head-to-head comparisons of different corticosteroids. The committee made it a priority to make a research recommendation for comparative studies on the effectiveness of the two most widely used systemic corticosteroids, dexamethasone and hydrocortisone, in preterm babies on respiratory support.

Only 1 RCT of very low quality evidence was identified on the use of nebulised budesonide in preterm babies on respiratory support. The committee highlighted the need for more evidence on nebulised budesonide and prioritised making a further research recommendation on the effectiveness of nebulised budesonide in preterm babies who require respiratory support. The committee also did not prioritise research on different doing strategies.

Benefits and harms

As defined in the protocol, the committee had requested that the initiation of corticosteroid therapy should be stratified into the following sub-groups where possible:

- Early (≤7 days after birth)
- Moderate delayed (8-20 days after birth)
- Late (>21 days after birth)

The committee agreed that the division of preterm babies requiring respiratory support into these 3 groups may be aligned to differences in critical and important outcomes, with early administration more often given as prophylaxis, and moderate delayed or late administration as treatment. The committee recognised that dividing moderate and late administration of corticosteroid therapy was difficult as the many of the studies overlapped these periods, in situations where this arose the committee agreed that 2 stratifications of early (≤7 days after birth) and later (≥8 days after birth) was more practical. The committee considered differentiation between prophylaxis and treatment in the evidence review key when weighing up the benefits and harms of the different corticosteroids and drafting recommendations.

The committee recognised the potential importance of differences in cumulative dose and duration of corticosteroid administration in the studies. However, they also recognised that due to the variations in dose and duration between studies that it was not feasible to take account of this in the analyses without reporting each trial separately and so foregoing the benefits of meta-analysis. The committee agreed that reporting the different corticosteroid regimens in the evidence table was sufficient to identify trials that had widely differing regimens.

Dexamethasone in preterm babies requiring respiratory support

In preterm babies requiring respiratory support, the committee decided that, taking into account the baby's risk factors for BPD (see recommendations A1 and A2), dexamethasone should be considered for babies who are 8 days or older.

The evidence in this population showed that dexamethasone reduced the incidence of BPD at 36 weeks PMA and, with late administration, at 28 days compared to placebo. Some studies showed an improvement in total days on invasive ventilation with dexamethasone administration at 8 days of age or older, although, as these studies could not be meta-analysed because the outcome was reported as means and medians in different studies , it was difficult to draw clear conclusions on these outcomes from consideration of the individual RCTs.

The committee also considered potential harms with dexamethasone. There was an increased risk of hypertension during hospitalisation with dexamethasone administration, although the committee observed that poor reporting in the studies made it difficult to determine the clinical significance of this outcome, because there was a lack of information as to whether the

hypertension was severe enough to require intervention or early stoppage of the dexamethasone and as to whether it was transient or persistent.

Despite the benefit identified with dexamethasone given at 8 days of age or older, the committee agreed that they could not make a recommendation that it should be 'offered', due to the uncertainty regarding the quality of evidence for any possible association between dexamethasone and neurodevelopmental outcomes, and in particular cerebral palsy. The lack of evidence on gastro-intestinal perforation with dexamethasone use at 8 days of age or older was an additional consideration in the decision not to make a firm recommendation to offer it.

The evidence on the use of dexamethasone in preterm babies of 7 days of age or younger requiring respiratory support also showed a reduction in BPD at 36 weeks PMA (although not at 28 days of age) compared to placebo and a reduction in days on ventilation. However, the committee decided not to make a recommendation for the use of dexamethasone in preterm babies of 7 days of age or younger as there was evidence for an increased risk of gastrointestinal perforation and no difference in mortality. When a fixed effects meta-analysis model was used there was also evidence of an increased risk of cerebral palsy with use of dexamethasone in preterm babies of 7 days of age or younger. However there was considerable heterogeneity in the individual study results and when using a random effects meta-analysis model there was no increased risk of cerebral palsy in this group. The committee noted that an RCT by Shinwell 2000 was the only trial that showed an increase in the risk of cerebral palsy with early dexamethasone in preterm babies on respiratory support, but that this study had the largest population of all studies meta-analysed. The committee looked at the balance of the evidence for cerebral palsy and agreed that, given the very low quality and inconsistency of the evidence regarding cerebral palsy, they could not conclusively determine the risk of cerebral palsy in babies 7 days of age or younger.

The committee considered that use of dexamethasone at 7 days of age or younger is deemed "prophylactic" (rather than actual "treatment", where healthcare professionals are trying to get preterm babies off respiratory support). Although there was evidence of benefit there was also evidence of increased risk of gastrointestinal perforation with dexamethasone in this age group, and uncertainty as described above over the risk of cerebral palsy. The committee therefore decided they did not wish to make a recommendation for or against its use. Although further evidence was desirable, the committee decided that this topic was not enough of a priority to make a research recommendation.

The committee agreed it was important to discuss the potential risks of gastro-intestinal perforation and cerebral palsy with dexamethasone with parents or carers before commencing therapy. The committee agreed that the use of dexamethasone, although the evidence suggested likely benefit in terms of preventing BPD, may have serious lifelong implications for a preterm baby, as well as an impact on the parents' or carers' lives and thus parents or carers should be involved in the decision to use dexamethasone.

Although, the combination of dexamethasone and non-steroidal anti-inflammatory drugs (NSAIDs) were not specifically assessed in this review, the committee recommended that dexamethasone and NSAIDs not be used concurrently because of the increased risk of gastrointestinal bleeding and perforation. The committee agreed that even though it is widely recognised and documented in the summary of product characteristics (SPC) that the combination of these drugs increase the risk of gastrointestinal bleeding and perforation, it is still important to highlight the risk to minimise their combinational use in clinical practice.

In view of the increased risk of hypertension with dexamethasone, the committee agreed that a recommendation to monitor blood pressure was appropriate. The length of monitoring and point of intervention would be decided by the neonatologist responsible for the preterm baby on respiratory support, depending on the degree of concern, as evidence on this aspect was not examined in the review.

The limited evidence on the different dexamethasone strategies with regards to dosing and initiation schedules did not show any clear favour in either direction for high versus low dose nor tailored versus continuous. Furthermore, the scarcity of evidence on neurodevelopmental outcomes precluded recommendations to be drawn based on these comparisons, but the committee did not prioritise these areas for further research.

Hydrocortisone in preterm babies on respiratory support

The committee decided not to make any recommendation on the use of hydrocortisone in preterm babies requiring respiratory support. Most of the evidence on the use of hydrocortisone was in preterm babies aged 7 days or younger, and showed no convincing difference between hydrocortisone and placebo for BPD at 36 weeks PMA, although there was a trend towards a reduced incidence of BPD with hydrocortisone in preterm babies aged 7 days or younger. The evidence suggested that there may be an improvement in mortality prior to discharge with hydrocortisone in preterm babies aged 7 days or younger, however given the absence of an effect on BPD the committee questioned whether the possible improvement in mortality was due to early cardiovascular stabilisation rather than an improvement in respiratory related mortality. No difference in neurodevelopmental outcomes, total days on invasive ventilation, gastro-intestinal perforation, or hypertension were seen from the analyses in preterm babies on respiratory support aged 7 days or younger, or in those 8 days of age or older.

The committee noted that the RCT by Watterberg 2004 did not show as strong a trend towards reduced BPD at 36 weeks PMA as other RCTs in the meta-analysis at 7 days of age or younger. The committee noted that there was a very high rate of prophylactic indomethacin in this study and this may have been the cause of the higher rates of GI perforation seen in this study. Nonetheless, the committee agreed that Watterberg 2004 was not particularly different to the other trials, thus there were no grounds to conduct a sensitivity analysis and exclude the trial from the analysis.

The evidence base for hydrocortisone versus placebo is smaller in quantity than that of dexamethasone versus placebo, and so it is difficult to determine whether there is any clear benefit from hydrocortisone over placebo, despite mortality prior to discharge and BPD outcomes tending towards benefit. The committee discussed the ongoing multi-centre SToP-BPD randomised controlled trial (Onland 2011), investigating the efficacy and safety of hydrocortisone versus placebo, started 7 to 14 days after birth. Promising preliminary results were presented in a recent conference, however absence of published data meant that the results could not be incorporated into the review. In view of this large RCT the committee did not think it was necessary to recommend a research study for hydrocortisone versus placebo, as this trial aims to answer this question.

Nebulised budesonide in preterm babies requiring respiratory support

The committee did not make any recommendation on the use of nebulised budesonide in preterm babies requiring respiratory support, because of the lack of evidence. Only 1 very low quality RCT was identified and only short term outcomes were captured. The committee did make a research recommendation however for a placebo controlled trial to study its effectiveness.

Dexamethasone versus hydrocortisone in preterm babies requiring respiratory support

In the absence of head-to-head comparisons between dexamethasone and hydrocortisone and inconsistency in use across different neonatal intensive care units, the committee highlighted the need for a high quality multicentre RCT to determine which if any is to be preferred in terms of short and long term outcomes, and made a research recommendation to this effect.

Cost effectiveness and resource use

There was no evidence on the cost effectiveness of corticosteroids in preterm babies who require respiratory support.

The committee noted that corticosteroids are cheap and the acquisition costs of different corticosteroids are comparable. Dexamethasone may have potential cost savings associated with the reduction in the short-term morbidity (that is, BPD at 36 weeks PMA) and the associated long-term respiratory consequences (including chronic lung disease) that may require expensive repeated hospital readmissions, prolonged invasive ventilation support at home, and expensive medical management in the future years of life. However, this finding was uncertain as BPD was reduced at 36 weeks PMA but not at 28 days of age. Even though improvement in BPD is a critical outcome the committee highlighted the importance of mortality and neurodevelopmental outcomes. The evidence suggested hydrocortisone may be associated with an improvement in survival and there is a potential for significant quality-adjusted life year gain gain. However, the committee noted that this finding was also uncertain. No such survival benefit was observed for dexamethasone.

The committee discussed the potential harms such as cerebral palsy associated with dexamethasone, particularly when it is given early (7 days of age or younger), an increase in GI perforation and hypertension. Such complications require resource intensive management and are costly to the NHS. However, it was noted that later administration of dexamethasone is associated with fewer adverse effects. Given the potential high risk of hypertension in babies receiving dexamethasone, the committee stressed the importance of monitoring blood pressure and discussed the optimal monitoring duration. The committee agreed that hypertension should be monitored even after dexamethasone is stopped but that it would be up to individual clinicians to decide the exact duration. The committee explained that these babies are closely monitored anyway and that monitoring blood pressure would be unlikely to result in an increase in costs. Overall, on balance, the committee were of a view that the benefits of giving dexamethasone late would outweigh any increase in costs associated with the management of potential adverse events. Also, the committee noted that the number of babies requiring treatment with corticosteroids is very small (most babies come off ventilation without the use of corticosteroids) and thus the financial impact of their use is not likely to be significant.

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Review question 3.5 What is the effectiveness of diuretics in preterm babies on respiratory support?

Introduction

Diuretics have been used with the aim of improving respiratory outcomes in preterm infants. However, there is limited knowledge on their impact on both short and long-term clinically important outcomes in preterm infants on respiratory support. There are significant variations in clinical practice regarding diuretic administration in bronchopulmonary dysplasia (BPD) including the choice of diuretic, dose, frequency and duration of treatment. Diuretics are also associated with certain adverse effects and have the potential to cause harm.

The aim of this review is to determine the optimal diuretic choice, dosing schedule, timing and mode of administration in ameliorating BPD and long-term sequelae. The review will also look at the adverse effects of the different diuretics.

Summary of the protocol

See Table 4 for a summary of the population, intervention, comparison and outcome (PICO) characteristics of this review

Table 4: Summary of the protocol (PICO table)

Population	Preterm babies requiring respiratory support: **Exclusions:** • Preterm babies with any congenital abnormalities except patent ductus arteriosus • Preterm babies who are ventilated solely due to a specific non-respiratory comorbidity, such as sepsis, necrotising enterocolitis, neurological disorders
Intervention	**Loop diuretics:** • Furosemide intravenous or oral **Aldosterone antagonists:** • Spironolactone (oral) • Potassium canrenoate (intravenous) **Thiazide diuretics:** • Chlorothiazide (oral)
Comparison	• Diuretic versus placebo/no intervention • Diuretic A versus diuretic B • Combination diuretic versus single diuretic

Outcome	**Critical outcomes:**
	• Mortality prior to discharge
	• Bronchopulmonary dysplasia (oxygen dependency at 36 weeks PMA or 28 days of age)
	• Neurodevelopmental outcomes at >18 months:
	  ○ Cerebral palsy (reported as presence or absence of condition, **not** severity of condition)
	  ○ Neurodevelopmental delay (reported as dichotomous outcomes, **not** continuous outcomes such as mean change in score)
	  - Severe (score of >2 SD below normal on validated assessment scales, **or** on Bayleys assessment scale of mental developmental index (MDI) or psychomotor developmental index (PDI) <70 or complete inability to assign score due to CP or severe cognitive delay)
	  - Moderate (score of 1-2 SD below normal on validated assessment scales, **or** on Bayleys assessment scale of MDI or PDI 70-84)
	  ○ Neurosensory impairment (reported as presence or absence of condition, **not** severity of condition)
	  - Severe hearing impairment (for example, deaf)
	  - Severe visual impairment (for example, blind)
	Important outcomes:
	• Days on invasive ventilation
	• Nephrocalcinosis
	• Ototoxicity
	• Hyponatraemia

CP: cerebral palsy; MDI: mental development index; PDI: psychomotor developmental index; RCT: randomised controlled trial; SD: standard deviation

For full details see review protocol in appendix A.

Clinical evidence

Included studies

In preterm babies on respiratory support, 2 randomised controlled trials (RCTs) were identified (Hoffman 2000; Kao 1994) comparing diuretic treatment to a placebo. Additionally, 1 observational study was included - a retrospective multi-centre cohort study comparing infants exposed to diuretics to infants were not (Laughon 2015).

See the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

Studies not included in this review with reasons for their exclusions are provided in appendix K.

Summary of clinical studies included in the evidence review

Table 5 provides a brief summary of the included studies

Table 5: Summary of included studies

Study and setting	Population	Intervention/ comparison	Outcomes	Comments
RCTs				
Hoffman 2000 RCT USA	N= 33 Preterm babies with CLD (defined as oxygen dependency beyond 28 days of life coexisting with characteristic radiographic abnormalities) and establishment of enteral feeding	Chlorothiazide (20mg/kg) + spironolactone (1.5mg/kg) orally twice daily vs chlorothiazide (20mg/kg) orally twice daily for 2-weeks	• Hyponatraemia (defined as sodium supplementation required)	
Kao 1994 RCT USA	N= 43 Preterm babies with typical radiographic appearance of Northway stage III or IV BPD, had received invasive ventilatory support for more than 1 month, were stable after extubation for more than 1 week, weighed more than 1.5kg	Chlorothiazide (40mg/kg) + spironolactone (4mg/kg) per day orally versus placebo continued until babies no longer required supplemental oxygen	• Nephrocalcinosis (1 year PMA) • Duration of oxygen supplementation days • Hearing loss (1 year PMA) • Supplemental electrolytes (defined as sodium or potassium)	Open label furosemide used in both study arms at discretion of attending physician
Cohort studies				
Laughon 2015 Retrospective multi-centre cohort study USA	N= 107,432 <32 weeks GA and <1500g birthweight. Diuretics being used to prevent or treat BPD.	Exposed to at least 1 diuretic of interest: acetazolamide, amiloride, bumetanide, chlorothiazide, diazoxide, ethracrynic acid, furosemide, hydrochlorothiazide, mannitol, metolazone, spironolactone	• Hyponatraemia	

BPD: bronchopulmonary dysplasia; CLD: chronic lung disease; GA: gestational age; PMA: post-menstrual age; RCT: randomised controlled trial

See appendix D for full evidence tables.

Quality assessment of clinical studies included in the evidence review

See appendix F for full GRADE tables.

Economic evidence

No economic evidence on the cost effectiveness of diuretics in preterm babies on respiratory support was identified by the literature searches of the economic literature undertaken for this review.

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation.

Clinical evidence statements

Comparison 1. Diuretic versus placebo/no intervention

Comparison 1.1 Chlorothiazide + spironolactone versus placebo

Critical outcomes

Mortality prior to discharge

- No studies reported on this critical outcome

Bronchopulmonary dysplasia (oxygen dependency at 36 weeks post-menstrual age *[PMA] or 28 days of age)*

- No studies reported on this critical outcome

Neurodevelopmental outcomes at ≥18 months

- No studies reported on this critical outcome

Important outcomes

Days on invasive ventilation

- No studies reported on this important outcome

Nephrocalcinosis

- Very low quality evidence from 1 RCT (n=43) showed no clinically significant difference in nephrocalcinosis at 1 year PMA among preterm babies on respiratory support with BPD who received chlorothiazide + spironolactone compared to those who received placebo.

Ototoxicty

- Very low quality evidence from 1 RCT (n=43) showed no clinically significant difference in hearing loss at 1 year PMA among preterm babies on respiratory support with BPD who received chlorothiazide + spironolactone compared to those who received placebo.

Hyponatraemia

- Very low quality evidence from 1 RCT (n=43) showed no clinically significant difference in the need for supplemental electrolytes among preterm babies on respiratory support with BPD who received chlorothiazide + spironolactone compared to those who received placebo.

Comparison 2. Diuretic A versus diuretic B

Comparison 2.1 Furosemide versus other diuretic(s)

Critical outcomes

Mortality before discharge

- No studies reported on this critical outcome

Bronchopulmonary dysplasia (oxygen dependency at 36 weeks PMA or 28 days of age)

- No studies reported on this critical outcome

Neurodevelopmental outcomes at ≥18 months

- No studies reported on this critical outcome

Important outcomes

Days on invasive ventilation

- No studies reported on this important outcome

Nephrocalcinosis

- No studies reported on this important outcome

Ototoxicty

- No studies reported on this important outcome

Hyponatraemia

- Very low quality evidence from 1 cohort study (n= 39,357) showed a reduction in the incidence of hyponatraemia (<125 mmol/L) among preterm babies <32 weeks PMA on respiratory support who received furosemide compared to other diuretics, but there was uncertainty about this estimate.
- Very low quality evidence from 1 cohort study (n= 39,357) showed no difference in the incidence of severe hyponatraemia (<115 mmol/L) among preterm babies <32 weeks PMA on respiratory support who received furosemide compared to other diuretics, but there was uncertainty about this estimate.

Comparison 3. Combination diuretic versus single diuretic

Comparison 3.1 Chlorothiazide + spironolactone versus chlorothiazide

Critical outcomes

Mortality prior to discharge

- No studies reported on this critical outcome

Bronchopulmonary dysplasia (oxygen dependency at 36 weeks PMA or 28 days of age)

- No studies reported on this critical outcome

Neurodevelopmental outcomes at ≥18 months

- No studies reported on this critical outcome

Important outcomes

Days on invasive ventilation

- No studies reported on this important outcome

Nephrocalcinosis

- No studies reported on this important outcome

Ototoxicty

- No studies reported on this important outcome

Hyponatraemia

- Low quality evidence from 1 RCT (n=33) showed no clinically significant difference in the need for sodium supplementation among preterm babies on respiratory support with BPD who received chlorothiazide + spironolactone compared to those who received chlorothiazide.

See appendix E for Forest plots

Economic evidence statements

- No economic evidence on the cost effectiveness of diuretics in preterm babies requiring respiratory support was available.

Recommendations

C2.1 The committee did not make any recommendations relating to the use of diuretics in preterm babies on respiratory support

Research recommendations

What is the effectiveness of diuretics compared with placebo in preventing bronchopulmonary dysplasia in preterm babies on respiratory support?

What is the effectiveness of diuretics compared with placebo in the treatment of bronchopulmonary dysplasia in preterm babies on respiratory support?

Rationale and impact

Why the committee didn't make any recommendations

The evidence on the use of diuretics in preterm babies on respiratory support was very limited. None of the studies identified assessed critical outcomes such as mortality before discharge, BPD or neurodevelopmental outcomes. Although the studies looked at short-term adverse effects associated with diuretics, it was not clear whether there was an increased risk of adverse effects because of the small sample size of the studies.

Because of the limited evidence and lack of clinical consensus, the committee could not make any recommendations for or against diuretic use in preterm babies on respiratory support. Instead, the committee recommended that further research be done in this area.

Impact of the recommendations on practice

Although they did not make any recommendations, some of the committee members thought that the lack of evidence identified may lead to healthcare professionals reviewing their use of diuretics. This may lead to a reduction in the use of diuretics in preterm babies on respiratory support, at least until further evidence is available.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee considered mortality prior to discharge, BPD, and neurodevelopmental outcomes as critical for decision making, due to their long term impact. Days on invasive ventilation was an important outcome as diuretics may be used to help wean babies off ventilation. Nephrocalcinosis, ototoxicity and hyponatraemia are all potential adverse effects of treatment with diuretics so were chosen to chosen as important outcomes to help balance the benefits and harms of diuretic treatment.

The quality of the evidence

The evidence in the pairwise comparisons was assessed using GRADE methodology. The quality of evidence in this review was very low. Most of the outcomes available were related to the safety of diuretic use and not its effectiveness. Critical outcomes in relation to efficacy such as mortality prior to discharge, BPD, and neurodevelopmental outcomes were not assessed in any of the identified studies.

The quality of evidence was most often downgraded because of the uncertainty around the risk estimate, which was generally attributable to the low event rates and small sample sizes of the studies included in the review.

There was an absence of evidence on the critical outcomes. Benefits and harms

In preterm babies on respiratory support, the committee decided to not make any recommendation on the use of diuretics. Instead, they made two research recommendation.

The evidence for this review was of very low quality and limited, and of the outcomes listed in the protocol none of the critical outcomes (mortality prior to discharge, BPD, neurodevelopmental outcomes) were available. Of the outcomes for which data were available (nephrocalcinosis, ototoxicity, and hyponatraemia) there was no clear association between diuretics and the outcomes due to the uncertainty around the estimates given the small sample sizes of the studies.

The committee discussed that the use of diuretics in preterm babies on respiratory support was based on historical trials conducted prior to 1990 and short-term improvements in pulmonary mechanics that were used as surrogate markers, and assumed to translate into longer term clinical benefits. Although the committee discussed the evidence pre-1990, the committee agreed that these pre-surfactant era preterm babies were different to the preterm babies on the NICU's today and that short-term improvements in pulmonary mechanics do not necessarily translate to long-term clinical outcomes, such as mortality prior to discharge and BPD.

The committee discussed the disparity across the UK in the use of diuretics in different units, and even within units by different clinicians. In view of the disparity and limited evidence, the committee agreed that they could not make recommendations for or against diuretic use in preterm babies on respiratory support. However, they strongly advocated the need for further research into the use of diuretics in the prevention and treatment of BPD in preterm babies on respiratory support. The committee discussed that although they could not make recommendations, they believed that the evidence review and clear lack of consensus on diuretic use in preterm babies on respiratory support may lead to some healthcare professionals re-evaluating their use of diuretics, at least until further studies in the area are published.

Cost effectiveness and resource use

There was no evidence for the clinical effectiveness of diuretics in preterm babies on respiratory support. As a result, diuretics are not likely to be cost effective. The committee noted a low acquisition cost of diuretics and any change in practice (such as a decrease in their use) which might arise would have a minimal impact on the NHS.

References

Hoffman 2000

Hoffman DJ., Gerdes JS., Abbasi SA. Pulmonary function and electrolyte balance following spironolactone treatment in preterm infants with chronic lung disease: a double-blind, placebo-controlled, randomised trial. Journal of Perinatology 2000; 1: 41-45

Kao 1994

Kao LC., Durand DJ., McCrea RC., Birch MB., Powers RJ., Nickerson BG. Randomised trial of long-term diuretic therapy for infants with oxygen-dependent bronchopulmonary dysplasia. Journal of Pediatrics 1994; 124: 772-81

Laughon 2015

Laughon MM., Chantala MS., Aliaga A., Herring AH., Hornik CP., Hughes R., Clark RH., Smith BP. Diuretic exposure in premature infants from 1997-2011. American Journal of Perinatology 2015: 32(1); 49-56

Review question 3.6 What is the effectiveness of caffeine in preterm babies requiring respiratory support

Introduction

Apnoea of prematurity (AOP) is usually defined as a cessation of breathing of at least 20 seconds, or for 10 seconds when it is accompanied by hypoxaemia and bradycardia. The prevalence of AOP is related to gestational age and is more common in babies born at less than 28 weeks gestation or with extremely low birth weight (less than 1000g). It usually resolves by 34 weeks PMA, but if not managed appropriately, can lead to adverse neurodevelopmental outcomes. The mainstay of therapy is pharmacological, with some respiratory support if required. Caffeine, a methylxanthine, is the most common pharmacological agent used for the management of AOP and has been suggested to improve neurodevelopmental outcomes by limiting hypoxic-induced white matter injury and by possible effects on the microstructure of developing white matter. However, there is a lack of consensus regarding the optimal use of caffeine and some concern over its adverse effects.

This review aims to clarify the role of caffeine in preterm babies requiring respiratory support, including the optimal treatment regimen and an evaluation of the potential benefits and harms.

Summary of the protocol

See Table 6 for a summary of the population, intervention, comparison and outcome (PICO) characteristics of this review.

Table 6: Summary of the protocol (PICO table)

Population	Preterm babies requiring respiratory support. **Exclusions:** • Preterm babies with any congenital abnormalities except patent ductus arteriosus • Preterm babies who are ventilated solely due to a specific non-respiratory comorbidity, such as sepsis, necrotising enterocolitis, neurological disorders
Intervention	Caffeine (citrate or base) – oral or intravenous
Comparison	**Control:** • Placebo • No intervention **Comparisons:** • Caffeine versus control • Lower dose caffeine versus higher dose caffeine • Earlier administration of caffeine versus later administration of caffeine • Shorter duration versus longer duration
Outcome	**Critical outcomes:**

	• Mortality prior to discharge
	• Bronchopulmonary dysplasia at 36 weeks postmenstrual age (PMA)
	• Neurodevelopmental outcomes at ≥18 months:
	  ○ Cerebral palsy (reported as presence or absence of condition, **not** severity of condition)
	  ○ Neurodevelopmental delay (reported as dichotomous outcomes, **not** continuous outcomes such as mean change in score)
	  - Severe (score of >2 SD below normal on validated assessment scales, **or** on Bayley's assessment scale of mental developmental index (MDI) or psychomotor developmental index (PDI) <70 or complete inability to assign score due to CP or severe cognitive delay)
	  - Moderate (score of 1-2 SD below normal on validated assessment scales, **or** on Bayley's assessment scale of MDI or PDI 70-84)
	  ○ Neurosensory impairment (reported as presence or absence of condition, **not** severity of condition)
	  - Severe hearing impairment (for example, deaf)
	  - Severe visual impairment (for example, blind)
	
	Important outcomes:
	• Continuing apnoea
	• Extubation failure
	• Tachycardia
	• Necrotising enterocolitis

CP: cerebral palsy; MDI: mental development index; PDI: psychomotor developmental index; PMA: postmenstrual age; RCT: randomised controlled trial; SD: standard deviation

For full details see review protocol in appendix A.

Clinical evidence

Included studies

In total, 17 study reports were included in this review (Amaro 2018; Borsdzewska-Kornacka 2017; CAP 2006; Davis 2010; Dobson 2014; Doyle 2014; Gray 2011; Lodha 2015; Lodha 2018; McPherson 2015; Murner-Lavenchy 2018; Schmidt 2007; Schmidt 2012; Schmidt 2017; Steer 2003; Steer 2004; Taha 2014)

Six were RCTs (Amaro 2018; CAP 2006; Gray 2011; McPherson 2015; Steer 2003; Steer 2004), 5 were retrospective cohort studies (Borsdzewska-Kornacka 2017; Dobson 2014; Lodha 2015; Lodha 2018; Taha 2014) and 6 were follow-up studies to the CAP trial that looked at longer-term neurodevelopemental outcomes (Davis 2010; Doyle 2014; Murner-Lavenchy 2018; Schmidt 2007; Schmidt 2012; Schmidt 2017). See Table 7: Summary of included studies for a description of the follow-up time frames. Gray 2011 and Steer 2004 reported on the same population of babies.

Two RCTs (Amaro 2018; CAP 2006) compared caffeine to placebo.

Four RCTs (Gray 2011; McPherson 2015; Steer 2003; Steer 2004) compared lower dose caffeine to higher dose caffeine.

Four retrospective cohort studies (Borszewska-Kornacka 2017; Dobson 2014; Lodha 2015; Taha 2014) compared earlier administration of caffeine to later administration of caffeine.

One retrospective cohort study (Lodha 2018) compared shorter with longer duration of caffeine.

See the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

Studies not included in this review, with reasons for their exclusion, are provided in appendix K.

Summary of clinical studies included in the evidence review

Table 7 provides a brief summary of the included studies.

Table 7: Summary of included studies

Study and setting	Population	Intervention/ comparison	Outcomes	Comments
RCTs				
Amaro 2018 USA	n= 83 Babies born at 23-30 weeks gestation and required invasive ventilation in the first 5 post-natal days	Caffeine versus placebo Intervention: Loading dose of caffeine citrate 20 mg/kg followed by a maintenance dose of 5 mg/kg/day Control: blinded loading dose of placebo before extubation.	• Mortality prior to discharge • BPD at 36 weeks PMA or 28 DOL • Extubation failure • NEC	
CAP trial 2006 Australia and Canada	n= 2006 Babies with a birth weight of 500-1250g and were considered to be candidates for methylxanthine therapy during the first 10 days of life	Caffeine versus placebo Intervention: Intravenous loading dose of 20mg/kg caffeine citrate, daily maintenance dose of 5mg/kg. If apnoeas persisted, the daily maintenance dose could be increased to a maximum doe of 10mg/kg. Control: Intravenous loading dose of 20mg/kg of normal saline, daily maintenance dose of 5mg/kg.	• Mortality prior to discharge • BPD at 36 weeks PMA • NEC	9.5% of participants received ≥ 1 dose of open-label methylxanthines
Gray 2011 Australia	n= 246	Lower dose caffeine versus higher dose caffeine	• Mortality prior to discharge • BPD at 36 weeks PMA	

Study and setting	Population	Intervention/ comparison	Outcomes	Comments
	Required methylxanthines for treatment of apnoea of prematurity or as part of per-extubation management	Low dose: 20mg/kg loading dose of caffeine citrate followed at 24 hour intervals of a maintenance dose of 5 mg/kg High dose: 80mg/kg loading dose of caffeine citrate followed at 24 hour intervals of a maintenance dose of 20 mg/kg	• Continued apnoea	
McPherson 2015 USA	n= 74 Babies born at ≤ 30 weeks gestation	Standard dose caffeine versus higher dose caffeine Standard dose: Administered intravenously as 20 mg/kg of caffeine citrate followed by 10 mg/kg 24 hours after the initial dose (30 mg/kg total over 36 hours) Higher dose: Administered intravenously as an initial loading dose of 40 mg/kg of caffeine citrate followed by 20 mg/kg 12 hours later, then 10 mg/kg at 24 and 36 hours after the initial dose (80 mg/kg total over 36 hours)	• Mortality prior to discharge • BPD at 36 weeks PMA • NEC	
Steer 2003 Australia	n=127 Babies born at a gestational age of < 31 weeks and who had received or were expected to receive at least 48 hours of invasive ventilation	Lower dose caffeine versus higher dose caffeine Loading dose of 2mL/kg caffeine citrate, with either 6, 30, or 60 mg/kg caffeine according to treatment group over a 15-minute period. Maintenance dose of 1mL/kg given at 24 hour intervals for the following 6 days, starting 24	• Extubation failure • Tachycardia • NEC	

Study and setting	Population	Intervention/ comparison	Outcomes	Comments
		hours after the loading dose.		
Steer 2004 Australia	n=234 Babies born at a gestational age of < 30 weeks and who had received or were expected to receive at least 48 hours of invasive ventilation	Lower dose caffeine versus higher dose caffeine Low dose: 20mg/kg loading dose of caffeine citrate followed at 24 hour intervals of a maintenance dose of 5 mg/kg High dose: 80mg/kg loading dose of caffeine citrate followed at 24 hour intervals of a maintenance dose of 20 mg/kg	• Mortality prior to discharge • BPD at 36 weeks PMA • Continued apnoea • Extubation failure • Tachycardia • NEC	
Follow up studies of CAP trial				
Davis 2010	See CAP trial 2006 for study details	18-21 months follow up	• Neurodevelopmental outcomes	
Doyle 2014	See CAP trial 2006 for study details	5 year follow up	• Neurodevelopmental outcomes	
Murner-Lavanchy 2018	See CAP trial 2006 for study details	11 year follow up	• Neurodevelopmental outcomes	
Schmidt 2007	See CAP trial 2006 for study details	18-21 months follow up	• Neurodevelopmental outcomes	
Schmidt 2012	See CAP trial 2006 for study details	5 year follow up	• Neurodevelopmental outcomes	
Schmidt 2017	See CAP trial 2006 for study details	11 year follow up	• Neurodevelopmental outcomes	
Retrospective cohort studies				
Borszewska-Kornacka 2017 Poland	n=286 Babies with a gestational age of ≤ 32 weeks gestation, had a diagnosis of RDS regardless of the severity of radiological findings on the chest X-ray and	Earlier administration (< 2 days) caffeine versus later administration (≥ 2 days) caffeine	• Mortality prior to discharge • BPD at 36 weeks PMA	

Study and setting	Population	Intervention/ comparison	Outcomes	Comments
	needed surfactant treatment			
Dobson 2014 USA	n= 28,706 Very-low birth weight babies (< 1500g), received caffeine during hospital course and were admitted to hospital within 1 day of birth	Earlier administration (< 3 days) caffeine versus later administration (≥ 3 days) caffeine	• Mortality prior to discharge • BPD at 36 weeks PMA or at 28 DOL • NEC	
Lodha 2015 Canada	n= 5101 Babies born at < 31 weeks gestation	Earlier administration (< 3 days) caffeine versus later administration (≥ 3 days) caffeine	• Mortality prior to discharge • BPD at 36 weeks PMA or at 28 DOL • NEC	
Lodha 2018 Canada	n= 448 Premature babies born before 30 weeks gestation, birth weight < 1250g, receiving CPAP, before extubation from the ventilator and for AOP	Early cessation of caffeine ≤ 14 days (ECC), intermediate cessation of caffeine 15-30 days (ICC) and late cessation of caffeine > 30 days (LCC)	• BPD at 36 weeks PMA • CP • Neurodevelopmental outcomes • NEC	
Taha 2014 USA	n= 2951 Babies admitted to the NICU, were ≤ 1250g, were treated with caffeine within the first 10 days of life	Earlier administration (< 3 days) caffeine versus later administration (≥ 3 days) caffeine	• Mortality prior to discharge • BPD at 36 weeks PMA • NEC	

AOP: apnoea of prematurity; BPD: bronchopulmonary dysplasia; CP: cerebral palsy; CPAP: continuous positive airway pressure; DOL: days of life; g: grams; GA: gestational age; n: number; NEC: necrotising enterocolitis; NICU: neonatal intensive care unit; PMA: post-menstrual age; RDS: respiratory distress syndrome

See appendix D for clinical evidence tables.

Quality assessment of clinical studies included in the evidence review

See appendix F for full GRADE tables.

Economic evidence

No economic evidence on the cost effectiveness of caffeine in preterm babies requiring respiratory support was identified by the literature searches of the economic literature undertaken for this review.

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation.

Clinical evidence statements

Comparison 1. Caffeine versus control

Critical outcomes

Mortality prior to discharge

- Low quality evidence from 2 RCTs (n=2087) showed no clinically significant difference in mortality prior to discharge between preterm babies with a gestational age of 23-30^{+6} weeks who received caffeine compared to those who received placebo.

Bronchopulmonary dysplasia at 36 weeks PMA

Bronchopulmonary dysplasia – at 36 weeks PMA or 28 days of age

Babies 23-30 weeks

- Low quality evidence from 1 RCT (n=83) showed no clinically significant difference in bronchopulmonary dysplasia at 36 weeks PMA or 28 days of age between preterm babies with a gestational age of 23-30 weeks who received caffeine compared to those who received placebo.

Bronchopulmonary dysplasia – at 36 weeks PMA

Babies < 31 weeks

- Moderate quality evidence from 1 RCT (n=2006) showed a clinically significant decrease in bronchopulmonary dysplasia at 36 weeks PMA between preterm babies with a gestational age of < 31 weeks who received caffeine compared to those who received placebo.

Neurodevelopmental outcomes at ≥ 18 months: cerebral palsy

18-21 months follow-up, all babies

- Moderate quality evidence from 1 RCT (n=1810) showed a clinically significant decrease in cerebral palsy at 18-21 months follow-up between preterm babies with a gestational age of < 31 weeks who received caffeine compared to those who received placebo.

18-21 months follow-up, respiratory indications – pre-extubation

- Moderate quality evidence from 1 RCT (n=644) showed a clinically significant decrease in cerebral palsy at 18-21 months follow-up between preterm babies with a gestational age of < 31 weeks who received caffeine for pre-extubation compared to those who received placebo.

18-21 months follow-up, respiratory indications – apnoea treatment

- Moderate quality evidence from 1 RCT (n=749) showed no clinically significant difference in cerebral palsy at 18-21 months follow-up between preterm babies with a gestational age of < 31 weeks who received caffeine for apnoea treatment compared to those who received placebo.

18-21 months follow-up, respiratory indications – apnoea prophylaxis

- Low quality evidence from 1 RCT (n=415) showed no clinically significant difference in cerebral palsy at 18-21 months follow-up between preterm babies with a gestational age of < 31 weeks who received caffeine for apnoea prophylaxis compared to those who received placebo.

18-21 months follow-up, respiratory support – no partial-pressure ventilation

- Low quality evidence from 1 RCT (n=306) showed no clinically significant difference in cerebral palsy at 18-21 months follow-up between preterm babies with a gestational age of < 31 weeks requiring no partial-pressure ventilation at randomisation who received caffeine compared to those who received placebo.

18-21 months follow-up, respiratory support – non-invasive ventilation

- Low quality evidence from 1 RCT (n=754) showed no clinically significant difference in cerebral palsy at 18-21 months follow-up between preterm babies with a gestational age of < 31 weeks requiring non-invasive ventilation at randomisation who received caffeine compared to those who received placebo.

18-21 months follow-up, respiratory support – endotracheal tube

- Moderate quality evidence from 1 RCT (n=956) showed a clinically significant decrease in cerebral palsy at 18-21 months follow-up between preterm babies with a gestational age of < 31 weeks requiring an endotracheal tube at randomisation who received caffeine compared to those who received placebo.

5 year follow-up

- Very low quality evidence from 1 RCT (n=1433) showed no clinically significant difference in cerebral palsy at 5 years follow-up between preterm babies with a gestational age of < 31 weeks who received caffeine compared to those who received placebo.

11 year follow-up

- Very low quality evidence from 1 RCT (n=968) showed no clinically significant difference in cerebral palsy at 11 years follow-up between preterm babies with a gestational age of < 31 weeks who received caffeine compared to those who received placebo.

Neurodevelopmental outcomes at ≥ 18 months: severe cognitive impairment (babies < 31 weeks)

18-21 months follow-up, MDI score < 85 on the BSID-II – All babies

- Moderate quality evidence from 1 RCT (n=1725) showed a statistically (but not clinically) significant decrease in severe cognitive impairment at 18-21 months follow-up between preterm babies with a gestational age of < 31 weeks who received caffeine compared to those who received placebo.

18-21 months follow-up, MDI score < 85 on the BSID-II, respiratory indications – pre-extubation

- Moderate quality evidence from 1 RCT (n=612) showed there may be a statistically significant decrease in severe cognitive impairment at 18-21 months follow-up between preterm babies with a gestational age of < 31 weeks who received caffeine for pre-extubation compared to those who received placebo, but there is uncertainty around the risk estimate.

18-21 months follow-up, MDI score < 85 on the BSID-II, respiratory indications – apnoea treatment

- Moderate quality evidence from 1 RCT (n=715) showed no clinically significant difference in severe cognitive impairment at 18-21 months follow-up between preterm babies with a gestational age of < 31 weeks who received caffeine for apnoea treatment compared to those who received placebo.

18-21 months follow-up, MDI score < 85 on the BSID-II, respiratory indications –apnoea prophylaxis

- Moderate quality evidence from 1 RCT (n=396) showed no clinically significant difference in severe cognitive impairment at 18-21 months follow-up between preterm babies with a gestational age of < 31 weeks who received caffeine for apnoea prophylaxis compared to those who received placebo.

18-21 months follow-up, MDI score < 85 on the BSID-II, respiratory support – no partial-pressure ventilation

- Moderate quality evidence from 1 RCT (n=291) showed no clinically significant difference in severe cognitive impairment at 18-21 months follow-up between preterm babies with a gestational age of < 31 weeks requiring no partial-pressure ventilation at randomisation who received caffeine compared to those who received placebo.

18-21 months follow-up, MDI score < 85 on the BSID-II, respiratory support – non-invasive ventilation

- Moderate quality evidence from 1 RCT (n=523) showed no clinically significant difference in severe cognitive impairment at 18-21 months follow-up between preterm babies with a gestational age of < 31 weeks requiring non-invasive ventilation at randomisation who received caffeine compared to those who received placebo.

18-21 months follow-up, MDI score < 85 on the BSID-II, respiratory support – endotracheal tube

- Moderate quality evidence from 1 RCT (n=910) showed no clinically significant difference in severe cognitive impairment at 18-21 months follow-up between preterm babies with a gestational age of < 31 weeks requiring an endotracheal tube at randomisation who received caffeine compared to those who received placebo.

5 year follow-up, Full Scale IQ < 70 on the Wechsler Preschool and Primary Scale of Intelligence III

- Very low quality evidence from 1 RCT (n=1518) showed no clinically significant difference in severe cognitive impairment at 5 years follow-up between preterm babies with a gestational age of < 31 weeks who received caffeine compared to those who received placebo.

11 year follow-up, Full Scale IQ < 85 on the Wechsler Abbreviated Sale of Intelligence-II

- Very low quality evidence from 1 RCT (n=785) showed no clinically significant difference in severe cognitive impairment at 11 years follow-up between preterm babies with a gestational age of < 31 weeks who received caffeine compared to those who received placebo.

Neurodevelopmental outcomes at ≥ 18 months: deafness

18-21 months follow-up

- Low quality evidence from 1 RCT (n=1814) showed no clinically significant difference in deafness at 18-21 months follow-up between preterm babies with a gestational age of < 31 weeks who received caffeine compared to those who received placebo.

5 year follow-up

- Very low quality evidence from 1 RCT (n=1571) showed no clinically significant difference in deafness at 5 years follow-up between preterm babies with a gestational age of < 31 weeks who received caffeine compared to those who received placebo.

11 year follow-up

- Very low quality evidence from 1 RCT (n=968) showed no clinically significant difference in deafness at 11 years follow-up between preterm babies with a gestational age of < 31 weeks who received caffeine compared to those who received placebo.

Neurodevelopmental outcomes at ≥ 18 months: blindness (babies < 31 weeks)

18-21 months follow-up

- Low quality evidence from 1 RCT (n=1816) showed no clinically significant difference in blindness at 18-21 months follow-up between preterm babies with a gestational age of < 31 weeks who received caffeine compared to those who received placebo.

5 year follow-up

- Very low quality evidence from 1 RCT (n=1555) showed no clinically significant difference in blindness at 5 years follow-up between preterm babies with a gestational age of < 31 weeks who received caffeine compared to those who received placebo.

11 year follow-up

- Low quality evidence from 1 RCT (n=968) showed a clinically significant decrease in blindness at 11 years follow-up between preterm babies with a gestational age of < 31 weeks who received caffeine compared to those who received placebo.

Important outcomes

Continuing apnoea

- There was no evidence for this important outcome.

Extubation failure

- Low quality evidence from 1 RCT (n=83) showed no clinically significant difference in extubation failure between preterm babies with a gestational age of 23-30 weeks who received caffeine compared to those who received placebo.

Tachycardia

- There was no evidence for this important outcome.

Necrotising enterocolitis

- Very low quality evidence from 2 RCTs (n=2089) showed no clinically significant difference in necrotising enterocolitis between preterm babies with a gestational age of 23-30^{+6} weeks who received caffeine compared to placebo.

Comparison 2. Lower dose caffeine versus higher dose caffeine

Critical outcomes

Mortality prior to discharge

5mg/kg versus 20mg/kg, all respiratory indications, babies < 30 weeks

- Low quality evidence from 1 RCT (n=246) showed no clinically significant difference in mortality prior to discharge between preterm babies with a gestational age of < 30 weeks who received lower dose caffeine compared to higher dose caffeine.

5mg/kg versus 20mg/kg, respiratory indication – peri-extubation, babies < 30 weeks

- Low quality evidence from 1 RCT (n=234) showed no clinically significant difference in mortality prior to discharge between preterm babies with a gestational age of < 30 weeks who received lower dose caffeine for peri-extubation compared to higher dose.

20mg/kg versus 80mg/kg, babies ≤ 30 weeks

- Very low quality evidence from 1 RCT (n=74) showed no clinically significant difference in mortality prior to discharge between preterm babies with a gestational age of ≤ 30 weeks who received lower dose caffeine compared to higher dose caffeine.

Bronchpulmonary dysplasia

Bronchopulmonary dysplasia – oxygen dependency at 36 weeks PMA

5 mg/kg versus 20 mg/kg, all respiratory indications, babies < 30 weeks

- Moderate quality evidence from 1 RCT (n=246) showed a clinically significant increase in bronchopulmonary dysplasia at 36 weeks PMA between preterm babies with a gestational age of < 30 weeks who received lower dose caffeine for all respiratory indications compared to those who received higher dose caffeine.

5 mg/kg versus 20 mg/kg, respiratory indication – peri-extubation, babies < 30 weeks

- Moderate quality evidence from 1 RCT (n=234) showed a clinically significant increase in bronchopulmonary dysplasia at 36 weeks PMA between preterm babies with a gestational age of < 30 weeks who received lower dose caffeine for peri-extubation compared to those who received higher dose caffeine.

20 mg/kg versus 80 mg/kg, babies ≤ 30 weeks

- Very low quality evidence from 1 RCT (n=74) showed no clinically significant difference in bronchopulmonary dysplasia at 36 weeks PMA between preterm babies with a gestational age of ≤ 30 weeks who received lower dose caffeine compared to those who received higher dose caffeine.

Bronchopulmonary dysplasia – oxygen dependency at 28 days of age

5mg/kg versus 20mg/kg, respiratory indication – peri-extubation, babies < 30 weeks

- Moderate quality evidence from 1 RCT (n=234) showed no clinically significant difference in bronchopulmonary dysplasia at 28 days of age between preterm babies with a gestational age of < 31 weeks who received lower dose caffeine compared to those who received higher dose caffeine.

Neurodevelopmental outcomes at ≥ 18 months

- There was no evidence for this critical outcome.

Important outcomes

Continuing apnoea, episodes of apnoea recorded by nursing staff within 7 days of the start of caffeine treatment

5 mg/kg versus 20 mg/kg, all respiratory indications, babies < 30 weeks

- Moderate quality evidence from 1 RCT (n=246) showed a clinically significant increase in documented apnoeic periods between preterm babies with a gestational age of < 30 weeks who received lower dose caffeine for all respiratory indications compared to those who received higher dose caffeine.

5 mg/kg versus 20 mg/kg, respiratory indication – peri-extubation, babies < 30 weeks

- Moderate quality evidence from 1 RCT (n=234) showed clinically significantly increase in documented apnoeic periods in preterm babies with a gestational age of < 30 weeks who received lower dose caffeine for peri-extubation compared to those who received higher dose caffeine.

Extubation failure

3mg/kg versus 15mg/kg, babies < 32 weeks

- Moderate quality evidence from 1 RCT (n=82) showed no clinically significant difference in extubation failure between preterm babies with a gestational age of < 32 weeks who received lower dose caffeine compared to higher dose caffeine.

3mg/kg versus 30mg/kg, babies < 32 weeks

- Moderate quality evidence from 1 RCT (n=87) showed a clinically significant increase in extubation failure between preterm babies with a gestational age of < 32 weeks who received lower dose caffeine compared to higher dose caffeine.

15mg/kg versus 30mg/kg, babies < 32 weeks

- Low quality evidence from 1 RCT (n=85) showed no clinically significant difference in extubation failure between preterm babies with a gestational age of < 32 weeks who received lower dose caffeine compared to higher dose caffeine.

5mg/kg versus 20mg/kg, respiratory indication – peri-extubation, babies < 30 weeks

- Moderate quality evidence from 1 RCT (n=234) showed a clinically significant increase in extubation failure between preterm babies with a gestational age of < 30 weeks who received lower dose caffeine for peri-extubation compared to higher dose caffeine.

Tachycardia

3mg/kg versus 15mg/kg, babies < 32 weeks

- Low quality evidence from 1 RCT (n=82) showed no clinically significant difference in tachycardia between preterm babies with a gestational age of < 32 weeks who received lower dose caffeine compared to higher dose caffeine.

3mg/kg versus 30mg/kg, babies < 32 weeks

- Moderate quality evidence from 1 RCT (n=87) showed no clinically significant difference in tachycardia between preterm babies with a gestational age of < 32 weeks who received lower dose caffeine compared to higher dose caffeine.

15mg/kg versus 30mg/kg, babies < 32 weeks

- Low quality evidence from 1 RCT (n=85) showed no clinically significant difference in tachycardia between preterm babies with a gestational age of < 32 weeks who received lower dose caffeine compared to higher dose caffeine.

5mg/kg versus 20mg/kg, respiratory indication – peri-extubation, babies < 30 weeks

- Low quality evidence from 1 RCT (n=234) showed no clinically significant difference in tachycardia between preterm babies with a gestational age of < 30 weeks who received lower dose caffeine for peri-extubation compared to higher dose caffeine.

Necrotising enterocolitis

3mg/kg versus 15mg/kg, babies < 32 weeks

- Low quality evidence from 1 RCT (n=82) showed no clinically significant difference in necrotising enterocolitis between preterm babies with a gestational age of < 32 weeks who received lower dose caffeine compared to higher dose caffeine.

3mg/kg versus 30mg/kg, babies < 32 weeks

- Low quality of evidence from 1 RCT (n=87) showed no clinically significant difference in necrotising enterocolitis between preterm babies with a gestational age of < 32 weeks who received lower dose caffeine compared to higher dose caffeine. No events were reported in either of the treatment arms.
- 15mg/kg versus 30mg/kg, babies < 32 weeks
- Low quality evidence from 1 RCT (n=85) showed no clinically significant difference in necrotising enterocolitis between preterm babies with a gestational age of < 32 weeks who received lower dose caffeine compared to higher dose caffeine.

5mg/kg versus 20mg/kg, respiratory indication – peri-extubation, babies < 30 weeks

- Low quality evidence from 1 RCT (n=234) showed no clinically significant difference in necrotising enterocolitis between preterm babies with a gestational age of < 30 weeks who received lower dose caffeine for peri-extubation compared to higher dose caffeine.

20mg/kg versus 80mg/kg, babies ≤ 32 weeks

- Very low quality evidence from 1 RCT (n=74) showed no clinically significant difference in necrotising enterocolitis between preterm babies with a gestational age of ≤ 32 weeks who received lower dose caffeine compared to higher dose caffeine.

Comparison 3. Earlier administration of caffeine versus later administration of caffeine

Critical outcomes

Mortality prior to discharge

Caffeine administration at < 2 days versus ≥ 2 days, babies ≤ 32 weeks

- Very low quality evidence from 1 retrospective cohort study (n=286) showed no clinically significant difference in mortality prior to discharge between preterm babies with a gestational age of ≤ 32 weeks who received earlier caffeine administration compared to later caffeine administration.

Caffeine administration at < 3 days versus ≥ 3 days

- Very low quality evidence from 1 retrospective cohort study (n=29070) showed no clinically significant difference in mortality prior to discharge between preterm babies who received earlier caffeine administration compared to later caffeine administration.

Caffeine administration at < 3 days versus ≥ 3 days, babies < 31 weeks

- Very low quality evidence from 1 retrospective cohort study (n=5101) showed no clinically significant difference in mortality prior to discharge between preterm babies with a gestational age of < 31 weeks who received earlier caffeine administration compared to later caffeine administration.

Caffeine administration at < 3 days versus ≥ 3 days

- Very low quality evidence from 1 retrospective cohort study (n=2951) showed no clinically significant difference in mortality prior to discharge between preterm babies who received earlier caffeine administration compared to later caffeine administration.

Bronchopulmonary dysplasia

Bronchopulmonary dysplasia – oxygen dependency at 36 weeks PMA

Caffeine administration at < 2 days versus ≥ 2 days, babies ≤ 32 weeks

- Very low quality evidence from 1 retrospective cohort study (n=286) showed no clinically significant difference in bronchopulmonary dysplasia prior to discharge between preterm babies with a gestational age of ≤ 32 weeks who received earlier caffeine administration compared to later caffeine administration.

Caffeine administration at < 3 days versus ≥ 3 days, babies < 31 weeks

- Low quality evidence from 1 retrospective cohort study (n=5101) showed no clinically significant difference in bronchopulmonary dysplasia between preterm babies with a gestational age of < 31 weeks who received earlier caffeine administration compared to later caffeine administration.

Caffeine administration at < 3 days versus ≥ 3 days

- Very low quality evidence from 1 retrospective cohort study (n=2951) showed a statistically but not clinically significant decrease in bronchopulmonary dysplasia between preterm babies who received earlier caffeine administration compared to later caffeine administration.

Bronchopulmonary dysplasia – oxygen dependency at 36 weeks PMA or 28 days of age

Caffeine administration at < 3 days versus ≥ 3 days

- Very low quality evidence from 1 retrospective cohort study (n=29070) showed a statistically but not clinically significant decrease in bronchopulmonary dysplasia between preterm babies who received earlier caffeine administration compared to later caffeine administration.

Bronchopulmonary dysplasia – oxygen dependency at 28 days of age

Caffeine administration at < 3 days versus ≥ 3 days, babies < 31 weeks

- Low quality evidence from 1 retrospective cohort study (n=5101) showed no clinically significant difference in mortality prior to discharge between preterm babies with a gestational age of < 31 weeks who received earlier caffeine administration compared to later caffeine administration.

Neurodevelopmental outcomes at ≥ 18 months

- There was no evidence for this critical outcome.

Important outcomes

Continuing apnoea

- There was no evidence for this important outcome.

Extubation failure

- There was no evidence for this important outcome.

Tachycardia

- There was no evidence for this important outcome.

Necrotising enterocolitis

NEC any stage

- Low quality evidence from 1 retrospective cohort study (n=29,070) showed no clinically significant difference in necrotising enterocolitis between preterm babies who received earlier caffeine administration compared to later caffeine administration.
- Very low quality evidence from 1 retrospective cohort study (n=2,951) showed no clinically significant difference in necrotising enterocolitis between preterm babies who received earlier caffeine administration compared to later caffeine administration.

NEC ≥ stage 2

Babies < 31 weeks

- Very low quality evidence from 1 retrospective cohort study (n=5,101) showed no clinically significant difference in necrotising enterocolitis between preterm babies with a gestational age of < 31 weeks who received earlier caffeine administration compared to later caffeine administration

Comparison 4. Shorter duration caffeine versus longer duration caffeine

Critical outcomes

Mortality prior to discharge

- There was no evidence for this critical outcome

Bronchopulmonary dysplasia – oxygen dependency at 36 weeks PMA (babies < 30 weeks)

Early cessation of caffeine ≤ 14 days (ECC) versus intermediate cessation of caffeine 15-30 days (ICC)

- Very low quality evidence from 1 retrospective cohort study (n=214) showed a clinically significant increase in bronchopulmonary dysplasia between preterm babies with a gestational age of < 30 weeks who received ECC compared to ICC.

ECC versus late cessation of caffeine > 30 days (LCC)

- Very low quality evidence from 1 retrospective cohort study (n=287) showed no clinically significant difference in bronchopulmonary dysplasia between preterm babies with a gestational age of < 30 weeks who received ECC compared to LCC.

ICC versus LCC

- Very low quality evidence from 1 retrospective cohort study (n=257) showed no clinically significant difference in bronchopulmonary dysplasia between preterm babies with a gestational age of < 30 weeks who received ICC compared to LCC.

Neurodevelopmental outcomes at ≥ 18 months: cerebral palsy (babies < 31 weeks)

ECC versus ICC

- Very low quality evidence from 1 retrospective cohort study (n=214) showed no clinically significant difference in cerebral palsy between preterm babies with a gestational age of < 30 weeks who received ECC compared to ICC.

ECC versus LCC

- Very low quality evidence from 1 retrospective cohort study (n=287) showed no clinically significant difference in cerebral palsy between preterm babies with a gestational age of < 30 weeks who received ECC compared to LCC.

ICC versus LCC

- Very low quality evidence from 1 retrospective cohort study (n=257) showed no clinically significant difference in cerebral palsy between preterm babies with a gestational age of < 30 weeks who received ICC compared to LCC.

Neurodevelopmental outcomes at ≥ 18 months: moderate cognitive impairment – full scale IQ 1-2 SD below the mean (babies < 30 weeks) (follow-up 11 years)

ECC versus ICC

- Very low quality evidence from 1 retrospective cohort study (n=214) showed no clinically significant difference in moderate cognitive impairment between preterm babies with a gestational age of < 30 weeks who received ECC compared to ICC.

ECC versus LCC

- Very low quality evidence from 1 retrospective cohort study (n=287) showed no clinically significant difference in moderate cognitive impairment between preterm babies with a gestational age of < 30 weeks who received ECC compared to LCC.

ICC versus LCC

- Very low quality evidence from 1 retrospective cohort study (n=257) showed no clinically significant difference in moderate cognitive impairment between preterm babies with a gestational age of < 30 weeks who received ICC compared to LCC.

Neurodevelopmental outcomes at ≥ 18 months: severe cognitive impairment – full scale IQ > 2 SD below the mean (babies < 30 weeks) (follow-up 11 years)

ECC versus ICC

- Very low quality evidence from 1 retrospective cohort study (n=214) showed no clinically significant difference in severe cognitive impairment between preterm babies with a gestational age of < 30 weeks who received ECC compared to ICC.

ECC versus LCC

- Very low quality evidence from 1 retrospective cohort study (n=287) showed no clinically significant difference in severe cognitive impairment between preterm babies with a gestational age of < 30 weeks who received ECC compared to LCC.

ICC versus LCC

- Very low quality evidence from 1 retrospective cohort study (n=257) showed no clinically significant difference in severe cognitive impairment between preterm babies with a gestational age of < 30 weeks who received ICC compared to LCC.

Neurodevelopmental outcomes at ≥ 18 months: deafness (babies < 30 weeks) (11 years follow-up)

ECC versus ICC

- Very low quality evidence from 1 retrospective cohort study (n=214) showed no clinically significant difference in deafness between preterm babies with a gestational age of < 30 weeks who received ECC compared to ICC.

ECC versus LCC

- Very low quality evidence from 1 retrospective cohort study (n=287) showed no clinically significant difference in deafness between preterm babies with a gestational age of < 30 weeks who received ECC compared to LCC.

ICC versus LCC

- Very low quality evidence from 1 retrospective cohort study (n=257) showed no clinically significant difference in deafness between preterm babies with a gestational age of < 30 weeks who received ICC compared to LCC.

Neurodevelopmental outcomes at ≥ 18 months: blindness (babies < 31 weeks)

ECC versus ICC

- Very low quality evidence from 1 retrospective cohort study (n=214) showed no clinically significant difference in blindness between preterm babies with a gestational age of < 30 weeks who received ECC compared to ICC.

ECC versus LCC

- Very low quality evidence from 1 retrospective cohort study (n=287) showed no clinically significant difference in blindness between preterm babies with a gestational age of < 30 weeks who received ECC compared to LCC.

ICC versus LCC

- Very low quality evidence from 1 retrospective cohort study (n=257) showed no clinically significant difference in blindness between preterm babies with a gestational age of < 30 weeks who received ICC compared to LCC.

Important outcomes

Continuing apnoea

- There was no evidence for this important outcome.

Extubation failure

- There was no evidence for this important outcome.

Tachycardia

- There was no evidence for this important outcome.

Necrotising enterocolitis

ECC versus ICC

- Very low quality evidence from 1 retrospective cohort study (n=214) showed no clinically significant difference in necrotising enterocolitis between preterm babies with a gestational age of < 30 weeks who received ECC compared to ICC.

ECC versus LCC

- Very low quality evidence from 1 retrospective cohort study (n=287) showed a clinically significant increase in necrotising enterocolitis between preterm babies with a gestational age of < 30 weeks who received ECC compared to LCC.

ICC versus LCC

- Very low quality evidence from 1 retrospective cohort study (n=257) showed no clinically significant difference in necrotising enterocolitis between preterm babies with a gestational age of < 30 weeks who received ICC compared to LCC.

See appendix E for Forest plots.

Economic evidence statements

- No economic evidence on the cost effectiveness of caffeine in preterm babies requiring respiratory support was available.

Recommendations

C3.1 Use caffeine citrate routinely in preterm babies born at or before 30 weeks, starting it as early as possible and ideally before 3 days of age.

C3.2 Consider stopping caffeine citrate at 33–35 weeks corrected gestational age if the baby is clinically stable.

C3.3 Consider caffeine citrate for any preterm baby with apnoea.

C3.4 Give a loading dose of 20 mg/kg of caffeine citrate, followed 24 hours later by a maintenance dosage of 5 mg/kg once daily, increasing up to 20 mg/kg[b] daily if apnoeas persist.

C3.5 Consider a maintenance dosage higher than 20 mg/kg daily[b] if therapeutic efficacy is not achieved, while ensuring that safe plasma levels are maintained.

Research recommendations

What is the optimal maintenance dose of caffeine citrate in order to optimise neurodevelopmental outcomes in preterm babies?

Rationale and impact

Why the committee made the recommendations

There was evidence that in preterm babies born before 31 weeks, caffeine reduces the incidence of BPD, cerebral palsy (at 18-21 months' follow-up), and blindness (at 11-year follow-up) compared to placebo. Based on their clinical experience, the committee agreed that administering caffeine would also reduce apnoea in older preterm babies

There was evidence that compared with lower doses, higher doses of caffeine reduce the incidence of BPD, continued apnoea and extubation failure.

Evidence showed that the treatment with caffeine before 3 days of age may lead to a reduction in BPD. There was also evidence that treatment with caffeine for 15-30 days reduces the incidence of BPD compared to a shorter duration, and that treatment for greater than 30 days reduces the incidence of necrotising enterocolitis compared with treatment for less than 15 days.

To determine when caffeine should be stopped, the committee referred back to the studies and identified the age at which caffeine was started, the duration of caffeine, and hence the age at which it had been stopped. The committee noted that caffeine had been stopped in

b At the time of consultation (October 2018), caffeine citrate did not have a marketing authorisation for use in children and young people at this dosage. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

the studies between 33 and 35 weeks. This reflected the clinical experience of the committee as the age at which preterm babies were no longer expected to suffer from apnoea, and so this figure was used by the committee to develop their recommendations.

The committee made their dosing recommendations based on evidence that a higher dose is more effective than a lower dose, and on currently recommended doses used in clinical practice. However, the variation in loading and maintenance doses used across different clinical trials made selecting an optimal dose difficult, and although higher doses appeared to improve early outcomes, there were few data on long-term outcomes. For this reason, the committee recommended further research to identify the maintenance dose of caffeine citrate needed to optimise neurodevelopmental outcomes.

The committee also discussed whether monitoring caffeine levels was necessary and noted that the Evelina London Paediatric Formulary advises that babies can receive 10 mg/kg of caffeine twice daily without monitoring blood plasma levels (Evelina London 2015). The committee noted that there are units that do not currently monitor blood levels, and increasing doses to higher than 20 mg/kg daily may be a concern if units did not test blood levels at these higher doses. Therefore the committee made an additional recommendation that if apnoea persists and a baby receives more than 20mk/kg daily, caffeine levels should be tested.

Impact of the recommendations on practice

The recommendations will have a minimal impact on current practice. The committee noted that there is some variation in dosage regimens across the NHS, so these recommendations should lead to greater consistency in the choice of dosage regimens. In addition, there may be a small increase in the number of blood tests performed to assess caffeine levels if higher doses are used.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The aim of the review was to assess the effectiveness and safety of caffeine in preterm babies requiring respiratory support. Mortality prior to discharge, bronchopulmonary dysplasia and neurodevelopmental outcomes at ≥ 18 months were prioritised as critical outcomes to inform decision making. Mortality prior to discharge was considered a critical outcome because the ultimate aim of caffeine for preterm babies is to act as a respiratory stimulant to prevent intermittent hypoxia. Bronchopulmonary dysplasia can develop with prolonged respiratory support which may be required in hypoxic babies and was therefore also considered a critical outcome. Neurodevelopmental outcomes such as cerebral palsy, cognitive impairments and sensory impairments such as blindness and deafness can have profound effects on a baby's later life and thus neurodevelopmental outcomes were also considered as critical outcomes.

Continued apnoea, extubation failure and necrotising enterocolitis (NEC) were considered important outcomes to decision making as they reflect the effectiveness of caffeine as a respiratory stimulant, while tachycardia is one of the most common side effects of caffeine and so was chosen to help balance the benefits and harms of caffeine therapy.

The quality of the evidence

The quality of the evidence in this review ranged from high to very low and was most often downgraded due to methodological limitations affecting the risk of bias, inconsistency in results and uncertainty around the risk estimate. While much of the evidence was of low or

very low quality, the majority of the clinically significant outcomes were based on evidence of moderate quality. This enabled the committee to make strong recommendations.

Methodological limitations affecting the risk of bias were studies not reporting the method for randomisation, treatment allocation or blinding. Additionally, neurodevelopmental outcomes were at a risk of bias as a result of sample attrition due to death or loss to follow-up.

Uncertainty around the risk estimate was generally attributable to low event rates and small sample sizes. Uncertainty was not estimable for some outcomes due to results being presented in medians, meaning that imprecision was not calculable and the quality of the evidence was downgraded by one level in these cases.

In addition, despite the evidence not being good quality, the committee were impressed with the body of evidence, and although limited meta-analysis was conducted, results from individual studie all provided evidence that all suggested similar benefits.

Benefits and harms

The evidence for the use of caffeine, doses, duration and time of administration was mixed, though evidence was available from studies with large sample sizes. There was evidence for a decrease in bronchopulmonary dysplasia (BPD) in babies less than 31 weeks (caffeine compared to placebo) and less than 30 weeks (high compared to low dose). Early administration of caffeine (before 2 or 3 days of age) did not lead to improved clinically significant outcomes, but did lead to a statistically significant reduction in BPD compared to later administration. In babies <30 weeks gestation, there was evidence for a clinically significant decrease in BPD in those who received caffeine for 15-30 days compared to <15 days

Compared to placebo, there was also evidence of a reduction in cerebral palsy at 18-21 months and in a sub-group of babies who were given caffeine for respiratory indications, pre-extubation and with an endotracheal tube in place. There was a statistically significant but not clinically significant decrease in severe cognitive impairment.

There was no evidence for continued apnoea in caffeine versus placebo comparisons, but evidence showed that higher compared to lower doses of caffeine reduced the indicidence of continued apnoea.

The manufacturer's summary of product characteristics for caffeine citrate recommends a loading dose of 20mg/kg followed by a maintenance dose of 5-10mg/kg every 24 hours, 24 hours after the initial loading dose with the option of increasing maintenance doses over 10mg/kg/day if the baby is not responding. There was evidence for a decrease in BPD, apnoea and extubation failure in babies receiving a higher dose of caffeine compared to a lower dose (reported doses ranged from 15mg/kg to 30 mg/kg compared to 3mg/kg or 5mg/kg). There was no increase in tachycardia with the higher dose. Therefore, the committee recommended a loading dose of 20mg/kg of caffeine followed by a maintenance dose of 5mg/kg, increasing to 20mg/kg per day if needed. The committee noted that the half-life of caffeine in preterm babies is prolonged compared to adults and has been estimated to be 102 hours, which makes it unnecessary to split the daily dose (Aranda 1979).

Additionally, the committee knew from their clinical experience that earlier initiation would lead to less apnoea, and that it is standard practice to start babies born at or before 30 weeks (an approximate equivalent for babies born at 1.25kg) on caffeine soon after birth on their admission to the neonatal unit, so they recommended earlier initiation. There was no evidence for the use of caffeine in babies older than 32 weeks but for preterm babies of any age who experienced apnoea, the committee knew from their clinical experience that caffeine would be beneficial and so they made a consider recommendation for this age group.

There was evidence that showed a clinically significant decrease in the incidence of NEC in babies <30 weeks gestation who received caffeine for >30 days compared to <15 days. Though this evidence was of very low quality and was from a single study, the committee agreed that this was similar to their clinical experience where longer durations of caffeine therapy seem to offer benefits.

Cost effectiveness and resource use

There was no evidence on the cost effectiveness of caffeine in preterm babies who require respiratory support. The committee noted that caffeine citrate has low acquisition costs and is widely used across the NHS. The committee agreed that even increasing the dose up to 20 mg/kg would have negligible effect on NHS costs given that most centres are already using 10 mg/kg. As indicated by the clinical review, caffeine is associated with important improvements in outcomes including lower risk of BPD, apnoea and extubation failure that otherwise may require expensive treatment. As caffeine may also result in improvements in neurodevelopmental outcomes the committee agreed that the use of caffeine was likely to be cost-effective. The committee noted that going above 20mg/kg will require regular blood tests to check caffeine levels and this may incur additional costs to the NHS. However, not many babies would require higher than 20mg/kg dose and the impact on NHS would therefore be negligible.

Other factors the committee took into account

The committee used the Guy's and Saint Thomas' Trust (GSTT) Paediatric Formulary and Summaries of Product Characteristics (SPCs) when discussing their dosing recommendations.

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Review question 3.8 What is the effectiveness of interventions for closing a patent ductus arteriosus in preterm babies requiring respiratory support?

Introduction

The ductus arteriosus is a vascular structure which connects the pulmonary artery to the descending aorta in the foetus, allowing most of the right ventricular output to be diverted directly from the pulmonary artery into the aorta, bypassing the lungs. The ductus normally closes after birth, but in preterm babies the usual stimuli for closure are not present and the blood vessel remains open, a condition called patent ductus arteriosus (PDA). The presence of a PDA allows oxygen-rich blood from the aorta to mix with oxygen-poor blood from the pulmonary artery and has been associated with bronchopulmonary dysplasia (BPD).

The PDA is likely to close spontaneously before discharge in over 80% of preterm babies, but the time to closure is longer in babies with a lower gestational age and there is uncertainty over whether it is better to try to close a PDA in preterm babies or to adopt a conservative “wait and see” approach.

Pharmacological closure of a hemodynamically significant PDA in preterm babies is often carried out, usually using a cycloxygenase (COX) inhibitor, but other strategies such as fluid restriction, administration of diuretics and paracetamol may also be used. Closure may also be carried out using surgical techniques.

This review aims to explore whether any of these of these treatment strategies (pharmacological agents, fluid restriction with or without diuretics, or surgical closure) improves outcomes in preterm infants requiring respiratory support.

Summary of the protocol

See Table 8: Summary of the protocol (PICO table) for a summary of the population, intervention, comparison and outcome (PICO) characteristics of this review.

Table 8: Summary of the protocol (PICO table)

Population	Preterm babies diagnosed with patent ductus arteriosus by an echocardiogram and who require respiratory support. **Exclusions:** • Preterm babies with any congenital abnormalities except patent ductus arteriosus • Preterm babies who are ventilated solely due to a specific non-respiratory comorbidity, such as sepsis, necrotising enterocolitis, neurological disorders

Intervention	**Pharmacological**
	• Ibuprofen – oral or intravenous
	• Paracetamol – oral or intravenous
	
	Fluid restriction
	• Fluid restriction only – oral or intravenous
	• Fluid restriction with diuretics:
	  ○ Furosemide – oral or intravenous
	  ○ Combined oral spironolactone and oral chlorothiazide
	  ○ Combined intravenous furosemide and intravenous potassium canrenoate

	Surgical • Surgical ligation **Control** • Placebo • No intervention
Comparison	• Pharmacological versus placebo • Surgery versus no surgery • Fluid restriction versus placebo • Pharmacological versus surgery • Pharmacological versus fluid restriction • Surgery versus fluid restriction If pharmacological is better than surgery and fluid restriction: • Ibuprofen versus paracetamol If fluid restriction is better than surgery and pharmacological: • Fluid restriction only versus fluid restriction with diuretics If fluid restriction with diuretics is better than fluid restriction only: • Fluid restriction with combination diuretics versus fluid restriction with single diuretics
Outcome	**Critical outcomes:** • Mortality prior to discharge • Bronchpulmonary dysplasia (oxygen dependency at 36 weeks postmenstrual age or 28 days of age) • Neurodevelopmental outcomes at ≥18 months: o Cerebral palsy (CP) (reported as presence or absence of condition, **not** severity of condition) o Neurodevelopmental delay (reported as dichotomous outcomes, not continuous outcomes such as mean change in score) - Severe (score of >2 SD below normal on validated assessment scales, **or** on Bayleys assessment scale of mental developmental index (MDI) or psychomotor developmental index (PDI) <70 or complete inability to assign score due to CP or severe cognitive delay) - Moderate (score of 1-2 SD below normal on validated assessment scales, **or** on Bayleys assessment scale of MDI or PDI 70-84) o Neurosensory impairment (reported as presence or absence of condition, **not** severity of condition) - Severe hearing impairment (for example, deaf) - Severe visual impairment (for example, blind) **Important outcomes:** • Failure of patent ductus arteriosus closure • Renal impairment • Gastrointestinal complications: o Gastrointestinal perforation o Gastrointestinal haemorrhage o Necrotising enterocolitis

CP: cerebral palsy; MDI: mental development index; PDI: psychomotor developmental index; RCT: randomised controlled trial; SD: standard deviation

C Clinical evidence

2 Included studies

3 Thirteen studies that examined treatment outcomes in preterm babies on respiratory support
4 were included in total.10 reports of 9 randomised controlled trials (RCTs) were identified
5 (Aranda 2009; Bagnoli 2013; De Carolis 2000; Gournay 2004; Harkin 2016; Kanmaz 2013;
6 Oncel 2014; Oncel 2017 [Oncel 2014]; Overmeire 2004; Sosenko 2012). In addition 3
7 retrospective cohort studies (Laughon 2007; Madan 2009; Mirea 2012) were identified.

8 Seven RCTs compared ibuprofen to placebo (Aranda 2009; Bagnoli 2013; De Carolis 2000;
9 Gournay 2004; Kanmaz 2013; Overmeire 2004; Sosenko 2012).

10 One RCT compared paracetamol to placebo (Harkin 2016).

11 Two RCTs compared ibuprofen to paracetamol (Oncel 2014; Oncel 2017 [Oncel 2014]).

12 Two retrospective cohort studies compared surgery to placebo (Laughon 2007; Madan
13 2009).

14 One retrospective cohort study compared surgery to fluid restriction (Mirea 2012).

15 No evidence was available for the following comparisons:

16 • Fluid restriction versus placebo
17 • Pharmacological versus surgery
18 • Pharmacological versus fluid restriction

19 See the literature search strategy in appendix B and study selection flow chart in appendix C.

2 Excluded studies

21 Studies not included in this review, with reasons for their exclusion, are provided in appendix
22 K.

2 Summary of clinical studies included in the evidence review

24 Table 9 and Table 10 provide a brief summary of the included studies.

25 **Table 9: RCTs included in the review**

Study details	Participants	Interventions	Outcomes and results	Comments
Aranda 2009 USA Multi-centre, double-blinded, randomised, placebo-controlled trial	N= 136 All preterm infants born ≤ 30 weeks gestation, who were admitted to the NICU, birth weight 500-1000g, < 72 hours postnatal age, non-symptomatic PDA, evidence of ductal shunting documented by echocardiogram	Intervention: 10mg/mL ibuprofen (L-lysine formulation) given intravenously for 10 minutes using a 10mg/kg loading dose followed by 5mg/kg/d on the second and third study day, using an umbilical venous catheter	• Mortality prior to discharge • BPD at 36 weeks PMA • Rescued who were ligated- on or before day 14 • NEC	

Study details	Participants	Interventions	Outcomes and results	Comments
		or peripheral IV site Control: normal saline solution given at same intervals as the intervention		
Bagnoli 2013 Italy Randomised, placebo-controlled, double-blind, parallel design trial	N=134 Babies with a gestational age ≤ 32 weeks, birth weight ≤ 1500g, PDA with evidence of ductal shunting documented by echocardiography, postnatal age > 72h	Intervention: Ibuprofen was given intravenously for 10 min using 10mg/kg loading doses, followed by 5 mg/kg/d on the second and third study days, using an umbilical venous catheter or peripheral IV site Control: The treatment course for the control group was not reported	• Creatinine levels • BUN	
De Carolis 2000 Italy RCT	N= 46 Babies with a gestational age less than 31 weeks, admitted to the NICU, PDA determined by echocardiographic evaluation	Intervention: Ibuprofen as lysine salt, according to the following therapeutic regime: 10mg/kg infused over 20 min via peripheral vein and commenced within a period of 2 h following birth. A further two treatments of 5mg/kg, using the same modality, were administered by infusion at 24 and 48 h after the first dose. Control: No placebo was	• Mortality prior to discharge • BPD at 28 days of life • Back-up treatment with indomethacin • Surgical ligation • Urine output • Serum creatinine • NEC • Renal impairment	Infants with significant PDA after receiving ibuprofen or placebo were treated with open-label indomethacin. Failure to respond to medical treatment was followed by surgical ligation

Study details	Participants	Interventions	Outcomes and results	Comments
		administered to the control group.		
Gournay 2004 France Multi-centre, double-blind, randomised, placebo-controlled RCT	N= 131 Babies with a gestational age less than 28 weeks , postnatal age < 6 hours	Intervention: 2mL vials containing 5g/L intravenous ibuprofen. Loading dose of 10mg/kg then two maintenance doses of 5mg/kg at 24-h interval Control: 2mL vials containing 0.9% saline. Equivalent volumes of saline	• Mortality prior to discharge • BPD at 36 weeks PMA • At least 1 episode of urinary output < 2mL/kg per h (day 1-3) • At least episode of serum creatinine > 140µmol/L (day 1-3) • NEC • Isolated intestinal perforation	Patients received open-label ibuprofen
Harkin 2016 Finland Single-centre, double-blind, randomised, placebo-controlled RCT	N= 48 Babies admitted to NICU with a very low gestational age	Intervention: intravenous paracetamol 10mg/mL Control: 0.45% saline solution	• Mortality prior to discharge • BPD at 28 days of life, • BPD at 36 weeks PMA, • Oliguria (<1mL/kg/h) • Polyuria (>5mL/kg/h) • NEC, stage 3	
Kanmaz 2013 Turkey Single-centre, double-blind RCT	N= 46 Babies with a gestational age < 28weeks and/or birth weight of <1000g	Intervention: oral ibuprofen 10mg/kg within 12–24h after birth followed by 5mg/kg at 24 and 48 h. Oral ibuprofen was given via an orogastric tube, which was flushed with 1mL of sterile water to ensure	• Mortality prior to discharge • BPD at 36 weeks PMA • Urea • Creatinine • NEC	

Study details	Participants	Interventions	Outcomes and results	Comments
		delivery of the drug. Control: no treatment		
Oncel 2014 Turkey RCT	N= 80 Babies with a gestational age ≤ 30 weeks, birth weight ≤1250g, postnatal age 48-96 hours, 1 of the following echocardiographic criteria: a duct size >1.5mm, a left atrium to aorta ratio > 1/5. end diastolic reversal of blood flow in the aorta, or poor cardia function in addition to clinical signs of PDA	Intervention 1: oral ibuprofen at an initial dose of 10mg/kg followed by 5mg/kg at 24 and 48 hours. Intervention 2: oral paracetamol 15mg/kg every 6 hours for 3 days	• Mortality prior to discharge • PDA closure rate (after the first course) • Reopening and closure with 2nd cure • Surgical ligation rate • NEC • Gastrointestinal bleeding • BUN • Serum creatinine • Urine output	
Oncel 2017 See Oncel 2014 for study details	N=61		• Neurodevelopmental impairment • Moderate to severe cerebral palsy • Blindness • Deafness	
Overmeire 2004 Belgium Multi-centre, placebo-controlled, double-blinded trial	N= 415 Babies with a gestational age 24-30 weeks, written informed consent signed by parents	Intervention: 3 doses of intravenous ibuprofen lysine as an initial dose of 10mg/kg within the first 6 h of life, followed by two doses of 5mg/kg after 24 h and 48 h Control: 3 doses of saline as an initial dose of 1mL/kg,	• Mortality prior to discharge • BPD at 36 weeks PMA • PDA closed on day 3 • Reopened after closure on day 3 • Rescue treatment • Ligated • Urine production • Oliguria	

Study details	Participants	Interventions	Outcomes and results	Comments
		followed by 0·5mL/kg after 24 h and 48 h	• Serum creatinine • NEC stage 3	
Sosenko 2012 USA Single-centre, placebo-controlled, double-blinded, randomised trial	N= 105 Babies with a birth weight 500-1250g, gestational age 23-32 weeks, >24 hours old but ≤ 14 days old	Intervention: ibuprofen lysine; initial dose of 10mg/kg, 2 doses of 5mg/kg each, every 24 hours, by slow intravenous infusion Control: placebo equivalent volumes of dextrose by slow intravenous infusion on the same schedule as the intervention group	• Mortality prior to discharge • BPD at 36 weeks PMA • Repeat course of blinded study drug, first 28 days • Open-label ibuprofen, first 28 days • NEC (requiring surgery) • Spontaneous intestinal perforation	Open-label ibuprofen was administered when PDA was confirmed with echo-cardiography

BPD: bronchopulmonary dysplasia; BUN: blood urea nitrogen; d: days; h: hours; IV: intravenous; n: number; NEC: necrotising enterocolitis; NICU: neonatal intensive care unit; PDA: patent ductus arteriosus; PMA: post-menstrual age

Table 10: Observational studies included in the review

Study details	Participants	Interventions	Outcomes and Results	Comments
Laughon 2007 USA Retrospective cohort study	N= 4587 Babies born 23-30 weeks gestation , cared for in NICUs managed by the Pediatrix Medical Group, discharged from the unit	Ligation only: ligation of the PDA was performed and in whom there was no report of prior use of indomethacin PDA without treatment: diagnosis of PDA and in whom there was no report of treatment (i.e. indomethacin or ligation)	• Mortality prior to discharge • NEC • Intestinal perforation	The database did not provide information on how PDA was diagnosed or how the clinician made the decision to treat the PDA. The authors could only evaluate the first course of therapy and did not have information on dose. The outcome of neonates exposed to multiple courses of indomethacin was not evaluated.

Study details	Participants	Interventions	Outcomes and Results	Comments
Madan 2009 USA Retrospective cohort study	N= 538 Babies who survived > 72 hours, developed clinically significant PDA, had 18 to 22 month neurodevelopmental follow up before October 27, 2006	Intervention: primary surgical closure Control: supportive treatment (met clinical criteria for significant PDA and who received no indomethacin treatment or surgical ligation for PDA. Some patients who received supportive treatment received prophylactic indomethacin before the diagnosis of PDA	• Mortality prior to discharge	Some patients in the control group received prophylactic indomethacin before the diagnosis of PDA. Information regarding clinicians' choice of therapy, several complications of prematurity and therapy for PDA other than indomethacin or surgery were not available.
Mirea 2012 Canada Retrospective cohort study	N= 904 Babies born between 2004-2008, GA ≤ 32 weeks, diagnosed with PDA from 22 NICUs in Canada	Surgical ligation only: performed in infants with PDA unresponsive to medical treatment or with contraindications to medical treatment Conservative management alone: including fluid restriction and/or diuretics, without medical or surgical intervention	• Mortality prior to discharge • BPD at 36 weeks PMA • NEC stages 2 or 3	Infants with PDA unresponsive to medical treatment or with contraindications to medical treatment received surgical ligation. Some infants classified as conservatively treated could have received prophylactic indomethacin, thereby contaminating the control group and reducing the observed impact of indomethacin treatment administered specifically for PDA; however, data regarding prophylactic indomethacin use were not available for adjustment.

BPD: bronchopulmonary dysplasia; BUN: blood urea nitrogen; GA: gestational age: n= number; NEC: necrotising enterocolitis; NICU: neonatal intensive care unit; PDA: patent ductus arteriosus; PMA: postmenstrual age

See appendix D for clinical evidence tables.

Quality assessment of clinical studies included in the evidence review

See appendix F for full GRADE tables.

Economic evidence

No economic evidence on the cost effectiveness of interventions for closing a patent ductus arteriosus in preterm babies requiring respiratory support was identified by the literature searches of the economic literature undertaken for this review.

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation.

Clinical evidence statements

Comparison 1. Pharmacological treatment versus placebo

Comparison 1.1 Ibuprofen versus placebo

Critical outcomes

Mortality prior to discharge

- Low quality evidence from 6 RCTs (n=879) showed no clinically significant difference in mortality prior to discharge between preterm babies with a gestational age of < 32 weeks who received ibuprofen compared to those who received placebo.

BPD at 36 weeks PMA or 28 days of life

BPD at 36 weeks PMA

- Moderate quality evidence from 4 RCTs (n=285) showed no clinically significant difference in BPD at 36 weeks PMA between preterm babies with a gestational age of < 32 weeks who received ibuprofen compared to those who received placebo.

BPD at 28 days of life

- High quality evidence from 3 RCTs (n=586) showed no clinically significant difference in BPD at 28 days of life between preterm babies with a gestational age of < 30 weeks who received ibuprofen compared to those who received placebo.

Neurodevelopmental outcomes at ≥ 18 months

- There was no evidence for this critical outcome.

Important outcomes

Failure of patent ductus arteriosus closure

PDA required back-up treatment with indomethacin

- High quality evidence from 2 RCTs (n=561) showed a clinically significant decrease in the number of babies requiring back-up treatment with indomethacin in preterm babies with a gestational age of < 31 weeks who received ibuprofen compared to those who received placebo.

PDA required surgical ligation

- Moderate quality evidence from 2 RCTs (n=561) showed no clinically significant difference in those who required surgical ligation between preterm babies with a gestational age of < 31 weeks who received ibuprofen compared to those who received placebo.

PDA failed to close on day 3

All infants 24-30 weeks

- Moderate quality evidence from 2 RCTs (n=586) showed a clinically significant decrease in failure to close on day 3 in all preterm aged 24-30 weeks babies who received ibuprofen compared to those who received placebo.

24-26 weeks

- High quality evidence from 1 RCT (n=101) showed a clinically significant decrease in failure to close on day 3 in preterm babies aged 24-26 weeks who received ibuprofen compared to those who received placebo.

27-30 weeks

- High quality evidence from 1 RCT (n=314) showed a clinically significant decrease in failure to close on day 3 in preterm babies aged 27-30 weeks who received ibuprofen compared to those who received placebo.

PDA reopened after closure on day 3

- Low quality evidence from 1 RCT (n=415) showed no clinically significant difference in reopening after closure on day 3 between preterm babies with a gestational age of 24-30 weeks who received ibuprofen compared to those who received placebo.

Repeated course of blinded study drug, first 28 days

- High quality evidence from 1 RCT (n=105) showed a clinically significant decrease in those needing a repeated course of blinded study drug during the first 28 days in preterm babies with a gestational age of 23-32 weeks who received ibuprofen compared to those who received placebo.

Open-label ibuprofen, first 28 days

- Low quality evidence from 1 RCT (n=105) showed no clinically significant difference in those needing open-label ibuprofen during the first 28 days between preterm babies with a gestational age of 23-32 weeks who received ibuprofen compared to those who received placebo.

Renal impairment

At least 1 episode of serum creatinine > 140µmol/L (Day 1-3)

- Moderate quality evidence from 1 RCT (n=131) showed no clinically significant difference in those with at least 1 episode of serum creatinine >140µmol/L between preterm babies with a gestational age < 28 weeks who received ibuprofen compared to those who received placebo

Serum creatinine (mg/dL)

Day 1

- Moderate quality evidence from 1 RCT (n=46) showed no clinically significant difference in serum creatinine levels on day 1 between preterm babies with a gestational age of < 28 weeks who received ibuprofen compared to those who received placebo.

Day 4

- Moderate quality evidence from 1 RCT (n=46) showed no clinically significant difference in serum creatinine levels on day 4 between preterm babies with a gestational age of < 28 weeks who received ibuprofen compared to those who received placebo.

Serum creatinine (µmol/L)

Day 1

- High quality evidence from 1 RCT (n=415) showed no clinically significant difference in serum creatinine levels on day 1 between preterm babies with a gestational age of 24-30 weeks who received ibuprofen compared to those who received placebo.

Day 3

- High quality evidence from 1 RCT (n=415) showed a clinically significant increase in serum creatinine levels on day 3 in preterm babies with a gestational age of 24-30 weeks who received ibuprofen compared to those who received placebo.

Median serum creatinine (mg/dl), day 7

- Low quality evidence from 1 RCT (n=134) showed a clinically significant increase at day 7 in median creatinine levels in preterm babies with a gestational age of ≤ 32 weeks who received ibuprofen compared to those who received placebo.

At least 1 episode of urinary output < 2 mL/kg/h (Day 1-3)

- Moderate quality evidence from 1 RCT (n=131) showed no clinically significant difference in the number of babies who had at least 1 episode of urinary output < 2 mL/kg/h between preterm babies with a gestational age of < 28 weeks who received ibuprofen compared to those who received placebo.

Urine production (mL/kg/h)

Day 1

- High quality evidence from 1 RCT (n=415) showed a clinically significant decrease in urine production on day 1 in preterm babies with a gestational age of 24-30 weeks who received ibuprofen compared to those who received placebo.

Day 3

- Moderate quality evidence from 1 RCT (n=415) showed no clinically significant difference in urine production on day 3 between preterm babies with a gestational age of 24-30 weeks who received ibuprofen compared to those who received placebo.

Median blood urea nitrogen (BUN) (mg/dl) – Day 7

- Low quality evidence from 1 RCT (n=134) showed a clinically significant increase in median BUN levels in preterm babies with a gestational age of ≤ 32 weeks who received ibuprofen compared to those who received placebo.

Urea (mg/dl)

Day 1

- Moderate quality evidence from 1 RCT (n=46) showed no clinically significant difference in urea on day 1 between preterm babies with a gestational age of < 28 weeks who received ibuprofen compared to those who received placebo.

Day 4

- Low quality evidence from 1 RCT (n=46) showed no clinically significant difference in urea on day 4 between preterm babies with a gestational age of < 28 weeks who received ibuprofen compared to those who received placebo.

Oliguria < 0.5mL/kg/h (Days 1-3)

- Moderate quality evidence from 1 RCT (n=415) showed a clinically significant increase in oliguria < 0.5mL/kg/h on days 1-3 in preterm babies with a gestational age of 24-30 weeks who received ibuprofen compared to those who received placebo.

Gastrointestinal complications

Intestinal perforation

- Very low quality evidence from 2 RCTs (n=236) showed no clinically significant difference in rates of intestinal perforation between preterm babies with a gestational age of < 32 weeks who received ibuprofen compared to those who received placebo.

NEC (requiring surgery)

- Low quality evidence from 1 RCT (n=105) showed no clinically significant difference in NEC requiring surgery between preterm babies with a gestational age of 23-32 weeks who received ibuprofen compared to those who received placebo.

NEC (stage 3)

- Low quality evidence from 1 RCT (n=415) showed no clinically significant difference in stage 3 NEC between preterm babies with a gestational age of 24-30 weeks who received ibuprofen compared to those who received placebo.

NEC (any stage)

- Very low quality evidence from 4 RCTs (n=343) showed no clinically significant difference in NEC at any stage between preterm babies with a gestational age of < 31 weeks who received ibuprofen compared to those who received placebo.

Comparison 1.2 Paracetamol versus placebo

Critical outcomes

Mortality prior to discharge

- Low quality evidence from 1 RCT (n=48) showed no clinically significant difference in mortality prior to discharge between preterm babies who received paracetamol compared to those who received placebo.

BPD at 36 weeks PMA

- Low quality evidence from 1 RCT (n=48) showed no clinically significant difference in BPD at 36 weeks PMA between preterm babies who received paracetamol compared to those who received placebo.

Neurodevelopmental outcomes at ≥ 18 months

- There was no evidence for this critical outcome.

Important outcomes

Failure of patent ductus arteriosus closure

- There was no evidence for this important outcome.

Renal impairment

Oliguria (< 1mL/kg/h)

- Low quality evidence from 1 RCT (n=48) showed no clinically significant difference in oliguria between preterm babies who received paracetamol compared to those who received placebo.

Polyuria (> 5mL/kg/h)

- Low quality evidence from 1 RCT (n=48) showed no clinically significant difference in polyuria between preterm babies who received paracetamol compared to those who received placebo.

Gastrointestinal complications

NEC (stage 3)

- Low quality evidence from 1 RCT (n=48) showed no clinically significant difference in stage 3 NEC between preterm babies who received paracetamol compared to those who received placebo.

Comparison 2. Surgery versus no surgery

Critical outcomes

Mortality prior to discharge

- Very low quality evidence from 2 observational studies (n=4587 and n=538) showed no clinically significant difference in mortality prior to discharge between preterm babies with a gestational age of < 30 weeks who received surgery compared to those who received no surgery.

BPD at 36 weeks PMA or 28 days of life

- There was no evidence for this critical outcome.

Neurodevelopmental outcomes at ≥ 18 months

- There was no evidence for this critical outcome.

Important outcomes

Failure of patent ductus arteriosus closure

- There was no evidence for this important outcome.

Renal impairment

- There was no evidence for this important outcome.

Gastrointestinal complications

Intestinal perforation

- Very low quality evidence from 1 observational study (n=4587) showed a clinically significant increase in intestinal perforation in preterm babies with a gestational age of 24-30 weeks who received surgery compared to those who received placebo.

NEC

- Very low quality evidence from 1 observational study (n=4587) showed a clinically significant increase in NEC in preterm babies with a gestational age of 24-30 weeks who received surgery compared to those who received placebo.

Comparison 3. Surgery versus fluid restriction

Critical outcomes

Mortality prior to discharge

- Very low quality evidence from 1 observational study (n=904) showed no clinically significant difference in mortality prior to discharge between preterm babies with a gestational age of ≤ 32 weeks who received surgery compared to those who received fluid restriction.

BPD at 36 weeks PMA or 28 days of life

- Very low quality evidence from 1 observational study (n=904) showed a clinically significant increase in BPD at 36 weeks PMA or 28 days of life in preterm babies with a gestational age of ≤ 32 weeks who received surgery compared to those who received fluid restriction.

Neurodevelopmental outcomes at ≥ 18 months

- There was no evidence for this critical outcome.

Important outcomes

Failure of patent ductus arteriosus closure

- There was no evidence for this important outcome.

Renal impairment

- There was no evidence for this important outcome.

Gastrointestinal complications

NEC (stages 2 or 3)

- Very low quality evidence from 1 observational study (n=904) showed a clinically significant increase in stage 2 or 3 NEC in preterm babies with a gestational age of ≤ 32 weeks who received surgery compared to those who received fluid restriction.

Comparison 4. Ibuprofen versus paracetamol

Critical outcomes

Mortality prior to discharge

- Very low quality evidence from 1 RCT (n=80) showed no clinically significant difference in mortality prior to discharge between preterm babies with a gestational age of ≤ 30 weeks who received ibuprofen compared to those who received paracetamol.

BPD at 36 weeks PMA or 28 days of life

- There was no evidence for this critical outcome.

Neurodevelopmental outcomes at ≥ 18 months: neurodevelopmental impairment

- Very low quality evidence from 1 RCT (n=61) showed no clinically significant difference in neurodevelopmental impairment between preterm babies with a gestational age of ≤ 30 weeks who received ibuprofen compared to those who received paracetamol.

Neurodevelopmental outcomes at ≥ 18 months: moderate to severe cerebral palsy

- Very low quality evidence from 1 RCT (n=61) showed no clinically significant difference in moderate to severe cerebral palsy between preterm babies with a gestational age of ≤ 30 weeks who received ibuprofen compared to those who received paracetamol.

Neurodevelopmental outcomes at ≥ 18 months: blindness

- Very low quality evidence from 1 RCT (n=61) showed no clinically significant difference in blindness between preterm babies with a gestational age of ≤ 30 weeks who received ibuprofen compared to those who received paracetamol.

Neurodevelopmental outcomes at ≥ 18 months: deafness

- Very low quality evidence from 1 RCT (n=61) showed no clinically significant difference in deafness between preterm babies with a gestational age of ≤ 30 weeks who received ibuprofen compared to those who received paracetamol.

Important outcomes

Failure of patent ductus arteriosus closure

PDA closure after first course of study drug

≤ 30 weeks

- Moderate quality evidence from 1 RCT (n=80) showed no clinically significant difference in PDA closure after the first course of the study drug between preterm babies at ≤ 30 weeks who received ibuprofen compared to those who received paracetamol.

< 28 weeks

- Low quality evidence from 1 RCT (n=42) showed no clinically significant difference in PDA closure after the first course of the study drug between preterm babies at < 28 weeks who received ibuprofen compared to those who received paracetamol.

≤ 26 weeks

- Very low quality evidence from 1 RCT (n=39) showed no clinically significant difference in PDA closure after the first course of the study drug between preterm babies at ≤ 26 weeks who received ibuprofen compared to those who received paracetamol.

Reopening and closure with second cure

≤ 30 weeks

- Very low quality evidence from 1 RCT (n=80) showed no clinically significant difference in reopening and closure with second cure between preterm babies at ≤ 30 weeks who received ibuprofen compared to those who received paracetamol.

< 28 weeks

- Very low quality evidence from 1 RCT (n=42) showed no clinically significant difference in reopening and closure with second cure between preterm babies at < 28 weeks who received ibuprofen compared to those who received paracetamol.

≤ 26 weeks

- Very low quality evidence from 1 RCT (n=39) showed no clinically significant difference in reopening and closure with second cure between preterm babies at ≤ 26 weeks who received ibuprofen compared to those who received paracetamol.

Surgical ligation rate

≤ 30 weeks

- Very low quality evidence from 1 RCT (n=80) showed no clinically significant difference in the surgical ligation rate between preterm babies at ≤ 30 weeks who received ibuprofen compared to those who received paracetamol.

< 28 weeks

- Very low quality evidence from 1 RCT (n=42) showed no clinically significant difference in the surgical ligation rate between preterm babies at < 28 weeks who received ibuprofen compared to those who received paracetamol.

≤ 26 weeks

- Very low quality evidence from 1 RCT (n=39) showed no clinically significant difference in the surgical ligation rate between preterm babies at ≤ 26 weeks who received ibuprofen compared to those who received paracetamol.

Renal impairment

Change in blood urea nitrogen (BUN) (mg/dL) from pre-treatment to post-treatment

- Low quality evidence from 1 RCT (n=80) showed no clinically significant difference in change in BUN from pre-treatment to post-treatment between preterm babies with a gestational age of ≤ 30 weeks who received ibuprofen compared to those who received paracetamol.

Change in serum creatinine (mg/dL) from pre-treatment to post-treatment

- Low quality evidence from 1 RCT (n=80) showed no clinically significant difference in deafness between preterm babies with a gestational age of ≤ 30 weeks who received ibuprofen compared to those who received paracetamol.

Change in urine output (mL/kg/h) from pre-treatment to post-treatment

- Low quality evidence from 1 RCT (n=80) showed no clinically significant difference in change in urine output from pre-treatment to post-treatment between preterm babies with a gestational age of ≤ 30 weeks who received ibuprofen compared to those who received paracetamol.

Gastrointestinal complications

NEC (any stage)

- Very low quality evidence from 1 RCT (n=80) showed no clinically significant difference in NEC at any stage between preterm babies with a gestational age of ≤ 30 weeks who received ibuprofen compared to those who received paracetamol.

NEC (stage > 2)

- Very low quality evidence from 1 RCT (n=80) showed no clinically significant difference in NEC at stage 2 or greater between preterm babies with a gestational age of ≤ 30 weeks who received ibuprofen compared to those who received paracetamol.

Gastrointestinal bleeding

- Very low quality evidence from 1 RCT (n=80) showed no clinically significant difference in gastrointestinal bleeding between preterm babies with a gestational age of ≤ 30 weeks who received ibuprofen compared to those who received paracetamol.

See appendix E for Forest plots.

Economic evidence statements

- No economic evidence on the cost effectiveness of interventions for closing a patent ductus arteriosus in preterm babies requiring respiratory support was available.

Recommendations

C4.1 Do not treat a patent ductus arteriosus (PDA) in a preterm baby unless it causes a significant clinical problem, for example, difficulty weaning the baby from a ventilator.

Research recommendations

Are any echocardiographic parameters able to improve predictive course of patent ductus arteriosus (PDA) and therefore suggest a group of babies who would benefit from PDA treatment?

Rationale and impact

Why the committee made the recommendations

There was no evidence of benefit from treating a PDA, and there was evidence for potential harms from treating it, with either medicines or surgery. However, the committee agreed that for some babies, treatment might be appropriate, for example, if there is difficulty weaning the baby from a ventilator. The committee agreed that further research was needed to identify which groups of babies would benefit most from PDA closure, and so made a research recommendation.

Impact of the recommendations on practice

The recommendation will reduce the unnecessary treatment of PDA and the number of babies exposed to potential harms from its treatment. The recommendations may result in cost savings because fewer procedures will be carried out.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The aim of the review was to assess the effectiveness of interventions for closing a PDA in preterm babies requiring respiratory support. The aim of closing a PDA is to reduce mortality prior to discharge and the incidence of BPD and therefore these were critical outcomes. As the haemodynamic disturbances associated with a large PDA can affect cerebral blood flow, neurodevelopmental delay (cerebral palsy, cognitive impairment and sensory impairments such as blindness and deafness) was also selected as a critical outcome, particularly as this can have profound and long-lasting effects on a baby's life, and their parents/carers too.

Failure of PDA closure was chosen as a measure of the effectiveness of interventions and an important outcome. As the range of possible treatment interventions can have adverse effects including renal impairment and gastrointestinal complications these were also considered as important outcomes.

There was evidence for all these outcomes across the range on interventions considered, but limited evidence for neurodevelopmental outcomes.

The quality of the evidence

No evidence was available for fluid restriction versus placebo, pharmacological treatment versus surgery, or pharmacological treatment versus fluid restriction. However these were not considered priorities for further research.

The quality of the evidence in this review ranged from very low to high with about half of the outcomes being rated as moderate to high.

The quality of evidence was most often downgraded because of methodological limitations affecting the risk of bias, inconsistency and the uncertainty around the risk estimate.

Methodological limitations affecting the risk of bias were generally attributed to several studies not reporting the method for randomisation, treatment allocation, or blinding.

Uncertainty around the risk estimate was generally attributable to low event rates and small sample sizes. Uncertainty was also not available for some outcomes due to results being presented in medians, meaning that imprecision was not calculable and the quality of the evidence was downgraded by one level in these cases.

The low quality of the evidence and failure of some studies to report the criteria for treating PDA or administering back up treatment made it more difficult for the committee to make any recommendations for the treatment of PDA.

Benefits and harms

There was evidence that ibuprofen was effective at closing the PDA, but there was no evidence for a reduction in mortality with any of the interventions, nor for a reduction in BPD. Indeed, with one comparison (surgery versus fluid restriction) there was evidence of an increase in BPD rates with surgical treatment. Similarly, there was evidence, but it showed no difference for any change in neurodevelopmental outcomes for the comparison of ibuprofen versus paracetamol (the only comparison where neurodevelopmental outcomes were available). However, there was evidence which showed there were side-effects from interventions including evidence for renal impairment with ibuprofen and gastrointestinal complications including intestinal perforation with surgery. Therefore, the committee agreed that the harms of routinely treating PDA outweighed the potential clinical benefits. The committee's recommendation to not routinely treat PDA would result in fewer babies receiving surgery unnecessarily and fewer side effects from drugs used to treat PDA.

The committee discussed that in some cases it might be appropriate to treat a PDA, for example in babies who were proving very difficult to wean from a ventilator. In these babies an individualised decision to treat the PDA might be made.

Cost effectiveness and resource use

There was no existing evidence on the cost-effectiveness of treatments for PDA in preterm babies requiring respiratory care. However, as evidence for the effectiveness of treatments for PDA showed no benefits, and the harms of treating PDA outweighed the potential clinical benefits it is unlikely that any interventions will be cost-effective in this population.

The committee explained that the unit cost for the PDA surgery depends on the presence of co-morbidities. According to the NHS Reference Costs 2016/17 (Non-Elective Long Stay) the unit cost for Intermediate Procedure for Congenital Heart Disease with CC Score 0-3 is £5,351 (EC14C), for a procedure with CC Score 4-8 it is £7,059 (EC14B), and for a procedure with a CC Score 9+ the unit cost is as much as £12,945 (EC14A). The committee noted that almost none will have EC14A, but many may have EC14B or EC14C. Also, the tariff will be brought down if another procedure of lower value is done concomitantly. The committee discussed the number of surgical PDA closures in premature babies that are done each year (approximately 260) and the cost of each procedure and agreed that there would, therefore, be cost-savings to the NHS if some of these procedures were not carried out. In addition, reducing the treatment of PDA will reduce the costs associated with transporting preterm babies to other centres for surgery.

Other factors the committee took into account

The committee took expert advice for this review question from a co-opted committee member who was a paediatric cardiologist and who provided an overview of the number of PDA closures carried out. The committee discussed the decision-making and referral process involving neonatologists, cardiologists and surgeons when the decision is being made whether to surgically repair a PDA. There was a particular concern that a baby's referral to a cardiologist would be interpreted by the cardiologist as a definitive request for a PDA closure, when it may not actually be the best treatment option.

The committee noted that there was an ongoing study called Baby-OSCAR (**O**utcome after **S**elective Early Treatment for **C**losure of Patent Ductus **AR**teriosus in Pre-term Babies) which was comparing the use of ibuprofen to placebo to close large PDAs in preterm babies and following them up for 2 years. The results of this study would provide further information to guide the use of pharmacologic treatment to close a PDA. The committee did not therefore

make a research recommendation for this review question. However, they did note that further studies using different echo physiological parameters from Baby-OSCAR to identify which babies would potentially benefit from PDA closure may allow treatment to be targeted more effectively in the future.

The committee also noted that it might be appropriate for the Neonatal Critical Care Clinical Reference Group (CRG) to incorporate their recommendations into the delivery of care in neonatal tertiary centres.

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Appendices

Appendix A – Review protocols

Review protocol for question 3.4 What is the effectiveness of corticosteroids in preterm babies requiring respiratory support?

Field (based on PRISMA-P	Content
Review question in SCOPE	What is the effectiveness and safety of corticosteroids in preventing or managing bronchopulmonary dysplasia?
Review question in guideline	What is the effectiveness of corticosteroids in preterm babies requiring respiratory support?
Type of review question	Intervention
Objective of the review	To determine the optimal corticosteroid choice, dosing schedule, mode of administration, in ameliorating BPD and longer-term sequelae in preterm babies requiring respiratory support.
Eligibility criteria – population/disease/condition/issue/domain	Preterm babies requiring respiratory support **Exclusions:** Preterm babies with any congenital abnormalities except patent ductus arteriosus Preterm babies who are ventilated solely due to a specific non-respiratory comorbidity, such as sepsis, NEC, neurological disorders.

Field (based on PRISMA-P	Content
	RCTs with <15 participants in each arm will not routinely be included. Consideration will be given to their inclusion if the evidence from larger RCTs is judged not to be sufficient – in quality or quantity. Studies where >2/3 of preterm babies receive respiratory support will be included in the review
Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	**Corticosteroids:** Intravenous dexamethasone Intravenous hydrocortisone Nebulised budesonide
Eligibility criteria – comparator(s)/control or reference (gold) standard	**Comparisons:** Corticosteroids versus placebo Corticosteroid A versus Corticosteroid B Lower dose corticosteroid A versus higher dose corticosteroid A Earlier administration of corticosteroid A versus Later administration of corticosteroid A
Outcomes and prioritisation	**Critical outcomes:** Mortality prior to discharge Bronchopulmonary Dysplasia (Oxygen dependency at 36 weeks gestation or 28 days of age) Neurodevelopmental outcomes at ≥18 months: • Cerebral Palsy (reported as presence or absence of condition, not severity of condition) • Neurodevelopmental delay (reported as dichotomous outcomes, not continuous outcomes such as mean change in score) ○ Severe (Score of >2 SD below normal on validated assessment scales, or on Bayleys assessment scale of mental developmental index (MDI) or psychomotor developmental

Field (based on PRISMA-P	Content
	index (PDI) <70 or complete inability to assign score due to CP or severe cognitive delay) ○ Moderate (Score of 1-2 SD below normal on validated assessment scales, or on Bayleys assessment scale of MDI or PDI 70-84) • Neurosensory impairment (reported as presence or absence of condition, not severity of condition) • Severe hearing impairment (e.g deaf) • Severe visual impairment (e.g blind) **Important outcomes:** Days on invasive ventilation GI perforation Hypertension
Eligibility criteria – study design	Systematic reviews of RCTs RCTs If insufficient RCTs: prospective cohort studies If insufficient prospective cohort studies: retrospective cohort studies
Other inclusion exclusion criteria	Inclusion: English language Developed countries with a neonatal care system similar to the UK (e.g. OECD countries) Studies conducted post 1990 Exclusion: Corticosteroid courses less than 2 days of duration
Proposed sensitivity/sub-group analysis, or meta-regression	Stratified analyses based on the following sub-groups of pre-term babies: Timing of corticosteroid administration: Early: <7 days gestational age Moderate: 8-20 days gestational age Late: >21 days gestational age

Field (based on PRISMA-P	Content
Selection process – duplicate screening/selection/analysis	Sifting, data extraction, appraisal of methodological quality and GRADE assessment will be performed by the systematic reviewer. Resolution of any disputes will be with the senior systematic review and the Topic Advisor. Quality control will be performed by the senior systematic reviewer. Dual sifting and data extraction will not be undertaken for this question.
Data management (software)	Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). 'GRADEpro' will be used to assess the quality of evidence for each outcome. NGA STAR software will be used for study sifting, data extraction, recording quality assessment using checklists and generating bibliographies/citations.
Information sources – databases and dates	Sources to be searched: Medline, Medline In-Process, CCTR, CDSR, DARE, HTA, Embase Limits (e.g. date, study design): Apply standard animal/non-English language exclusion Limit to RCTs and systematic reviews in first instance but download all results Dates: from 1990 Studies conducted post 1990 will be considered for this review question, as the GC felt that significant advances have occurred in ante-natal and post-natal respiratory management since this time period and outcomes for preterm babies prior to 1990 are not the same as post 1990.
Identify if an update	Not an update
Author contacts	Developer: NGA
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual
Search strategy	For details please see appendix B
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix D (clinical evidence tables) or H (economic evidence tables)

Field (based on PRISMA-P	Content
Data items – define all variables to be collected	For details please see evidence tables in appendix D (clinical evidence tables) or H (economic evidence tables).
Methods for assessing bias at outcome/study level	Standard study checklists were used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis (where suitable)	For details please see section 6.4 of Developing NICE guidelines: the manual
Methods for analysis – combining studies and exploring (in)consistency	Appraisal of methodological quality: The methodological quality of each study will be assessed using an appropriate checklist: • AMSTAR for systematic reviews • Cochrane risk of bias tool for RCTs • Cochrane risk of bias tool for non-randomised studies The quality of the evidence for an outcome (i.e. across studies) will be assessed using GRADE. Synthesis of data: Pairwise meta-analysis will be conducted where appropriate. When meta-analysing continuous data, final and change scores will be pooled and if any studies reports both, the method used in the majority of studies will be analysed. Minimally important differences: Default values will be used of: 0.8 and 1.25 for dichotomous outcomes; 0.5 times SD for continuous outcomes, unless more appropriate values are identified by the guideline committee or in the literature. Mortality prior to discharge – any change (statistically significant)

Field (based on PRISMA-P	Content
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual. If sufficient relevant RCT evidence is available, publication bias will be explored using RevMan software to examine funnel plots. Trial registries will be examined to identify missing evidence: Clinical trials.gov, NIHR Clinical Trials Gateway
Assessment of confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual
Rationale/context – Current management	For details please see the introduction to the evidence review in the full guideline.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by The National Guideline Alliance and chaired by Dr Janet Rennie in line with section 3 of Developing NICE guidelines: the manual. Staff from The National Guideline Alliance undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see the methods chapter of the full guideline.
Sources of funding/support	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Name of sponsor	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Roles of sponsor	NICE funds The National Guideline Alliance to develop guidelines for those working in the NHS, public health, and social care in England
PROSPERO registration number	Not registered

1

Review protocol for question 3.5 What is the safety and effectiveness of diuretics in preterm babies on respiratory support?

Field (based on PRISMA-P	Content
Review question in SCOPE	What is the effectiveness and safety of diuretics in preventing or managing bronchopulmonary dysplasia?
Review question in guideline	What is the effectiveness of diuretics in preterm babies requiring respiratory support?
Type of review question	Intervention
Objective of the review	To determine the optimal diuretic choice, dosing schedule and mode of administration, in ameliorating BPD and longer-term sequelae in preterm babies requiring respiratory support.
Eligibility criteria – population/disease/condition/issue/domain	Preterm babies who require respiratory support: Exclusions: Preterm babies with congenital abnormalities except patent ductus arteriosus Preterm babies who are ventilated solely due to a specific non-respiratory comorbidity, such as sepsis, NEC, neurological disorders. RCTs with <15 participants in each arm will not routinely be included. Consideration will be given to their inclusion if the evidence from larger RCTs is judged not to be sufficient – in quality or quantity. Studies where >2/3 of preterm babies receive respiratory support will be included in the review
Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	Loop diuretics: Furosemide intravenous or oral Aldosterone antagonists: Spironolactone oral Potassium canrenoate intra-venous

Field (based on PRISMA-P	Content
	Thiazide diuretic: Chlorothiazide oral
Eligibility criteria – comparator(s)/control or reference (gold) standard	Comparisons: Diuretic vs placebo/no intervention Diuretic A vs Diuretic B Combination diuretic vs single diuretic
Outcomes and prioritisation	Critical outcomes: Mortality prior to discharge Bronchopulmonary dysplasia (oxygen dependency at 36 weeks corrected gestation or 28 days of age) Neurodevelopmental outcomes at >18 months: Cerebral Palsy (reported as presence or absence of condition, not severity of condition) Neurodevelopmental delay (reported as dichotomous outcomes, not continuous outcomes such as mean change in score) Severe (Score of >2 SD below normal on validated assessment scales, or on Bayleys assessment scale of mental developmental index (MDI) or psychomotor developmental index (PDI) <70 or complete inability to assign score due to CP or severe cognitive delay) Moderate (Score of 1-2 SD below normal on validated assessment scales, or on Bayleys assessment scale of MDI or PDI 70-84) Neurosensory impairment (reported as presence or absence of condition, not severity of condition) Severe hearing impairment (e.g deaf) Severe visual impairment (e.g blind) Important outcomes: Days on invasive ventilation Nephrocalcinosis

Field (based on PRISMA-P	Content
	Ototoxicity Hyponatraemia
Eligibility criteria – study design	Systematic reviews of RCTs RCTs If insufficient RCTs: prospective cohort studies If insufficient prospective cohort studies: retrospective cohort studies
Other inclusion exclusion criteria	Inclusion: English language Developed countries with a neonatal care system similar to the UK (e.g. OECD countries) Studies conducted post 1990
Proposed sensitivity/sub-group analysis, or meta-regression	Stratified analyses based on the following sub-groups of ventilated preterm babies receiving diuretics: Age at start of diuretic treatment <7 days after birth 8-20 days after birth >21 days after birth Duration of treatment course: <14 days >15 days Gestational age: ≤26+6 weeks 27-31+6 weeks 32-36+6 weeks
Selection process – duplicate screening/selection/analysis	Sifting, data extraction, appraisal of methodological quality and GRADE assessment will be performed by the systematic reviewer. Resolution of any disputes will be with the senior systematic review and the Topic Advisor. Quality control will be performed by the senior systematic reviewer. Dual quality assessment and data extraction will be performed when capacity allows

Field (based on PRISMA-P	Content
Data management (software)	Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). 'GRADEpro' will be used to assess the quality of evidence for each outcome. NGA STAR software will be used for study sifting, data extraction, recording quality assessment using checklists and generating bibliographies/citations.
Information sources – databases and dates	Sources to be searched: Medline, Medline In-Process, CCTR, CDSR, DARE, HTA, Embase Limits (e.g. date, study design): Apply standard animal/non-English language exclusion Limit to RCTs and systematic reviews in first instance but download all results Dates: from 1990 Studies conducted post 1990 will be considered for this review question, as the GC felt that significant advances have occurred in ante-natal and post-natal respiratory management since this time period and outcomes for preterm babies prior to 1990 are not the same as post 1990.
Identify if an update	Not an update
Author contacts	Developer: NGA
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual
Search strategy	For details please see appendix B
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix D (clinical evidence tables) or H (economic evidence tables).
Data items – define all variables to be collected	For details please see evidence tables in appendix D (clinical evidence tables) or H (economic evidence tables).
Methods for assessing bias at outcome/study level	Standard study checklists were used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/

Field (based on PRISMA-P	Content
	Please document any deviations/alternative approach when GRADE isn't used or if a modified GRADE approach has been used for non-intervention or non-comparative studies.
Criteria for quantitative synthesis (where suitable)	For details please see section 6.4 of Developing NICE guidelines: the manual
Methods for analysis – combining studies and exploring (in)consistency	Appraisal of methodological quality: The methodological quality of each study will be assessed using an appropriate checklist: • AMSTAR for systematic reviews • Cochrane risk of bias tool for RCTs • Cochrane risk of bias tool for non-randomised studies The quality of the evidence for an outcome (i.e. across studies) will be assessed using GRADE. Synthesis of data: Pairwise meta-analysis will be conducted where appropriate. When meta-analysing continuous data, final and change scores will be pooled and if any studies reports both, the method used in the majority of studies will be analysed. Minimally important differences: Default values will be used of: 0.75 and 1.25 for dichotomous outcomes; 0.5 times SD for continuous outcomes, unless more appropriate values are identified by the guideline committee or in the literature. Mortality – any change (statistically significant)
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual. If sufficient relevant RCT evidence is available, publication bias will be explored using RevMan software to examine funnel plots. Trial registries will be examined to identify missing evidence: Clinical trials.gov, NIHR Clinical Trials Gateway
Assessment of confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual

Field (based on PRISMA-P	Content
Rationale/context – Current management	For details please see the introduction to the evidence review in the full guideline.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by The National Guideline Alliance and chaired by Dr Janet Rennie in line with section 3 of Developing NICE guidelines: the manual. Staff from The National Guideline Alliance undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see the methods chapter of the full guideline.
Sources of funding/support	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Name of sponsor	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Roles of sponsor	NICE finds The National Guideline Alliance to develop guidelines for those working in the NHS, public health, and social care in England
PROSPERO registration number	Not registered to PROSPERO

1

Review protocol for question 3.6 What is the effectiveness of caffeine in preterm babies requiring respiratory support?

Field (based on PRISMA-P	Content
Review question in SCOPE	What is the effectiveness and safety of caffeine in preventing or managing bronchopulmonary dysplasia?
Review question in guideline	What is the effectiveness of caffeine in preterm babies requiring respiratory support?
Type of review question	Intervention
Objective of the review	To determine the optimal caffeine dosing schedule, mode of administration, in ameliorating BPD and longer-term sequelae in preterm babies
Eligibility criteria – population/disease/condition/issue/domain	Preterm babies who require respiratory support. Exclusions: • Preterm babies with congenital abnormalities excluding patent ductus arteriosus • Preterm babies who are ventilated solely due to a specific non-respiratory comorbidity, such as sepsis, NEC, neurological disorders. • RCTs with <15 participants in each arm will not routinely be included. Consideration will be given to their inclusion if the evidence from larger RCTs is judged not to be sufficient – in quality or quantity. Studies where >2/3 of preterm babies receive respiratory support will be included in the review
Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	**Caffeine (citrate or base) – oral or IV**
Eligibility criteria – comparator(s)/control or reference (gold) standard	**Control:** • Placebo • No intervention **Comparisons:** • Caffeine versus control

Field (based on PRISMA-P	Content
	• Lower dose caffeine versus higher dose caffeine • Earlier administration of caffeine versus later administration of caffeine • Shorter duration versus longer duration

Outcomes and prioritisation	**Critical outcomes:**
	• Mortality before discharge
	• Bronchopulmonary dysplasia at 36 weeks PMA or 28 days of age
	• Neurodevelopmental outcomes at ≥18 months:
	  ○ Cerebral palsy (reported as presence or absence of condition, not severity of condition)
	  ○ Neurodevelopmental delay (reported as dichotomous outcomes, not continuous outcomes such as mean change in score)
	  ▪ Severe (score of >2 SD below normal on validated assessment scales, or on Bayleys assessment scale of mental developmental index (MDI) or psychomotor developmental index (PDI) <70 or complete inability to assign score due to CP or severe cognitive delay)
	  ▪ Moderate (score of 1-2 SD below normal on validated assessment scales, or on Bayleys assessment scale of MDI or PDI 70-84)
	  ○ Neurosensory impairment (reported as presence or absence of condition, not severity of condition)
	  ▪ Severe hearing impairment (e.g deaf)
	  ▪ Severe visual impairment (e.g blind)
	
	Important outcomes:
	• Continuing apnoea
	• Extubation failure
	• Tachycardia
	• Necrotising enterocolitis (NEC)

Field (based on PRISMA-P	Content
Eligibility criteria – study design	Systematic reviews of RCTs RCTs If insufficient RCTs: prospective cohort studies If insufficient prospective cohort studies: retrospective cohort studies
Other inclusion exclusion criteria	Inclusion: • English language • Developed countries with a neonatal care system similar to the UK (e.g. OECD countries) • Studies conducted post 1990
Proposed sensitivity/sub-group analysis, or meta-regression	Stratified analyses based on the following sub-groups of preterm babies receiving caffeine: **Respiratory support:** • Invasive • Non-invasive **Gestational age:** • <26^{+6} weeks • 27-31^{+6} weeks • 32-36^{+6} weeks **Respiratory indications:** • Prevention of extubation failure • Apnoea of prematurity
Selection process – duplicate screening/selection/analysis	Sifting, data extraction, appraisal of methodological quality and GRADE assessment will be performed by the systematic reviewer. Resolution of any

Field (based on PRISMA-P	Content
	disputes will be with the senior systematic reviewer and the Topic Advisor. Quality control will be performed by the senior systematic reviewer. Dual sifting and data extraction will not be undertaken for this question.
Data management (software)	Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). 'GRADEpro' will be used to assess the quality of evidence for each outcome. NGA STAR software will be used for study sifting, data extraction, recording quality assessment using checklists and generating bibliographies/citations.
Information sources – databases and dates	Sources to be searched: Medline, Medline In-Process, CCTR, CDSR, DARE, HTA, Embase Limits (e.g. date, study design): Apply standard animal/non-English language exclusion Limit to RCTs and systematic reviews in first instance but download all results Dates: from 1990 Studies conducted post 1990 will be considered for this review question, as the GC felt that significant advances have occurred in ante-natal and post-natal respiratory management since this time period and outcomes for preterm babies prior to 1990 are not the same as post 1990.
Identify if an update	Not an update
Author contacts	Developer: NGA
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual
Search strategy	For details please see appendix B
Data collection process – forms/duplicate	A standardised evidence table format will be used and published as appendix D (clinical evidence tables) or H (economic evidence tables).

Field (based on PRISMA-P	Content
Data items – define all variables to be collected	For details please see evidence tables in appendix D (clinical evidence tables) or H (economic evidence tables).
Methods for assessing bias at outcome/study level	Standard study checklists were used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis (where suitable)	For details please see section 6.4 of Developing NICE guidelines: the manual
Methods for analysis – combining studies and exploring (in)consistency	Appraisal of methodological quality: The methodological quality of each study will be assessed using an appropriate checklist: • AMSTAR for systematic reviews • Cochrane risk of bias tool for RCTs • Cochrane risk of bias tool for non-randomised studies The quality of the evidence for an outcome (i.e. across studies) will be assessed using GRADE. Synthesis of data: Pairwise meta-analysis will be conducted where appropriate. When meta-analysing continuous data, final and change scores will be pooled and if any studies reports both, the method used in the majority of studies will be analysed. Minimally important differences: Default values will be used of: 0.75 and 1.25 for dichotomous outcomes; 0.5 times SD for continuous outcomes, unless more appropriate values are identified by the guideline committee or in the literature. Mortality – any change (statistically significant)
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual. If sufficient relevant RCT evidence is available, publication bias will be explored using RevMan software to examine funnel plots.

Field (based on PRISMA-P	Content
	Trial registries will be examined to identify missing evidence: Clinical trials.gov, NIHR Clinical Trials Gateway
Assessment of confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual
Rationale/context – Current management	For details please see the introduction to the evidence review in the full guideline.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by The National Guideline Alliance and chaired by Dr Janet Rennie in line with section 3 of Developing NICE guidelines: the manual. Staff from The National Guideline Alliance undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate and drafted the guideline in collaboration with the committee. For details please see the methods chapter of the full guideline.
Sources of funding/support	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Name of sponsor	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Roles of sponsor	NICE finds The National Guideline Alliance to develop guidelines for those working in the NHS, public health and social care in England
PROSPERO registration number	Not registered to PROSPERO

1

Review protocol for question 3.8: What is the effectiveness of interventions for closing a patent ductus arteriosus in preterm babies requiring respiratory support?

Field (based on PRISMA-P)	Content
Review question in SCOPE	What is the effectiveness and safety of interventions for closing a patent ductus arteriosus in preventing or managing bronchopulmonary dysplasia?
Review question in guideline	What is the effectiveness of interventions for closing a patent ductus arteriosus in preterm babies requiring respiratory support?
Type of review question	Intervention
Objective of the review	To determine the optimal intervention for closing a patent ductus arteriosus in preterm babies requiring respiratory support
Eligibility criteria – population/disease/condition/issue/domain	Preterm babies diagnosed with patent ductus arteriosus by an echocardiogram and require respiratory support. Exclusions: • Preterm babies with any congenital abnormalities except PDA • Preterm babies who are ventilated solely due to a specific non-respiratory comorbidity, such as sepsis, NEC, neurological disorders • RCTs with <15 participants in each arm will not routinely be included. Consideration will be given to their inclusion if the evidence from larger RCTs is judged not to be sufficient – in quality or quantity. • Studies where >2/3 of preterm babies receive respiratory support will be included in the review
Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	**Pharmacological:** • Ibuprofen - oral or intravenous • Paracetamol – oral or intravenous **Fluid Restriction:** • Fluid restriction only – oral or iv • Fluid restriction with diuretics: • Furosemide – oral or iv • Combined oral spironolactone and oral chlorothiazide

Field (based on PRISMA-P)	Content
	• Combined IV frusemide and IV potassium canrenoate **Surgical:** • Surgical ligation **Control:** • Placebo • No intervention
Eligibility criteria – comparator(s)/control or reference (gold) standard	**Comparisons:** • Pharmacological vs placebo • Surgery vs placebo • Fluid restriction vs placebo • Pharmacological vs surgery • Pharmacological vs fluid restriction • Surgery vs fluid restriction If pharmacological is better than surgery and fluid restriction: • Ibuprofen vs paracetamol If fluid restriction is better than surgery and pharmacological: • Fluid restriction only vs fluid restriction with diuretics • If fluid restriction with diuretics is better than fluid restriction only: • Fluid restriction with combination diuretics vs fluid restriction with single diuretics
Outcomes and prioritisation	**Critical outcomes:** • Mortality prior to discharge • Bronchpulmonary dysplasia (Oxygen dependency at 36 weeks postmenstrual age or 28 days of age) • Neurodevelopmental outcomes at ≥18 months: ○ Cerebral Palsy (reported as presence or absence of condition, not severity of condition)

Field (based on PRISMA-P)	Content
	○ Neurodevelopmental delay (reported as dichotomous outcomes, not continuous outcomes such as mean change in score) ○ Severe (Score of >2 SD below normal on validated assessment scales, or on Bayleys assessment scale of mental developmental index (MDI) or psychomotor developmental index (PDI) <70 or complete inability to assign score due to CP or severe cognitive delay) ○ Moderate (Score of 1-2 SD below normal on validated assessment scales, or on Bayleys assessment scale of MDI or PDI 70-84) ○ Neurosensory impairment (reported as presence or absence of condition, not severity of condition) ○ Severe hearing impairment (e.g deaf) ○ Severe visual impairment (e.g blind) **Important outcomes:** • Failure of patent ductus arteriosus closure • Renal impairment • Gastrointestinal complications: ○ gastrointestinal perforation ○ gastrointestinal haemorrhage ○ necrotising enterocolitis (NEC)
Eligibility criteria – study design	Systematic reviews of RCTs RCTs If insufficient RCTs: prospective cohort studies If insufficient prospective cohort studies: retrospective cohort studies
Other inclusion exclusion criteria	Inclusion: • English language

Field (based on PRISMA-P)	Content
	• Developed countries with a neonatal care system similar to the UK (e.g. OECD countries) • Studies conducted post 1990
Proposed sensitivity/sub-group analysis, or meta-regression	Stratified analyses based on the following sub-groups of ventilated preterm babies receiving caffeine: Gestational age: • <26+6 weeks • 27-31+6 weeks • 32-36+6 weeks Post-natal age at start of PDA treatment: • <7 days • 8-14 days • >15 days
Selection process – duplicate screening/selection/analysis	Dual sifting, data extraction and methodological quality assessment: Sifting, data extraction, appraisal of methodological quality and GRADE assessment will be performed by the systematic reviewer. Dual weeding will be performed by a second systematic reviewer on 5% or 10% of records (depending on database size), with resolution of discrepancies in discussion with the senior reviewer if necessary. Quality control will be performed by the senior systematic reviewer. Dual data extraction and quality assessment will be performed as capacity allows.
Data management (software)	Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). 'GRADEpro' will be used to assess the quality of evidence for each outcome. NGA STAR software will be used for study sifting, data extraction, recording quality assessment using checklists and generating bibliographies/citations,

Field (based on PRISMA-P)	Content
Information sources – databases and dates	Sources to be searched: Medline, Medline In-Process, CCTR, CDSR, DARE, HTA, Embase • Limits (e.g. date, study design): • Apply standard animal/non-English language exclusion • Limit to RCTs and systematic reviews in first instance but download all results • Dates from 1990 Studies conducted post 1990 will be considered for this review question, as the GC felt that significant advances have occurred in ante-natal and post-natal respiratory management since this time period and outcomes for preterm babies prior to 1990 are not the same as post 1990.
Identify if an update	Not an update
Author contacts	Developer: NGA
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual
Search strategy	For details please see appendix B
Data collection process – forms/duplicate	A standardised evidence table format will be used and published as appendix D (clinical evidence tables) or H (economic evidence tables).
Data items – define all variables to be collected	For details please see evidence tables in appendix D (clinical evidence tables) or H (economic evidence tables).
Methods for assessing bias at outcome/study level	Standard study checklists were used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis (where suitable)	For details please see section 6.4 of Developing NICE guidelines: the manual
Methods for analysis – combining studies and exploring (in)consistency	Appraisal of methodological quality:

Field (based on PRISMA-P)	Content
	The methodological quality of each study will be assessed using an appropriate checklist: • AMSTAR for systematic reviews • Cochrane risk of bias tool for RCTs • Cochrane risk of bias tool for non-randomised studies The quality of the evidence for an outcome (i.e. across studies) will be assessed using GRADE. Synthesis of data: Pairwise meta-analysis will be conducted where appropriate. When meta-analysing continuous data, final and change scores will be pooled and if any studies reports both, the method used in the majority of studies will be analysed. For details regarding inconsistency, please see the methods chapter of the full guideline Minimally important differences: Default values will be used of: 0.75 and 1.25 for dichotomous outcomes; 0.5 times SD for continuous outcomes, unless more appropriate values are identified by the guideline committee or in the literature. Mortality – any change (statistically significant)
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual. If sufficient relevant RCT evidence is available, publication bias will be explored using RevMan software to examine funnel plots. Trial registries will be examined to identify missing evidence: Clinical trials.gov, NIHR Clinical Trials Gateway
Assessment of confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual

Field (based on PRISMA-P)	Content
Rationale/context – Current management	For details please see the introduction to the evidence review in the full guideline.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by The National Guideline Alliance and chaired by Dr Janet Rennie in line with section 3 of Developing NICE guidelines: the manual. Staff from The National Guideline Alliance undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate and drafted the guideline in collaboration with the committee. For details please see the methods chapter of the full guideline.
Sources of funding/support	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Name of sponsor	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Roles of sponsor	NICE finds The National Guideline Alliance to develop guidelines for those working in the NHS, public health and social care in England
PROSPERO registration number	Not registered to PROSPERO

1
2

Appendix B – Literature search strategies

Literature search strategies for question 3.4 What is the effectiveness of corticosteroids in preterm babies requiring respiratory support?

Systematic reviews and RCTs

Date of initial search: 10/05/2017

Database: Embase 1980 to 2017 Week 19, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Date of updated search: 26/06/2018

Database(s): Embase 1980 to 2018 Week 26, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

#	Searches
1	exp Infant, Newborn/ use ppez
2	newborn/ use emez
3	prematurity/ use emez
4	exp low birth weight/ use emez
5	(infan* or neonat* or newborn* or new-born* or baby or babies).ti,ab,jw,nw.
6	(preterm or pre-term or prematur* or pre-matur* or pre?mie* or premie*1).tw.
7	(low adj3 birth adj3 weigh*).tw.
8	(LBW or VLBW).tw.
9	exp Respiratory Distress Syndrome, Newborn/ use ppez
10	neonatal respiratory distress syndrome/ use emez
11	exp Intensive Care, Neonatal/ use ppez
12	newborn intensive care/ use emez
13	exp Intensive Care Units, Neonatal/ use ppez
14	neonatal intensive care unit/ use emez
15	special care baby unit*.tw.
16	((newborn or neonatal) adj ICU*1).tw.
17	(SCBU or NICU).tw.
18	or/1-17
19	exp Respiration, Artificial/ use ppez
20	exp artificial ventilation/ use emez
21	exp assisted ventilation/ use emez
22	exp Ventilators, Mechanical/ use ppez
23	exp ventilator/ use emez
24	(((mechanic* or artificial or assisted or continu* or control* or high frequency or invasive or mandatory or oscillat* or pressure* or pulmonary or support* or trigger* or volume) adj3 (ventilat* or respirate or respiration or breathing or airway*)) or ventilat* or respirator or respirators).tw.
25	(ACV or CMV or SIMV or PCV or PTV or SIPPV or VGV or PCVG or HFOV).tw.
26	assist* control*.tw.
27	volume control*.tw.
28	volume guarantee.tw.
29	or/19-28
30	Budesonide/ use ppez
31	budesonide/ use emez
32	(budesonide or budelin or pulmicort).tw.
33	exp Dexamethasone/ use ppez
34	dexamethasone/ use emez
35	(dexamethasone or dexsol or martapen).tw.
36	exp Hydrocortisone/ use ppez
37	hydrocortisone/ use emez
38	(hydrocortisone or efcortesol or solu cortef or solucortef or corlan).tw.
39	(steroid* or corticosteroid* or glucocortico*).tw.
40	or/30-39
41	18 and 29 and 40
42	limit 41 to english language

#	Searches
43	limit 42 to yr="1990 -Current"
44	Letter/ use ppez
45	letter.pt. or letter/ use emez
46	note.pt.
47	editorial.pt.
48	Editorial/ use ppez
49	News/ use ppez
50	exp Historical Article/ use ppez
51	Anecdotes as Topic/ use ppez
52	Comment/ use ppez
53	Case Report/ use ppez
54	case report/ or case study/ use emez
55	(letter or comment*).ti.
56	or/44-55
57	randomized controlled trial/ use ppez
58	randomized controlled trial/ use emez
59	random*.ti,ab.
60	or/57-59
61	56 not 60
62	animals/ not humans/ use ppez
63	animal/ not human/ use emez
64	nonhuman/ use emez
65	exp Animals, Laboratory/ use ppez
66	exp Animal Experimentation/ use ppez
67	exp Animal Experiment/ use emez
68	exp Experimental Animal/ use emez
69	exp Models, Animal/ use ppez
70	animal model/ use emez
71	exp Rodentia/ use ppez
72	exp Rodent/ use emez
73	(rat or rats or mouse or mice).ti.
74	or/61-73
75	43 not 74
76	Meta-Analysis/
77	Meta-Analysis as Topic/
78	systematic review/
79	meta-analysis/
80	(meta analy* or metanaly* or metaanaly*).ti,ab.
81	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
82	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
83	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
84	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
85	(search* adj4 literature).ab.
86	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
87	cochrane.jw.
88	((pool* or combined) adj2 (data or trials or studies or results)).ab.
89	or/76-77,80,82-87 use ppez
90	or/78-81,83-88 use emez
91	or/89-90
92	clinical Trials as topic.sh. or (controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or (placebo or randomi#ed or randomly).ab. or trial.ti.
93	92 use ppez
94	(controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or drug therapy.fs. or (groups or placebo or randomi#ed or randomly or trial).ab.
95	94 use ppez
96	crossover procedure/ or double blind procedure/ or randomized controlled trial/ or single blind procedure/ or (assign* or allocat* or crossover* or cross over* or ((doubl* or singl*) adj blind*) or factorial* or placebo* or random* or volunteer*).ti,ab.
97	96 use emez
98	93 or 95
99	97 or 98
100	91 or 99
101	75 and 100
102	remove duplicates from 101

1 Observational studies

1 Date of initial search: 10/05/2017

2 Database: Embase 1980 to 2017 Week 19, Ovid MEDLINE(R) Epub Ahead of Print, In-
3 Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)
4 1946 to Present

5 Date of updated search: 26/06/2018

6 Database(s): Embase 1980 to 2018 Week 26, Ovid MEDLINE(R) Epub Ahead of Print, In-
7 Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)
8 1946 to Present

#	Searches
1	exp Infant, Newborn/ use ppez
2	newborn/ use emez
3	prematurity/ use emez
4	exp low birth weight/ use emez
5	(infan* or neonat* or newborn* or new-born or baby or babies).ti,ab,jw,nw.
6	(preterm or pre-term or prematur* or pre-matur* or pre?mie* or premie*1).tw.
7	(low adj3 birth adj3 weigh*).tw.
8	(LBW or VLBW).tw.
9	exp Respiratory Distress Syndrome, Newborn/ use ppez
10	neonatal respiratory distress syndrome/ use emez
11	exp Intensive Care, Neonatal/ use ppez
12	newborn intensive care/ use emez
13	exp Intensive Care Units, Neonatal/ use ppez
14	neonatal intensive care unit/ use emez
15	special care baby unit*.tw.
16	((newborn or neonatal) adj ICU*1).tw.
17	(SCBU or NICU).tw.
18	or/1-17
19	exp Respiration, Artificial/ use ppez
20	exp artificial ventilation/ use emez
21	exp assisted ventilation/ use emez
22	exp Ventilators, Mechanical/ use ppez
23	exp ventilator/ use emez
24	(((mechanic* or artificial or assisted or continu* or control* or high frequency or invasive or mandatory or oscillat* or pressure* or pulmonary or support* or trigger* or volume) adj3 (ventilat* or respirate or respiration or breathing or airway*)) or ventilat* or respirator or respirators).tw.
25	(ACV or CMV or SIMV or PCV or PTV or SIPPV or VGV or PCVG or HFOV).tw.
26	assist control.tw.
27	volume control*.tw.
28	volume guarantee.tw.
29	or/19-28
30	Budesonide/ use ppez
31	budesonide/ use emez
32	(budesonide or budelin or pulmicort).tw.
33	exp Dexamethasone/ use ppez
34	dexamethasone/ use emez
35	(dexamethasone or dexsol or martapen).tw.
36	exp Hydrocortisone/ use ppez
37	hydrocortisone/ use emez
38	(hydrocortisone or efcortesol or solu cortef or solucortef or corlan).tw.
39	(steroid* or corticosteroid* or glucocortico*).tw.
40	or/30-39
41	18 and 29 and 40
42	limit 41 to english language
43	limit 42 to yr="1990 -Current"
44	Letter/ use ppez
45	letter.pt. or letter/ use emez
46	note.pt.
47	editorial.pt.
48	Editorial/ use ppez
49	News/ use ppez
50	exp Historical Article/ use ppez
51	Anecdotes as Topic/ use ppez
52	Comment/ use ppez
53	Case Report/ use ppez

#	Searches
54	case report/ or case study/ use emez
55	(letter or comment*).ti.
56	or/44-55
57	randomized controlled trial/ use ppez
58	randomized controlled trial/ use emez
59	random*.ti,ab.
60	or/57-59
61	56 not 60
62	animals/ not humans/ use ppez
63	animal/ not human/ use emez
64	nonhuman/ use emez
65	exp Animals, Laboratory/ use ppez
66	exp Animal Experimentation/ use ppez
67	exp Animal Experiment/ use emez
68	exp Experimental Animal/ use emez
69	exp Models, Animal/ use ppez
70	animal model/ use emez
71	exp Rodentia/ use ppez
72	exp Rodent/ use emez
73	(rat or rats or mouse or mice).ti.
74	or/61-73
75	43 not 74
76	Epidemiologic Studies/
77	Case Control Studies/
78	Retrospective Studies/
79	Cohort Studies/
80	Longitudinal Studies/
81	Follow-Up Studies/
82	Prospective Studies/
83	Cross-Sectional Studies/
84	or/76-83 use ppez
85	clinical study/
86	case control study/
87	family study/
88	longitudinal study/
89	retrospective study/
90	prospective study/
91	cohort analysis/
92	or/85-91 use emez
93	((retrospective* or cohort* or longitudinal or follow?up or prospective or cross section*) adj3 (stud* or research or analys*)).ti.
94	84 or 92 or 93
95	75 and 94
96	remove duplicates from 95

1 **Health economics**

2 Date of initial search: 10/05/2017

3 Database: Embase 1980 to 2017 Week 19, Ovid MEDLINE(R) Epub Ahead of Print, In-
4 Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)
5 1946 to Present

6 Date of updated search: 26/06/2018

7 Database(s): Embase 1980 to 2018 Week 26, Ovid MEDLINE(R) Epub Ahead of Print, In-
8 Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)
9 1946 to Present

#	Searches
1	exp Infant, Newborn/ use ppez
2	newborn/ use emez
3	prematurity/ use emez
4	exp low birth weight/ use emez
5	(infan* or neonat* or newborn* or new-born* or baby or babies).ti,ab,jw,nw.
6	(preterm or pre-term or prematur* or pre-matur* or pre?mie* or premie*1).tw.

#	Searches
7	(low adj3 birth adj3 weigh*).tw.
8	(LBW or VLBW).tw.
9	exp Respiratory Distress Syndrome, Newborn/ use ppez
10	neonatal respiratory distress syndrome/ use emez
11	exp Intensive Care, Neonatal/ use ppez
12	newborn intensive care/ use emez
13	exp Intensive Care Units, Neonatal/ use ppez
14	neonatal intensive care unit/ use emez
15	special care baby unit*.tw.
16	((newborn or neonatal) adj ICU*1).tw.
17	(SCBU or NICU).tw.
18	or/1-17
19	exp Respiration, Artificial/ use ppez
20	exp artificial ventilation/ use emez
21	exp assisted ventilation/ use emez
22	exp Ventilators, Mechanical/ use ppez
23	exp ventilator/ use emez
24	(((mechanic* or artificial or assisted or continu* or control* or high frequency or invasive or mandatory or oscillat* or pressure* or pulmonary or support* or trigger* or volume) adj3 (ventilat* or respirate or respiration or breathing or airway*)) or ventilat* or respirator or respirators).tw.
25	(ACV or CMV or SIMV or PCV or PTV or SIPPV or VGV or PCVG or HFOV).tw.
26	assist control.tw.
27	volume control*.tw.
28	volume guarantee.tw.
29	or/19-28
30	Budesonide/ use ppez
31	budesonide/ use emez
32	(budesonide or budelin or pulmicort).tw.
33	exp Dexamethasone/ use ppez
34	dexamethasone/ use emez
35	(dexamethasone or dexsol or martapen).tw.
36	exp Hydrocortisone/ use ppez
37	hydrocortisone/ use emez
38	(hydrocortisone or efcortesol or solu cortef or solucortef or corlan).tw.
39	(steroid* or corticosteroid* or glucocortico*).tw.
40	or/30-39
41	18 and 29 and 40
42	limit 41 to english language
43	limit 42 to yr="1990 -Current"
44	Letter/ use ppez
45	letter.pt. or letter/ use emez
46	note.pt.
47	editorial.pt.
48	Editorial/ use ppez
49	News/ use ppez
50	exp Historical Article/ use ppez
51	Anecdotes as Topic/ use ppez
52	Comment/ use ppez
53	Case Report/ use ppez
54	case report/ or case study/ use emez
55	(letter or comment*).ti.
56	or/44-55
57	randomized controlled trial/ use ppez
58	randomized controlled trial/ use emez
59	random*.ti,ab.
60	or/57-59
61	56 not 60
62	animals/ not humans/ use ppez
63	animal/ not human/ use emez
64	nonhuman/ use emez
65	exp Animals, Laboratory/ use ppez
66	exp Animal Experimentation/ use ppez
67	exp Animal Experiment/ use emez
68	exp Experimental Animal/ use emez
69	exp Models, Animal/ use ppez
70	animal model/ use emez
71	exp Rodentia/ use ppez

#	Searches
72	exp Rodent/ use emez
73	(rat or rats or mouse or mice).ti.
74	or/61-73
75	43 not 74
76	Economics/
77	Value of life/
78	exp "Costs and Cost Analysis"/
79	exp Economics, Hospital/
80	exp Economics, Medical/
81	Economics, Nursing/
82	Economics, Pharmaceutical/
83	exp "Fees and Charges"/
84	exp Budgets/
85	or/76-84 use ppez
86	health economics/
87	exp economic evaluation/
88	exp health care cost/
89	exp fee/
90	budget/
91	funding/
92	or/86-91 use emez
93	budget*.ti,ab.
94	cost*.ti.
95	(economic* or pharmaco?economic*).ti.
96	(price* or pricing*).ti,ab.
97	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
98	(financ* or fee or fees).ti,ab.
99	(value adj2 (money or monetary)).ti,ab.
100	or/93-98
101	85 or 92 or 100
102	75 and 101
103	remove duplicates from 102
97	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
98	(financ* or fee or fees).ti,ab.
99	(value adj2 (money or monetary)).ti,ab.
100	or/93-98
101	85 or 92 or 100
102	75 and 101
103	remove duplicates from 102

1 **Systematic reviews, RCTs, health economics**

2 Date of initial search: 10/05/2017

3 Databases: The Cochrane Library, issue 5 of 12, May 2017

4 Date of updated search: 27/06/2018

5 Databases: The Cochrane Library, issue 6 of 12, June 2018

ID	Search
#1	MeSH descriptor: [Infant, Newborn] explode all trees
#2	(infan* or neonat* or newborn* or new-born* or baby or babies or preterm or pre-term or prematur* or pre-matur* or pre?mie* or premie or premies)
#3	((low near/3 birth near/3 weigh*) or (LBW or VLBW))
#4	MeSH descriptor: [Respiratory Distress Syndrome, Newborn] explode all trees
#5	MeSH descriptor: [Intensive Care, Neonatal] explode all trees
#6	MeSH descriptor: [Intensive Care Units, Neonatal] explode all trees
#7	(special care baby unit* or ((newborn or neonatal) near ICU*1) or (SCBU or NICU))
#8	{or #1-#7}
#9	MeSH descriptor: [Respiration, Artificial] explode all trees
#10	MeSH descriptor: [Ventilators, Mechanical] explode all trees
#11	(((mechanic* or artificial or assisted or continu* or control* or high frequency or invasive or mandatory or oscillat* or pressure* or pulmonary or support* or trigger* or volume) near/3 (ventilat* or respirate or respiration or breathing or airway*)) or ventilat* or respirator or respirators)
#12	(ACV or CMV or SIMV or PCV or PTV or SIPPV or VGV or PCVG or HFOV)
#13	(assist* control* or volume control* or volume guarantee)
#14	{or #9-#13}

ID	Search
#15	MeSH descriptor: [Budesonide] this term only
#16	(budesonide or budelin or pulmicort)
#17	MeSH descriptor: [Dexamethasone] explode all trees
#18	(dexamethasone or dexsol or martapen)
#19	MeSH descriptor: [Hydrocortisone] explode all trees
#20	(hydrocortisone or efcortesol or solu cortef or solucortef or corlan)
#21	(steroid* or corticosteroid* or glucocortico*)
#22	{or #15-#21}
#23	#8 and #14 and #22 Publication Year from 1990 to 2017

Literature search strategies for question 3.5 What is the safety and effectiveness of diuretics in preterm babies on respiratory support?

Systematic reviews and RCTs

Date of initial search: 03/10/2017

Database(s): Embase 1980 to 2017 Week 40, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Date of updated search: 26/06/2018

Database(s): Embase 1980 to 2018 Week 26, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

#	Searches
1	exp Infant, Newborn/ use ppez
2	newborn/ use emez
3	prematurity/ use emez
4	(infan* or neonat* or neo-nat* or newborn* or baby or babies).ti,ab,jw,nw.
5	(preterm or pre-term or prematur* or pre-matur* or pre?mie* or premie*1).tw.
6	exp low birth weight/ use emez
7	(low adj3 birth adj3 weigh$).tw.
8	(LBW or VLBW).tw.
9	exp Respiratory Distress Syndrome, Newborn/ use ppez
10	neonatal respiratory distress syndrome/ use emez
11	exp Intensive Care, Neonatal/ use ppez
12	newborn intensive care/ use emez
13	exp Intensive Care Units, Neonatal/ use ppez
14	neonatal intensive care unit/ use emez
15	Neonatal Nursing/ use ppez
16	exp newborn nursing/ use emez
17	newborn care/ use emez
18	(special and care and baby and unit*).tw.
19	((newborn or neonatal or neo-natal) adj ICU*1).tw.
20	((newborn or neonat* or neo-nat*) adj2 (unit or care or department* or facilit* or hospital*)).tw.
21	(SCBU or NICU).tw.
22	((infan* or baby or babies or preterm or pre-term or prematur* or pre?mie* or premie*1) adj2 (unit* or care or department* or facilit* or hospital*)).tw.
23	or/1-22
24	Diuretics/ use ppez
25	diuretic agent/ use emez
26	Sodium Potassium Chloride Symporter Inhibitors/ use ppez
27	diuretic*.tw.
28	loop diuretic agent/ use emez
29	Furosemide/ use ppez
30	furosemide/ use emez
31	(furosemid* or frusemide or furantral).tw.
32	Mineralocorticoid Receptor Antagonists/ use ppez
33	aldosterone antagonist/ use emez
34	Canrenoic Acid/ use ppez

#	Searches
35	canrenoate potassium/ use emez
36	((potassium adj canrenoate) or (aldadiene adj kalium) or canrenoic acid).tw.
37	Spironolactone/ use ppez
38	spironolactone/ use emez
39	(spironolact?on* or acetylthiospirolactone).tw.
40	Thiazides/ use ppez
41	thiazide diuretic agent/ use emez
42	thiazide*.tw.
43	exp Chlorothiazide/ use ppez
44	chlorothiazide/ use emez
45	(chlorothiazid* or mechlozid or uroflux).tw.
46	or/24-44
47	23 and 46
48	limit 47 to english language
49	limit 48 to yr="1990 -Current"
50	Letter/ use ppez
51	letter.pt. or letter/ use emez
52	note.pt.
53	editorial.pt.
54	Editorial/ use ppez
55	News/ use ppez
56	exp Historical Article/ use ppez
57	Anecdotes as Topic/ use ppez
58	Comment/ use ppez
59	Case Report/ use ppez
60	case report/ or case study/ use emez
61	(letter or comment*).ti.
62	or/50-61
63	randomized controlled trial/ use ppez
64	randomized controlled trial/ use emez
65	random*.ti,ab.
66	or/63-65
67	62 not 66
68	animals/ not humans/ use ppez
69	animal/ not human/ use emez
70	nonhuman/ use emez
71	exp Animals, Laboratory/ use ppez
72	exp Animal Experimentation/ use ppez
73	exp Animal Experiment/ use emez
74	exp Experimental Animal/ use emez
75	exp Models, Animal/ use ppez
76	animal model/ use emez
77	exp Rodentia/ use ppez
78	exp Rodent/ use emez
79	(rat or rats or mouse or mice).ti.
80	or/67-79
81	49 not 80
82	Meta-Analysis/
83	Meta-Analysis as Topic/
84	systematic review/
85	meta-analysis/
86	(meta analy* or metanaly* or metaanaly*).ti,ab.
87	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
88	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
89	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
90	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
91	(search* adj4 literature).ab.
92	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
93	cochrane.jw.
94	((pool* or combined) adj2 (data or trials or studies or results)).ab.
95	or/82-83,86,88-93 use ppez
96	or/84-87,89-94 use emez
97	or/95-96
98	clinical Trials as topic.sh. or (controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or (placebo or randomi#ed or randomly).ab. or trial.ti.
99	98 use ppez

#	Searches
100	(controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or drug therapy.fs. or (groups or placebo or randomi#ed or randomly or trial).ab.
101	100 use ppez
102	crossover procedure/ or double blind procedure/ or randomized controlled trial/ or single blind procedure/ or (assign* or allocat* or crossover* or cross over* or ((doubl* or singl*) adj blind*) or factorial* or placebo* or random* or volunteer*).ti,ab.
103	102 use emez
104	99 or 101
105	103 or 104
106	97 or 105
107	81 and 106
108	remove duplicates from 107

Observational studies

Date of initial search: 03/10/2017

Database(s): Embase 1980 to 2017 Week 40, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Date of updated search: 26/06/2018

Database(s): Embase 1980 to 2018 Week 26, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

#	Searches
1	exp Infant, Newborn/ use ppez
2	newborn/ use emez
3	prematurity/ use emez
4	(infan* or neonat* or neo-nat* or newborn* or baby or babies).ti,ab,jw,nw.
5	(preterm or pre-term or prematur* or pre-matur* or pre?mie* or premie*1).tw.
6	exp low birth weight/ use emez
7	(low adj3 birth adj3 weigh$).tw.
8	(LBW or VLBW).tw.
9	exp Respiratory Distress Syndrome, Newborn/ use ppez
10	neonatal respiratory distress syndrome/ use emez
11	exp Intensive Care, Neonatal/ use ppez
12	newborn intensive care/ use emez
13	exp Intensive Care Units, Neonatal/ use ppez
14	neonatal intensive care unit/ use emez
15	Neonatal Nursing/ use ppez
16	exp newborn nursing/ use emez
17	newborn care/ use emez
18	(special and care and baby and unit*).tw.
19	((newborn or neonatal or neo-natal) adj ICU*1).tw.
20	((newborn or neonat* or neo-nat*) adj2 (unit or care or department* or facilit* or hospital*)).tw.
21	(SCBU or NICU).tw.
22	((infan* or baby or babies or preterm or pre-term or prematur* or pre?mie* or premie*1) adj2 (unit* or care or department* or facilit* or hospital*)).tw.
23	or/1-22
24	Diuretics/ use ppez
25	diuretic agent/ use emez
26	Sodium Potassium Chloride Symporter Inhibitors/ use ppez
27	diuretic*.tw.
28	loop diuretic agent/ use emez
29	Furosemide/ use ppez
30	furosemide/ use emez
31	(furosemid* or frusemide or furantral).tw.
32	Mineralocorticoid Receptor Antagonists/ use ppez
33	aldosterone antagonist/ use emez
34	Canrenoic Acid/ use ppez
35	canrenoate potassium/ use emez
36	((potassium adj canrenoate) or (aldadiene adj kalium) or canrenoic acid).tw.
37	Spironolactone/ use ppez
38	spironolactone/ use emez

#	Searches
39	(spironolact?on* or acetylthiospirolactone).tw.
40	Thiazides/ use ppez
41	thiazide diuretic agent/ use emez
42	thiazide*.tw.
43	exp Chlorothiazide/ use ppez
44	chlorothiazide/ use emez
45	(chlorothiazid* or mechlozid or uroflux).tw.
46	or/24-44
47	23 and 46
48	limit 47 to english language
49	limit 48 to yr="1990 -Current"
50	Letter/ use ppez
51	letter.pt. or letter/ use emez
52	note.pt.
53	editorial.pt.
54	Editorial/ use ppez
55	News/ use ppez
56	exp Historical Article/ use ppez
57	Anecdotes as Topic/ use ppez
58	Comment/ use ppez
59	Case Report/ use ppez
60	case report/ or case study/ use emez
61	(letter or comment*).ti.
62	or/50-61
63	randomized controlled trial/ use ppez
64	randomized controlled trial/ use emez
65	random*.ti,ab.
66	or/63-65
67	62 not 66
68	animals/ not humans/ use ppez
69	animal/ not human/ use emez
70	nonhuman/ use emez
71	exp Animals, Laboratory/ use ppez
72	exp Animal Experimentation/ use ppez
73	exp Animal Experiment/ use emez
74	exp Experimental Animal/ use emez
75	exp Models, Animal/ use ppez
76	animal model/ use emez
77	exp Rodentia/ use ppez
78	exp Rodent/ use emez
79	(rat or rats or mouse or mice).ti.
80	or/67-79
81	49 not 80
82	Epidemiologic Studies/
83	Case Control Studies/
84	Retrospective Studies/
85	Cohort Studies/
86	Longitudinal Studies/
87	Follow-Up Studies/
88	Prospective Studies/
89	Cross-Sectional Studies/
90	or/82-89 use ppez
91	clinical study/
92	case control study/
93	family study/
94	longitudinal study/
95	retrospective study/
96	prospective study/
97	cohort analysis/
98	or/91-97 use emez
99	((retrospective$ or cohort$ or longitudinal or follow?up or prospective or cross section$) adj3 (stud$ or research or analys$)).ti.
100	90 or 98 or 99
101	81 and 100
102	remove duplicates from 101

1 Health economics

2 Date of initial search: 03/10/2017

3 Database(s): Embase 1980 to 2017 Week 40, Ovid MEDLINE(R) Epub Ahead of Print, In-
4 Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)
5 1946 to Present

6 Date of updated search: 26/06/2018

7 Database(s): Embase 1980 to 2018 Week 26, Ovid MEDLINE(R) Epub Ahead of Print, In-
8 Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)
9 1946 to Present

#	Searches
1	exp Infant, Newborn/ use ppez
2	newborn/ use emez
3	prematurity/ use emez
4	(infan* or neonat* or neo-nat* or newborn* or baby or babies).ti,ab,jw,nw.
5	(preterm or pre-term or prematur* or pre-matur* or pre?mie* or premie*1).tw.
6	exp low birth weight/ use emez
7	(low adj3 birth adj3 weigh$).tw.
8	(LBW or VLBW).tw.
9	exp Respiratory Distress Syndrome, Newborn/ use ppez
10	neonatal respiratory distress syndrome/ use emez
11	exp Intensive Care, Neonatal/ use ppez
12	newborn intensive care/ use emez
13	exp Intensive Care Units, Neonatal/ use ppez
14	neonatal intensive care unit/ use emez
15	Neonatal Nursing/ use ppez
16	exp newborn nursing/ use emez
17	newborn care/ use emez
18	(special and care and baby and unit*).tw.
19	((newborn or neonatal or neo-natal) adj ICU*1).tw.
20	((newborn or neonat* or neo-nat*) adj2 (unit or care or department* or facilit* or hospital*)).tw.
21	(SCBU or NICU).tw.
22	((infan* or baby or babies or preterm or pre-term or prematur* or pre?mie* or premie*1) adj2 (unit* or care or department* or facilit* or hospital*)).tw.
23	or/1-22
24	Diuretics/ use ppez
25	diuretic agent/ use emez
26	Sodium Potassium Chloride Symporter Inhibitors/ use ppez
27	diuretic*.tw.
28	loop diuretic agent/ use emez
29	Furosemide/ use ppez
30	furosemide/ use emez
31	(furosemid* or frusemide or furantral).tw.
32	Mineralocorticoid Receptor Antagonists/ use ppez
33	aldosterone antagonist/ use emez
34	Canrenoic Acid/ use ppez
35	canrenoate potassium/ use emez
36	((potassium adj canrenoate) or (aldadiene adj kalium) or canrenoic acid).tw.
37	Spironolactone/ use ppez
38	spironolactone/ use emez
39	(spironolact?on* or acetylthiospirolactone).tw.
40	Thiazides/ use ppez
41	thiazide diuretic agent/ use emez
42	thiazide*.tw.
43	exp Chlorothiazide/ use ppez
44	chlorothiazide/ use emez
45	(chlorothiazid* or mechlozid or uroflux).tw.
46	or/24-44
47	23 and 46
48	limit 47 to english language
49	limit 48 to yr="1990 -Current"
50	Letter/ use ppez
51	letter.pt. or letter/ use emez

#	Searches
52	note.pt.
53	editorial.pt.
54	Editorial/ use ppez
55	News/ use ppez
56	exp Historical Article/ use ppez
57	Anecdotes as Topic/ use ppez
58	Comment/ use ppez
59	Case Report/ use ppez
60	case report/ or case study/ use emez
61	(letter or comment*).ti.
62	or/50-61
63	randomized controlled trial/ use ppez
64	randomized controlled trial/ use emez
65	random*.ti,ab.
66	or/63-65
67	62 not 66
68	animals/ not humans/ use ppez
69	animal/ not human/ use emez
70	nonhuman/ use emez
71	exp Animals, Laboratory/ use ppez
72	exp Animal Experimentation/ use ppez
73	exp Animal Experiment/ use emez
74	exp Experimental Animal/ use emez
75	exp Models, Animal/ use ppez
76	animal model/ use emez
77	exp Rodentia/ use ppez
78	exp Rodent/ use emez
79	(rat or rats or mouse or mice).ti.
80	or/67-79
81	49 not 80
82	Economics/
83	Value of life/
84	exp "Costs and Cost Analysis"/
85	exp Economics, Hospital/
86	exp Economics, Medical/
87	Economics, Nursing/
88	Economics, Pharmaceutical/
89	exp "Fees and Charges"/
90	exp Budgets/
91	or/82-90 use ppez
92	health economics/
93	exp economic evaluation/
94	exp health care cost/
95	exp fee/
96	budget/
97	funding/
98	or/92-97 use emez
99	budget*.ti,ab.
100	cost*.ti.
101	(economic* or pharmaco?economic*).ti.
102	(price* or pricing*).ti,ab.
103	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
104	(financ* or fee or fees).ti,ab.
105	(value adj2 (money or monetary)).ti,ab.
106	or/99-104
107	91 or 98 or 106
108	81 and 107
109	remove duplicates from 108

1 **Systematic reviews, RCTs and health economics**

2 Date of initial search: 03/10/2017

3 Database(s): Cochrane Library, issue 10 of 12, October 2017

4 Date of updated search: 27/06/2018

Database(s): Cochrane Library, issue 6 of 12, June 2018

ID	Search
#1	MeSH descriptor: [Infant, Newborn] explode all trees
#2	(infan* or neonat* or neo-nat* or newborn* or baby or babies or preterm or pre-term or prematur* or pre-matur* or pre?mie* or premie or premies or low birth weight or very low birth weight)
#3	(LBW or VLBW)
#4	MeSH descriptor: [Respiratory Distress Syndrome, Newborn] explode all trees
#5	MeSH descriptor: [Intensive Care, Neonatal] explode all trees
#6	MeSH descriptor: [Intensive Care Units, Neonatal] explode all trees
#7	MeSH descriptor: [Neonatal Nursing] explode all trees
#8	((newborn or neonat* or neo-nat*) near/2 (unit or care or department* or facilit* or hospital* or ICU*))
#9	(special near baby next unit*)
#10	(SCBU or NICU)
#11	((infan* or baby or babies or preterm or pre-term or prematur* or pre?mie* or premie* or premies) near/2 (unit* or care or department* or facilit* or hospital*))
#12	{or #1-#11}
#13	MeSH descriptor: [Diuretics] this term only
#14	MeSH descriptor: [Sodium Potassium Chloride Symporter Inhibitors] this term only
#15	diuretic*
#16	MeSH descriptor: [Furosemide] this term only
#17	(furosemid* or frusemide or furantral)
#18	MeSH descriptor: [Mineralocorticoid Receptor Antagonists] this term only
#19	MeSH descriptor: [Canrenoic Acid] this term only
#20	((potassium next canrenoate) or (aldadiene next kalium) or canrenoic acid)
#21	MeSH descriptor: [Spironolactone] this term only
#22	(spironolacton* or acetylthiospirolactone)
#23	MeSH descriptor: [Thiazides] this term only
#24	thiazide*
#25	MeSH descriptor: [Chlorothiazide] explode all trees
#26	(chlorothiazid* or mechlozid or uroflux)
#27	{or #13-#26}
#28	#12 and #27

Literature search strategies for question 3.6 What is the effectiveness of caffeine in preterm babies requiring respiratory support?

Date of initial search: 13/03/2018

Database: Embase 1980 to 2018 Week 11, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Date of updated search: 12/06/2018

Database(s): Embase 1980 to 2018 Week 24, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

#	Searches
1	exp Infant, Newborn/ use ppez
2	newborn/ use emez
3	prematurity/ use emez
4	(infan* or neonat* or newborn* or baby or babies).ti,ab,jw,nw.
5	(preterm or pre-term or prematur* or pre-matur* or pre?mie* or premie*1).tw.
6	exp low birth weight/ use emez
7	(low adj3 birth adj3 weigh*).tw.
8	(LBW or VLBW).tw.
9	exp Intensive Care, Neonatal/ use ppez
10	newborn intensive care/ use emez
11	exp Intensive Care Units, Neonatal/ use ppez
12	neonatal intensive care unit/ use emez
13	(special and care and baby and unit*).tw.
14	((newborn or neonatal) adj ICU*1).tw.
15	(SCBU or NICU).tw.

#	Searches
16	exp Respiratory Distress Syndrome, Newborn/ use ppez
17	neonatal respiratory distress syndrome/ use emez
18	or/1-17
19	Caffeine/ use ppez
20	caffeine/ use emez
21	caffeine citrate/ use emez
22	caffeine benzoate/ use emez
23	caffeine.tw.
24	or/19-23
25	18 and 24
26	Letter/ use ppez
27	letter.pt. or letter/ use emez
28	note.pt.
29	editorial.pt.
30	Editorial/ use ppez
31	News/ use ppez
32	exp Historical Article/ use ppez
33	Anecdotes as Topic/ use ppez
34	Comment/ use ppez
35	Case Report/ use ppez
36	case report/ or case study/ use emez
37	(letter or comment*).ti.
38	or/26-37
39	randomsied controlled trial/ use ppez
40	randomsied controlled trial/ use emez
41	random*.ti,ab.
42	or/39-41
43	38 not 42
44	animals/ not humans/ use ppez
45	animal/ not human/ use emez
46	nonhuman/ use emez
47	exp Animals, Laboratory/ use ppez
48	exp Animal Experimentation/ use ppez
49	exp Animal Experiment/ use emez
50	exp Experimental Animal/ use emez
51	exp Models, Animal/ use ppez
52	animal model/ use emez
53	exp Rodentia/ use ppez
54	exp Rodent/ use emez
55	(rat or rats or mouse or mice).ti.
56	or/43-55
57	25 not 56
58	limit 57 to english language
59	limit 58 to yr="1990 -Current"
60	remove duplicates from 59

1 **Health economics**

2 Date of initial search: 14/03/2018

3 Database: Embase 1980 to 2018 Week 11, Ovid MEDLINE(R) Epub Ahead of Print, In-
4 Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)
5 1946 to Present

6 Date of updated search: 12/6/2018

7 Database(s): Embase 1980 to 2018 Week 24, Ovid MEDLINE(R) Epub Ahead of Print, In-
8 Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)
9 1946 to Present

#	Searches
1	exp Infant, Newborn/ use ppez
2	newborn/ use emez
3	prematurity/ use emez
4	(infan* or neonat* or newborn* or baby or babies).ti,ab,jw,nw.
5	(preterm or pre-term or prematur* or pre-matur* or pre?mie* or premie*1).tw.

#	Searches
6	exp low birth weight/ use emez
7	(low adj3 birth adj3 weigh*).tw.
8	(LBW or VLBW).tw.
9	exp Intensive Care, Neonatal/ use ppez
10	newborn intensive care/ use emez
11	exp Intensive Care Units, Neonatal/ use ppez
12	neonatal intensive care unit/ use emez
13	(special and care and baby and unit*).tw.
14	((newborn or neonatal) adj ICU*1).tw.
15	(SCBU or NICU).tw.
16	exp Respiratory Distress Syndrome, Newborn/ use ppez
17	neonatal respiratory distress syndrome/ use emez
18	or/1-17
19	Caffeine/ use ppez
20	caffeine/ use emez
21	caffeine citrate/ use emez
22	caffeine benzoate/ use emez
23	caffeine.tw.
24	or/19-23
25	18 and 24
30	Economics/
31	Value of life/
32	exp "Costs and Cost Analysis"/
33	exp Economics, Hospital/
34	exp Economics, Medical/
35	Economics, Nursing/
36	Economics, Pharmaceutical/
37	exp "Fees and Charges"/
38	exp Budgets/
39	(or/30-38) use ppez
40	health economics/
41	exp economic evaluation/
42	exp health care cost/
43	exp fee/
44	budget/
45	funding/
46	(or/40-45) use emez
47	budget*.ti,ab.
48	cost*.ti.
49	(economic* or pharmaco?economic*).ti.
50	(price* or pricing*).ti,ab.
51	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
52	(financ* or fee or fees).ti,ab.
53	(value adj2 (money or monetary)).ti,ab.
54	or/47-53
55	39 or 46 or 54
56	25 and 55
57	limit 56 to english language
58	limit 57 to yr="1990 -Current"
59	remove duplicates from 58

1 Date of initial search: 13/03/2018

2 Database: The Cochrane Library, issue 3 of 12, March 2018

3 Date of updated search: 13/06/2018

4 Database: The Cochrane Library, issue 6 of 12, June 2018

ID	Search
#1	MeSH descriptor: [Infant, Newborn] explode all trees
#2	(infan* or neonat* or neo-nat* or newborn* or baby or babies)
#3	(preterm or pre-term or prematur* or pre-matur* or pre?mie* or premie*1)
#4	(low near birth near weigh*)
#5	MeSH descriptor: [Intensive Care, Neonatal] this term only
#6	MeSH descriptor: [Intensive Care Units, Neonatal] this term only
#7	(special and care and baby and unit*)
#8	((newborn or neonatal or neo-natal) near (ICU*1 or unit*))

ID	Search
#9	(SCBU or NICU)
#10	{or #1-#9}
#11	MeSH descriptor: [Caffeine] this term only
#12	caffeine
#13	#11 or #12
#14	#10 and #13 Publication Year from 1990 to 2018

Literature search strategies for question 3.8 What is the effectiveness of interventions for closing a patent ductus arteriosus in preterm babies requiring respiratory support?

Systematic reviews and RCTs

Date of initial search: 15/11/2017

Database(s): Embase 1980 to 2017 Week 46, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Date of updated search: 05/06/2018

Database(s): Embase 1980 to 2018 Week 23, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

#	Searches
1	exp Infant, Newborn/ use ppez
2	newborn/ use emez
3	prematurity/ use emez
4	(infan* or neonat* or neo-nat* or newborn* or baby or babies).ti,ab,jw,nw.
5	(preterm or pre-term or prematur* or pre-matur* or pre?mie* or premie*1).tw.
6	exp low birth weight/ use emez
7	(low adj3 birth adj3 weigh$).tw.
8	(LBW or VLBW).tw.
9	exp Respiratory Distress Syndrome, Newborn/ use ppez
10	neonatal respiratory distress syndrome/ use emez
11	exp Intensive Care, Neonatal/ use ppez
12	newborn intensive care/ use emez
13	exp Intensive Care Units, Neonatal/ use ppez
14	neonatal intensive care unit/ use emez
15	Neonatal Nursing/ use ppez
16	exp newborn nursing/ use emez
17	newborn care/ use emez
18	(special and care and baby and unit*).tw.
19	((newborn or neonatal or neo-natal) adj ICU*1).tw.
20	((newborn or neonat* or neo-nat*) adj2 (unit or care or department* or facilit* or hospital*)).tw.
21	(SCBU or NICU).tw.
22	((infan* or baby or babies or preterm or pre-term or prematur* or pre?mie* or premie*1) adj2 (unit* or care or department* or facilit* or hospital*)).tw.
23	or/1-22
24	Ductus Arteriosus, Patent/ use ppez
25	exp patent ductus arteriosus/ use emez
26	(patent ductus or persistent ductus or ductus arteriosus or PDA).tw.
27	or/24-26
28	23 and 27
29	drug therapy.fs.
30	surgery.fs.
31	29 or 30
32	Cyclooxygenase Inhibitors/ use ppez
33	prostaglandin synthase inhibitor/ use emez
34	Acetaminophen/ use ppez
35	paracetamol/ use emez

#	Searches
36	(paracetamol or acetaminophen or acetamidophen* or acetylaminophen* or panadol or tylenol).tw.
37	Anti-Inflammatory Agents, Non-Steroidal/ use ppez
38	nonsteroid antiinflammatory agent/ use emez
39	Ibuprofen/ use ppez
40	ibuprofen/ use emez
41	(ibuprofen* or ibuprophen or isobutylphenyl propionic acid or NSAID*).tw.
42	or/32-41
43	Fluid Therapy/ use ppez
44	fluid therapy/ use emez
45	Dehydration/ use ppez
46	dehydration/ use emez
47	or/43-46
48	(((fluid* or water) adj3 (restrict* or balanc* or deplet* or depriv* or imbalanc* or intake* or loss or manag* or remov* or therap* or treatment*)) or (dehydrat* or dishydrat*)).tw.
49	diuretic*.tw.
50	48 or (48 and 49)
51	Diuretics/ use ppez
52	diuretic agent/ use emez
53	51 or 52
54	47 and 53
55	Furosemide/ use ppez
56	furosemide/ use emez
57	(furosemid* or frusemide or furantral).tw.
58	or/55-57
59	Spironolactone/ and exp Chlorothiazide/ use ppez
60	spironolactone/ and chlorothiazide/ use emez
61	Furosemide/ and Canrenoic Acid/ use ppez
62	((spironolact?on* or acetylthiospirolactone) and (chlorothiazid* or mechlozid or uroflux)).tw.
63	furosemide/ and canrenoate potassium/ use emez
64	((furosemid* or frusemide or furantral) and ((potassium adj canrenoate) or (aldadiene adj kalium) or canrenoic acid)).tw.
65	or/59-64
66	Ligation/ use ppez
67	ductus arteriosus obliteration/ use emez
68	exp cardiovascular procedure/ use emez
69	exp Cardiac Catheterization/ use ppez
70	heart catheterization/ use emez
71	clip/ use emez
72	*Cardiovascular Surgical Procedures/ or *Cardiac Surgical Procedures/ use ppez
73	*cardiovascular surgery/ or *heart surgery/ use emez
74	(ligation* or catheter* or clip or clips* or closure or coil* or device* or intervention* or occlusion* or surgery or suture* or suturing or transcatheter* or trans-catheter*).tw.
75	or/66-74
76	31 or 42 or 47 or 50 or 54 or 58 or 65 or 75
77	28 and 76
78	limit 77 to english language
79	limit 78 to yr="1990 -Current"
80	Letter/ use ppez
81	letter.pt. or letter/ use emez
82	note.pt.
83	editorial.pt.
84	Editorial/ use ppez
85	News/ use ppez
86	exp Historical Article/ use ppez
87	Anecdotes as Topic/ use ppez
88	Comment/ use ppez
89	Case Report/ use ppez
90	case report/ or case study/ use emez
91	(letter or comment*).ti.
92	or/80-91
93	randomised controlled trial/ use ppez
94	randomised controlled trial/ use emez
95	random*.ti,ab.
96	or/93-95
97	92 not 96
98	animals/ not humans/ use ppez
99	animal/ not human/ use emez
100	nonhuman/ use emez

#	Searches
101	exp Animals, Laboratory/ use ppez
102	exp Animal Experimentation/ use ppez
103	exp Animal Experiment/ use emez
104	exp Experimental Animal/ use emez
105	exp Models, Animal/ use ppez
106	animal model/ use emez
107	exp Rodentia/ use ppez
108	exp Rodent/ use emez
109	(rat or rats or mouse or mice).ti.
110	or/97-109
111	79 not 110
112	Meta-Analysis/
113	Meta-Analysis as Topic/
114	systematic review/
115	meta-analysis/
116	(meta analy* or metanaly* or metaanaly*).ti,ab.
117	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
118	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
119	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
120	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
121	(search* adj4 literature).ab.
122	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
123	cochrane.jw.
124	((pool* or combined) adj2 (data or trials or studies or results)).ab.
125	or/112-113,116,118-123 use ppez
126	or/114-117,119-124 use emez
127	or/125-126
128	clinical Trials as topic.sh. or (controlled clinical trial or pragmatic clinical trial or randomised controlled trial).pt. or (placebo or randomi#ed or randomly).ab. or trial.ti.
129	128 use ppez
130	(controlled clinical trial or pragmatic clinical trial or randomised controlled trial).pt. or drug therapy.fs. or (groups or placebo or randomi#ed or randomly or trial).ab.
131	130 use ppez
132	crossover procedure/ or double blind procedure/ or randomised controlled trial/ or single blind procedure/ or (assign* or allocat* or crossover* or cross over* or ((doubl* or singl*) adj blind*) or factorial* or placebo* or random* or volunteer*).ti,ab.
133	132 use emez
134	129 or 131
135	133 or 134
136	127 or 135
137	111 and 136
138	remove duplicates from 137

1 **Observational studies**

2 Date of initial search:15/11/2017

3 Database(s): Embase 1980 to 2017 Week 46, Ovid MEDLINE(R) Epub Ahead of Print, In-
4 Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)
5 1946 to Present

6 Date of updated search: 06/06/2018

7 Database(s): Embase 1980 to 2018 Week 23, Ovid MEDLINE(R) Epub Ahead of Print, In-
8 Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)
9 1946 to Present

#	Searches
1	exp Infant, Newborn/ use ppez
2	newborn/ use emez
3	prematurity/ use emez
4	(infan* or neonat* or neo-nat* or newborn* or baby or babies).ti,ab,jw,nw.
5	(preterm or pre-term or prematur* or pre-matur* or pre?mie* or premie*1).tw.
6	exp low birth weight/ use emez
7	(low adj3 birth adj3 weigh$).tw.

#	Searches
8	(LBW or VLBW).tw.
9	exp Respiratory Distress Syndrome, Newborn/ use ppez
10	neonatal respiratory distress syndrome/ use emez
11	exp Intensive Care, Neonatal/ use ppez
12	newborn intensive care/ use emez
13	exp Intensive Care Units, Neonatal/ use ppez
14	neonatal intensive care unit/ use emez
15	Neonatal Nursing/ use ppez
16	exp newborn nursing/ use emez
17	newborn care/ use emez
18	(special and care and baby and unit*).tw.
19	((newborn or neonatal or neo-natal) adj ICU*1).tw.
20	((newborn or neonat* or neo-nat*) adj2 (unit or care or department* or facilit* or hospital*)).tw.
21	(SCBU or NICU).tw.
22	((infan* or baby or babies or preterm or pre-term or prematur* or pre?mie* or premie*1) adj2 (unit* or care or department* or facilit* or hospital*)).tw.
23	or/1-22
24	Ductus Arteriosus, Patent/ use ppez
25	exp patent ductus arteriosus/ use emez
26	(patent ductus or persistent ductus or ductus arteriosus or PDA).tw.
27	or/24-26
28	23 and 27
29	drug therapy.fs.
30	surgery.fs.
31	29 or 30
32	Cyclooxygenase Inhibitors/ use ppez
33	prostaglandin synthase inhibitor/ use emez
34	Acetaminophen/ use ppez
35	paracetamol/ use emez
36	(paracetamol or acetaminophen or acetamidophen* or acetylaminophen* or panadol or tylenol).tw.
37	Anti-Inflammatory Agents, Non-Steroidal/ use ppez
38	nonsteroid antiinflammatory agent/ use emez
39	Ibuprofen/ use ppez
40	ibuprofen/ use emez
41	(ibuprofen* or ibuprophen or isobutylphenyl propionic acid or NSAID*).tw.
42	or/32-41
43	Fluid Therapy/ use ppez
44	fluid therapy/ use emez
45	Dehydration/ use ppez
46	dehydration/ use emez
47	or/43-46
48	(((fluid* or water) adj3 (restrict* or balanc* or deplet* or depriv* or imbalanc* or intake* or loss or manag* or remov* or therap* or treatment*)) or (dehydrat* or dishydrat*)).tw.
49	diuretic*.tw.
50	48 or (48 and 49)
51	Diuretics/ use ppez
52	diuretic agent/ use emez
53	51 or 52
54	47 and 53
55	Furosemide/ use ppez
56	furosemide/ use emez
57	(furosemid* or frusemide or furantral).tw.
58	or/55-57
59	Spironolactone/ and exp Chlorothiazide/ use ppez
60	spironolactone/ and chlorothiazide/ use emez
61	Furosemide/ and Canrenoic Acid/ use ppez
62	((spironolact?on* or acetylthiospirolactone) and (chlorothiazid* or mechlozid or uroflux)).tw.
63	furosemide/ and canrenoate potassium/ use emez
64	((furosemid* or frusemide or furantral) and ((potassium adj canrenoate) or (aldadiene adj kalium) or canrenoic acid)).tw.
65	or/59-64
66	Ligation/ use ppez
67	ductus arteriosus obliteration/ use emez
68	exp cardiovascular procedure/ use emez
69	exp Cardiac Catheterization/ use ppez
70	heart catheterization/ use emez
71	clip/ use emez
72	*Cardiovascular Surgical Procedures/ or *Cardiac Surgical Procedures/ use ppez

#	Searches
73	*cardiovascular surgery/ or *heart surgery/ use emez
74	(ligation* or catheter* or clip or clips* or closure or coil* or device* or intervention* or occlusion* or surgery or suture* or suturing or transcatheter* or trans-catheter*).tw.
75	or/66-74
76	31 or 42 or 47 or 50 or 54 or 58 or 65 or 75
77	28 and 76
78	limit 77 to english language
79	limit 78 to yr="1990 -Current"
80	Letter/ use ppez
81	letter.pt. or letter/ use emez
82	note.pt.
83	editorial.pt.
84	Editorial/ use ppez
85	News/ use ppez
86	exp Historical Article/ use ppez
87	Anecdotes as Topic/ use ppez
88	Comment/ use ppez
89	Case Report/ use ppez
90	case report/ or case study/ use emez
91	(letter or comment*).ti.
92	or/80-91
93	randomised controlled trial/ use ppez
94	randomised controlled trial/ use emez
95	random*.ti,ab.
96	or/93-95
97	92 not 96
98	animals/ not humans/ use ppez
99	animal/ not human/ use emez
100	nonhuman/ use emez
101	exp Animals, Laboratory/ use ppez
102	exp Animal Experimentation/ use ppez
103	exp Animal Experiment/ use emez
104	exp Experimental Animal/ use emez
105	exp Models, Animal/ use ppez
106	animal model/ use emez
107	exp Rodentia/ use ppez
108	exp Rodent/ use emez
109	(rat or rats or mouse or mice).ti.
110	or/97-109
111	79 not 110
112	Epidemiologic Studies/
113	Case Control Studies/
114	Retrospective Studies/
115	Cohort Studies/
116	Longitudinal Studies/
117	Follow-Up Studies/
118	Prospective Studies/
119	Cross-Sectional Studies/
120	or/112-119 use ppez
121	clinical study/
122	case control study/
123	family study/
124	longitudinal study/
125	retrospective study/
126	prospective study/
127	cohort analysis/
128	or/121-127 use emez
129	((retrospective$ or cohort$ or longitudinal or follow?up or prospective or cross section$) adj3 (stud$ or research or analys$)).ti.
130	120 or 128 or 129
131	111 and 130
132	remove duplicates from 131

1 **Health economics**

2 Date of initial search:15/11/2017

Database(s): Embase 1980 to 2017 Week 46, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Date of updated search: 05/06/2018

Database(s): Embase 1980 to 2018 Week 23, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

#	Searches
1	exp Infant, Newborn/ use ppez
2	newborn/ use emez
3	prematurity/ use emez
4	(infan* or neonat* or neo-nat* or newborn* or baby or babies).ti,ab,jw,nw.
5	(preterm or pre-term or prematur* or pre-matur* or pre?mie* or premie*1).tw.
6	exp low birth weight/ use emez
7	(low adj3 birth adj3 weigh$).tw.
8	(LBW or VLBW).tw.
9	exp Respiratory Distress Syndrome, Newborn/ use ppez
10	neonatal respiratory distress syndrome/ use emez
11	exp Intensive Care, Neonatal/ use ppez
12	newborn intensive care/ use emez
13	exp Intensive Care Units, Neonatal/ use ppez
14	neonatal intensive care unit/ use emez
15	Neonatal Nursing/ use ppez
16	exp newborn nursing/ use emez
17	newborn care/ use emez
18	(special and care and baby and unit*).tw.
19	((newborn or neonatal or neo-natal) adj ICU*1).tw.
20	((newborn or neonat* or neo-nat*) adj2 (unit or care or department* or facilit* or hospital*)).tw.
21	(SCBU or NICU).tw.
22	((infan* or baby or babies or preterm or pre-term or prematur* or pre?mie* or premie*1) adj2 (unit* or care or department* or facilit* or hospital*)).tw.
23	or/1-22
24	Ductus Arteriosus, Patent/ use ppez
25	exp patent ductus arteriosus/ use emez
26	(patent ductus or persistent ductus or ductus arteriosus or PDA).tw.
27	or/24-26
28	23 and 27
29	drug therapy.fs.
30	surgery.fs.
31	29 or 30
32	Cyclooxygenase Inhibitors/ use ppez
33	prostaglandin synthase inhibitor/ use emez
34	Acetaminophen/ use ppez
35	paracetamol/ use emez
36	(paracetamol or acetaminophen or acetamidophen* or acetylaminophen* or panadol or tylenol).tw.
37	Anti-Inflammatory Agents, Non-Steroidal/ use ppez
38	nonsteroid antiinflammatory agent/ use emez
39	Ibuprofen/ use ppez
40	ibuprofen/ use emez
41	(ibuprofen* or ibuprophen or isobutylphenyl propionic acid or NSAID*).tw.
42	or/32-41
43	Fluid Therapy/ use ppez
44	fluid therapy/ use emez
45	Dehydration/ use ppez
46	dehydration/ use emez
47	or/43-46
48	(((fluid* or water) adj3 (restrict* or balanc* or deplet* or depriv* or imbalanc* or intake* or loss or manag* or remov* or therap* or treatment*)) or (dehydrat* or dishydrat*)).tw.
49	diuretic*.tw.
50	48 or (48 and 49)
51	Diuretics/ use ppez
52	diuretic agent/ use emez
53	51 or 52
54	47 and 53
55	Furosemide/ use ppez

#	Searches
56	furosemide/ use emez
57	(furosemid* or frusemide or furantral).tw.
58	or/55-57
59	Spironolactone/ and exp Chlorothiazide/ use ppez
60	spironolactone/ and chlorothiazide/ use emez
61	Furosemide/ and Canrenoic Acid/ use ppez
62	((spironolact?on* or acetylthiospirolactone) and (chlorothiazid* or mechlozid or uroflux)).tw.
63	furosemide/ and canrenoate potassium/ use emez
64	((furosemid* or frusemide or furantral) and ((potassium adj canrenoate) or (aldadiene adj kalium) or canrenoic acid)).tw.
65	or/59-64
66	Ligation/ use ppez
67	ductus arteriosus obliteration/ use emez
68	exp cardiovascular procedure/ use emez
69	exp Cardiac Catheterization/ use ppez
70	heart catheterization/ use emez
71	clip/ use emez
72	*Cardiovascular Surgical Procedures/ or *Cardiac Surgical Procedures/ use ppez
73	*cardiovascular surgery/ or *heart surgery/ use emez
74	(ligation* or catheter* or clip or clips* or closure or coil* or device* or intervention* or occlusion* or surgery or suture* or suturing or transcatheter* or trans-catheter*).tw.
75	or/66-74
76	31 or 42 or 47 or 50 or 54 or 58 or 65 or 75
77	28 and 76
78	limit 77 to english language
79	limit 78 to yr="1990 -Current"
80	Letter/ use ppez
81	letter.pt. or letter/ use emez
82	note.pt.
83	editorial.pt.
84	Editorial/ use ppez
85	News/ use ppez
86	exp Historical Article/ use ppez
87	Anecdotes as Topic/ use ppez
88	Comment/ use ppez
89	Case Report/ use ppez
90	case report/ or case study/ use emez
91	(letter or comment*).ti.
92	or/80-91
93	randomised controlled trial/ use ppez
94	randomised controlled trial/ use emez
95	random*.ti,ab.
96	or/93-95
97	92 not 96
98	animals/ not humans/ use ppez
99	animal/ not human/ use emez
100	nonhuman/ use emez
101	exp Animals, Laboratory/ use ppez
102	exp Animal Experimentation/ use ppez
103	exp Animal Experiment/ use emez
104	exp Experimental Animal/ use emez
105	exp Models, Animal/ use ppez
106	animal model/ use emez
107	exp Rodentia/ use ppez
108	exp Rodent/ use emez
109	(rat or rats or mouse or mice).ti.
110	or/97-109
111	79 not 110
112	Economics/
113	Value of life/
114	exp "Costs and Cost Analysis"/
115	exp Economics, Hospital/
116	exp Economics, Medical/
117	Economics, Nursing/
118	Economics, Pharmaceutical/
119	exp "Fees and Charges"/
120	exp Budgets/

#	Searches
121	or/112-120 use ppez
122	health economics/
123	exp economic evaluation/
124	exp health care cost/
125	exp fee/
126	budget/
127	funding/
128	or/122-127 use emez
129	budget*.ti,ab.
130	cost*.ti.
131	(economic* or pharmaco?economic*).ti.
132	(price* or pricing*).ti,ab.
133	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
134	(financ* or fee or fees).ti,ab.
135	(value adj2 (money or monetary)).ti,ab.
136	or/129-134
137	121 or 128 or 136
138	111 and 137
139	remove duplicates from 138

1 **Systematic reviews, RCTs, health economics**

2 Date of initial search: 15/11/2017

3 Database: The Cochrane Library, issue11 of 12, November 2017

4 Date of updated search: 05/06/2018

5 Database: The Cochrane Library, issue 6 of 12, June 2018

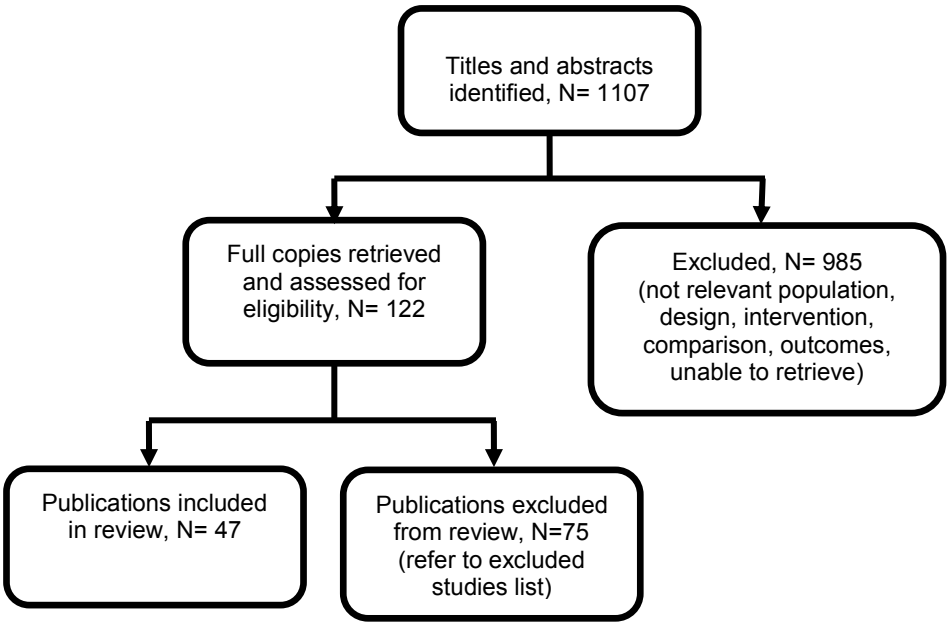
ID	Search
#1	MeSH descriptor: [Infant, Newborn] explode all trees
#2	(infan* or neonat* or neo-nat* or newborn* or baby or babies)
#3	(preterm or pre-term or prematur* or pre-matur* or pre?mie* or premie*1)
#4	(low near birth near weigh*)
#5	MeSH descriptor: [Intensive Care, Neonatal] this term only
#6	MeSH descriptor: [Intensive Care Units, Neonatal] this term only
#7	(special and care and baby and unit*)
#8	((newborn or neonatal or neo-natal) near (ICU*1 or unit*))
#9	(SCBU or NICU)
#10	{or #1-#9}
#11	MeSH descriptor: [Ductus Arteriosus, Patent] this term only
#12	(patent ductus or persistent ductus or ductus arteriosus or PDA)
#13	#11 or #12
#14	#10 and #13
#15	MeSH descriptor: [Cyclooxygenase Inhibitors] explode all trees
#16	MeSH descriptor: [Acetaminophen] this term only
#17	MeSH descriptor: [Ibuprofen] this term only
#18	MeSH descriptor: [Anti-Inflammatory Agents, Non-Steroidal] this term only
#19	(paracetamol or acetaminophen or acetamidophen* or acetylaminophen* or panadol or tylenol)
#20	(ibuprofen* or ibuprophen or isobutylphenyl propionic acid or NSAID*)
#21	{or #15-#20}
#22	MeSH descriptor: [Fluid Therapy] explode all trees
#23	MeSH descriptor: [Dehydration] this term only
#24	#22 or #23
#25	MeSH descriptor: [Diuretics] this term only
#26	#24 and #25
#27	{or #24-#26}
#28	((fluid* or water) N3 (rrestrict* or balanc* or deplet* or depriv* or imbalanc* or intake* or loss or manag* or remov* or therap* or treatment*))
#29	(dehydrat* or dishydrat*)
#30	#28 or #29
#31	diuretic*
#32	#30 and #31
#33	{or #30-#32}
#34	MeSH descriptor: [Furosemide] this term only
#35	(furosemid* or frusemide or furantral)

ID	Search
#36	#34 or #35
#37	MeSH descriptor: [Spironolactone] this term only
#38	MeSH descriptor: [Chlorothiazide] explode all trees
#39	#37 and #38
#40	MeSH descriptor: [Furosemide] this term only
#41	MeSH descriptor: [Canrenoic Acid] explode all trees
#42	#40 and #41
#43	((spironolacton* or acetylthiospirolactone) and (chlorothiazid* or mechlozid or uroflux))
#44	((furosemid* or frusemide or furantral) and ((potassium adj canrenoate) or (aldadiene N2 kalium) or canrenoic acid))
#45	#43 or #44
#46	MeSH descriptor: [Ligation] this term only
#47	MeSH descriptor: [Cardiac Catheterization] explode all trees
#48	MeSH descriptor: [Cardiovascular Surgical Procedures] this term only
#49	MeSH descriptor: [Cardiac Surgical Procedures] this term only
#50	(ligation* or catheter* or clip or clips* or closure or coil* or device* or intervention* or occlusion* or surgery or suture* or suturing or transcatheter* or trans-catheter*)
#51	{or #46-#50}
#52	{or #21, #27, #33, #36, #39, #42, #45, #51}
#53	#14 and #52 Publication Year from 1990 to 2017

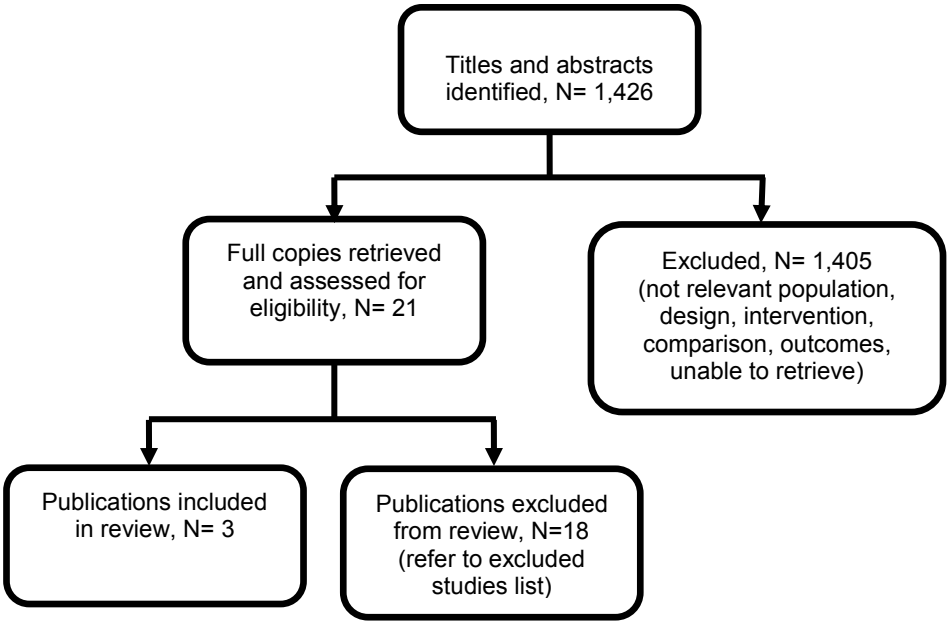
1
2

Appendix C – Clinical evidence study selection

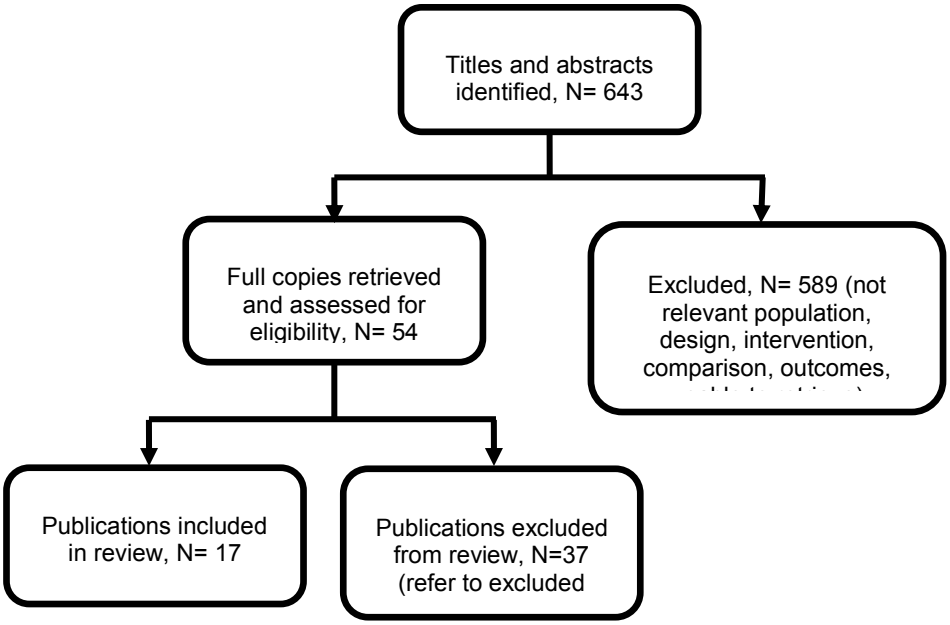
Clinical evidence study selection for question 3.4 What is the effectiveness of corticosteroids in preterm babies requiring respiratory support?



Clinical evidence study selection for question 3.5 What is the safety and effectiveness of diuretics in preterm babies on respiratory support?

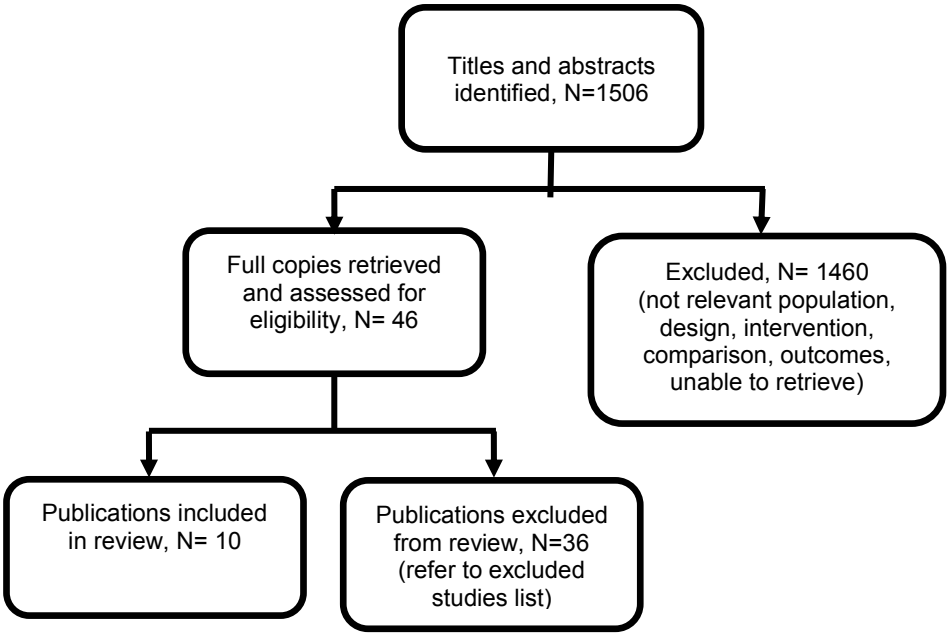


Clinical evidence study selection for question 3.6 What is the effectiveness of caffeine in preterm babies requiring respiratory support?

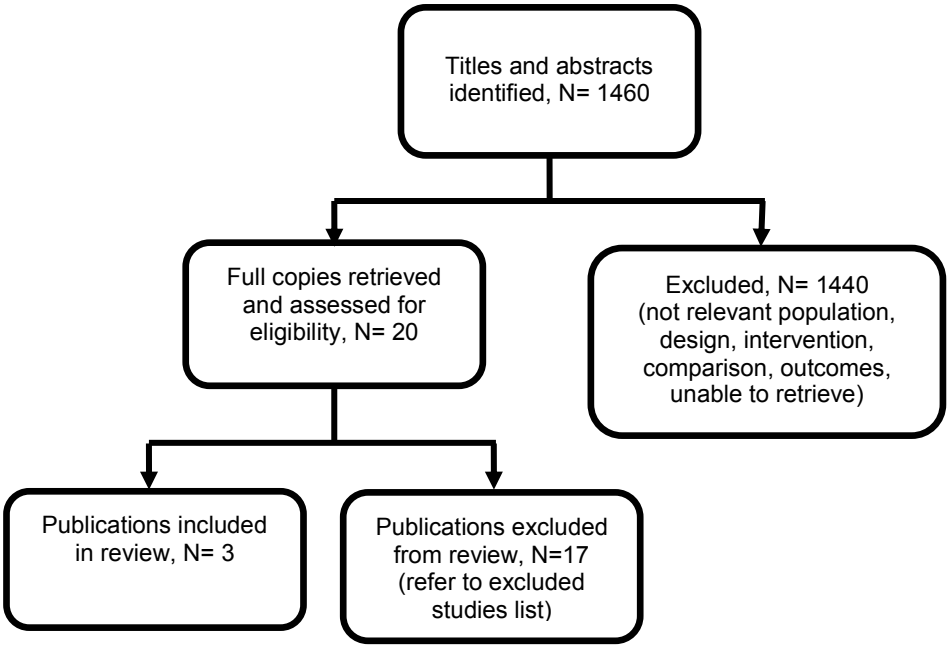


Clinical evidence study selection for question 3.8 What is the effectiveness of interventions for closing a patent ductus arteriosus in preterm babies requiring respiratory support?

Systematic reviews and RCTS:



Observational studies:



Appendix D – Clinical evidence tables

Clinical evidence tables for question 3.4 What is the effectiveness of corticosteroids in preterm babies requiring respiratory support?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Armstrong,D.L., Penrice,J., Bloomfield,F.H., Knight,D.B., Dezoete,J.A., Harding,J.E., Follow up of a randomised trial of two different courses of dexamethasone for preterm babies at risk of chronic lung disease, Archives of Disease in Childhood Fetal and Neonatal Edition, 86, F102-F107, 2002 **Ref Id** 254070 **Country/ies where the study was carried out** **Study type**	**Sample size** Follow-up study to Bloomfield 1998. Please see Onland 2017 Cochrane systematic review **Characteristics** **Inclusion criteria** **Exclusion criteria**	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study **Study dates** **Source of funding**					
Full citation Baud, O, Maury, L, Lebail, F, Ramful, D, Moussawi, F, Nicaise, C, Zupan-Simunek, V, Coursol, A, Beuchée, A, Bolot, P, Andrini, P, Mohamed, D, Alberti, C, Effect of early low-dose hydrocortisone on survival without bronchopulmonary dysplasia in extremely preterm infants (PREMILOC): a double-blind, placebo-controlled, multicentre, randomised trial, Lancet (London,	**Sample size** n=523 randomised (n=256 hydrocortisone; n=257 placebo) **Characteristics** Geststional age (weeks in median, with IQR in parentheses): Hydrocortisone= 26.4 (25.6-27); placebo=26.5 (25.7-27.1) **Inclusion criteria** Inborn (born in a maternity ward that is at the same site	**Interventions** 1) Hydrocortisone hemisuccinate, 1mg/kg per day divided into 2 doses per day for 7 days, followed by one dose of 0.5mg/kg per day for 3 days. 2) Control infants were given equal volumes of i.v glucose (5% placebo) **Total cumulative dose: 8.5mg/kg** **Timing of administration: Within first 24 hours**	**Details** **Methods** Randomisation: Randomisation was generated electronically with nQuery (verion 6.01) Allocation concealment: Treatment assignment was done with a secure study website (Cleanweb Telemedicine Technologies, Boulogne-Billancourt, France) after verification of eligibility and consent status. Randomisation	**Results** Outcome: Mortality prior to discharge Hydrocortisone: 48/255; placebo: 67/266 Outcome: Bronchopulmonary dysplasia at 36 weeks corrected gestation Hydrocortisone: 55/255; placebo: 70/266 Outcome: Gastro-intestinal perforation Hydrocortisone: 13/255; placebo: 11/266	**Limitations** **Quality of study:** Risk of bias assessed using Cochrane risk of bias tool Random sequence generation: Low risk (Randomisation was generated electronically with nQuery (verion 6.01) a computer generated randomisation tool) Allocation concealment: Lows risk (Treatment assignment was done with a secure study website [Cleanweb Telemedicine Technologies, Boulogne-Billancourt, France] after

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
England), 387, 1827-36, 2016 **Ref Id** 619449 **Country/ies where the study was carried out** France **Study type** Double-blind, placebo-controlled, multicentre, randomised trial **Aim of the study** To assess whetehr low-dose hydrocortisoneimproved survival without bronchopulmonary dysplasia **Study dates** May 25, 2008 - Jan 31, 2014 **Source of funding**	as the NICU) and delivered between 24+0 and 27+6 weeks gestation (randomised within 24 hrs of birth) **Exclusion criteria** Rupture of membranes occured before 22 weeks of gestation, if birht weight was less than the third percentile for gestational age according to French gender-customised curves, if they had severe perinatal asphyxia (defined as Apgar score of 0-3 for more than 5 min, a cord blood pH of less than 7.00, or both) and were expected to die shortly after birth, or if they had congenital malformations (defined as birht defects or major structural abnormalities detectable prenatally) or known chromosomal aberrations.		was stratified by gestational age (2 groups: 24-25 weeks and 26-27 weeks of gestation). Blinding: The appearance of hysrocortisone and placebo vials was strictly identical, and patient information and treatment groups were masked from all participants in the research (i.e parents, nurses, and physicians) Attrition: ITT analysis, 2 babies' parents withdrew consent (1 from each arm) Selective reporting: All outcomes in the protocol reported in the full RCT **Outcomes** Survival without BPD, Death, BPD, extubated patients on day 10, weaning from any ventilatory support at 36 PMA, weaning from an supplemental oxygen		verification of eligibility and consent status. Randomisation was stratified by gestational age [2 groups: 24-25 weeks and 26-27 weeks of gestation]) Blinding of participants and personnel: Low risk (The appearance of hydrocortisone and placebo vials was strictly identical) Blinding of outcome assessment: Low risk (patient information and treatment groups were masked from all participants in the research [i.e parents, nurses, and physicians]) Incomplete outcome data: Low risk (ITT analysis, 2 babies' parents withdrew consent [1 from each arm]) Selective reporting: Low risk (All outcomes in the protocol reported in the full RCT) Other bias: None reported

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Assistance Publique-Hospitaux de Paris			at 36 weeks PMA, PDA ligation, air leaks, pulmonary haemorrhage, insulin requirement, necrolising entrerocolitis, gastrointestinal perforation, late-onset sepsis, severe IVH, cystic PVL, severe ROP, death before discharge.		**Other information**
Full citation Bloomfield, Fh, Knight, Db, Harding, Je, Side effects of 2 different dexamethasone courses for preterm infants at risk of chronic lung disease: a randomized trial, The Journal of Pediatrics, 133, 395-400, 1998 **Ref Id** 619468	**Sample size** Please see Onland 2017 Cochrane systematic review **Characteristics** **Inclusion criteria** **Exclusion criteria**	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out **Study type** **Aim of the study** **Study dates** **Source of funding**					
Full citation Bonsante,F., Latorre,G., Iacobelli,S., Forziati,V., Laforgia,N., Esposito,L., Mautone,A., Early low-dose hydrocortisone in very preterm infants: a randomized, placebo-controlled trial, Neonatology, 91, 217-221, 2007 **Ref Id** 253998	**Sample size** Please see Doyle et al 2014 (early administration of corticosteroids) cochrane systematic review **Characteristics** **Inclusion criteria** **Exclusion criteria**	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out **Study type** **Aim of the study** **Study dates** **Source of funding**					
Full citation Brozanski,B.S., Jones,J.G., Gilmour,C.H., Balsan,M.J., Vazquez,R.L., Israel,B.A., Newman,B., Mimouni,F.B., Guthrie,R.D., Effect of pulse dexamethasone therapy on the incidence and severity of chronic lung disease in the very low birth weight infant,	**Sample size** Please see Doyle et al 2014 (late administration of corticosteroids) cochrane systematic review **Characteristics** **Inclusion criteria** **Exclusion criteria**	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Journal of Pediatrics, 126, 769-776, 1995 **Ref Id** 208645 **Country/ies where the study was carried out** **Study type** **Aim of the study** **Study dates** **Source of funding**					
Full citation Doyle, Lw, Davis, Pg, Morley, Cj, McPhee, A, Carlin, Jb, Low-dose dexamethasone facilitates extubation among chronically ventilator-dependent infants: a multicenter,	**Sample size** Please see Doyle et al 2014 (late administration of corticosteroids) cochrane systematic review **Characteristics**	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
international, randomized, controlled trial, Pediatrics, 117, 75-83, 2006 **Ref Id** 619539 **Country/ies where the study was carried out** **Study type** **Aim of the study** **Study dates** **Source of funding**	**Inclusion criteria** **Exclusion criteria**				
Full citation Doyle, L. W., Davis, P. G., Morley, C. J., McPhee, A., Carlin, J. B., Kaimakamis, M., Callanan, C., Davis, N., Ford, G., Kelly, E., Ung,	**Sample size** Please see Doyle et al 2014 (late administration of corticosteroids) cochrane systematic review	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
L., Yu, V., Hayes, M., Li, R., Carse, E., Charlton, M., Fraser, S., Gill, A., Wooderson, S., Vimpani, A., Lontis, R., Goodchild, L., French, N., Benninger, H., Evans, N., Reid, S., Rieger, I., Darlow, B., Kuschel, C., Dezoete, A., Alvaro, R., Chiu, A., Sankaran, K., Andreychuk, B., Jamsen, K., Chionh, C., Hiller, J., Lumley, J., Sinclair, J. C., Outcome at 2 years of age of infants from the DART study: A multicenter, international, randomized, controlled trial of low-dose dexamethasone, Pediatrics, 119, 716-721, 2007 **Ref Id** 619541 **Country/ies where the study was carried out** **Study type**	**Characteristics** **Inclusion criteria** **Exclusion criteria**				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study **Study dates** **Source of funding**					
Full citation Doyle, L. W., Ehrenkranz, R. A., Halliday, H. L., Late (> 7 days) postnatal corticosteroids for chronic lung disease in preterm infants, Cochrane Database of Systematic Reviews, 5, CD001145, 2014 **Ref Id** 357360 **Country/ies where the study was carried out** **Study type** Cochrane systematic review	**Sample size** **Of relevant studies:** **Brozanski 1995** n=88 randomised **CDTG 1991** n=287 randomised (n=145 dexamethasone; n=142 placebo) **Doyle 2006** n=70 randomised (n=35 dexamethasone; n=35 placebo) **Durand 1995** n=43 randomised (n=23 dexamethasone; n= 20 placebo) **Kari 1993** n=41 randomised (n=17 dexamethason; n=24 placebo) **Kothadia 1999**	**Interventions** **Of relevant studies:** **Brozanski 1995** 1) Dexamethasone 0.25 mg/kg/day 12-hourly for 2 days, repeated every 10 days until 36 weeks' PMA or no longer needs ventilator support or supplemental oxygen. An occasional dose of study drug was administered as an intramuscular injection when intravenous access was not possible. **Total cumulative dose: Dependent on gestational age**	**Details** **Of relevant studies** **Brozanski 1995** Methods: Double-blind, randomised, controlled trial Outcomes: Inspired oxygen concentration, duration of supplemental oxygen, survival without oxygen at 30 days and 34 weeks, CLD, GI bleeding, IVH, death, NEC, ROP (> stage II), hyperglycaemia, pulmonary air leak, sepsis and worsening IVH (grade > II) **Doyle 2006**	**Results** Outcome: Mortality prior to discharge **Brozanski 1995** Dexamethasone: 4/30; control: 9/39 **Doyle 2006** Dexamethasone: 3/35; control: 5/35 **Durand 1995** Dexamethasone: 2/23; control: 4/20 **Kari 1993** Dexamethasone: 1/17; control: 3/24 **Kothadia 1999** Dexamethasone: 7/57; control: 10/61 **Kovacs 1998** Dexamethasone: 8/30; control: 5/30 **Parikh 2013**	**Limitations** **Quality of Cochrane SR:** Systematic review assessed using AMSTAR checklist. Total score: 10/11 All checklist items adressed, with the exception of: Checklist item 4: Was the status of publication (i.e. grey literature) used as an inclusion criterion? No details provided **Quality of individual studies:** Risk of bias assessment taken from Cochrane systematic reivew (Cochrane risk of bias tool)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study To determine the relative benefits and adverse effects associated with late (> 7 days) postnatal systemic corticosteroid treatment compared with control (placebo or nothing) in the preterm infant with evolving or established chronic lung disease. **Study dates** Search up to August 2013 **Source of funding** Action research grant to study long-term folow-up, UK. Action research (UK) grant to study the effects of postnantal steroids, UK. National health and medical research council, Australia. Eunice Kennedy Shriver	n=118 randomised (n=57 dexamethasone; n=61 placebo) **Kovacs 1998** n=60 randomised (n=30 steroid; n=60 placebo) **Parikh 2013** n=64 randomised (n=31 hydrocortisone group; n=33 placebo group) **Romagnoli 1998** n=30 randomised (n=15 dexamethasone; n=15 placebo) **Walther 2003** n=36 randomised (n=17 dexamethasone; n=17 placebo) **Characteristics Of relevant studies included:** **Bronzanski 1995*** Setting: USA Gestational age (weeks in mean, with SD in parentheses): Dexamethasone= 25.6 (± 0.3); Placebo=26.0 (± 0.3) Apgar score ≤ 5 at 5 min: Dexamethasone=7/38; placebo=7/38	**Timing of administration: ≥7 days (mean age 8 days or older)** 2)Control infants were given an equivalent volume of saline intravenously twice daily for 3 days **Doyle 2006** 1) A 10-day tapering course of dexamethasone (0.15 mg/kg/day for 3 days, 0.10 mg/kg/day for 3 days, 0.05 mg/kg/day for 2 days and 0.02 mg/kg/day for 2 days). **Total cumulative dose: 0.89 mg/kg** **Timing of administration: ≥7 days (mean age 8 days or older)** 2) Control infants were given equivalent volumes of normal saline placebo A repeat course of the same blinded drug was allowed at the discretion of the attending clinicians **Durand 1995**	Methods: Multi-centre, double-blind, randomised controlled trial Outcomes: Ventilator settings, oxygen requirements, hyperglycaemia, hypertension, growth, BPD (any oxygen at 36 weeks) severe BPD (> 30% oxygen at 36 weeks' PMA), mortality, infections, NEC, GI bleeding, PDA, ROP, cardiac hypertrophy, cranial ultrasound abnormalities. Long-term follow-up at 2 years of age by staff blinded to treatment allocation for neurological impairments and disabilities, including cerebral palsy **Durand 1995** Methods: Randomised controlled trial Outcomes: Pulmonary function tests, inspired oxygen	Hydrocortisone: 8/31; control: 8/33 **Romagnoli 1998** Dexamethasone: 0/15; control: 0/15 **Walther 2003** Dexamethasone: 2/17; control:2/19 Outcome: Bronchopulmonary dysplasia at 36 weeks corrected gestation **Brozanski 1995** Dexamethasone: 20/39; control: 23/39 **Doyle 2006** Dexamethasone: 28/35; control: 29/35 **Durand 1995** Dexamethasone: 2/23; control: 8/20 **Kothadia 1999** Dexamethasone: 32/57; control: 45/61 **Kovacs 1998** Dexamethasone: 10/30; control: 14/30 **Parikh 2013** Hydrocortisone: 20/31; control: 20/33 **Romagnoli 1998** Dexamethasone: 5/15; control: 11/15	**Brozanski 1995** Random sequence generation: Low risk (Random allocation using sealed envelopes kept in the pharmacy. Stratified by gender and birth weight [< 1000 g versus > 1000 g]) Allocation concealment: Lows risk (Random allocation using sealed envelopes kept in the pharmacy. Stratified by gender and birth weight [< 1000 g versus > 1000 g] Blinding of randomisation: yes) Blinding of participants and personnel: Low risk (blinding of intervention) Blinding of outcome assessment: Low risk (blinding of outcome) Incomplete outcome data: Unclear risk (Complete follow-up: no; results given for 78 out of 88 infants enrolled) Other bias: None reported **Doyle 2006** Random sequence generation: Low risk

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
National Institute of Child Health and Human Development National Institutes of Health, Department of Health and Human Services, USA	Surfactant use: Dexamethasone=35/39; Placebo=34/39 FiO2 (mean, with SD in parentheses): Dexamethasone=0.43 (±0.03); placebo=0.39 (±0.03) **Doyle 2006*** Setting: Australia Gestational age (weeks in median, IQR in parentheses): Dexamethasone= 24 (24-25); placebo= 25 (24-26) Apgar score (median, IQR in parentheses) at: 1 min: Dexamethasone=5 (4-6); placebo=5 (3-6) 5 min: Dexamethasone=7 (7-8); placebo=7 (6-9) Surfactant (%): Dexamethasone= 33 (94.3); placebo=34 (97.1) **Durand 1995*** Setting: USA Gestational age (weeks in mean, with SD in parentheses): Dexamethasone=27.4 (±1.6); placebo=27.4 (±1.7) Apgar score (median, range in parentheses) at:	1) Intravenous dexamethasone 0.5 mg/kg/day for 3 days, then 0.25 mg/kg/day for 3 days and 0.10 mg/kg for 1 day **Total cumulative dose: 2.35 mg/kg** **Timing of administration: 7-14 days** 2) Control infants were not given a placebo **Kari 1993** 1) Dexamethasone 0.5 mg/kg/day given intravenously 12-hourly for 7 days **Total cumulative dose: 3.5mg/kg** **Timing of administration: 10 days** 2) Infants in the control group received normal saline as a placebo **Kothadia 1999** 1) 42-day tapering course of dexamethasone. Dexamethasone 0.25mg/kg 12-hourly for 3 days, 0.15 mg/kg 12-hourly for 3 days,	concentration, ventilator settings, CLD (36 weeks' PMA), infection, ROP and IVH **Kari 1993** Methods: Multi-centre, double-blind, randomised, controlled trial Outcomes: BPD, duration of IPPV, hypertension, hyperglycaemia, sepsis, perforated colon, cryotherapy for ROP **Kothadia 1999** Methods: Double-blind, randomised, controlled trial Outcomes: Duration of ventilation, oxygen, hospital stay; death, oxygen at 36 weeks' PMA, ROP (stage 3), infection, hypertension and hyperglycaemia. Follow-up: Bayley MDI and PDI, cerebral palsy, abnormal neurological examination	**Walther 2003** Dexamethasone: 4/17; control:8/19 Outcome: Bronchopulmonary dysplasia at 28 days corrected gestation **Brozanski 1995** Dexamethasone: 33/39; control: 31/39 **Durand 1995** Dexamethasone: 7/23; control: 14/20 **Kari 1993** Dexamethasone: 15/17; control: 22/24 **Kovacs 1998** Dexamethasone: 24/30; control: 26/30 **Romagnoli 1998** Dexamethasone: 10/15; control: 15/15 Outcome: Cerebral Palsy **Kothadia 1999 - extracted from O'Shea 2007* (based on combination of follow-up [15 diagnosed at 1 year, 2 diagnosed at 4-6 years** - denominator = population at follow-up, excludes 15 children who were free from CP at 1 year but were not	(Random allocation was computer-generated centrally, independent of investigators except the statistician, and was stratified by centre, with randomly permuted blocks of 2 to 8 infants) Allocation concealment: Low risk (blinding of randomisation) Blinding of participants and personnel: Low risk (blinding of intervention) Blinding of outcome assessment: Low risk (blinding of outcome measure) Incomplete outcome data: Low risk (complete follow-up) Other bias: None reported **Durand 1995** Random sequence generation: Unclear risk (Blind drawing of random cards in sealed envelopes) Allocation concealment: Low (specifics not reported by Doyle 2014) Blinding of participants and personnel: High risk

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	1 min: Dexamethasone=4 (1-9); placebo=4 (1-8) 5 min: Dexamethasone: 6 (4-9); placebo= 7 (4-9) **Kari 1993*** Setting: Finland Gestational age (weeks in mean, with SD in parentheses): Dexamethasone= 27 (± 2); Placebo=27 (± 2) **Kothadia 1999*** Setting: USA Gestational age: (weeks median, range in parentheses): Dexamethasone 26 (23-29); placebo=25 (23-31) Surfactant (%): Dexamethasone=56 (99%); placebo: 61 /(100%) FiO2 at entry (median, range in parentheses): Dexamethasone=0.60 (0.30-1.0); placebo=0.60 (0.34-1.0) **Kovacs 1998*** Setting: Canada Gestational age (weeks in mean, with SD in parentheses): Steroid= 25.8 (±1.6); placebo=25.9 (±1.8) Apgar score (median, range in parentheses) at:	then a 10% reduction in dose every 3 days until a dose of 0.1 mg/kg had been given for 3 days, from which time 0.1 mg/kg every other day until 42 days after entry **Total cumulative dose: 6.7 mg/kg** **Timing of administration: 15-25 days** 2) 42-tapering course of control, using an equal volume of saline **Kovacs 1998** 1) Dexamethasone given systemically in a dose of 0.25mg/kg twice daily for 3 days followed by nebulised budesonide 500 µg twice daily for 18 days **Total cumulative dose: 1.5mg/kg dexamethasone + 1.8mg of budesonide** **Timing of administration: ≥7 days (mean age 8 days or older)**	**Kovacs 1998** Methods: Double-blind, randomised, controlled trial Outcomes: Survival to discharge, ventilatory support between 9 and 17 days, supplemental oxygen between 8 and 10 days, pulmonary compliance at 10 days, elastase/albumin ratios in tracheal aspirates, need for rescue dexamethasone, time to extubation, duration of oxygen in survivors, CLD at 36 weeks' PMA in survivors, duration of hospital stay **Parikh 2013** Methods: Double-blind, randomised, controlled trial Outcomes: Main outcomes was brain tissue volumes on MRI at term-equivalent age. Other outcomes included	examined at 4-6 years and 1 child who was only seen at 9 years**)** Dexamethasone: 13/45; placebo: 4/34 **Doyle 2006 - extracted from Doyle 2007* (diagnosed at 2 years-** denominator = population at follow-up**)** Dexamethasone: 4/29; control: 6/27 **Romagnoli 1998 - extracted from Romagnoli 2002* (diagnosed at 36-42 months of age-** denominator = population at follow-up**)** Dexamethasone: 2/15; control: 3/15 **Durand 1995 (diagnosed at 1-3 years and at last reported age-** denominator = population at follow-up**)** Dexamethasone: 2/16; control: 2/13 **Kovacs 1998 (diagnosed at 1-3 years and at last reported age-** denominator = population at follow-up**)** Dexamethasone: 1/15; control: 1/18 **Walther 2003 (diagnosed at 1-3 years and at last**	(no blinding of intervention) Blinding of outcome assessment: High risk (blinding of outcome measurement only for respiratory mechanics) Incomplete outcome data: Low risk (Complete follow-up: almost [43 of 44 randomised]) Other bias: None reported **Kari 1993** Random sequence generation: Unclear risk (method not stated) Allocation concealment: Low risk (specifics not reported by Doyle 2014) Blinding of participants and personnel: Low risk (blinding of intervention) Blinding of outcome assessment: Low risk (blinding of outcome measure) Incomplete outcome data: Low risk (complete follow-up) Other bias: None reported **Kothadia 1999**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	1 min: Steroid=5 (1-8); placebo=3 (1-7) 5 min: Steroid= 7 (1-10); placebo= 7 (2-8) Surfactant (%): Steroid= 14 (46.7); Placebo= 14 (46.7) **Parikh 2013*** Setting: USA Gestational age: (weeks median, range in parentheses): Hydrocortisone=25 (24-26); placebo=25 (24-27) Apgar at 5 min, median (IQR): Hydrocortisone=7 (5-8); placebo=7 (5-8) Surfactant use (%): Hydrocortisone= 31 (100%); placebo=32 (97%) FiO2 at randomisation, median (IQR); Hydrocortisone=0.44 (0.38-0.60); placebo= 0.46(0.36-0.52) **Romagnoli 1998*** Setting: Italy Gestational age (weeks in mean, with SD in parentheses): dexamethasone=27.5 (±1.4); placebo= 27.1 (±1.4) **Walther 2003*** Setting: USA	2) Control infants received systemic and inhaled saline placebos **Parikh 2013** 1) Hydrocortisone total of 17 mg/kg over 7 days (3 mg/kg/day for 4 days, 2 mg/kg/day for 2 days and 1 mg/kg/day for 1 day) **Total cumulative dose: 17mg/kg** **Timing of administration: 10-21 days** 2) Identical volume saline placebo **Romagnoli 1998** 1) Dexamethasone 0.50 mg/kg/day for 6 days, 0.25 mg/kg/day for 6 days and 0.125 mg/kg/day for 3 days (total dose 4.75 mg/kg) from 10th day intravenously. **Total cumulative dose: 4.75mg/kg** **Timing of administration: 10 days** 2) Control group received no placebo **Walther 2003**	mortality, BPD and acute complications. *Follow-up: Long-term follow up at 18-22 months of age for Cerebral palsy, language delay (defined by Bayley <80), cognitive delay (defined by Bayley <80), and other neurodevelopmental outcomes. Bayleys testing was done by examiner blinded to treatment allocation. *Data extracted from original paper by the NGA technical team **Romagnoli 1998** Methods: Randomised controlled trial Outcomes: Failure to extubate at 28 days, CLD (28 days and 36 weeks' PMA), infection, hyperglycaemia, hypertension, PDA, severe IVH, NEC, received late steroids, severe ROP, left	**reported age-** denominator = population at follow-up**)** Dexamethasone: 1/12: control: 3/13 Outcome: Major cognitive impairment **Kothadia 1999 - extracted from O'Shea 2007* (based on combination of follow up of DAS and VABS at 4-6 years [2 diagnosed] WISC-III and VABS at 8-11 years [10 diagnosed] and defined as mental retardation-** denominator = population at follow-up, untestable children not included in analysis**)** Dexamethasone: 8/45; placebo: 4/37 **Durand 1995 (defined as MDI <-2 SD on Bayley scale, no time frame of diagnosis or edition of Bayley scale used -** denominator = population at follow-up**)** Dexamethasone: 2/16; control: 3/13 **Walther 2003 (defined as MDI <-2 SD on Bayley scale, no time frame of diagnosis or edition of**	Random sequence generation: Low risk (Random allocation within 6 strata according to birth weight [500 g to 800 g, 801 g to 1100 g and 1101 g to 1500 g] and gender. Method not stated) Allocation concealment: Low risk (Random allocation within 6 strata according to birth weight [500 g to 800 g, 801 g to 1100 g and 1101 g to 1500 g] and gender. Method not stated. Blinding of randomisation) Blinding of participants and personnel: Low risk (blinding of intervention) Blinding of outcome assessment: Low risk (blinding of outcome) Incomplete outcome data: Low risk (Complete follow-up: yes for outcomes measured within first year; no for outcomes at 5 or more years) Other bias: None reported

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Gestational age (weeks in mean, with SD in parentheses): dexamethasone=28.5 (±1.7); placebo= 28.6 (±1.9) Apgar score (median, range in parentheses) at: 1 min: Dexamethasone=6 (1-9); placebo=6 (2-9) 5 min: Dexamethasone= 6 (3-9); placebo= 8 (3-9) Antenatal steroids %: Dexamethasone=76; placebo=42 Surfactant %: Dexamethasone=100; placebo=100 FiO2 at study entry (mean, with SD in parentheses): Dexamethasone=0.41 (±0.19); placebo=0.41 (±0.19) *Data extracted from original paper by the NGA technical team **Inclusion criteria** **Of relevant studies included:** **Brozanski 1995**	1) 14-day course of dexamethasone (0.20 mg/kg/day for 4 days, 0.15 mg/kg/day for 4 days, 0.10 mg/kg/day for 4 days and 0.05 mg/kg/day for 2 days). Total dose of dexamethasone 1.9 mg/kg over 14 days **Total cumulative dose: 1.9mg/kg** **Timing of administration: 7-14 days** 2)Control infants received equivalent amounts of normal saline placebo	ventricular hypertrophy **Walther 2003** Methods: Double-blind, randomised, controlled trial Outcomes: Ventilator settings, MAP, inspired oxygen concentration, extubation within 7 to 14 days, hyperglycaemia, hypertension, serum cortisol, received late dexamethasone, BPD (oxygen at 36 weeks' PMA) and survival without BPD	**Bayley scale used-** denominator = population at follow-up**)** Dexamethasone: 1/12: control: 3/13 Outcome: Developmental delay **Doyle 2006 - extracted from Doyle 2007* (diagnosed at 2 years and defined as MDI <85 on Bayley scale II edition-** denominator = population at follow-up- denominator = population at follow-up**)** Dexamethasone: 16/27; control: 12/24 Outcome: Intellectual impairment **Romagnoli 1998 - extracted from Romagnoli 2002* (diagnosed at 36-42 months of age and defined as IQ <70 on Scale of Intelligence Stanford-Binet 3rd revision-** denominator = population at follow-up**)** Dexamethasone: 2/15; control: 3/15 Outcome: Blindness	**Kovacs 1998** Random sequence generation: Low risk (Random allocation in pharmacy, with stratification by gestational age (22 to 26 weeks versus 27 to 29 weeks) Allocation concealment: Low risk (specifics not reported by Doyle 2014) Blinding of participants and personnel: Low risk (blinding of intervention) Blinding of outcome assessment: Low risk (blinding of outcome) Incomplete outcome data: Low risk (complete follow-up) Other bias: None reported **Parikh 2013** Random sequence generation: Unclear risk (Random allocation by an individual not involved with the study. Birth weight (<= 750 g versus 751 g to 1000 g) and respiratory index score [2 to 4 versus >4] strata)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Preterm infants < 1501 g who were ventilator-dependent at 7 days **Doyle 2006** Preterm infants < 28 weeks' gestation or < 1000 g birth weight, ventilator-dependent after 7 days **Durand 1995** Preterm babies, 7 to 14 days old with birth weight 501 g to 1500 g, gestational age 24 to 32 weeks, needing mechanical ventilation with < 30% oxygen **Kari 1993** Preterm infants 10 days old, weighing < 1500 g and with gestational age > 23 weeks, and ventilator-dependent. **Kothadia 1999** Preterm infants, < 1501 g age 15 to 25 days, ventilator-dependent over 30% oxygen **Kovacs 1998** Ventilator-dependent preterm infants of < 30 weeks' gestation and < 1501 g birth weight **Parikh 2013** Preterm infants with birth weight < 1001 g, ventilator-			**Doyle 2006 - extracted from Doyle 2007* (diagnosed at 2 years and defined as visual acuity in both eyes worse than 6/60-** denominator = population at follow-up**)** Dexamethasone: 1/27; control: 0/27 **Romagnoli 1998 - extracted from Romagnoli 2002* (diagnosed at 36-42 months of age and defined as blind-** denominator = population at follow-up**)** Dexamethasone: 1/15; control: 1/15 **Durand 1995 (no time frame for diagnosis or criteria for diagnosis-** denominator = population at follow-up**)** Dexamethasone: 1/16; control: 1/13 **Kovacs 1998 (no time frame for diagnosis or criteria for diagnosis-** denominator = population at follow-up**)** Dexamethasone: 0/15; control: 1/18 **Walther 2003 (no time frame for diagnosis or criteria for**	Allocation concealment: Low risk (specifics not reported by Doyle 2014) Blinding of participants and personnel: Low risk (blinding of intervention) Blinding of outcome assessment: Low risk (blinding of outcomes measured before discharge) Incomplete outcome data: Low risk (complete follow-up) Other bias: None reported **Romagnoli 1998** Random sequence generation: Unclear risk (random allocation using numbered sealed envelopes) Allocation concealment: Low risk (specifics not reported by Doyle 2014) Blinding of participants and personnel: High risk (No blinding of intervention) Blinding of outcome assessment: Unclear risk (Can't tell if done for short term outcomes)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	dependent between 10 to 21 days of age with a respiratory index ≥ 2 with estimated 75% risk of developing CLD **Romagnoli 1998** Preterm infants, oxygen- and ventilator-dependent on 10th day and at high risk of CLD by authors' own scoring system (90% risk) **Walther 2003** Preterm infants of gestation 24 to 32 weeks and birth weight > 599 g with respiratory distress syndrome requiring mechanical ventilation with > 29% oxygen or respiratory index (MAP x inspired oxygen) > 1.9 and ventilator rate > 16/min on day 7 to 14 after birth **Exclusion criteria** **Of relevant studies included:** **Brozanski 1995** Complex congenital anomalies, pulmonary hypoplasia or haemodynamic instability			**diagnosis-** denominator = population at follow-up**)** Dexamethasone: 0/12: control: 0/13 Outcome: Deafness **Doyle 2006 - extracted from Doyle 2007* (diagnosed at 2 years and defined as hearing loss requiring amplification or worse-** denominator = population at follow-up**)** Dexamethasone: 2/27; control: 4/27 **Romagnoli 1998 - extracted from Romagnoli 2002* (diagnosed at 36-42 months of age and defined as severe deafness-** denominator = population at follow-up**)** Dexamethasone: 0/15; control: 2/15 **Durand 1995 (no time frame for diagnosis or criteria for diagnosis-** denominator = population at follow-up**)** Dexamethasone: 0/16; control: 0/13 **Kovacs 1998 (no time frame for diagnosis or criteria for**	*For long-term outcomes both paediatrician and paediatric neurologist were completely blinded to group assignment. Incomplete outcome data: Low risk (Complete follow-up) Other bias: None reported **Walther 2003** Random sequence generation: Low risk (Random allocation by staff pharmacist with investigators and clinicians unaware of treatment assignment) Allocation concealment: Low risk (specifics not reported by Doyle 2014) Blinding of participants and personnel: Low risk (blinding of intervention) Blinding of outcome assessment: Low risk (blinding of outcome) Incomplete outcome data: Low risk (complete follow-up) Other bias: None reported

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Doyle 2006 Congenital neurological defects, chromosomal anomalies or other disorders likely to cause long-term neurological deficits **Durand 1995** Congenital heart disease, IVH (grade IV) and multiple anomalies **Kari 1993** PDA, sepsis, GI bleeding and major malformation **Kothadia 1999** PDA, major malformation, HIV or Hepatitis B virus infection **Kovacs 1998** None noted **Parikh 2013** None noted **Romagnoli 1998** None noted **Walther 2003** Sepsis, congenital heart disease, hypertension, unstable clinical status (renal failure, grade IV IVH) and multiple congenital anomalies			**diagnosis-** denominator = population at follow-up**)** Dexamethasone: 0/15; control: 0/18 Outcome: Days on invasive ventilation **Durand 1995*(median [range])** Dexamethasone: 20 (17-33); control: 35 (25-75); p-value≤0.01 **Kari 1993* (median [range])** Dexamethasone: 24 (20-40); control: 40 (22-50); p-value reported as not significant **Kothadia 1999* (median [range])** Dexamethasone: 13 (1-64); control: 25 (6-104); p-value=0.005 **Parikh 2013* (adjusted mean [95% CI], reported for survivors only)** Hydrocortisone: 68.7 (63.4-74.0) ; control: 65.9 (59.7-72) **Walther 2003* (mean ± SD)** Dexamethasone: 28 (± 21); control: 38 (± 45)	**Other information** Neurodevelopmental outcomes recorded for Brozanski 1995, Durand 1995, Kovacs 1998, and Walther 2003 in review, however no time-frame of when the neurodevelopmental outcomes were taken could be reported as there was no follow-up study associated with the primary paper and the authors did not indicate this in their write up or in the notes that they contacted the authors.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				***Data extracted from original paper by the NGA technical team** Outcome: Gastro-intestinal perforation **Doyle 2006** Dexamethasone: 0/35; control: 0/35 **Parikh 2013** Hydrocortisone: 2/31; control: 0/33 Outcome: Hypertension **Brozanski 1995** Dexamethasone: 0/39; control: 0/39 **Durand 1995** Dexamethasone: 2/23; control: 1/20 **Kari 1993** Dexamethasone: 7/17; control: 1/24 **Kothadia 1999** Dexamethasone: 7/57; control: 3/61 **Parikh 2013** Hydrocortisone: 17/31; control: 13/33 **Romagnoli 1998** Dexamethasone: 0/15; control: 0/15	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Doyle, Lex W, Ehrenkranz, Richard A, Halliday, Henry L, Early (< 8 days) postnatal corticosteroids for preventing chronic lung disease in preterm infants, Cochrane Database of Systematic Reviews, 2014 **Ref Id** 619542 **Country/ies where the study was carried out** **Study type** Cochrane systematic review **Aim of the study** To examine the relative benefits and adverse effects of postnatal steroids commenced within the first seven	**Sample size** **Of relevant studies included:** **Anttila 2005** n=109 randomised (n=53 dexamethasone; n=56 placebo) **Bosante 2007*** n=50 randomised (n=25 hydrocortisone; n=25 placebo) **Garland 1999** n=241 randomised (n=118 dexamethasone; n=123 placebo) **Lauterbach 2006** n=150 randomised (n=50 dexamethasone; n=50 placebo; n=50 pentoxifylline) **Peltoniemi 2005** n=51 randomised (n=25 hydrocortisone; n=26 placebo) **Rastogi 1996** n=70 randomised (n=36 dexamethasone; n=34 placebo) **Romagnoli 1999**	**Interventions** **Of relevant studies:** **Anttila 2005** 1) 4 doses of dexamethasone 0.25mg/kg each at 12-hourly intervals 2) normal saline or placebo in same regimen **Total cumulative dose: 1mg/kg** **Timing of administration: Before 6 hours** **Bosante 2007** 1) hydrocortisone 0.5mg/kg/12 hourly for 9 days, then 0.5mg/kg/24 hourly for 3 days 2) Equal volume of 0.9% saline **Total cumulative dose: 10.5mg/kg** **Timing of adminstration: Before 48 hours** **Garland 1999** 1) 3-day course of dexamethasone	**Details** **Of relevant studies included:** **Anttila 2005** Methods: multicentre, double-blind, placebo-controlled, randomised trial Outcomes: Survivial to 36 weeks without IVH (grade III-IV), PVL (echodensities after 1st week or periventricular cysts on ultrasound) or BPD (oxygen at 36 weeks), growth, duration of assisted ventilation and oxygen, late corticosteroid treatment, infection, hyperglycaemia, hypertension, ROP, PDA, GI bleeding, and perforation and NEC **Bosante 2007*** Methods: two-centre, randomised, double-	**Results** Outcome: Mortality prior to discharge Dexamethasone **Anttila 2005** Dexamethasone: 11/53; control: 12/56 **Garland 1999** Dexamethasone: 19/118; control: 25/123 **Rastogi 1996** Dexamethasone: 4/36; control: 2/34 **Romagnoli 1999** Dexamethasone: 2/25; control: 3/25 **Shinwell 1996** Dexamethasone: 31/132; control: 22/116 **Soll 1999** Dexamethasone: 76/273; control: 62/269 **Stark 2001** Dexamethasone: 23/111; control: 28/109 **Subhedar 1997** Dexamethasone: 9/21; control: 8/21 **Tapia 1998** Dexamethasone: 17/55; control: 18/54	**Limitations** **Quality of Cochrane SR:** Systematic review assessed using AMSTAR checklist. Total score: 10/11 All checklist items adressed, with the exception of: Checklist item 4: Was the status of publication (i.e. grey literature) used as an inclusion criterion? No details provided **Quality of individual studies:** Risk of bias taken from Cochrane systematic review (Cochrane risk of bias tool) **Anttila 2005** Random sequence generation (selection bias): unclear risk (random allocation by use of coded vials prepared in the pharmacy of each centre) Allocation concealment (selection bias): low risk

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
days of life to preterm infants at risk of developing chronic lung disease **Study dates** Search up to August 2013 **Source of funding** Action research UK grant to study the effects of postnatal steroids, UK. Action research UK grant to study long-term follow-up, UK. National health and medical research council, Australia. Eunice Kennedy Shriver National instituite of child health and human development national institutes of health, department of health and human services, USA.	n=50 randomised (n=25 dexamethasone; n=25 placebo) **Shinwell 1996** n=248 randomised (n=132 dexamethasone; n=116 placebo) **Soll 1999** n=542 randomised (n=273 dexamethasone; n=269 placebo) **Stark 2001** n=220 randomised (n=111 dexamethasone; n=109 placebo) **Subhedar 1997** n=42 (n=21 dexamethasone; n=21 placebo) **Tapia 1998** n=113 (4 exclusions for congenital abnormality, early sepsis and failure to obtain follow-up data, n=55 dexamethasone; n=54 placebo) **Watterberg 1999** n=40 randomised (n=20 hydrocortisone; n=20 placebo) **Watterberg 2004** n=360 randomised (n=180 hydrocortisone; n=180 placebo)	beginning at 24 to 48 hours. The first 2 doses were 0.4mg/kg, 3rd and the doses 0.2/kg and the 5th and 6th doses 0.1mg/kg and 0.05mgkg respectively** 2) Similar volume of normal saline was given to control infants **Total cumultive dose: 1.35 mg/kg** **Timing of administration: 24 hours** **At first interim analysis (n=75) an increased risk of GI perforation was noted in the dexamethasone group. The data monitoring committee recommended reducing the dexamethasone dose to 4 doses of 0.25mg/kg/dose every 12 hours begun at 24 hours to 48 hours followed by doses 0.125mg/kg and 0.05mg/kg at the next	blind, placebo-controlled trial Outcomes: Primary outcomes - survival free of disability at 2 years of age, mortality up to 2 years of age and neurological outcome after discharge. Secondary outcomes - rate of CLD, death or CLD, failure to extubate, other complications during primary hospital stay including GI perforation, severe IVH (grade III or IV) and cystic PVL, long-term neurosensory impairment (blindness, deafness, developmental delay assessed by MDI on Bayleys scales, cerebral palsy) and disabilities (severe - any of severe cerebral palsy [not likely to walk], blindness or severe developmental delay [MDI <55], moderate - cerebral palsy [not walking at 2	Hydrocortisone **Bosante 2007** Hydrocortisone: 4/25; control: 10/25 **Peltoniemi 2005** Hydrocortisone: 2/25; control: 3/26 **Watterberg 1999** Hydrocortisone: 3/20; control: 3/20 **Watterberg 2004** Hydrocortisone: 31/180: control: 32/180 Outcome: Bronchopulmonary dysplasia at 36 weeks corrected gestation Dexamethasone **Anttila 2005** Dexamethasone: 11/53; control: 15/56 **Garland 1999** Dexamethasone: 16/118; control: 27/123 **Lauterbach 2006** Dexamethasone: 16/50; control: 21/50 **Rastogi 1996** Dexamethasone: 0/36; control: 6/34 **Romagnoli 1999** Dexamethasone: 3/25; 17/25	(allocation concealment: yes) Blinding of participants and personnel (performance bias) all outcomes: low risk (blinding of intervention: yes) Blinding of outcome assessment (detection bias) all outcomes: low risk (blinding of outcome measurements: yes) Incomplete outcome data (attrition bias) all outcomes: low risk (complete follow-up: yes) **Bosante 2007** Random sequence generation (selection bias): low risk (computer-generated randomisation centrally) Allocation concealment (selection bias): low risk (allocation concealment: yes) Blinding of participants and personnel (performance bias) all outcomes: low risk (blinding of intervention: yes)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Characteristics Of relevant studies included: **Anttila 2005*** Setting: Multicentre, European Gestational age (weeks in mean, SD in parentheses): dexamethasone=26.3 (1.4); placebo=27.0 (1.5) Apgar scores (mean, SD in parentheses): at 1 min: dexamethasone=5.0 (2.1); placebo=4.9 (2.4) at 5 min dexamethasone=6.8 (1.7); placebo=6.5 (2.2) Surfactant: dexamethasone=48/53 (91%); placebo=50/56 (91%) **Bosante 2007*** Setting: Italy Gestational age (weeks in median, range in parentheses): hydrocortisone= 26.2 (25.2-27.4); placebo=26.5 (25.0-28.1)	12-hour periods respectively. **Lauterbach 2006** 1) Dexamethasone 0.25 mg/kg/dose every 12 hours for 3 days 2) nebulised distilled water *Total cumulative dose: 1.5mg/kg* **Timing of administration: 4th day of life** **Peltoniemi 2005** 1) Hydrocortisone 2.0mg/kg/day intravenously 8-hrly for 2 days, 1.5mg/kg/day 8-hrly for 2 days, 0.75 mg/kg/day 12-hrly for 6 days 2) Control infants received isotonic saline as placebo **Total cumulative dose: 11.5mg/kg** **Timing of administration: Before 36 hours** **Rastogi 1996** 1) Intravenous dexamethasone 0.5mg/kg/day for 3 days, 0.25mg/kg/day	years but likely to do so], deafness, moderate developmental delay [MDI 55-<70], mild - mild cerebral palsy [walking at 2 years] or mild developmental delay [MDI 70-<85]) **Garland 1999** Methods: Multi-centre, placebo-controlled, randomised trial Outcomes: Primary outcomes - survival without CLD defined as oxygen therapy at 36 weeks to maintain SaO2 above 91% and mortality. Secondary outcomes - duration of ventilation and supplemental oxygen, respiratory support at 28 days, length of stay for survivors, use of subsequent dexamethasone therapy and usual complications of prematurity **Lauterbach 2006** Methods: Single-centre, randomised,	**Shinwell 1996** Dexamethasone: 15/132; control: 11/116 **Soll 1999** Dexamethasone: 62/273; control: 84/269 **Stark 2001** Dexamethasone: 47/111; control: 49/109 **Subhedar 1997** Dexamethasone: 11/21; 13/21 **Tapia 1998** Dexamethasone: 3/55; control: 12/54 Hydrocortisone **Bosante 2007** Hydrocortisone: 6/25; control: 8/25 **Peltroniemi 2005** Hydrocortisone: 7/25; control: 11/26 **Watterberg 1999** Hydrocortisone: 5/20; control: 10/20 **Watterberg 2004** Hydrocortisone: 90/180; control: 92/180 Outcome: Bronchopulmonary dysplasia at 28 days corrected gestation	Blinding of outcome assessment (detection bias) all outcomes: low risk (blinding of outcome measurements: yes) Incomplete outcome data (attrition bias) all outcomes: low risk (complete follow-up: yes for outcomes during primary hospital stay - 98% of surviving infants traced to 2 years of age) **Garland 1999** Random sequence generation (selection bias): low risk (randomisation by study pharmacists at each study centre) Allocation concealment (selection bias): low risk (allocation concealment: yes) Blinding of participants and personnel (performance bias) all outcomes: low risk (blinding of intervention: yes) Blinding of outcome assessment (detection bias) all outcomes: low

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	FiO2 at entry, % (range): hydrocortisone= 28 (25-36); placebo=26 (24-40) **Garland 1999*** Setting: USA Gestational age (weeks in mean, SEM in parentheses): dexamethasone=26 (±0.2); placebo= 26.1 (±0.2) 5 min Apgar scores ≤3: dexamethasone=6 (7%); placebo=6 (7%) **Lauterbach 2006*** Setting: Poland Gestational age (weeks in mean, SD in parentheses): dexamethasone= 28.5 (2); placebo= 28.8 (2.05) 1 min Apgar score (median, range in parentheses): dexamethasone= 7 (1-8); placebo= 6 (0-8) **Peltoniemi 2005** Setting: Finland **Rastogi 1996*** Setting: USA Gestational age (weeks in mean, SD in parentheses): dexamethasone=28.8 (2); placebo=28.2 (2) Apgar scores (mean, SD in parentheses):	for 3 days, 0.15 mg/kg/day for 3 days, 0.05mg/kg/day for 3 days 2) Control group given saline placebo **Total cumulative dose: 3.03mg/kg** **Timing of administration: <12 hours** **Romagnoli 1999** 1) Dexamethasone 0.5mg/kg/day for 3 days, 0.25mg/kg/day for 3 days and 0.125mg/kg/day for 1 day 2) no details reported **Total cumulative dose: 2.375mg/kg** **Timing of administration: 72 hours** **Shinwell 1996** 1) Intravenous dexamethasone 0.25mg/kg every 12 hours 6 times 2) Controls given saline placebo **Total cumulative dose: 3mg/kg**	3-armed, placebo-controlled trial Outcomes: BPD (oxygen dependency at 36 weeks), PDA, IVH and PVL. **Peltoniemi 2005** Methods: Multi-centre, double-blind, randomised controlled trial Outcomes: Survival without BPD (oxygen at 36 weeks), IVH (grades III-IV), cystic PVL, durations of ventilation, oxygen and hospital stay, sepsis, hyperglycaemia, hypertension, PDA, GI bleeding, GI perforation, NEC, ROP, and cortisol levels. Long-term outcomes: neurosensory impairment (blindness, deafness, developmental delay assessed by MDI on Bayleys scales, cerebral palsy) and disabilites (severe -	Dexamethasone **Garland 1999** Dexamethasone: 73/118; control: 76/123 **Rastogi 1996** Dexamethasone: 5/36; control: 21/34 **Romagnoli 1999** Dexamethasone: 11/25; control: 24/25 **Shinwell 1996** Dexamethasone: 29/132; contol: 23/116 **Soll 1999** Dexamethasone: 181/273; control: 186/269 **Stark 2001** Dexamethasone: 71/111; control: 82/109 **Tapia 1998** Deamethasone: 11/55; control: 16/54 Outcome: Cerebral Palsy Dexamethasone **Stark 2001 - extracted from Stark 2014* (diagnosed at 18 to 22 months of age)** Dexamethasone: 11/76; control: 12/68 **Shinwell 1996 - extracted from Shinwell 2000* (diagnosed up to 6 years**	risk (blinding of outcome measurements: yes) Incomplete outcome data (attrition bias) all outcomes: low risk (complete follow-up: yes) **Lauterbach 2006** Random sequence generation (selection bias): low risk (computer generated randomisation table) Allocation concealment (selection bias): unclear risk (not stated) Blinding of participants and personnel (performance bias) all outcomes: high risk (blinding of intervention: no) Blinding of outcome assessment (detection bias) all outcomes: high risk (blinding of outcome measurements: no) Incomplete outcome data (attrition bias) all outcomes: low risk (complete follow-up: yes) **Peltoniemi 2005** Random sequence generation (selection bias): unclear risk

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	at 1 min: dexamethasone=5.0 (2.1); placebo=4.9 (2.2) at 5 min dexamethasone=7.0 (1.6); placebo=6.9 (1.6) **Romagnoli 1999*** Setting: Italy Gestational age (weeks in median, range in parentheses): dexamethasone= 28 (25-31); placebo=28 (25-30) FiO2 at entry, (median, range in parentheses): dexamethasone= 0.30 (0.23-0.55); placebo=0.3 (0.23-0.6) **Shinwell 1996*** Setting: Israel Gestational age (weeks in mean, SEM in parentheses): dexamethasone=29 (±0.2); placebo 29 (±0.2) 5 min Apgar scores (mean, SEM in parentheses): dexamethasone=7.5 (0.2); placebo=7.8 (0.2) Oxygenation index before study drug (mean, SEM in parentheses): dexamethasone= 12 (0.8); placebo= 12.8 (0.8)	**Timing of administration: <12 hours** **Soll 1999** 1) Dexamethasone 0.5mg/kg/day for 3 days, 0.25mg/kg/day for 3 days, 0.10mg/kg/day for 3 days and 0.05mg/kg/day for 3 days. 2) Conrol infants a similar volume of normal saline **Total cumulative dose: 2.7mg/kg** **Timing of administration: 12 hours** **Stark 2001** 1) Dexamethasone 0.15mg/kg/day for 3 days, then tapered over 7 days 2) Saline placebo **Total cumulative dose: 0.89/kg** **Timing of administration: <24 hours** **Subheadar 1997** 1) Intravenous dexamethasone at 12-	any of severe cerebral palsy [not likely to walk], blindness or severe developmental delay [MDI <55, moderate - moderate cerebral palsy [not walking at 2 years of age but likely to do so], deafness, moderate developmental delay [MDI 55-<70], mild - mild cerebral palsy [walking at 2 years] or mild developmental delay [MDI 70-<85]) **Rastogi 1996** Methods: Double-blind, randomised controlled trial Outcomes: FiO2, MAPM BPD (28 days and CXR), severe BPD (36 weeks), duration of O2, infections, deaths, pneumothorax, pulmonary haemorrhage, PDA, IVH, NEC, hyperglycaemia, insulin use, hypertension, ROP	**of age [range 24-71 months])** Dexamethasone: 39/80; control: 12/79 **Romagnoli 1999 (no time frame of diagnosis or criteria for diagnosis)** Dexamethasone: 2/25; control: 3/25 **Subhedar 1997 (no time frame of diagnosis or criteria for diagnosis)** Dexamethasone: 0/21; control: 2/21 Hydrocortisone **Watterberg 2004 - extracted from Watterberg 2007* (diagnosed at 18 to 22 months of age)** Hydrocortisone: 16/126; control: 18/126 **Peltoniemi 2005 - extracted from Peltoniemi 2009* (diagnosed at 2 years of age)** Hydrocortisone: 2/23; control: 0/22 **Bosante 2007 (no time frame of diagnosis or criteria for diagnosis)** Hydrocortisone: 2/25; control: 2/25	(random allocation in each centre using identical coded syringes. Stratified by birth weight [501g to 750g vs 750g to 999g vs 1000g to 1250g]) Allocation concealment (selection bias): low risk (allocation concealment: yes) Blinding of participants and personnel (performance bias) all outcomes: low risk (blinding of intervention: yes) Blinding of outcome assessment (detection bias) all outcomes: low risk (blinding of outcome measurements: yes) Incomplete outcome data (attrition bias) all outcomes: low risk (complete follow-up: yes) **Rastogi 1996** Random sequence generation (selection bias): low risk (random allocation: using a pharmacy list, stratified for birth weight) Allocation concealment (selection bias): low risk

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Soll 1999* Setting: USA Gestational age (weeks in mean, SD in parentheses): dexamethasone=25.8 (0.1); placebo=25.7 (0.1) Apgar scores (median): at 1 min: dexamethasone=4; placebo=4 at 5 min dexamethasone=7; placebo=7 **Stark 2001*** Setting: USA Gestational age (weeks in mean, SD in parentheses): dexamethasone=25.3 (1.7); placebo=25.4 (1.6) Apgar scores ≤3: at 1 min: dexamethasone=48/111 (43%); placebo=42/109 (39%) at 5 min dexamethasone=7/111 (6%); placebo=8/109 (7%) Surfactant: dexamethasone=106/111 (95%); placebo=105/109 (96%) **Subhedar 1997*** Setting: UK Gestational age (weeks in median, range in	hrly intervals for 6 days; 0.5mg/kg/dose for 6 doses and 0.25mg/kg/dose for a further 6 doses 2) Control groups were given placebo **Total cumulative dose: 4.5mg/kg Timing of administration: 96 hours** **Tapia 1998** 1) Intravenous dexamethasone 0.5mg/kg/day for 3 days, 0.25mg/kg/day for 3 days, 0.12mg/kg/day for 3 days and 0.06mg/kg/day for 3 days 2) Placebo group recevied an equivalent volume of saline solution **Total cumulative dose: 2.79mg/kg Timing of administration: 36 hours** **Watterberg 1999** 1) Hydrocortisone 1.0mg/kg/day every 12	**Romagnoli 1999** Methods: Randomised, non-blinded, controlled trial Outcomes: Survival to 28 days, survival to discharge, PDA, IVH (grades III-IV), PVL, sepsis, NEC, ROP (stages III and above), requiring ventilation at 28 days, CLD at 28 days and 36 weeks, hyperglycaemia, hypertension, needed late corticosteroids, growth failure and left ventricular hypertrophy **Shinwell 1996** Methods: Multi-centre, double-blind, randomised controlled trial Outcomes: Mortality, survival with no O2, mechanical ventilation at 3 and 7 days, CLD, duration in hospital, IVH, PVL, pneumothorax, PIE, PDA, sepsis,	**Watterberg 1999 (no time frame of diagnosis or criteria for diagnosis)** Hydrocortisone: 1/13; control: 2/13 Outcome: Major mental developmental delay Dexamethasone **Stark 2001 - extracted from Stark 2014* (diagnosed at 18 to 22 months of age and defined as MDI <70 Bayley scale II -** denominator = population at follow-up**)** Dexamethasone: 35/76; control: 25/68 Hydrocortisone **Watterberg 2004 - extracted from Watterberg 2007* (diagnosed at 18 to 22 months of age and defined as MDI <70 Bayley scale II -** denominator = population at follow-up**)** Hydrocortisone: 34/126; control: 47/126 **Peltoniemi 2005 - extracted from Peltoniemi 2009* (diagnosed at 2 years of age and defined as MDI <70 Bayley scale II**	(allocation concealment: yes) Blinding of participants and personnel (performance bias) all outcomes: unclear risk (blinding of intervention: yes) Blinding of outcome assessment (detection bias) all outcomes: unclear risk (blinding of outcome measurements: yes) Incomplete outcome data (attrition bias) all outcomes: low risk (complete follow-up: yes) **Romagnoli 1999** Random sequence generation (selection bias): low risk (random allocation using random numbers, concealed in numbered sealed envelopes) Allocation concealment (selection bias): low risk (allocation concealment: yes) Blinding of participants and personnel (performance bias) all outcomes: high risk

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	parentheses): dexamethasone=27 (22-31); placebo= 27 (22-31) 5 min Apgar scores (median, range in parentheses): dexamethasone=8 (3-10); placebo=8 (2-10) **Tapia 1998*** Setting: Chile Gestational age (weeks in mean, SD in parentheses): dexamethasone=29.1 (2); placebo=28.7 (1.8) Low Apgar score (<4 at 1 min or <7 at 5 min): dexamethasone=23/55 (42%); placebo=24/54 (44%) **Watterberg 1999*** Setting: USA Gestational age (weeks in mean, SD in parentheses): hydrocortisone=25.2 (1.3); placebo=25.4 (1.5) **Watterberg 2004*** Setting: USA Gestational age (weeks in mean, SD in parentheses): hydrocortisone=25.2 (1.5); placebo=25.3 (1.7) Apgar scores (median, 25th-75th percentile in parentheses):	hours for 9 days, 0.5mg/kg/day for 3 days 2) Control infants were given an equal volume of normal saline **Total cumulative dose: 10.5mg/kg** **Timing of administration: <48 hours** **Watterberg 2004** 1) Hydrocortisone 1mg/kg/day for 12 days, then 0.5mg/kg/day for 3 days 2) Control group infants received an equal volume of normal saline placebo **Total cumulative dose: 13.5mg/kg** **Timing of administration: 12-48 hours**	hypertension, hyperglycaemia **Soll 1999** Methods: multicentre, randomised, double-blind trial Outcomes: Primary outcome - CLD or death at 36 weeks adjusted age. Secondary outcome - clinical status at 14 days and 28 days, duration of assisted ventilation, supplemental oxygen and hospital stay, treatment with late post-natal corticosteroids, proven sepsis, hypertension and hyperglycaemia requiring therapy, weight at 36 weeks and the usual complications of prematurity **Stark 2001** Methods: multicentre, randomised, double-blind trial Outcomes: death or CLD, oxygen at 28	**-** denominator = population at follow-up**)** Hydrocortisone: 2/23; control: 1/22 Outcome: Moderate mental developmental delay Hydrocortisone **Peltoniemi 2005 - extracted from Peltoniemi 2009* (diagnosed at 2 years of age and defined as MDI 70-84 Bayley scale II -** denominator = population at follow-up**)** Hydrocortisone: 5/23; control: 1/22 Outcome: Major psychmotor developmental delay Dexamethasone **Stark 2001 - extracted from Stark 2014* (diagnosed at 18 to 22 months of age and defined as PDI <70 Bayley scale II -** denominator = population at follow-up**)** Dexamethasone: 21/74; control: 22/62 Hydrocortisone **Watterberg 2004 - extracted from Watterberg**	(blinding of intervention: no) Blinding of outcome assessment (detection bias) all outcomes: high risk (blinding of outcome measurements: no) Incomplete outcome data (attrition bias) all outcomes: low risk (complete follow-up: yes) **Shinwell 1996** Random sequence generation (selection bias): low risk (random allocation, stratified by centre and birth weight, from random numbers list in the pharmacy) Allocation concealment (selection bias): low risk (allocation concealment: yes) Blinding of participants and personnel (performance bias) all outcomes: low risk (blinding of intervention: yes) Blinding of outcome assessment (detection bias) all outcomes: low risk (blinding of outcome measurements: yes)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	at 1 min: hydrocortisone=4 (2-6); placebo=4 (2-6) at 5 min dexamethasone=7 (6-8); placebo=7 (5-8) Surfactant: dexamethasone=152/180 (84%); placebo=158/180 (88%) ***Data extracted from original paper by the NGA technical team** **Inclusion criteria** **Of relevant studies included:** **Anttila 2005** Preterm infants with birthweight 500g to 999g, gestation <32 weeks, need for mechanical ventilationand supplemental oxygen by 4 hours of age. **Bosante 2007** Preterm infants either <1000g birht weight or <28 weeks gestation, ventilator dependent after 7 days pf age and considered to be a candidate for corticosteroids **Garland 1999**		days, PIE, late corticosteroid treatment, hypertension, hyperglycaemia, GI perforation **Subhedar 1997** Methods: randomised, controlled trial - factorial design Outcomes: mortality, CLD at 28 days and >36 weeks with abnormal chest radiograph, duration of ventilation, time to extubation, duration of hopsitalisation, maximum grade of IVH, pulmonary haemorrhage, pneumothorax, severe PDA, NEC, ROP (stages 3 or 4), complications including ileal perforation, upper GI haemorrhage, hyperglycaemia, hypertension, septicaemia **Note factorial design - which means than half of the treated**	**2007* (diagnosed at 18 to 22 months of age and defined as PDI <70 Bayley scale II-** denominator = population at follow-up**)** Hydrocortisone: 33/126; control: 29/126 Outcome: Intellectual impairment **Romagnoli 1999 (defined as IQ <70 no details on methods used for diagnosis nor time frame of diagnosis)** Dexamethasone: 3/25; control: 3/25 Outcome: Deafness **Stark 2001 - extracted from Stark 2014* (diagnosed at 18 to 22 months of age and defined as disability with bilateral hearing amplification-** denominator = population at follow-up**)** Dexamethasone: 2/75 control: 2/67 **Shinwell 1996 - extracted from Shinwell 2000* (diagnosed up to 6 years of age [range 24-71 months]-** denominator = population at follow-up**)**	Incomplete outcome data (attrition bias) all outcomes: low risk (complete follow-up: yes for short term, 84% for long-term) **Soll 1999** Random sequence generation (selection bias): unclear risk (random allocation in hospital pharmacies by opening opaque, sealed envelopes. Precise method of randomisation not stated) Allocation concealment (selection bias): low risk (allocation concealment: yes) Blinding of participants and personnel (performance bias) all outcomes: low risk (blinding of intervention: yes) Blinding of outcome assessment (detection bias) all outcomes: low risk (blinding of outcome measurements: yes) Incomplete outcome data (attrition bias) all

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Preterm infants weighing between 500g and 1500g, received surfactant, at significant risk for CLD or death using a model to predict at 24 hours **Lauterbach 2006** Preterm infants weighing < 1500g who needed oxygen on fourth day of life, regardless of the need for assisted ventilation **Peltoniemi 2005** Preterm infants with a birth weght 501g to 1250g, gestation 23 to 29 weeks, needing mechanical ventilation before age of 24 hours. The subgroup 1000g to 1250g had to need supplemental oxyfen and mechanical ventilation > 24 hours despite surfactant. **Rastogi 1996** Preterm infants <12 hours old, wighing 700g to 1500g with respiratory distress syndrome (RDS), confirmed clinically abd radiologically, infants needed mechanical ventilation >30% O2 and/or MAP 7cm H2O a/A <0.25 after surfactant treatment **Romagnoli 1999**		**and half of the control infants also received 72 hours of inhaled nitric oxide** **Tapia 1998** Methods: multicentre, doible-blind, placebo-controlled, randomised trial Outcomes: primary outcomes - death before hospital discharge, BPD (oxygen need at 28 days and X-ray changes), death or BPD and oxygen need at 36 weeks. Other outcomes included time on ventilator, time in over 40% oxygen and time in oxygen. Major morbidity and complications included pneumothorax, PIE, PDA, pulmonary haemorrhage, pneumonia, sepsis, NEC, ROP, hypertension, hyperglycaemia and	Dexamethasone: 1/80; control: 0/79 **Romagnoli 1999 (no time frame of diagnosis or criteria for diagnosis)** Dexamethasone: 0/23; control: 2/22 **Subhedar 1997 (no time frame of diagnosis or criteria for diagnosis)** Dexamethasone: 1/10; control: 0/21 Hydrocortisone **Watterberg 1999 (no time frame of diagnosis or criteria for diagnosis)** Hydrocortisone: 0/10; control: 0/8 Outcome: Blindness Dexamethasone **Stark 2001 - extracted from Stark 2014* (diagnosed at 18 to 22 months of age and defined as no useful vision in either eye-** denominator = population at follow-up**)** Dexamethasone: 1/76; control: 0/67 **Shinwell 1996 - extracted from Shinwell 2000* (diagnosed up to 6 years of age [range 24-71**	outcomes: low risk (complete follow-up: yes) **Stark 2001** Random sequence generation (selection bias): low risk (random allocation using numbers generated by a random, permuted block algorithm, stratified by birth weight) Allocation concealment (selection bias): low risk (allocation concealment: yes) Blinding of participants and personnel (performance bias) all outcomes: low risk (blinding of intervention: yes) Blinidng of outcome assessment (detection bias) all outcomes: low risk (blinding of outcome measurements: yes) Incomplete outcome data (attrition bias) all outcomes: low risk (complete follow-up: yes) **Subhedar 1997** Random sequence generation (selection bias): low risk (random

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Preterm infants <1251g or <33 weeks, oxyen-dependent at 72 hours and at high risk of CLD according to a scoring system predicting 90% risk of CLD **Shinwell 1996** Preterm infants with birth weight 500g to 2000g, 1-3 days old, requiring mechanical ventilation with more than 40% oxygen. **Soll 1999** Preterm infants weighing 501g to 100g who required assisted ventilation <12 hours, had received surfactant by 12 hours, were physiologically stable and had no life-threatening congenital abnormalities **Stark 2001** Preterm infants with birth weight 501g to 1000g, mechanically ventilated <12 hours. Infants >750g also needed to receive surfactant and have FiO2 >0.29 **Subhedar 1997** Preterm infants, entry at 96 hours if gestation <32 weeks, mechanical		IVH (grades I-II and III-IV) **Watterberg 1999** Methods: two-centre, double-blind, randomised controlled trial Outcomes: primary outcome - survival without supplemental oxygen at 36 weeks post-conception. Secondary outcome in survivors - CLD at 36 weeks, duration of mechanical ventilation, >40% oxygen, >25% oxygen, hospital stay, and weightand head circumference at 36 weeks **Watterberg 2004** Methods: Multi-centre, double-blind, randomised controlled trial Outcomes: Survival without BPD (oxygen at 36 weeks), physiological BPD, death before 36 weeks, death before discharge, BPD in	**months] defined as blind-** denominator = population at follow-up**)** Dexamethasone: 3/79; control: 1/80 **Romagnoli 1999 (no time frame of diagnosis or criteria for diagnosis-** denominator = population at follow-up**)** Dexamethasone: 2/23; control: 1/22 **Subhedar 1997 (no time frame of diagnosis or criteria for diagnosis-** denominator = population at follow-up**)** Dexamethasone: 0/10; control: 0/11 Hydrocortisone **Watterberg 1999 (no time frame of diagnosis or criteria for diagnosis-** denominator = population at follow-up**)** Hydrocortisone: 0/10; control: 0/8 Outcome: Days on invasive ventilation Dexamethasone **Garland 1999* (median [range]) - survivors only**	allocation by computer-generated random numbers and sealed envelopes. Factorial design provided 4 groups: early dexamethasone, inhaled nitric oxide, both drug together and neither drug) Allocation concealment (selection bias): low risk (allocation concealment: yes) Blinding of participants and personnel (performance bias) all outcomes: high risk (blinding of intervention: no) Blinidng of outcome assessment (detection bias) all outcomes: high risk (blinding of outcome measurements: no) Incomplete outcome data (attrition bias) all outcomes: low risk (complete follow-up: yes) **Tapia 1998** Random sequence generation (selection bias): unclear risk (random allocation using

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	ventilation from birth, surfactant treatment and high risk of developing CLD by a score. **Tapia 1998** Preterm infants with birth weight between 700g and 1600g, clinical and radiological diagnosis of RDS, needing mechanical ventilation at <36 hours of age **Watterberg 1999** Preterm infants weighing between 500g and 999g who were AGAand needed machanical ventilation <48 hours of age **Watterberg 2004** Preterm infants 500g to 999g birth weight, needing mechanical ventilation and aged 12 to 48 hours **Exclusion criteria** **Of relevant studies included:** **Anttila 2005** Life threatening congenital anomalies or known chromosomal anomaly **Bosante 2007**		survivors, durations of mechanical ventilation, oxygen and hospital stay, weight and OFC at 36 weejs, PDA, infection, NEC, GI perforation, major IVH (grades III or IV), cystic PVL, ROP, and open label corticosteroid therapy. Longer term outcomes included neurosensory impairments (any cerebral palsy, blindness, deafness, or developmental or motor delay assessed by the Bayley scales (MDI or PDI, respectively)	Dexamethasone: 27 (2-120); control: 30 (3-69); p-value=0.2 **Romagnoli 1999* (mean [SD])** Dexamethasone: 16.1 (±10.2); control: 34.2 (±22.2) **Shinwell 1996* (mean [SD])** Dexamethasone: 9 (1.2); control: 11 (1) **Soll 1999* (mean [SD])** Dexamethasone: 22.2 (2): control 27.7 (1.8) **Subhedar 1997* (median [range])** Dexamethasone: 23 (6-44); control: 13 (5-39); p-value not reported **Tapia 1998* (mean [SD])** Dexamethasone: 6 (7); placebo: 11 (12) Hydrocortisone **Bosante 2007* (median [range])** Hydrocortisone: 4 (2-7); control: 15 (2-7); p-value reported as not significant **Watterberg 1999* (median [range, 25th-75th percentile]) - survivors only** Hydrocortisone: 25 (14-34); control: 32 (11-45); p-value=0.03	ampoules of dexamethasone and saline prepared in the hospital pharmacy. Exact method of randomisation not described) Allocation concealment (selection bias): low risk (allocation concealment: yes) Blinding of participants and personnel (performance bias) all outcomes: low risk (blinding of intervention: yes) Blinidng of outcome assessment (detection bias) all outcomes: low risk (blinding of outcome measurements: yes) Incomplete outcome data (attrition bias) all outcomes: low risk (complete follow-up: almost 109/113) **Watterberg 1999** Random sequence generation (selection bias): low risk (random allocation at each centre by constant bloack design with 4 patients per block to minimise bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Major anomaly likely to affect long-tem neurological outcome **Garland 1999** Not reported **Lauterbach 2006** Major malformations and grade 3 or 4 IVH **Peltoniemi 2005** Lethal malformations or suspected chromosomal abnormalities **Rastogi 1996** Major malformations, chromosome abnormalitie, severe infection, apgar <3 at 5 min **Romagnoli 1999** Not reported **Shinwell 1996** Active bleeding, hypertension, hyperglycaemia, active infection and lethal congenital abnormalities **Soll 1999** Not reported **Stark 2001** Not reported **Subhedar 1997** Major congenital anomaly, structural cardiac defect, significant ductus shunting, culture-positive sepsis, IVH			**Watterberg 2004* (median [range, 25th-75th percentile]) - survivors only** Hydrocortisone: 32 (13-54); control: 35 (17-47); adjusted p-value=0.86 Outcome: Hypertension Dexamethasone **Garland 1999** Dexamethasone: 95/118; control: 56/123 **Rastogi 1996** Dexamethasone: 1/36; control: 1/34 **Romagnoli 1999** Dexamethasone: 2/25; control: 0/25 **Shinwell 1996** Dexamethasone: 8/132; control: 2/116 **Soll 1999** Dexamethasone: 68/272; control: 50/257 **Stark 2001** Dexamethasone: 30/111; control: 4/109 **Subhedar 1997** Dexamethasone: 0/21; control: 0/21 **Tapia 1998**	over time. Seperate randomisation tables were used for infants exposed to antenatal corticosteroids) Allocation concealment (selection bias): low risk (allocation concealment: yes) Blinding of participants and personnel (performance bias) all outcomes: low risk (blinding of intervention: yes) Blinidng of outcome assessment (detection bias) all outcomes: low risk (blinding of outcome measurements: yes) Incomplete outcome data (attrition bias) all outcomes: low risk (complete follow-up: yes) **Watterberg 2004** Random sequence generation (selection bias): low risk (random allocation, stratified by centre and birth weight [500g to 749g vs 750g to 999g] using permuted-blocks scheme with blocks of 6 in each

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	with parenchymal involvement, pulmonary or GI haemorrhage, abnormal coagulation or thrombocytopenia (platelets <50,000) **Tapia 1998** Life-threatening congenital malformation or chromosome abnormality, a strong suspicionof infection at birth (maternal chorioamnionitis) or early sepsis (positive blood culture in the first 36 hours of life) **Watterberg 1999** Maternal diabetes, congenital sepsis, SGA **Watterberg 2004** Major congenital anomaly, congenital sepsis, postnatal corticosteroids, triplet or higher order gestation			Dexamethasone: 3/55; control 2/54 Hydrocortisone **Bosante 2007** Hydrocortisone: 3/25; control: 1/25 Outcome: Gastro-intestinal perforation Dexamethasone **Anttila 2005** Dexamethasone: 3/53; control: 1/56 **Garland 1999** Dexamethasone: 12/118: control: 7/123 **Rastogi 1996** Dexamethasone: 0/36; control: 0/34 **Soll 1999** Dexamethasone: 31/271; control: 20/267 **Stark 2001** Dexamethasone: 15/111; control: 8/109 **Subhedar 1997** Dexamethasone: 2/21; control: 1/21 Hydrocortisone **Bosante 2007** Hydrocortisone: 2/25; control: 1/25	stratum. Randomisation lists in each pharmacy in sealed envelopes) Allocation concealment (selection bias): low risk (allocation concealment: yes) Blinding of participants and personnel (performance bias) all outcomes: low risk (blinding of intervention: yes) Blinidng of outcome assessment (detection bias) all outcomes: low risk (blinding of outcome measurements: yes) Incomplete outcome data (attrition bias) all outcomes: low risk (complete follow-up: yes) Other notes: The sample size estimate was 712 but the study was stopped early because an increased incidence of apparantly spontaneous GI perforation in the hydrocortisone group. ***Significant difference in the incidence on GI perforation between groups of infants who**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Peltroniemi 2005 Hydrocortisone: 4/25; control: 0/26 **Watterberg 1999** Hydrocortisone: 1/20: control: 1/20 **Watterberg 2004** Hydrocortisone: 22/180; control: 11/180 ***Data extracted from original paper by the NGA technical team**	**received hydrocortisone alone (n=1/41) and combination of hydrocortisone and indomethacin (n=16/139), p-value=0.0009.** ***Data extracted from original paper by the NGA technical team** **Other information** Neurodevelopmental outcomes recorded for Bosante 2007, Romagnoli 1999, Subhedar 1997, and Watterberg 1999 in review, however no time-frame of when the neurodevelopmental outcomes were taken could be reported as there was no follow-up study associated with the primary paper and the authors did not indicate this in their write up or in the notes that they contacted the authors.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Durand,M., Mendoza,M.E., Tantivit,P., Kugelman,A., McEvoy,C., A randomized trial of moderately early low-dose dexamethasone therapy in very low birth weight infants: dynamic pulmonary mechanics, oxygenation, and ventilation, Pediatrics, 109, 262-268, 2002 **Ref Id** 208742 **Country/ies where the study was carried out** **Study type** **Aim of the study** **Study dates**	**Sample size** Please see Onland 2017 Cochrane systematic review **Characteristics** **Inclusion criteria** **Exclusion criteria**	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding					
Full citation Durand,M., Sardesai,S., McEvoy,C., Effects of early dexamethasone therapy on pulmonary mechanics and chronic lung disease in very low birth weight infants: a randomized, controlled trial, Pediatrics, 95, 584-590, 1995 **Ref Id** 208741 **Country/ies where the study was carried out** **Study type** **Aim of the study** **Study dates**	**Sample size** Please see Doyle et al 2014 (late administration of corticosteroids) cochrane systematic review **Characteristics** **Inclusion criteria** **Exclusion criteria**	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding					
Full citation Garland,J.S., Alex,C.P., Pauly,T.H., Whitehead,V.L., Brand,J., Winston,J.F., Samuels,D.P., McAuliffe,T.L., A three-day course of dexamethasone therapy to prevent chronic lung disease in ventilated neonates: a randomized trial, Pediatrics, 104, 91-99, 1999 **Ref Id** 253884 **Country/ies where the study was carried out** **Study type** **Aim of the study**	**Sample size** Please see Doyle et al 2014 (early administration of corticosteroids) cochrane systematic review **Characteristics** **Inclusion criteria** **Exclusion criteria**	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates **Source of funding**					
Full citation Gilmour,C.H., Sentipal-Walerius,J.M., Jones,J.G., Doyle,J.M., Brozanski,B.S., Balsan,M.J., Mimouni,F.B., Pulse dexamethasone does not impair growth and body composition of very low birth weight infants, Journal of the American College of Nutrition, 14, 455-462, 1995 **Ref Id** 208785 **Country/ies where the study was carried out** **Study type**	**Sample size** Please see Doyle et al 2014 (late administration of corticosteroids) cochrane systematic review **Characteristics** **Inclusion criteria** **Exclusion criteria**	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study **Study dates** **Source of funding**					
Full citation Halliday, H. L., Patterson, C. C., Halahakoon, C. W. N. L., A multicenter, randomized open study of early corticosteroid treatment (OSECT) in preterm infants with respiratory illness: Comparison of early and late treatment and of dexamethasone and inhaled budesonide, Pediatrics, 107, 232-240, 2001 **Ref Id**	**Sample size** Please see Onland 2017 Cochrane systematic review **Characteristics** **Inclusion criteria** **Exclusion criteria**	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
619623 **Country/ies where the study was carried out** **Study type** **Aim of the study** **Study dates** **Source of funding**					
Full citation Jonsson,B., Eriksson,M., Soder,O., Broberger,U., Lagercrantz,H., Budesonide delivered by dosimetric jet nebulization to preterm very low birthweight infants at high risk for development of chronic lung disease, Acta Paediatrica, 89, 1449-1455, 2000	**Sample size** n=30 randomised (budesonide: n=15; control: n=15) **Characteristics** Gestational age (weeks in median, range in parentheses): budesonide: n=25 (23-27); control: n=26 (24-29)	**Interventions** 1) Budesonide (Pulmicort) 500mcg twice daily for 14 days via jet nebulisation 2) Placebo vehilce without active corticosteroid	**Details** **Methods:** Randomisation: computer-generated randomisation Allocation concealment: Envelopes were numbered consequtively from 1-30. Clinical staff were blinded to the group assignment during the	**Results** Outcome: Total days on ventilator budesonide: 11 (1-40); control: 14 (1-38); p-value reported as not significant Outcome: Supplemental oxygen at 28 days budesonide: 13/13; control: 14/14 Outcome: Supplemental oxygen at 36 weeks	**Limitations** Risk of bias assessed by Cochrane risk of bias tool Random sequence generation: unclear risk (computer-generated, method of sequencing unknown) Allocation concealment: unclear risk (Envelopes were numbered consequtively from 1-30. Clinical staff were blinded

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ref Id 253931 **Country/ies where the study was carried out** Sweden **Study type** Prospective, placebo-controlled, double-blinded randmised design **Aim of the study** To examine if an aerosolized corticosteroid, budesonide (Pulmicort) could decrease the oxygen requirement of infants at high risk of developing CLD. **Study dates** February 1996 - February 1998	5-min Apgar score (median, range in parentheses): budesonide: n=7 (2-8); control: n=8 (2-10) Surfactant treatment: budesonide: n=14/15 (93%); control: n=15/15 (100%)m **Inclusion criteria** Preterm infants on mechanical ventilation on day 6 of life, or if extubated, nCPAP with Fi02 >0.3. **Exclusion criteria** Congenital malformations, congenital heart disease and IVH (grades III-IV). Infants could be excluded through the study period by the decsion of the attending neonatologist if they remained on mechanical ventilation with an increasing FiO2 requirement greater than 0.6 and/or pCO2 greater than 8.5kPa. Patients on HFOV on day 7 of life could not be included, since		patients hospital stay. The code was broken after the last patient was finished with inhalations. Blinding of participants and personnel all outcomes: budesonide and placebo vehicle without active corticosteroid was supplied in identical opaque, unmarked, plastic vials by Astra-Draco. Blinding of outcome measures: For outcome measures during trial yes, however code was broken after last patient thus not clear if outcomes at 36 weeks were blinded Incomplete outcome data: complete follow-up: 90% (all accounted for; 1 declined inclusion in study, 2 could not be included due to	budesonide: 8/13; control: 11/13	to the group assignment during the patients hospital stay. The code was broken after the last patient was finished with inhalations) Blinding of participants and personnel all outcomes: low risk (budesonide and placebo vehicle without active corticosteroid was supplied in identical opaque, unmarked, plastic vials by Astra-Draco) Blinding of outcome measures: Unclear risk (For outcome measures during trial yes, however code was broken after last patient thus not clear if outcomes at 36 weeks were blinded) Incomplete outcome data: low risk (complete follow-up: 90% [all accounted for; 1 declined inclusion in study, 2 could not be included due to ongoing HFOV on day 7 of life])

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding Grants from Sallskapet Barnavard amd Stoftelsen Barnhuset, Stockholm	inhalations could not be given through this device.1)		ongoing HFOV on day 7 of life) **Outcomes:** Ventilator time in days, supplemental oxygen at 28 days, supplemental oxygen at 36 weeks		Selective reporting: unclear risk (no published protocol available) **Other information**
Full citation Kari, M. A., Heinonen, K., Ikonen, R. S., Koivisto, M., Raivio, K. O., Dexamethasone treatment in preterm infants at risk for bronchopulmonary dysplasia, Archives of Disease in Childhood, 68, 566-569, 1993 **Ref Id** 410798 **Country/ies where the study was carried out** **Study type**	**Sample size** Please see Doyle et al 2014 (late administration of corticosteroids) cochrane systematic review **Characteristics** **Inclusion criteria** **Exclusion criteria**	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study **Study dates** **Source of funding**					
Full citation Kothadia, J. M., O'Shea, T. M., Roberts, D., Auringer, S. T., Weaver, Iii R. G., Dillard, R. G., Randomized placebo-controlled trial of a 42-day tapering course of dexamethasone to reduce the duration of ventilator dependency in very low birth weight infants, Pediatrics, 104, 22-27, 1999 **Ref Id** 619715 **Country/ies where the study was carried out**	**Sample size** Please see Doyle et al 2014 (late administration of corticosteroids) cochrane systematic review **Characteristics** **Inclusion criteria** **Exclusion criteria**	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study type **Aim of the study** **Study dates** **Source of funding**					
Full citation Kovacs,L., Davis,G.M., Faucher,D., Papageorgiou,A., Efficacy of sequential early systemic and inhaled corticosteroid therapy in the prevention of chronic lung disease of prematurity, Acta Paediatrica, 87, 792-798, 1998 **Ref Id** 254048	**Sample size** Please see Doyle et al 2014 (late administration of corticosteroids) cochrane systematic review **Characteristics** **Inclusion criteria** **Exclusion criteria**	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out **Study type** **Aim of the study** **Study dates** **Source of funding**					
Full citation Lauterbach,R., Szymura-Oleksiak,J., Pawlik,D., Warchol,J., Lisowska-Miszczyk,I., Rytlewski,K., Nebulized pentoxifylline for prevention of bronchopulmonary dysplasia in very low birth weight infants: a pilot clinical study, Journal of Maternal-Fetal and Neonatal Medicine, 19, 433-438, 2006	**Sample size** Please see Doyle et al 2014 (early administration of corticosteroids) cochrane systematic review **Characteristics** **Inclusion criteria** **Exclusion criteria**	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ref Id 208932 **Country/ies where the study was carried out** **Study type** **Aim of the study** **Study dates** **Source of funding**					
Full citation McEvoy,C., Bowling,S., Williamson,K., McGaw,P., Durand,M., Randomized, double-blinded trial of low-dose dexamethasone: II. Functional residual capacity and pulmonary outcome in very low birth weight infants at risk for	**Sample size** Please see Onland 2017 Cochrane systematic review **Characteristics** **Inclusion criteria**	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
bronchopulmonary dysplasia, Pediatric Pulmonology, 38, 55-63, 2004 **Ref Id** 208981 **Country/ies where the study was carried out** **Study type** **Aim of the study** **Study dates** **Source of funding**	**Exclusion criteria**				
Full citation Odd,D.E., Armstrong,D.L., Teele,R.L., Kuschel,C.A., Harding,J.E., A randomized trial of two dexamethasone	**Sample size** Please see Onland 2017 Cochrane systematic review **Characteristics**	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
regimens to reduce side-effects in infants treated for chronic lung disease of prematurity, Journal of Paediatrics and Child Health, 40, 282-289, 2004 **Ref Id** 253880 **Country/ies where the study was carried out** **Study type** **Aim of the study** **Study dates** **Source of funding**	**Inclusion criteria** **Exclusion criteria**				
Full citation Onland, W., De Jaegere, A. P., Offringa, M., van Kaam, A., Systemic	**Sample size** **Of relevant studies:** **Bloomfield 1998** n=40 randomised (n=19 pulse course	**Interventions** **Of relevant studies:** **Bloomfield 1998** 1) Pulse arm: infants received	**Details** **Of relevant studies:** **Bloomfield 1998** Methods: Randomized	**Results** Outcome: Mortality prior to discharge **Bloomfield 1998**	**Limitations** **Quality of Cochrane SR:**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
corticosteroid regimens for prevention of bronchopulmonary dysplasia in preterm infants, Cochrane Database of Systematic Reviews, 1, CD010941, 2017 **Ref Id** 619815 **Country/ies where the study was carried out** **Study type** Cochrane systematic review **Aim of the study** To assess the effects of different corticosteroid treatment regimens on mortality, pulmonary morbidity, and neurodevelopmental outcome in very low birth weight (VLBW) infants.	dexamethasone; n=21 long course dexamethasone) **Durand 2002** n=47 randomised (n=23 high-dose course of dexamethasone; n=24 low-dose course of dexamethasone) **Halliday 2001** n=285 randomised (n=135 early dexamethasone; n=150 delayed dexamethasone) **McEvoy 2004** n=62 randomised (n= high dose dexamethasone; n=33 low dose dexamethasone) **Odd 2004** n=33 randomised (n=16 long course of dexamethasone; n=17 to the individual course of dexamethasone) **Papile 1998** n=371 randomised (n=182 early dexamethasone; n=189 late dexamethasone) **Characteristics Of relevant studies:** **Bloomfield 1998***	dexamethasone 0.5 mg/kg/day for 3 consecutive days. The pulse course was repeatable every 10 days if still ventilated or supplemental oxygen and < 36 weeks' post menstrual age 2) Continuous arm: starting at 14 days of age if still ventilated at ≥ 15 cycles/min and ≥ 30% supplemental oxygen, a high-dosage regimen with a cumulative dose of 7.9mg/kg of dexamethasone administered over a 42-day course: 0.5 mg/kg/day for 3 days, 0.3 mg/kg/day for 3 days, a 10% decrease every 3 days until 0.1 mg/kg/day, 0.1 mg/kg/day for 3 days, 0.1 mg/kg/day on alternate days for 7 days. The initial dosage administration of 0.5 mg/kg/day was in 2	controlled trial comparing a pulse course against high-dosage regimen dexamethasone Outcomes: The primary outcomewas linear growth,measured as weight gain, crown-heel length, and head circumference. Secondary outcomes were hypertension, hyperglycemia requiring insulin therapy, necrotizing enterocolitis, retinopathy of prematurity, proven infections, myocardial hypertrophy, supplemental oxygen at 28 days' PNA and 36 weeks' PMA, BPD at 28 days' PNA and 36 weeks' PMA. In addition a Synacthen test was performed 1 week after discontinuation of the dexamethasone. The long-term follow-up	Long-group dexamethasone: 2/37; pulse-group dexamethasone: 5/39 **Durand 2002** High-dose dexamethasone: 1/23; low-dose dexamethasone: 1/24 **Halliday 2001** Early dexamethasone: 43/135; delayed dexamethasone: 39/150 **McEvoy 2004** high-dose dexamethasone: 2/29; low dose: 1/33 **Odd 2004** Individual course dexamethasone: 5/17; long course dexamethasone: 4/16 **Papille 1998** Early dexamethasone: 17/182; delayed dexamethasone: 26/189 Outcome: Bronchopulmonary dysplasia at 36 weeks corrected gestation **Bloomfield 1998** Long-group dexamethasone: 11/37; pulse-group dexamethasone: 13/39 **Durand 2002**	Systematic review assessed using AMSTAR checklist. Total score: 10/11 All checklist items adressed, with the exception of: Checklist item 4: Was the status of publication (i.e. grey literature) used as an inclusion criterion? No details provided **Quality of individual studies:** Risk of bias assessment taken from Cochrane systematic reivew (Cochrane risk of bias tool): **Bloomfield 1998** Random sequence generation: Low risk (computer randomisation) Allocation concealment: Low risk (computer randomisation, no additional details. Randomisation was balanced in blocks of 6 and stratified by sex and birth weight) Blinding of participants and personnel: High risk

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates Search up to March 2016 **Source of funding** Eunice Kennedy Shriver National Institute of Child Health and Human Development National Institutes of Health, USA. Editorial support of the Cochrane Neonatal Review Group has been funded with federal funds from the Eunice Kennedy Shriver National Institute of Child Health and Human Development National Institutes of Health, Department of Health and Human Services, USA, under Contract No. HHSN275201100016C	- Setting: New Zealand - Gestational age (weeks in median, with ranges in parentheses): Pulse =25.5 (23-30); Long=25.2 (24-30) - Oxygenation index (median, with ranges in parentheses): Pulse =3.7 (1.8-18.6); Long=3.8 (2.5-6.6) **Durand 2002*** - Setting: USA - Gestational age (weeks in mean, with ± SD in parentheses): High-dose=27.1 (±1.8); Low-dose=26.9 (±1.6) - Gender (% female): High-dose=39%; Low-dose=54% - Apgar score 1 min (median, with ranges in parentheses): high-dose=6 (1-9); low-dose=5 (1-9) - Apgar score 5 min (median, with ranges in parentheses): high-dose=8 (3-9); low-dose=7 (3-9) - Surfactant (%): high-dose=87%; low-dose=88% - FiO2 (mean, with ± SD in parentheses): high-dose=0.43 (±0.11); low-dose=0.41 (±0.1) **Halliday 2001***	**Total cumulative dose: Pulse (5.3 mg/kg) vs Long (7.1 mg/kg)** **Timing of administration: Pulse (7 days) vs long (14 days)** **Durand 2002** 1) A moderate-dosage regimen with a cumulative dose of 2.4 mg/kg of dexamethasone administered over a 7-day course: 0.5 mg/kg/day for 3 days, then 0.25mg/kg/day for 3 days, then 0.1 mg/kg/day for 1 day; 2) A low-dosage regimen with a cumulative dose of 1.0 mg/kg of dexamethasone administered over a 7-day course: 0.2 mg/kg/day for 3 days, then 0.1 mg/kg/day for 4 days. All medication was given divided into 2 dosages per day.	manuscript reported on neurodevelopmental outcome with an extended inclusion rate. **Durand 2002** Methods: Single center randomized controlled trial. Outcomes: The primary outcomes were the dynamic respiratory mechanics, measured before and on days 2, 5 and 7 of dexamethasone therapy. Secondary outcomes were ventilator settings, occurrence of CLD, defined as dependence on oxygen supplementation at 36 weeks' PMA, survival without CLD, duration of mechanical ventilation, duration of hospitalizations, hyperglycemia, hypertension, ROP, NEC, spontaneous GI	High-dose dexamethasone: 3/23; low-dose dexamethasone: 2/24 **Halliday 2001** Early dexamethasone: 32/135; delayed dexamethasone: 54/150 **McEvoy 2004** high-dose dexamethasone: 5/29; low dose: 8/33 **Odd 2004** Individual course dexamethasone: 9/17; long course dexamethasone: 8/16 **Papille 1998** Early dexamethasone: 121/182; delayed dexamethasone: 127/189 Outcome: Bronchopulmonary dysplasia at 28 days of age **Bloomfield 1998** Long-group dexamethasone: 17/37; pulse-group dexamethasone: 25/39 **Halliday 2001** Early dexamethasone: 71/135; delayed dexamethasone: 91/150 **Odd 2004** Individual course dexamethasone: 14/17; long	(no blinding of intervention) Blinding of outcomes assessors: High risk (no blinding of outcome assessment) Incomplete outcome data: Low risk (Intention-to-treat analysis. 1 infant was found to have a birth weight of > 1250 grams. 3 infants were lost to follow-up) Selective reporting: Low risk (All predefined outcomes were mentioned in the manuscript) Other bias: No concerns of other biases **Durand 2002** Random sequence generation: Low risk (blind drawing of random cards) Allocation concealment: Low risk (opaque sealed envelopes) Blinding of participants and personnel: High risk (no blinding of intervention)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	- Setting: Multinational (47 neonatal units) - Gestational age (weeks): < 25: early dexamethasone=11 (8%); late dexamethasone=11 (7%) 25-29: early dexamethasone=106 (79%); late dexamethasone=125 (83%) 30-34: early dexamethasone=18 (13%); late dexamethasone=14 (9%) - Mean (SD): early dexamethasone=27.4 (1.9); late dexamethasone=27.1 (1.9) - Apgar score 1 min (median, with ranges in parentheses): early dexamethasone=5 (0-10); late dexamethasone=5 (0-9) - Apgar score 5 min (median, with ranges in parentheses): early dexamethasone=7 (1-10); late dexamethasone=7 (1-10) - Surfactant (%): early dexamethasone=95%; late dexamethasone=92% **McEvoy 2004***	Administration of open-label dexamethasone was allowed after the study period at the discretion of the attending neonatologist **Total cumulative dose: moderate dose (2.35 mg/kg) vs low dose (1 mg/kg)** **Timing of administration: 7-14 days** **Halliday 2001** Eligible infants were randomized in 1 of 4 arms, of which 2 contained inhaled corticosteroids. These infants were excluded from this review The remaining infants were randomized into 1 of 2 arms. 1) Early (< 72 hours) dexamethasone: initial dose of 0.5 mg/kg/day for 3 days, followed by 0.25 mg/kg/day for 3 days, followed by 0.1 mg/kg/day for 3 days and finally 0.05 mg/kg/day for 3 days.	perforation, sepsis and pulmonary air leaks. **Halliday 2001** Methods: Multicenter partly double-blinded randomized controlled trial with a factorial design investigating early versus late administration of inhaled and systemic dexamethasone Outcomes: Primary outcome was death or oxygen dependency at 36 weeks' PMA. Secondary outcomes were death or major cerebral abnormality, death or oxygen dependency at 28 days and expected date of delivery, duration of > 40% oxygen, duration of any oxygen, duration of mechanical ventilation, and duration of hospital stay. Furthermore, complications such as pneumothorax, necrotizing	course dexamethasone 15/16 **Papille 1998** Early dexamethasone: 141/182; delayed dexamethasone: 168/189 Outcome: Cerebral Palsy **Halliday 2001 - extracted from Wilson 2006* (diagnosed at 7 years of age -** denominator = population at follow-up) Early dexamethasone: 2/22; Delayed dexamethasone: 6/34 **Durand 2002 (no time frame for diagnosis or criteria for diagnosis-** denominator = population at follow-up**)** High-dose dexamethasone: 2/18; low-dose dexamethasone: 2/18 **McEvoy 2004 (diagnosed at 9-15 months)** High-dose dexamethasone: 2/21; low-dose dexamethasone: 2/18 Outcome: Major cognitive impairment **Durand 2002 (criteria for diagnosis Bayley scale**	Blinding of outcomes assessors: High risk (an outside investigator blinded to the group assignment evaluated the dynamic pulmonary mechanics and graphics. However, assessment of clinical diagnosis was not blinded) Incomplete outcome data: Low risk (Of the 59 infants eligible, 7 parents were unavailable and 5 parents refused. 1 included participant had a few doses of dexamethasonewithheld because of suspected infection) Selective reporting: Low risk (All predefined outcomes were mentioned in the manuscript) Other bias: No concerns of other biases **Halliday 2001** Random sequence generation: Unclear risk (method not mentioned) Allocation concealment: Low risk (supervising clinician telephoned the

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	- Setting: USA - Gestational age (weeks in mean, with ± SD in parentheses): high-dose=26.1 (2.0); low-dose=26.3 (1.8) - Surfactant (%): high-dose=97; low-dose=82 - Apgar score 1 min (median, with ranges in parentheses): high-dose=4 (1-8); low-dose= 4 (1-9) - Apgar score 5 min (median, with ranges in parentheses): high-dose=7 (2-10); low-dose= 8 (4-9) - FiO2 at study (% in mean, with ± SD in parentheses)): high-dose=44 (13); low-dose= 42 (13) **Odd 2004*** - Setting: New Zealand - Gestational age (weeks in median, with ranges in parentheses): individual course=24 (23-27); long course=24 (23-26) - Cumulative dexamethasone dose (mg/kg in median, with ranges in parentheses): individual course=3.8 (2.0-5.7); long course=6.5 (3.8-7.3)	2) Moderate early (15 days postnatal age) dexamethasone: infants randomized to the late dexamethasone group had to fulfill the inclusion criteria at 15 days to be eligible for treatment. Initial dose of 0.5 mg/kg/day for 3 days, followed by 0.25 mg/kg/day for 3 days, followed by 0.1 mg/kg/day for 3 days and finally 0.05 mg/kg/day for 3 days. All medication was given divided into 2 dosages per day **Total cumulative dose: 2.7 mg/kg** **Timing of administration: Early (< 72 hours) vs moderate early (> 15 days)** **McEvoy 2004** 1) A moderate-dosage regimen with a cumulative dose of 2.4 mg/kg of dexamethasone	enterocolitis, hypertension, hyperglycemia, sepsis, pneumonia, persistent ductus arteriosus requiring therapy, pulmonary hemorrhage, seizures, recurrent apnea, retinopathy of prematurity, gastric hemorrhage, gastrointestinal perforation were reported. The follow-up manuscript reported on neurodevelopmental outcome at 7 years of age, including level of disability, cerebral palsy, cognitive ability using the British Ability Scales (BAS 2nd edition), behavioral difficulties using the Strengths and Difficulties Questionnaire (SDQ), competencies using the Child Behavior Checklist for Children, growth, and respiratory symptoms.	**MDI <-2 SD, but no time frame for diagnosis - denominator = whole population)** High-dose dexamethasone: 4/23; low-dose dexamethasone: 3/24 **McEvoy 2004 (diagnosed at 9-15 months)** High-dose dexamethasone: 5/29; low-dose dexamethasone: 3/33 Outcome: Neurodevelopmental outcome of Severe Disability (defined as >-2 SD on Bayleys II mental score, bilateral blindness, sensoneural deafness requiring hearing aids, or the presence of severe cerebral palsy) **Bloomfield 1998 - extracted from Armstrong 2002* (diagnosed at 18 months of age,** denominator = population at follow-up) Long-group dexamethasone: 1/32; pulse-group dexamethasone: 4/32	randomization center in Belfast) Blinding of participants and personnel: High risk (Of the 47 participating NICUs, 11 conducted a double-blinded study. In the remaining centers the design was open because some clinicians wanted to prescribe broad spectrum antibiotics or H2 blockers, or both. In the 11 double-blinded centers intravenous saline was given) Blinding of outcomes assessors: High risk (see blinding of participants and personnel) Incomplete outcome data: Low risk (Analyses were on intention-to-treat analyses. 5 infants allocated to early treatment were not treated within 5 days, whereas 10 infants allocated to themoderately early period were treated before the 10th day. 2

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Papille 1998* - Setting: USA - Gestational age (weeks in mean, with ± SD in parentheses): early dexamethasone=25.7 (1.9); late dexamethasone=25.6 (1.6) - Apgar score ≤3 1 min (% in mean, with ± SD in parentheses): early dexamethasone=93 (51); late dexamethasone=96 (51) 5 min (% in mean, with ± SD in parentheses): early dexamethasone=29 (16); late dexamethasone=22 (12) - Surfactant therapy (n, with % in parentheses): early dexamethasone=165 (91); late dexamethasone=169 (89) - Patent ductus arteriosus requiring treatment (n, with % in parentheses): early dexamethasone=128 (70); late dexamethasone=113 (60)	administered over a 7-day course: 0.5 mg/kg/day for 3 days, then 0.25mg/kg/day for 3 days, then 0.1 mg/kg/day for 1 day. 2) A low-dosage regimen with a cumulative dose of 1.0 mg/kg of dexamethasone administered over a 7-day course: 0.2 mg/kg/day for 3 days, then 0.1 mg/kg/day for 4 days. All medication was given divided into 2 dosages per day. **The use of open-label dexamethasone therapy was discouraged, but could be administered at the discretion of the attending neonatologist** **Total cumulative dose: high dose (2.35 mg/kg) vs low dose (1mg/kg)** **Odd 2004**	Impairment was defined as BAS cluster score < 10th percentile, weight or height < 2nd percentile,head circumference < 2nd or > 98th percentile, seizures, borderline SDQtotal difficulties score (14 to 16), strabismus, or nystagmus. **McEvoy 2004** Methods: Single center randomized controlled trial Outcomes: The primary outcomes were the functional residual capacity and passive respiratory compliance before and during the 7-day therapy. Secondary outcome measurements were the ventilator settings, the duration of mechanical ventilation, the duration of hospitalizations, CLD (defined as oxygen	Outcome: Neurodevelopmental outcome of Severe Disability (defined as GCA score of <55) **Halliday 2001 - extracted from Wilson 2006* (diagnosed at 7 years of age,** denominator = population at follow-up) Early dexamethasone: 2/24; delayed dexamethasone: 4/37 Outcome: Neurodevelopmental outcome of moderate disability (defined as -1-2 SD on Bayleys II mental score or mild-moderate cerebral palsy without developmental delay) **Bloomfield 1998 - extracted from Armstrong 2002* (diagnosed at 18 months of age,** denominator = population at follow-up) Long-group dexamethasone: 16/32; pulse-group dexamethasone: 11/32 Outcome: Neurodevelopmental	infants were given the wrong drug) Selective reporting: Low risk (All predefined outcomes were mentioned in the manuscript) Other bias: Unclear risk (A large proportion of the total included infants randomized to delayed selective treatment either died or did not fulfill the entry criteria) **McEvoy 2004** Random sequence generation: Low risk (group assignment was done by the pharmacy using a randomization table) Allocation concealment: Low risk (Investigators and clinical staff was unaware of treatment allocation, because a staff pharmacist was in charge of randomization and study drug preparation) Blinding of participants and personnel: Low risk

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	***Data extracted from original paper by the NGA technical team** **Inclusion criteria** **Of relevant studies:** **Bloomfield 1998** Preterm infants with a birth weight ≤ 1250 grams, and ventilated at ≥ 15 cycles/min at 7 days of age. **Durand 2002** Infants were included when having a birth weight between 501 and 1500 grams, a gestational age between 24 weeks and 32 weeks, postnatal age between 7 and 14 days and at entry on ventilation support with a rate of 15 cycles per minute or more,	1) Continuous dosage regimen: 0.5 mg/kg/day for 3 days, 0.3 mg/kg/day for 3 days, then a dose decreasing by 10% every 3 days to 0.1 mg/kg per day over a further 30 days, followed by 0.1 mg/kg/day on alternate days for 1 week. Total duration was 42 days. 2) Individual course: 0.5 mg/kg/day for 3 days, 0.3 mg/kg/day for 3 days, 0.1 mg/kg/day for 3 days, followed by 0.1 mg/kg every 72 hours until the infant was extubated and required a FiO2 ≤ 0.25 for 3 doses. In case of clinical deterioration (increase in FiO2 ≥ 0.15 or MAP ≥ 2 cmH2O) the dose reverted to 0.3 mg/kg/day for 3 days, after which the same schedule was followed. **Total cumulative dose: individual**	dependence at 36 weeks' PMA), survival without CLD, PDA, hyperglycemia, hypertension, IVH, periventricular leukomalacia, ROP, NEC, spontaneous GI perforation, sepsis, pulmonary air leaks. At 1 year of corrected age the infants were assessed for early neurodevelopmental follow-up (cerebral palsy and Bayley Scales of Infant Development) by a developmental pediatrician, a pediatric neurologist and specialized personnel. Cerebral palsy was defined as non-progressive motor impairment characterized by abnormal muscle tone and decreased range/control of movements. Severe cognitive delay was defined as lower than 70 on the mental	outcome of Moderate Disability (defined as GCA score of 55-69) **Halliday 2001 - extracted from Wison 2006* (diagnosed at 7 years of age,** denominator = population at follow-up) Early dexamethasone: 1/24; delayed dexamethasone: 1/37 Outcome: Blind **Haliday 2001 - extracted from Wilson 2006* (diagnosed at 7 years of age,** denominator = population at follow-up) No reported events in either arm **Durand 2002 (labelled as severe blindness, no criteria defined nor time frame for diagnosis - denominator = whole population)** High-dose dexamethasone: 1/23; low-dose dexamethasone: 0/24 **McEvoy 2004 (diagnosed at 9-15 months)** High-dose dexamethasone: 1/29; low-dose dexamethasone: 0/33	(Although method not specified in manuscripts.) Blinding of outcomes assessors: Low risk (Although method not specified in manuscripts.) Incomplete outcome data: High risk (In 3 patients of the high-dose group, 1 dose of dexamethasone was withheld due to blood in the gastric tube or hypertension. For 1 patient of the low dose group, a dose was inadvertently not given. 66% of the survivors were assessed for follow-up. No statement on the influence on the neurodevelopmental outcome) Selective reporting: Low risk (All predefined outcomes were mentioned in the manuscript) Other bias: Low risk **Odd 2004** Random sequence generation: Low risk

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	and 30% supplemental oxygen or more to maintain a pulse oxymeter oxygen saturation of 90% or higher, despite weaning trials. **Halliday 2001** Intubated infants < 30 weeks' gestational age, a postnatal age < 72 hours and with an inspired oxygen concentration > 30%. Infants with a gestational age between 30 and 31 weeks could be included if needing inspired oxygen > 50% **McEvoy 2004** Preterm infants were included when between 7 and 21 days of postnatal age, with a birth weight of > 501 grams and < 1500 grams, a gestational age of > 24 weeks and < 32 weeks. The infants were dependent on ventilation support with 15 cycles per minute or more and oxygen levels of 30% or more at entry. **Odd 2004** Preterm infants ≤ 1250 grams, ventilated between postnatal age of 7 days and	**course (median 3.8 mg/kg [2-5.7]) vs continuous course (median 6.5 mg/kg [3.8-7.3])** **Timing of administration: 7 days** **Papille 1998** 1) Moderately early initiation: infants received 2 weeks of dexamethasone regimen, followed by 2 weeks' saline. 2) Late initiation: infants started with 2 weeks of saline, after which they started with 2 weeks of dexamethasone if the respiratory index still was ≥ 2.4. Both dexamethasone regimens started with 0.5 mg/kg/day (divided in 2 doses) for 5 days, followed by 0.15 mg/kg, 0.07 mg/kg, and 0.03 mg/kg for 3 days each. **Total cumulative dose: 4 mg/kg**	developmental index (MDI) score. **Odd 2004** Methods: Single center randomized controlled trial investigating a continuous dosage regimen versus an individualized course tailored to the infants' respiratory status Outcomes: The primary outcome was linear growth, measured by knemometry, weight, crown-heel length, and head circumference. Secondary outcomes were hypertension, myocardial hypertrophy, respiratory status (mode, peak inspiratory pressure, and end expiratory pressure and FiO at enrolment, study days 14, 42, 28 days' postnatal age and 36 weeks' corrected gestational age,	Outcomes: Deaf **Halliday 2001 - extracted from Wilson 2006* (diagnosed at 7 years of age,** denominator = population at follow-up) No reported events in either arm Outcome: Days of invasive ventilation (mean [SD]) **McEvoy 2004** high-dose dexamethasone: 36 (30.2); low dose: 34.9 (20.9) **Odd 2004** Individual course dexamethasone: 27.75 (9.75); long course dexamethasone: 20.25 (5.25) Outcome: Gastro-intestinal perforation **Durand 2002** High-dose dexamethasone: 1/23; low-dose dexamethasone: 1/24 **Halliday 2001** Early dexamethasone: 6/135; delayed dexamethasone: 5/150	(computer generated random numbers) Allocation concealment: Low risk (Stratified by sex and birth weight) Blinding of participants and personnel: High risk Blinding of outcomes assessors: High risk (Clinical outcome assessment was not blinded, although the primary outcome was (knemometry), as well as ultrasounds performed by staff unaware of treatment allocation. The developmental psychologist was also unaware of the treatment allocation) Incomplete outcome data: Low risk (In 1 infant in the individual group, the dexamethasone treatment was stopped on day 10. Intention-to-treat analyses were performed) Selective reporting: Low risk (All predefined outcomes were mentioned in the manuscript)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	28 days for which dexamethasone was indicated **Papille 1998** Ventilator-dependent preterm infants with birth weight 501 to 1500 grams, at a postnatal age between 13 and 15 days, with a respiratory index of ≥ 2.4 **Exclusion criteria** **Of relevant studies:** **Bloomfield 1998:** Infants with major congenital malformations or who were ventilated for surgical reasons were excluded **Durand 2002** Infants were excluded from the randomization if they had multiple congenital anomalies or chromosomal abnormalities, systemic hypertension, congenital heart disease, IVH grade IV, renal failure or sepsis at entry **Halliday 2001**	**Timing of administration: moderately early (14 days) vs late (28 days)**	hyperglycemia requiring insulin therapy, renal and cranial ultrasounds, proven and suspected infections. In addition a Synacthen test was performed 1 week after discontinuation of the dexamethasone. The long-term neurodevelopmental outcome were assessed at 9 and 18 months using the Bayley Scales of Infant Development II (median age at ND follow up: individual course: 54 weeks [21-115]; long course: 64 weeks [21-113]) **Papile 1998** Methods: Multicenter double-blinded randomized controlled trial investigating dexamethasone therapy initiated moderately early versus late Outcomes: Primary outcome was the	**McEvoy 2004** high-dose dexamethasone: 1/29; low dose: 1/33 **Odd 2004** Individual course dexamethasone: 9/17; long course dexamethasone: 8/16 Outcome: Hypertension **Bloomfield 1998** Long-group dexamethasone: 0/37; pulse-group dexamethasone: 0/39 **Durand 2002** High-dose dexamethasone: 3/23; low-dose dexamethasone: 1/24 **Halliday 2001** Early dexamethasone: 25/135; delayed dexamethasone: 22/150 **McEvoy 2004** high-dose dexamethasone: 6/29; low dose: 3/33 **Odd 2004** Individual course dexamethasone: 9/17; long course dexamethasone: 8/16 **Papille 1998** Early dexamethasone: 17/182; delayed dexamethasone: 23/189	Other bias: Low risk **Papille 1998** Random sequence generation: Low risk (an order form was sent to each center's pharmacy,where the infants were randomly assigned to 1 of 2 treatment groups) Allocation concealment: Unclear risk (No information provided) Blinding of participants and personnel: Low risk (To blind clinical staff, different volumes of placebo were prepared to match the various doses of dexamethasone) Blinding of outcomes assessors: Low risk (see blinding of participants and personnel) Incomplete outcome data: Low risk (3 infants did not receive any of the assigned treatments. Of the 173 infants in the late dexamethasone group who were alive on treatment day 14, 31 did not meet the criteria for starting

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Infants with lethal congenital anomalies, severe IVH > III, and proven infections were excluded. When strong suspicion of infection, hypertension or hyperglycemia, inclusion was postponed until resolved **McEvoy 2004** Infants with multiple congenital anomalies, systemic hypertension, congenital heart disease, IVH grade IV, renal failure, and sepsis at entry were excluded **Odd 2004** Infants with congenital anomalies and surgical problems were excluded **Papille 1998** Infants who received glucocorticoid therapy after birth, had proven or suspected sepsis, or congenital anomaly of cardiovascular, pulmonary, or central nervous system were excluded		number of days from randomization to ventilator independence. Secondary outcomes were death before hospital discharge, duration of assisted ventilation, supplemental oxygen, and hospital stay, BPD at 36 weeks, hyperglycemia, hypertension, changes in weight and head circumference, proven sepsis, necrotizing enterocolitis, and gastric hemorrhage.	***Data extracted from original paper by the NGA technical team**	dexamethasone treatment. Results were analyzed on intention-to-treat method) Selective reporting: Low risk (All predefined outcomes were mentioned in the manuscript) Other bias: Low risk **Other information** Neurodevelopmental outcomes recorded for Durand 2002 and McEvoy 2004 in review, however not reported as no follow-up study associated with the primary paper, no indication of contacting authors in the notes, and no time-frame of when neurodevelopmental outcomes were taken

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation O'Shea,T.M., Washburn,L.K., Nixon,P.A., Goldstein,D.J., Follow-up of a randomized, placebo-controlled trial of dexamethasone to decrease the duration of ventilator dependency in very low birth weight infants: neurodevelopmental outcomes at 4 to 11 years of age, Pediatrics, 120, 594-602, 2007 **Ref Id** 209028 **Country/ies where the study was carried out** **Study type** **Aim of the study** **Study dates**	**Sample size** Follow-up study to Kothadia 1999. Please see Doyle et al 2014 (late administration of corticosteroids) cochrane systematic review **Characteristics** **Inclusion criteria** **Exclusion criteria**	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding					
Full citation Papile, L. A., Tyson, J. E., Stoll, B. J., Wright, L. L., Donovan, E. F., Bauer, C. R., Krause-Steinrauf, H., Verter, J., Korones, S. B., Lemons, J. A., Fanaroff, A. A., Stevenson, D. K., Oh, W., Ehrenkranz, R. A., Shankaran, S., A multicenter trial of two dexamethasone regimens in ventilator-dependent premature infants, New England Journal of Medicine, 338, 1112-1118, 1998 **Ref Id** 619825 **Country/ies where the study was carried out** **Study type**	**Sample size** Please see Onland 2017 Cochrane systematic review **Characteristics** **Inclusion criteria** **Exclusion criteria**	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study **Study dates** **Source of funding**					
Full citation Parikh, Na, Kennedy, Ka, Lasky, Re, Tyson, Je, Neurodevelopmental Outcomes of Extremely Preterm Infants Randomized to Stress Dose Hydrocortisone, PLoS ONE, 10, e0137051, 2015 **Ref Id** 619830 **Country/ies where the study was carried out** USA	**Sample size** See Parikh 2013 **Characteristics** See Parikh 2013 **Inclusion criteria** See Parikh 2013 **Exclusion criteria** See Parikh 2013	**Interventions** See Parikh 2013	**Details** **Methods:** Randomisation: See Parikh 2013 Allocation concealment: See Parikh 2013 Bliniding of participants and personnel: See Parikh 2013 Blinding of outcome assessment: A certified examiner blinded to group assignment performed all Bayley testing. Bilateral deafness was defined as bilateral hearing	**Results** Outcome: Cerebral Palsy at corrected age of 18-22 months (**denominator = population at follow-up)** Hydrocortisone: 3/20; control: 1/17 Outcome: Cognitive delay (defined as a Bayley [3rd edition] cognitive score of less than 80) at corrected age of 18-22 months (**denominator = population at follow-up)** Hydrocortisone: 4/19; control: 8/17 Outcome: Language delay (defined as a Bayley [3rd edition] language score of less than 80) at corrected	**Limitations** Risk of bias assessment assesed wuth Cochrane risk of bias tool Random sequence generation: Unclear risk (random allocation by an individual not involved in the study. Birth weight [≤750g versus 751g to 1000g] and respiratory index score[2-4 versus >4] strata) Allocation concealment: Low risk (specifics not reported by Doyle 2014) Blinding of participants and personnel: Low risk (blinding of intervention)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study type RCT **Aim of the study** To compare the effects of stress dose hydrocortisone therapy with placebo on survival without neurodevelopmental impairments in high-risk preterm infants **Study dates** See Parikh 2013 Neurodevelopmental assessments October 2007-November 2010 **Source of funding** Supported by the National institutes of health (national institutes of neurological disorders and stroke) K23-NS048152 grant and the research insititute at nationwide children's			loss requiring amplification and bilateral blindness as bilateral vision loss with only form or shadow vision or no useful vision. Cerebral palsy was defined as the presence of any two of the following 3 abnormalities: 1) Delay in motor milestones, 2) Abnormalities observed in the neuromotor exam (tone, deep tendon reflexes, coordination, and movement) and 3) aberrations in primitive reflexes or postural reactions. Incomplete outcome data: Complete follow-up: 91%, 6 participants lost to follow-up (hydrocortisone: n=2, control: n=4) for death or impairment. However, for cognitive delay assessment follow-up: 63%; language delay	age of 18-22 months (**denominator = population at follow-up)** Hydrocortisone: 9/18; control: 10/17 Outcome: Bilateral blindness (**denominator = population at follow-up)** No cases reported in either study group Outcome: Bilateral deafness (**denominator = population at follow-up)** 1 case reported, however group assignment was not specified	Blinidng of outcome assessment: Low risk (A certified examiner blinded to group assignment performed all Bayley testing. Bilateral deafness was defined as bilateral hearing loss requiring amplification and bilateral blindness as bilateral vision loss with only form or shadow vision or no useful vision. Cerebral palsy was defined as the presence of any two of the following 3 abnormalities: 1) Delay in motor milestones, 2) Abnormalities observed in the neuromotor exam (tone, deep tendon reflexes, coordination, and movement) and 3) aberrations in primitive reflexes or postural reactions) Incomplete outcome data: high risk (Complete follow-up: 91%, 6 participants lost to follow-up (hydrocortisone: n=2, control: n=4) for death or impairment. However, for

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
hospiital to NAP. The funders had no role in study design, data collection and analysis, decision to publish or preparation of manuscript.			assessment follow-up:61%; cerebral palsy assessment follow-up: 65% **Outcomes:** Cognitive delay (Bayleys cognitive score <80), language delay (Bayleys language score <80), cerebral palsy, bilateral deafness and bilateral blindness,		cognitive delay assessment follow-up: 63%; language delay assessment follow-up:61%; cerebral palsy assessment follow-up: 65%) Selective reporting: All outcomes reported in protocol **Other information**
Full citation Parikh,N.A., Kennedy,K.A., Lasky,R.E., McDavid,G.E., Tyson,J.E., Pilot randomized trial of hydrocortisone in ventilator-dependent extremely preterm infants: effects on regional brain volumes, Journal of Pediatrics, 162, 685-690, 2013 **Ref Id**	**Sample size** Please see Doyle et al 2014 (late administration of corticosteroids) cochrane systematic review **Characteristics** **Inclusion criteria** **Exclusion criteria**	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
325938 **Country/ies where the study was carried out** **Study type** **Aim of the study** **Study dates** **Source of funding**					
Full citation Peltoniemi, O. M., Lano, A., Yliherva, A., Kari, M. A., Hallman, M., Randomised trial of early neonatal hydrocortisone demonstrates potential undesired effects on neurodevelopment at preschool age, 105, 159-164, 2016 **Ref Id**	**Sample size** See Peltoniemi 2005 **Characteristics** See Peltonniemi 2005 **Inclusion criteria** See Peltoniemi 2005	**Interventions** See Peltoniemi 2005	**Details** **Methods:** Randomisation: See Peltoniemi 2005 Allocation concealment: See Peltoniemi 2005 Blinding of participants and personnel: See Peltoniemi 2005 Blinding of outcome assessment: The	**Results** Outcome: Cerebral palsy at 5-7 years of age (**denominator = population at follow-up)** Hydrocortisone: 2/17; control 0/18 Outcome: Hearing loss at 5-7 years of age (**denominator = population at follow-up)** Hydrocortisone: 1/17; control: 0/18	**Limitations** Risk of bias assessed using Cochrane risk of bias tool Random sequence generation: unclear risk (random allocation in each centre using identical coded syringes. Stratified by birth weight [501g to 750g vs 750g to 999g vs 1000g to 1250g])

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
443280 **Country/ies where the study was carried out** Finland **Study type** RCT **Aim of the study** To evaluate the neurodevelopment and growth of five to seven year old children who had participated in a randomised trial of early low-dose hydrocortisone treatment to prevent bronchopulmonary dysplasia **Study dates** See Peltoniemi 2005 Dates of follow-up for this study not stipulated **Source of funding**	**Exclusion criteria** See Peltoniemi 2005		examiners were not aware of the child's post natal exposure to the study drugs. Incomplete outcome data: High risk (Complete follow-up: 72% all accounted for in both groups; hydrocortisone [group 2 died during initial study period, 2 refused to participate, 1 could not be located, 2 had language problems]; control group [3 died during initial study period, 1 refused to participate, 4 could not be located]) Selective reporting: unclear risk (unable to find published protocol)	Outcome: Blindness at 5-7 years of age (**denominator = population at follow-up)** Hydrocortisone: 0/17; control: 0/18 Outcome: Mild speech and language abnormality at 5-7 years of age (defined as scores of between -1-2 SD on the Reynell Development Language Scale III [RDS III] using both expressive and receptive langauge skills as well as total RDLS III performance, **denominator = population at follow-up**) Hydrocortisone: 3/17; Control: 5/17 Outcome: Severe speech and language abnormality at 5-7 years of age (defined as scores of between >-2 SD on the Reynell Development Language Scale III [RDS III] using both expressive and receptive langauge skills as well as total RDLS III performance, **denominator = population at follow-up**) Hydrocortisone: 5/17; control: 2/17 Outcome: Mentally retarded - Cognitive development at 5-7 years of age (using	Allocation concealment: low risk (allocation concealment: yes) Blinding of participants and personnel all outcomes: low risk (blinding of intervention: yes) Blinding of outcome measures all outcomes: low risk (The examiners were not aware of the child's post natal exposure to the study drugs) Incomplete outcome data all data: high risk (**Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Foundation of paediatric research, the alma and K.A Snellman foundation (Oulu, Finland)				Weschsler Primary and Preschool scales of Intelligence -revised [WPPSI-R] for functional IQ, defined as a score <69, **denominator = population at follow-up**) Hydrocortisone: 2/17; control; 1/17	
Full citation Rastogi,A., Akintorin,S.M., Bez,M.L., Morales,P., Pildes,R.S., A controlled trial of dexamethasone to prevent bronchopulmonary dysplasia in surfactant-treated infants, Pediatrics, 98, 204-210, 1996 **Ref Id** 253867 **Country/ies where the study was carried out** **Study type**	**Sample size** Please see Doyle et al 2014 (early administration of corticosteroids) cochrane systematic review **Characteristics** **Inclusion criteria** **Exclusion criteria**	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study **Study dates** **Source of funding**					
Full citation Romagnoli, C, Vento, G, Zecca, E, Tortorolo, L, Papacci, P, De, Cp, Maggio, L, Tortorolo, G, A controlled trial of dexamethasone in preterm infants at risk of chronic lung disease: <ORIGINAL> IL DESAMETAZONE NELLA PREVENZIONE DELLA PATOLOGIA POLMONARE CRONICA DEL NEONATO PRETERMINE: STUDIO PROSPETTICO RANDOMIZZATO, Rivista Italiana Di	**Sample size** Please see Doyle et al 2014 (late administration of corticosteroids) cochrane systematic review **Characteristics** **Inclusion criteria** **Exclusion criteria**	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Pediatria, 24, 283-8, 1998 **Ref Id** 619868 **Country/ies where the study was carried out** **Study type** **Aim of the study** **Study dates** **Source of funding**					
Full citation Romagnoli,C., Zecca,E., Luciano,R., Torrioli,G., Tortorolo,G., A three year follow up of preterm infants after moderately early treatment with dexamethasone, Archives of Disease in	**Sample size** Folllow-up study to Romagnoli 1998. Please see Doyle et al 2014 (late administration of corticosteroids) cochrane systematic review	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Childhood Fetal and Neonatal Edition, 87, F55-F58, 2002 **Ref Id** 253885 **Country/ies where the study was carried out** **Study type** **Aim of the study** **Study dates** **Source of funding**	**Characteristics** **Inclusion criteria** **Exclusion criteria**				
Full citation Romagnoli,C., Zecca,E., Vento,G., De Carolis,M.P., Papacci,P., Tortorolo,G., Early postnatal dexamethasone for the prevention of chronic	**Sample size** Please see Doyle et al 2014 (early administration of corticosteroids) cochrane systematic review **Characteristics**	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
lung disease in high-risk preterm infants, Intensive Care Medicine, 25, 717-721, 1999 **Ref Id** 254006 **Country/ies where the study was carried out** **Study type** **Aim of the study** **Study dates** **Source of funding**	**Inclusion criteria** **Exclusion criteria**				
Full citation Shinwell, E. S., Dollberg, S., Arbel, E., Goldberg, M., Gur, I., Naor, N., Sirota, L., Mogilner, S., Zaritsky, A., Barak, M., Gottfried, E., Karplus, M.,	**Sample size** Follow-up study to Shinwell 1996. Please see Doyle et al 2014 (early administration of corticosteroids) cochrane systematic review	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Reich, D., Weintraub, Z., Blazer, S., Bader, D., Yurman, S., Dolfin, T., Kogan, A., Early postnatal dexamethasone treatment and increased incidence of cerebral palsy, Archives of Disease in Childhood: Fetal and Neonatal Edition, 83, F177-F181, 2000 **Ref Id** 336891 **Country/ies where the study was carried out** **Study type** **Aim of the study** **Study dates** **Source of funding**	**Characteristics** **Inclusion criteria** **Exclusion criteria**				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Shinwell,E.S., Karplus,M., Zmora,E., Reich,D., Rothschild,A., Blazer,S., Bader,D., Yurman,S., Dolfin,T., Kuint,J., Milbauer,B., Kohelet,D., Goldberg,M., Armon,Y., Davidson,S., Sirota,L., Amitai,M., Zaretsky,A., Barak,M., Gottfried,S., Failure of early postnatal dexamethasone to prevent chronic lung disease in infants with respiratory distress syndrome, Archives of Disease in Childhood Fetal and Neonatal Edition, 74, F33-F37, 1996 **Ref Id** 254060 **Country/ies where the study was carried out** **Study type**	**Sample size** Please see Doyle et al 2014 (early administration of corticosteroids) cochrane systematic review **Characteristics** **Inclusion criteria** **Exclusion criteria**	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study **Study dates** **Source of funding**					
Full citation Stark, A. R., Carlo, W. A., Tyson, J. E., Papile, L. A., Wright, L. L., Shankaran, S., Donovan, E. F., Oh, W., Bauer, C. R., Saha, S., Poole, W. K., Stoll, B. J., National Institute of Child, Health, Human Development Neonatal Research, Network, Adverse effects of early dexamethasone treatment in extremely-low-birth-weight infants. National Institute of Child Health and Human Development Neonatal Research Network, New England Journal of	**Sample size** Please see Doyle et al 2014 (early administration of corticosteroids) cochrane systematic review **Characteristics** **Inclusion criteria** **Exclusion criteria**	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Medicine, 344, 95-101, 2001 **Ref Id** 619922 **Country/ies where the study was carried out** **Study type** **Aim of the study** **Study dates** **Source of funding**					
Full citation Tapia,J.L., Ramirez,R., Cifuentes,J., Fabres,J., Hubner,M.E., Bancalari,A., Mercado,M.E., Standen,J., Escobar,M., The effect of early dexamethasone	**Sample size** Please see Doyle et al 2014 (early administration of corticosteroids) cochrane systematic review **Characteristics**	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
administration on bronchopulmonary dysplasia in preterm infants with respiratory distress syndrome, Journal of Pediatrics, 132, 48-52, 1998 **Ref Id** 254245 **Country/ies where the study was carried out** **Study type** **Aim of the study** **Study dates** **Source of funding**	**Inclusion criteria** **Exclusion criteria**				
Full citation Vermont Oxford Network Steroid Study, Group, Early postnatal	**Sample size** Follow-up study to Soll 1999. Please see Doyle et al 2014 (early administration	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
dexamethasone therapy for the prevention of chronic lung disease, Pediatrics, 108, 741-8, 2001 **Ref Id** 619973 **Country/ies where the study was carried out** **Study type** **Aim of the study** **Study dates** **Source of funding**	of corticosteroids) cochrane systematic review **Characteristics** **Inclusion criteria** **Exclusion criteria**				
Full citation Walther,F.J., Findlay,R.D., Durand,M., Adrenal suppression and extubation rate after moderately early low-	**Sample size** Please see Doyle et al 2014 (late administration of corticosteroids) cochrane systematic review	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
dose dexamethasone therapy in very preterm infants, Early Human Development, 74, 37-45, 2003 **Ref Id** 253891 **Country/ies where the study was carried out** **Study type** **Aim of the study** **Study dates** **Source of funding**	**Characteristics** **Inclusion criteria** **Exclusion criteria**				
Full citation Watterberg,K.L., Gerdes,J.S., Cole,C.H., Aucott,S.W., Thilo,E.H., Mammel,M.C., Couser,R.J.,	**Sample size** Please see Doyle et al 2014 (early administration of corticosteroids) cochrane systematic review	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Garland,J.S., Rozycki,H.J., Leach,C.L., Backstrom,C., Shaffer,M.L., Prophylaxis of early adrenal insufficiency to prevent bronchopulmonary dysplasia: a multicenter trial, Pediatrics, 114, 1649-1657, 2004 **Ref Id** 209223 **Country/ies where the study was carried out** **Study type** **Aim of the study** **Study dates** **Source of funding**	**Characteristics** **Inclusion criteria** **Exclusion criteria**				
Full citation	**Sample size**	**Interventions**	**Details**	**Results**	**Limitations**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Watterberg,K.L., Gerdes,J.S., Gifford,K.L., Lin,H.M., Prophylaxis against early adrenal insufficiency to prevent chronic lung disease in premature infants, Pediatrics, 104, 1258-1263, 1999 **Ref Id** 87841 **Country/ies where the study was carried out** **Study type** **Aim of the study** **Study dates** **Source of funding**	Please see Doyle et al 2014 (early administration of corticosteroids) cochrane systematic review **Characteristics** **Inclusion criteria** **Exclusion criteria**				**Other information**
Full citation	**Sample size**	**Interventions**	**Details**	**Results**	**Limitations**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Watterberg,K.L., Shaffer,M.L., Mishefske,M.J., Leach,C.L., Mammel,M.C., Couser,R.J., Abbasi,S., Cole,C.H., Aucott,S.W., Thilo,E.H., Rozycki,H.J., Lacy,C.B., Growth and neurodevelopmental outcomes after early low-dose hydrocortisone treatment in extremely low birth weight infants, Pediatrics, 120, 40-48, 2007 **Ref Id** 209225 **Country/ies where the study was carried out** **Study type** **Aim of the study** **Study dates**	Follow-up study to Watterberg 2004. Please see Doyle et al 2014 (early administration of corticosteroids) cochrane systematic review **Characteristics** **Inclusion criteria** **Exclusion criteria**				**Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding					
Full citation Stark, A. R., Carlo, W. A., Vohr, B. R., Papile, L. A., Saha, S., Bauer, C. R., Oh, W., Shankaran, S., Tyson, J. E., Wright, L. L., Poole, W. K., Das, A., Stoll, B. J., Fanaroff, A. A., Korones, S. B., Ehrenkranz, R. A., Stevenson, D. K., Peralta-Carcelen, M., Wilson-Costello, D. E., Bada, H. S., Heyne, R. J., Johnson, Y. R., Lee, K. G., Steichen, J. J., Death or neurodevelopmental impairment at 18 to 22 months corrected age in a randomized trial of early dexamethasone to prevent death or chronic lung disease in extremely low birth weight infants, Journal of Pediatrics, 164, 34-39.e2, 2014	**Sample size** Follow-up study to Stark 2001. Please see Doyle et al 2014 (early administration of corticosteroids) cochrane systematic review **Characteristics** **Inclusion criteria** **Exclusion criteria**	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ref Id 414988 **Country/ies where the study was carried out** **Study type** **Aim of the study** **Study dates** **Source of funding**					
Full citation Wilson,T.T., Waters,L., Patterson,C.C., McCusker,C.G., Rooney,N.M., Marlow,N., Halliday,H.L., Neurodevelopmental and respiratory follow-up results at 7 years for children from the United Kingdom and Ireland	**Sample size** Follow-up study to Halliday 2001. Please see Onland 2017 Cochrane systematic review **Characteristics** **Inclusion criteria**	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
enrolled in a randomized trial of early and late postnatal corticosteroid treatment, systemic and inhaled (the Open Study of Early Corticosteroid Treatment), Pediatrics, 117, 2196-2205, 2006 **Ref Id** 325933 **Country/ies where the study was carried out** **Study type** **Aim of the study** **Study dates** **Source of funding**	**Exclusion criteria**				
Full citation Baud, O., Trousson, C., Biran, V., Leroy, E.,	**Sample size** See Baud 2016	**Interventions** See Baud 2016	**Details** **Methods** Randomisation: Randomisation was	**Results** Neurodevelopmental outcome: Cerebral	**Limitations** **Quality of study:**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Mohamed, D., Alberti, C., Association Between Early Low-Dose Hydrocortisone Therapy in Extremely Preterm Neonates and Neurodevelopmental Outcomes at 2 Years of Age, JamaJama, 317, 1329-1337, 2017 **Ref Id** 664038 **Country/ies where the study was carried out** France **Study type** RCT **Aim of the study** To assess whether early hydrocortisone therapy in extremely preterm infants is associated with neurodevelopmental impairment at 2 years of age	**Characteristics** See Baud 2016 **Inclusion criteria** See Baud 2016 **Exclusion criteria** See Baud 2016		generated electronically with nQuery (verion 6.01). Allocation concealment: Treatment assignment was done with a secure study website (Cleanweb Telemedicine Technologies, Boulogne-Billancourt, France) after verification of eligibility and consent status. Randomisation was stratified by gestational age (2 groups: 24-25 weeks and 26-27 weeks of gestation). Blinding: The appearance of hydrocortisone and placebo vials was strictly identical, and patient information and treatment groups were masked from all participants in the research (i.e parents, nurses, and physicians). All revised brunet-lezine	palsy (**denominator = population at follow-up)** Hydrocortisone: 12/194; Placebo: 10/185 Neurodevelopmental outcome: Global developmental quotient score (using revised Brunet-Lezine [RBL] scale, **denominator = population at follow-up**) >85 (no disability) Hydrocortisone: 121/158; Placebo: 110/146 70-84 (mild disability) Hydrocortisone: 30/158; Placebo: 25/146 <70 (moderate to severe disability) Hydrocortisone: 7/158; Placebo: 11/146 Neurodevelopmental outcome: Severe auditory impairment (**denominator = population at follow-up)** No children deaf Neurodevelopmental outcome: Severe visual impairment (**denominator = population at follow-up)** No children blind	Risk of bias assessed using Cochrane risk of bias tool Random sequence generation: Low risk (Randomisation was generated electronically with nQuery (verion 6.01) a computer generated randomisation tool) Allocation concealment: Lows risk (Treatment assignment was done with a secure study website [Cleanweb Telemedicine Technologies, Boulogne-Billancourt, France] after verification of eligibility and consent status. Randomisation was stratified by gestational age [2 groups: 24-25 weeks and 26-27 weeks of gestation]) Blinding of participants and personnel: Low risk (The appearance of hydrocortisone and placebo vials was strictly identical) Blinding of outcome assessment: Low risk (patient information and

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates See Baud 2016 Neurodevelopmental assessments 2010-2016 **Source of funding** See Baud 2016			(RBL) examiners were unaware of treatment assignment, which remained masked throughout the follow-up period Attrition: ITT analysis (complete follow-up: no, for cerebral palsy, hearing and visual impairment, 24% drop out rate for hydrocortisone and 30% drop out rate for placebo [patients lost to follow-up not explained, only deaths]; for RBL assessment additional 14% in the hydrocortisone were not assessed due to infants unable to be tested due to severity or parents missed the appointment and 15% in the placebo group were not assessed due to infants unable to be tested due to severity or parents missed the appointment)		treatment groups were masked from all participants in the research [i.e parents, nurses, and physicians]. All revised brunet-lezine [RBL] examiners were unaware of treatment assignment, which remained masked throughout the follow-up period) Incomplete outcome data: High risk (ITT analysis. Complete follow-up: almost all >90% in survivors for cerebral palsy, hearing and visual impairment; for RBL assessment additional only 76% in the hydrocortisone were assessed due to infants unable to be tested due to severity or parents missed the appointment and only 73% in the placebo group were assessed due to infants unable to be tested due to severity or parents missed the appointment) Selective reporting: Low risk (All outcomes in the

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			Selective reporting: All outcomes in the protocol reported in the full RCT **Outcomes** Neurdevelopmental outcomes (18 months-3 years)		protocol reported in the full RCT) Other bias: None reported **Other information**
Full citation Anttila, E., Peltoniemi, O., Haumont, D., Herting, E., ter Horst, H., Heinonen, K., Kero, P., Nykanen, P., Oetomo, S. B., Hallman, M., Early neonatal dexamethasone treatment for prevention of bronchopulmonary dysplasia. Randomised trial and meta-analysis evaluating the duration of dexamethasone therapy, European Journal of Pediatrics, 164, 472-81, 2005 **Ref Id** 510451	**Sample size** Please see Doyle et al 2014 (early administration of corticosteroids) cochrane systematic review **Characteristics** **Inclusion criteria** **Exclusion criteria**	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out **Study type** **Aim of the study** **Study dates** **Source of funding**					
Full citation Peltoniemi, O., Kari, M. A., Heinonen, K., Saarela, T., Nikolajev, K., Andersson, S., Voutilainen, R., Hallman, M., Pretreatment cortisol values may predict responses to hydrocortisone administration for the prevention of bronchopulmonary dysplasia in high-risk	**Sample size** Please see Doyle et al 2014 (early administration of corticosteroids) cochrane systematic review **Characteristics** **Inclusion criteria** **Exclusion criteria**	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
infants, The Journal of pediatrics, 146, 632-7, 2005 **Ref Id** 461589 **Country/ies where the study was carried out** **Study type** **Aim of the study** **Study dates** **Source of funding**					
Full citation Peltoniemi, O. M., Lano, A., Puosi, R., Yliherva, A., Bonsante, F., Kari, M. A., Hallman, M., Trial of early neonatal hydrocortisone: Two-year	**Sample size** Follow-up study to Peltoniemi 2005. Please see Doyle et al 2014 (early administration of corticosteroids) cochrane systematic review	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
follow-up, Neonatology, 95, 240-247, 2009 **Ref Id** 347302 **Country/ies where the study was carried out** **Study type** **Aim of the study** **Study dates** **Source of funding**	**Characteristics** **Inclusion criteria** **Exclusion criteria**				
Full citation Subhedar,N.V., Ryan,S.W., Shaw,N.J., Open randomised controlled trial of inhaled nitric oxide and early dexamethasone in high risk preterm infants, Archives of Disease in	**Sample size** Please see Doyle et al 2014 (early administration of corticosteroids) cochrane systematic review **Characteristics**	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Childhood Fetal and Neonatal Edition, 77, F185-F190, 1997 **Ref Id** 254144 **Country/ies where the study was carried out** **Study type** **Aim of the study** **Study dates** **Source of funding**	**Inclusion criteria** **Exclusion criteria**				

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Clinical evidence tables for question 3.5 What is the safety and effectiveness of diuretics in preterm babies on respiratory support?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Hoffman, D. J., Gerdes, J. S., Abbasi, S., Pulmonary function and electrolyte balance following spironolactone treatment in preterm infants with chronic lung disease: a double-blind, placebo-controlled, randomized trial, Journal of Perinatology, 20, 41-5, 2000 **Ref Id** 410667 **Country/ies where the study was carried out** USA **Study type** Randomised controlled trial	**Sample size** n=33 preterm babies 26-36 weeks PMA Spironolactone n=17; Placebo n=16 **Characteristics** Birthweight in g (SD): chlorothiazide + spironolactone = 838 (±204); chlorothiazide + placebo = 859 (±160) Study weight in g (SD): chlorothiazide + spironolactone = 1357 (±370); chlorothiazide + placebo = 1438 (±323) Gestational age in weeks (SD): chlorothiazide + spironolactone = 26.1 (±1.4); chlorothiazide + placebo = 26.2 (±1.7) Apgar score at 5 minutes: chlorothiazide + spironolactone = 7; chlorothiazide + placebo = 7	**Interventions** 1. Chlorothiazide 20mg/kg per dose orally twice daily and spironolactone 1.5mg/kg per dose orally twice daily 2. Chlorothiazide same dose as above and placebo *2/52 study period	**Details** Randomisation: No details Allocation concealment: Only pharmacists were aware of the randomisation schedule Blinding: To mask the identities of of either spironolactone or placebo, the order was written for "chlorothiazide" and "study medication", respectively. The placebo and spironolactone doses were prepared in identical unit aliquots with equal volumes and colours of the solutions. Attrition: No drop-outs Statistical analysis: A power analysis, performed during the KCL supplementation	**Results** Outcome: Hyponatraemia (sodium supplementation required when sodium level less than 130mEq/L) chlorothiazide + spironolactone: 11/17; chlorothiazide + placebo: 7/16	**Limitations** **Quality of study:** Risk of bias assessed using Cochrane risk of bias tool Random sequence generation: Unclear risk (no details reported) Allocation concealment: Low risk (Only pharmacists were aware of the randomisation schedule) Blinding of participants and personnel: Low risk (To mask the identities of of either spironolactone or placebo, the order was written for "chlorothiazide" and "study medication", respectively. The placebo and spironolactone doses were prepared in identical unit aliquots with equal volumes and colours of the solutions)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study To study the effect of spironolactone on dietary electrolyte supplementation, pulmonary function, and electrolyte imbalance in premature infants with chronic lung disease. **Study dates** Not reported **Source of funding** Newborn Pediatrics Research Fund. The main author was supported in part by a training grant from the NIH	**Inclusion criteria** Eligibility criteria were: the presence of chronic lung disease (defined as oxygen dependency beyond 28 days of life coexisting with characteristic radiographic abnormalities), the establishment of enteral feeding, and the decision by the attending physician to prescribe oral diuretics **Exclusion criteria** Infants were excluded from the study if at the time of enrollment that they were receiving the early portion of a course of dexamethasone (0.1 to 0.5 mg/kg per day), hyperalimentation, intravenous fluids, or frusemide, or if renal anomalies were known.		for infants who received the combination of chlorothiazide and spironolactone (spironolactone group) and those that received chlorothiazide and placebo (placebo group). The two treatments would have been considered equivalent with regard to the need for potassium supplementation if the difference between the 2 groups was not >25%. A minimum of 15 infants in each group was required to test this hypothesis with 80% power and a significance level of 0.05. Two way t-tests were used to compare each experimental variable.		Blinding of outcome assessment: Low risk (To mask the identities of of either spironolactone or placebo, the order was written for "chlorothiazide" and "study medication", respectively. The placebo and spironolactone doses were prepared in identical unit aliquots with equal volumes and colours of the solutions) Incomplete outcome data: Low risk (no dropouts) Selective reporting: Low risk (All outcomes reported) Other bias: None reported **Other information**
Full citation	**Sample size**	**Interventions**	**Details**	**Results**	**Limitations**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Kao, L. C., Durand, D. J., McCrea, M. R. C., Birch, M., Powers, R. J., Nickerson, B. G., Randomized trial of long-term diuretic therapy for infants with oxygen-dependent bronchopulmonary dysplasia, Journal of Pediatrics, 124, 772-781, 1994 **Ref Id** 687685 **Country/ies where the study was carried out** USA **Study type** Randomised controlled trial **Aim of the study** To determine whetehr long-term oral diuretic therapy would improve	n=49 enrolled n=43 (n=6 not included in analysis, n=5 requested code to be broken, n=1 moved out of state) Diuretic n=22; placebo n=21 **Characteristics** Male/female subjects: diuretic = 17/5; placebo = 14/7 Received surfactant: diuretic = 7 (32%); placebo = 7 (33%) Birthweight in kg (SD): diuretic = 0.96 (±0.4); placebo = 1.03 (±0.58) Gestational age in weeks (SD): diuretic = 28 (±3); 28 (±4) Duration of ventilation in weeks (SD): diuretics = 8.7 (±4.3); 8.4 (±3.9) Treated with steroids for BPD: diuretics = 9; placebo = 7 Age at study entry in weeks (SD): diuretics = 12.1 (±3.9); placebo = 11.1 (+4)	1. Diuretic group: chlorothiazide 40mg/kg per day and spironolactone 4mg/kg per day by mouth 2. Placebo *All infants were clinically stable for at least 3 weeks before entry into the study. Diuretics or placebo were continued as long as the infant required supplemental oxygen. When the infants condition was stable without supplemental oxygen for 1 week, the doses were tapered for a period of 1 to 2 weeks and then discontinued.	Randomisation: No details Allocation concealment: Only one investigator (DJD) knew whether a patient was assigned to the diuretic or the placebo group; the remainder of the nursery staff remained uninformed until the entire study was completed. Blinding: Infants in the placebo group received medications dispensed in bottles, with volume and dosage identical to those for the diuretics. Attrition: 6 drop outs Statistical analysis: Dichotomous variables were analysed with the Fisher Exact Test. Parametric variables were compared between the diuretic and placebo group by means of the two-tailed unpaired	Outcome: Nephrocalcinosis (1 year postterm corrected age) Diuretic group = 7/22; Placebo group = 5/21 Outcome: Duration of oxygen supplementation days Diuretic group: 133 (±53); Placebo group: 147 (±71) Outcome: Hearing loss (1 year postterm corrected age) Diuretic group: 2/22; placebo group: 1/21 Outcome: Supplemental electrolytes (given if sodium was less than 125 mmol/L or potassium <2.8 mmol/L) Diuretic group: 2/22; placebo group: 0/21	**Quality of study:** Risk of bias assessed using Cochrane risk of bias tool Random sequence generation: Unclear risk (no details reported) Allocation concealment: Unclear risk (Unclear the involvement of DJD in the study) Blinding of participants and personnel: Unclear risk (Unclear the involvement of DJD in the study) Blinding of outcome assessment: Unclear risk (no details reported) Incomplete outcome data: High risk (43/49 participants finished the study) Selective reporting: Low risk (All outcomes reported) Other bias: None reported **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
the pulmonary function of preterm infants with bronchopulmonary dysplasia **Study dates** June 1989-June 1992 **Source of funding** Not reported	**Inclusion criteria** Infants were eligible for the study if they had the typical radiographic appearance of Northway stage III or IV BPD, had received mechanicl ventilatory support for more than 1 month, were stable after extubation for more than 1 wee, weighed more than 1.5kg, and required supplemental oxygen with a fraction of inspired oxygen of 0.3-0.5. **Exclusion criteria** Rib cage deformities, congenital heart disease, or chromosomal abnormalities.		student t test. Changes in parametric variables with time were analysed with one-way analysis of variance, with the student-newman-keuls post hoc test		Infants in both groups received furosemide at any one time the attending physician thought that the therapy was clinically indicated. 3/22 infants from the diuretic group and 9/21 infants from the placebo group received at least one dose of furosemide. Significantly more infants in the placebo group received more than 10 doses of furosemide.
Full citation Laughon, M. M., Chantala, K., Aliaga, S., Herring, A. H., Hornik, C. P., Hughes, R., Clark, R. H.,	**Sample size** n=107,542 Exposed to diuretic: 39,357; Not exposed to diuretic: 68,185	**Interventions** 1. Cohort exposed to at least 1 diuretic (acetazolamide, amiloride, bumetanide, chlorthiazide, diazoxide,	**Details** Statistical analysis Standard summary statistics were used to describe demographic characteristics;	**Results** Outcome: Hyponatraemia (<125 mmol/L) Furosemide = 1.8 per 1000 infant days; Any	**Limitations** Quality of Study Risk of bias assessed using Newcastle-Ottawa tool for cohort studies **Selection**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Smith, P. B., Diuretic exposure in premature infants from 1997 to 2011, American Journal of Perinatology, 32, 49-56, 2015 **Ref Id** 687725 **Country/ies where the study was carried out** USA **Study type** Retrospective cohort study **Aim of the study** Diuretics are often prescribed off-label to premature infants, particularly to prevent or treat BPD. This study examined their use and safety in this group.	**Characteristics** Gestational age weeks (%): <23 weeks: exposed = 150 (<1); not exposed = 498 (1) 23-34 weeks: exposed = 6697 (17); not exposed = 6441 (10) 25-26 weeks: exposed = 12,537 (32); not exposed = 9523 (14) 27-28 weeks: exposed = 11,892 (30); not exposed = 17,346 (25) 29-30 weeks: exposed = 6728 (17); not exposed = 24,501 (36) 31-32 weeks: exposed = 1353 (3); not exposed = 9876 (15) Birthweight grams (%): <1000: exposed = 25,975 (66); not exposed 25,371 (37) >100-1500: exposed = 13,382 (34); not exposed = 42,814 (63) Antenatal steroids (%): exposed = 29,207 (74); 50,023 (73)	ethacrynic acid, furosemide, hydrochlorothiazide, amnnitol, metolazone, spironolactone) 2. Cohort exposed to diuretic *Furosemide most commonly used diuretic. Next most commonly used diuretics were spironolactone, chlorothiazide, hydrochlorothiazide, bumetanide, and acetazolamide. The most common combinations of diuretics were: frusemide plus spironolactone (40 per 1000 infants); follwoed by furosemide plus chlorothiazide (36 per 1000 infants), then chlorothiazide plus spironolactone (36 per 1000 infants)	continuous variables are presented as median, and categorical variables are presented as counts. Laboratory AEs and SAEs were described at the infant day level (number of days with abnormal laboratory values/1000 infant days exposed to diuretics). The proportion of infants exposed to diuretics by the total number of infants discharged from the Pediatrix Medical Group in the same year. The proportion of infants exposed to diuretics by the total number of infants of the same GA. The proportion of infants exposed to diuretics by NICU is calculated by dividing the number of infants exposed to diuretics by the total number of infants discharged	diuretic = 2.9 per 1000 infant days Outcome: Severe hyponatraemia (<115 mmol/L) Frusemide = 0.1 per 1000 infant days; Any diuretic = 0.1 per 1000 infant days	1) Representativeness of the exposed cohort a) Truly representative (one star) 2) Selection of the non-exposed cohort a) Drawn from the same community as the exposed cohort (one star) 3) Ascertainment of exposure a) Secure record (Pediatrix medical group database) (one star) 4) Demonstration that outcome of interest was not present at start of study b) No (retrospective cohort study) **Comparability** 1) Comparability of cohorts on the basis of the design or analysis controlled for confounders c) Cohorts are not comparable on the basis of the design or analysis controlled for confounders

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates 1997-2011 **Source of funding** Not reported	Male sex (%): exposed = 21,821 (56); not exposed = 33,752 (50) **Inclusion criteria** <32 weeks gestational age and <1500g birthweight discharged from 1 of the 333 NICUs managed by the Padiatrix Medical Group between 1997 and 2011 who were exposed to at least diuretic of interest (acetazolamide, amiloride, bumetanide, chlorthiazide, diazoxide, ethacrynic acid, furosemide, hydrochlorothiazide, amnnitol, metolazone, spironolactone). **Exclusion criteria** Not reported		from each NICU during the study period. All statistical analyses were performed in STATA 12.0		**Outcome** 1) Assessment of outcome b) Record linkage (one star) 2) Was follow-up long enough for outcomes to occur a) Yes (hyponatraemia does not need a long duration of follow-up to capture, usually evident quite soon after starting treatment) (one star) 3) Adequacy of follow-up cohorts d) No statement - retrospective design **Overall quality** Poor quality due to 0 stars in comparability domain **Other information**

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Clinical evidence tables for question 3.6 What is the effectiveness of caffeine in preterm babies requiring respiratory support?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Amaro, C. M., Bello, J. A., Jain, D., Ramnath, A., D'Ugard, C., Vanbuskirk, S., Bancalari, E., Claure, N., Early Caffeine and Weaning from Mechanical Ventilation in Preterm Infants: A Randomized, Placebo-Controlled Trial, Journal of pediatrics, 06, 06, 2018 **Ref Id** 804202 **Country/ies where the study was carried out** US **Study type** Single-centre, double-blind,	**Sample size** n= 83 Caffeine=41; Control=42 **Characteristics** Caffeine, n=41 Birth weight, g, median (IQR)= 25.7 (24.3-27.0) Gestational age, weeks, median (IQR)= 670 (605-915) Antenatal steroids, n (%)= 37 (90) 5-minute Apgar score of < 5, n (%)= 10 (24) Received surfactant, n (%)= 39 (95) Control, n=42 Birth weight, g, median (IQR)= 26.1 (24.2-28.4) Gestational age, weeks, median (IQR)= 720 (643-894) Antenatal steroids, n (%)= 40 (95) 5-minute Apgar score of < 5, n (%)= 4 (9.5) Received surfactant, n (%)= 40 (95)	**Interventions** Early caffeine versus control Early caffeine: loading dose of caffeine citrate 20 mg/kg followed by a maintenance dose of 5 mg/kg/day. Infants in the early caffeine group received a blinded loading dose of placebo before extubation. Control: an equivalent volume of normal saline bolus and maintenance. Infants in the control group received a blinded loading dose of caffeine citrate 20 mg/kg before extubation, as is routinely done in this NICU. After extubation, clinical teams considered reintubation only if the infant met ≥1 of the	**Details** Randomisation: not reported Allocation concealment: allocation determined through sealed, opaque envelopes Blinding: Investigators and the clinical team were blind to treatment assignment Attrition: Intention to treat; no attrition Statistical analysis: Categorical variables were compared by the Pearson X^2 or Fisher exact test. Continuous variables were compared by the Student t test or Mann-Whitney U test, depending on the distribution. The Kaplan-Meier log-rank test was used to compare time-to-event variables, such as age at first successful extubation. P < .05 was considered statistically significant. Outcomes: Primary endpoint was age at first successful extubation; secondary endpoints included BPD, defined as requiring oxygen at 28 days of age or 35 weeks, mortality prior to discharge, necrotising enterocolotis, defined as Bell's stage II or III, successful extubation, defined as remaining extubated for > 24 hours	**Results** Outcome: Mortality prior to discharge, n (%) Caffeine= 9/41; Control= 5/42 Outcome: BPD at 28 days or 36 weeks PMA Caffeine= 15/41; Control= 20/42 Outcome: Failed extubation and required reintubation within 24 hours Caffeine= 8/41; Control=8/42 Outcome: NEC Caffeine= 7/41; Control= 2/42	**Limitations** Risk of bias assessing using Cochrane risk of bias tool Random sequence generation: Unclear risk (method of randomisation not reported) Allocation concealment: Low risk (sealed, opaque envelopes) Blinding of participants and personnel: Low risk (investigators and clinical team blinded to treatment allocation throughout trial) Blinding of outcome assessment: Low risk (study personnel blind to treatment allocation; clear guidelines reported and followed for reintubation) Selective reporting:

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
placebo-controlled, RCT **Aim of the study** The aim of the study was to assess the effect of early caffeine on the age of the first successful extubation in preterm babies. **Study dates** January 2013 to December 2015 **Source of funding** Not reported	**Inclusion criteria** • 23-30 weeks gestation • Required mechanical ventilation in the first 5 post-natal days **Exclusion criteria** • Major congenital anomalies • Small for gestational age (birth weight <3rd percentile)	following criteria: ≥2 episodes of severe apnea or bradycardia requiring bag-mask ventilation in a 4-hour period, an increase in FiO_2 of >0.2 above the pre-extubation baseline and of >0.5, or an increase in $PaCO_2$ of >15 mm Hg above the pre-extubation baseline and of >70 mm Hg. Enrolled infants were followed until 36 weeks postmenstrual age, discharge, or death, whichever came first.			Low risk (all outcomes reported in Methods reported in Results) Other bias: Low risk **Other information**
Full citation Borszewska-Kornacka, M. K., Hozejowski, R., Rutkowska, M.,	**Sample size** n=286 Early=143; Late=143	**Interventions** Early caffeine administration versus late caffeine administration	**Details** Data collection: The study is a retrospective cohort study of the NeoPro study, which was a non-interventional, observational study and aimed at assessing adherence to the European	**Results** Outcome: Mortality prior to discharge, n/N Early=12/143; Late=12/143	**Limitations** Risk of bias assessed using the Newcastle-Ottawa Quality Assessment Scale for Cohort Studies

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Lauterbach, R., Shifting the boundaries for early caffeine initiation in neonatal practice: Results of a prospective, multicenter study on very preterm infants with respiratory distress syndrome, Plos one, 12 (12) (no pagination), 2017 **Ref Id** 804233 **Country/ies where the study was carried out** Poland **Study type** Retrospective cohort study **Aim of the study** The aim of the study was to compare outcomes in preterm	**Characteristics** Early, n=143 Birth weight, g, mean (SD)=1174 (357) Gestational age, weeks, mean (SD)=28.6 (2.1) Antenatal steroids, n (%)=106 (74.1) 5-minute Apgar score, mean (SD)=6.6 (2.1) Late, n=143 Birth weight, g, mean (SD)=1168 (406) Gestational age, weeks, mean (SD)=28.5 (2.4) Antenatal steroids, n (%)=106 (74.1) 5-minute Apgar score, mean (SD)=6.5 (6.5) **Inclusion criteria** Gestational age ≤ 32 weeks, diagnosis of RDS regardless of the severity of radiological findings on chest X-ray, need for surfactant treatment **Exclusion criteria**	Early: Caffeine citrate was administered during the first 24 hours after birth Late: Caffeine citrate was administered on the second day of life or after	Guidelines on the Management of RDS in neonatal departments in Poland. Statistical analysis: The study used propensity score matching (PSM) to adjust for the affects of baseline characteristic difference between treatment groups. PSM mimics the randomisation process whereby participants in each treatment arm are matched based on baseline covariates, allowng for the selection of a control group that is similar to the intervention group. The variables used to match the two arms were age, gestational age, birth weight, inborn/outborn, mode of delivery, 5-minute APGAR score, use of antenatal steroids and need for intubation in the delivery room. The nearest neighbour without replacement method was used. A standard deviation to 0.05 of the standard deviation of the propensity score was used. Two-sided Student's t-test or U-Mann-Whitney tests were used to assess differences between independent variables. Dichotomous variables were assessed using Yate's continuity corrected chi-square test or Fisher's exact test. A p-value of 0.05 was considered significant. Follow up: Not reported Primary outcomes: Incidence of BPD (oxygen dependency at 36 weeks postmenstrual age or prior to discharge), Secondary outcomes: Mortality prior to discharge	Outcome: BPD at 36 weeks PMA, n/N Early=43/143; Late= 49/143	Selection Representativeness of the exposed cohort: a) truly representative of the average preterm requiring respiratory support in the community* Selection of the non exposed cohort: a) drawn from the same community as the exposed cohort* Ascertainment of exposure: a) secure record (hospital questionnaire)* Demonstration that outcome of interest was not present at start of study: a) yes* Comparability Study controls for: Age, gestational age, birth weight, place of birth (inborn/outborn), mode of delivery, 5-minute APGAR score, use of antenatal steroids and need for

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
infants receiving early and late doses of caffeine therapy **Study dates** November 2014 to December 2015 **Source of funding** Chiesi Poland Sp. z.o.o	Presence of clinically significant congenital defects				intubation in the delivery room* Study controls for any additional factor: a) yes* Outcome Assessment of outcome: b) record linkage* Was follow-up long enough for outcomes to occur: a) yes (prior to discharge)* Adequacy of follow-up of cohorts: a) complete follow up - all subjects accounted for* **Other information**
Full citation Davis, P. G., Schmidt, B., Roberts, R. S., Doyle, L. W., Asztalos, E., Haslam, R., Sinha, S., Tin, W., Caffeine for Apnea of	**Sample size** Follow up study; see Schmidt 2006 (CAP trial 2006) for study details **Characteristics**	**Interventions**	**Details** Follow up: 18 to 21 months Outcomes: Cerebral palsy (diagnosed if the child had a nonprogressive motor impairment by abnormal muscle tone and decrease range or control of movements). Cognitive delay (MDI score < 85 on the BSID-II). Severe hearing loss (audiometry	**Results** Outcome: Cognitive delay (MDI < 85), n/N **Subgroup: Reason for treatment** Apnoea treatment	**Limitations** Risk of bias assessed using Cochrane risk of bias tool Blinding of outcome assessment: Low risk Incomplete outcome

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Prematurity Trial: Benefits May Vary in Subgroups, Journal of pediatrics, 156, 382-387.e3, 2010 **Ref Id** 804275 **Country/ies where the study was carried out** **Study type** **Aim of the study** **Study dates** **Source of funding**	**Inclusion criteria** **Exclusion criteria**		was performed to determine the presence or absence of hearing loss). Blindness was defined as corrected visual acuity less than 20/200. Subgroup analyses: subgroup analyses were performed for reasons for why the infant was considered a candidate for methylxanthine treatment i.e. to prevent apnoea, to treat apnoea, or to facilitate removal of an endotracheal tube. Stratifications were also performed on the basis of the level of respiratory support at randomisation, i.e. no respiratory support, non-invasive respiratory support, or ventilation via endotracheal tube.	Caffeine= 110/374; Placebo=117/341 Apnoea prophylaxis Caffeine=78/207; Placebo= 66/189 Pre-extubation Caffeine= 105/285; Placebo= 145/327 **Subgroup: Level of respiratory support** No PPV Caffeine=55/162; Placebo= 33/129 Non-invasive ventilation Caffeine=77/263; Placebo= 91/260 Endotracheal tube Caffeine= 161/442; Placebo= 204/468 Outcome: CP, n/N **Subgroup: Reason for treatment** Apnoea treatment Caffeine= 11/388; Placebo= 18/361 Apnoea prophylaxis	data: High risk (6.9% attrition due to death or loss to follow up) For all other areas, please see Schmidt 2006 **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Caffeine=10/215; Placebo=9/200 Pre-extubation Caffeine= 19/305; Placebo= 39/339 **Subgroup: Level of respiratory support** No PPV Caffeine=3/168; Placebo=4/138 Non-invasive ventilation Caffeine=8/273; Placebo=13/274 Endotracheal tube Caffeine=29/468; Placebo=49/488	
Full citation Dobson, N. R., Patel, R. M., Smith, P. B., Kuehn, D. R., Clark, J., Vyas-Read, S., Herring, A., Laughon, M. M., Carlton, D., Hunt, C. E., Trends in caffeine use and association between	**Sample size** n=28,706 Early=14,535; Late= 14,535 **Characteristics** Early, n=14535 Birth weight, g, median (IQR)=1055 (630-1447)	**Interventions** Early caffeine administration versus late caffeine Early caffeine: Initiation of caffeine therapy before 3 days of life Late caffeine: Initiation of caffeine	**Details** Data collection: This retrospective cohort study assessed a multi-centre dataset from the Pediatrix Medical Group, which included infants discharged from 1997 to 2919 Statistical analysis: The study authors used baseline demographic and early clinical variables to match babies babies between groups, including gestational age, birth weight, sex, race, small for	**Results** Outcome: Mortality prior to discharge, n/N Early=659/14535; Late=542/14535 Outcome: BPD at 36 weeks PMA, n/N* Early=3070/14535; Late=4154/14535	**Limitations** Risk of bias assessed using the Newcastle-Ottawa Quality Assessment Scale for Cohort Studies Selection Representativeness of the exposed cohort: a) truly representative of the

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
clinical outcomes and timing of therapy in very low birth weight infants, Journal of Pediatrics, 164, 992-998.e3, 2014 **Ref Id** 726255 **Country/ies where the study was carried out** US **Study type** Retrospective cohort study **Aim of the study** The aim of the study was to assess the effect of early administration of caffeine compared to late administration in very low birth weight infants.	Gestational age, weeks, median (IQR)= 28.1 (25.0-31.0) Antenatal steroids, n (%)=11427 (78.6) Apgar score at 1 minute, median (IQR)=6 (4-7) Apgar score at minutes, median (IQR)=6 (4-7) Late, n=14535 Birth weight, g, median (IQR)=1054 (590-1460) Gestational age, weeks, median (IQR)=28.0 (24.0-32.0) Antenatal steroids, n (%)=11475 (79) Apgar score at 1-minute, median (IQR)=6 (4-7) Apgar score at minutes, median (IQR)=8 (7-9) **Inclusion criteria** • Receipt of caffeine during hospital course • VLBW (<1500 g birth weight)	therapy on or after 3 days of life	gestational age, Apgar score at 5 minutes, any receipt of antenatal steroids, outborn, centre, and birth year. The following early clinical variables were used: apnea on day of life 0 or 1, level of respiratory support on day of life 1, maximal fraction of inspired oxygen on day of life 1, and the use of high-frequency oscillatory ventilation on day of life 1. A greedy match algorithm was used to match infants receiving early and late caffeine therapy. Subjects were matched without replacement down to a 1-digit match, and any subjects who could not be matched beyond this were excluded. 'For propensity-matched patients, McNemar's test for categorical variables was used for binary categorical variables, Bhakpar's generalszed McNemar's test was used for multiple categorical variables, and paired t-tests or Wilcoxon rank sum tests were used for continuous variables. A P<0.01 was considered significant.' Follow up: Not reported Primary outcomes: Death (mortality prior to discharge), BPD (need for any respiratory support at a postmenstrual age of 36 0/7 to 36 6/7 weeks if < 32 weeks gestational age at birth or at 28 to 34 postnatal days if ≥ 32 weeks gestational age at birth).	Outcome: NEC, n/N Early=1219/14535; Late=1187/14535 *Number taken for whole sample population, not just survivors	population* Selection of the non exposed cohort: a) drawn from the same community as the exposed cohort* Ascertainment of exposure: a) secure record (database)* Demonstration that outcome of interest was not present at start of study: a) yes* Comparability Study controls for: gestational age* Study controls for any additional factor: postnatal age at caffeine initiation* Outcome Assessment of outcome: record linkage* Was follow-up long enough for outcomes to occur: yes* Adequacy of follow-up of cohorts: b) 1031 (3.5%) propensity score-matched infants (early: 558; late: 473) with

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates 1997-2010 **Source of funding** National Center for Advancing Translational Sciences of the National Institutes of Health Eunice Kennedy Shriver National Institutes of Child Health and Human Development American Recovery and Reinvestment Act National Center for Advancing Translational Sciences of the National Institutes of Health	• Admission within 1 day of birth **Exclusion criteria** • Treatment with multiple methylxanthines and early mortality (death on day of life 0–3)		Secondary outcomes: NEC (diagnosis of medical or surgical NEC)		missing data for BPD, but small proportion unlikely to introduce bias* **Other information**
Full citation	**Sample size** For study details please see Schmidt 2006	**Interventions**	**Details** Follow up: 5 years Outcomes: Severe cognitive impairment	**Results** Outcome: Cerebral palsy, n/N	**Limitations**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Doyle, L. W., Schmidt, B., Anderson, P. J., Davis, P. G., Moddemann, D., Grunau, R. E., O'Brien, K., Sankaran, K., Herlenius, E., Roberts, R., Reduction in developmental coordination disorder with neonatal caffeine therapy, Journal of Pediatrics, 165, 356-359.e2, 2014 **Ref Id** 444776 **Country/ies where the study was carried out** **Study type** **Aim of the study**	**Characteristics** **Inclusion criteria** **Exclusion criteria**		(Full-Scale IQ <70 (< -2 SD relative to the normative mean of 100) on the Wechsler Preschool and Primary Intelligence III. The Full-Scale IQ was assumed to be <70 if the child could not complete the testing because of severe intellectual delay or severe autism). Cerebral palsy (diagnosed at 5 years of age by a pediatrician).	Caffeine= 28/735; Placebo= 34/698	Risk of bias assessed using Cochrane risk of bias tool Blinding of outcome assessment: Low risk Incomplete outcome data: High risk (29% attrition due to incomplete assessments or loss to follow up) For all other areas, please see Schmidt 2006 **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates **Source of funding**					
Full citation Gray, P. H., Flenady, V. J., Charles, B. G., Steer, P. A., Caffeine citrate for very preterm infants: Effects on development, temperament and behaviour, Journal of Paediatrics and Child Health, 47, 167-172, 2011 **Ref Id** 434970 **Country/ies where the study was carried out** Australia	**Sample size** n= 246 5mg/kg= 126; 20mg/kg= 120 **Characteristics** 5mg/kg, n=126 Birth weight, g, mean (SD)= 1032 (238) Gestational age, weeks, mean (SD)= 27.5 (1.4) Antenatal steroids, n (%)= 80 (63) Exogenous surfactant, n (%)= 85 (67) 20mg/kg, n=120 Birth weight, g, mean (SD)= 1051 (281) Gestational age, weeks, mean (SD)= 27.3 (1.4) Antenatal steroids, n (%)= 75 (63)	**Interventions** Babies were stratified by indication for caffeine therapy (peri-extubation and treatment), For Intervention details see Steer 2004	**Details** For Details see Steer 2004	**Results** Outcome: Mortality prior to discharge* 5 mg/kg= 7/126; 20mg/kg= 5/120 Outcome: BPD at 36 weeks PMA 5 mg/kg= 52/126; 20mg/kg= 35/120 Outcome: Documented apnoeic periods, median (IQR) 5mg/kg=6 (2-20); 20mg/kg=4 (1-12) p= 0.05 *N taken for whole population	**Limitations** For Risk of Bias assessment see Steer 2004 **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study type See Steer 2004 **Aim of the study** **Study dates** **Source of funding**	Exogenous surfactant, n (%)= 76 (63) **Inclusion criteria** • Requiring methylxanthines for treatment of apnoea of prematurity or as part of peri-extubation management **Exclusion criteria** • Major congenital abnormality, sepsis, grade III or IV intraventricular haemorrhage, and previous methylxanthine therapy				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	• Received short-term caffeine (≤ 7 days)				
Full citation Lodha, A., Seshia, M., McMillan, D. D., Barrington, K., Yang, J., Lee, S. K., Shah, P. S., Association of early caffeine administration and neonatal outcomes in very preterm neonates, JAMA PediatricsJama, Pediatr, 169, 33-38, 2015 **Ref Id** 727831 **Country/ies where the study was carried out** Canada **Study type**	**Sample size** n= 5101 Early= 3806 Late=1295 **Characteristics** Early, n=3806 Birth weight, g, median (IQR)= 1070 (850-1310) Antenatal steroids, n (%)= 3533 (94.4) 5-minute Apgar score, median (IQR)= 8 (6-9) Intubation at birth, n (%)= 1363 (38.3) Conventional ventilation on day 2, n (%)=1496 (39.3) High-frequency ventilation on day 2, n (%)=236 (6.2) CPAP on day 2, n (%)=1447 (38.0)	**Interventions** Early caffeine administration versus late caffeine administration Early: received caffeine within the first 2 days of life Late: received caffeine starting ≥ 3 days after birth	**Details** Data collection: Data was collected from 29 neonatal intensive care units in the Canadian Neonatal Network (CNN) between January 1, 2010 and December 31, 2012. Data on daily use of caffeine was collected for each baby by data abstractors at each site a dichotomous yes/no variables. Data on demographic and outcome data were collected from the baby's medical record by trained research assistants using a computerised data entry program and standardised definitions according to the CNN manual. Statistical analysis: Pearson X^2 tests were used for categorical variables and t-test for continuous variables. The Wilcoxon rank test was used for non-normally distributed continuous data. Multivariable logistic regression analysis was used to examine the effect of significant outcomes from the univariate analysis fo the early versus late groups on the primary and secondary outcomes. Follow up: Data were collected until death or discharge from the NICU	**Results** Outcome: Mortality prior to discharge, n/N Early= 217/3806; Late=75/1295 Outcome: BPD at 36 weeks PMA, n/N Early=999/3806; Late= 340/1296 Outcome: BPD at 28 days of life, n/N Early=1535/3806; Late=502/1295 Outcome: NEC (≥ stage 2), n/N Early=240/3806; Late=78/1295	**Limitations** Risk of bias assessed using the Newcastle-Ottawa Quality Assessment Scale for Cohort Studies Selection Representativeness of the exposed cohort: a) truly representative of the average preterm baby requiring respiratory support in the community* Selection of the non exposed cohort: a) drawn from the same community as the exposed cohort* Ascertainment of exposure:a) secure record (hospital record)* Demonstration that outcome of interest

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Retrospective cohort study **Aim of the study** The aim of the study was to assess the effect of early initiation of caffeine citrate on preterm outcomes in very preterm babies born in Canada **Study dates** January 1, 2010 to December 31, 2012 **Source of funding** Canadian Institutes of Health Research Ministry of Health and Long-Term Care, Ontario, Canada	Late, n=1295 Birth weight, g, mean (SD)=1050 (790-1360) Antenatal steroids, n (%)=1173 (92.9) 5-minute Apgar score, median (IQR)= 7 (6-8) Intubation at birth, n (%)= 427 (34.8) Conventional ventilation on day 2, n (%)=496 (38.3) High-frequency ventilation on day 2, n (%)=251 (19.4) CPAP on day 2, n (%)=350 (27.0) **Inclusion criteria** • < 31 weeks gestation **Exclusion criteria** • Neonates born outside a tertiary-level NICU,		Outcomes: Death (before discharge from the NICU), bronchopulmonary dysplasia (supplemental oxygen use at 36weeks' postmenstrual age or at discharge from the NICU) and necrotising enterocolitis (Bell criteria and was classified as medical or surgical)		was not present at start of study: a) yes* Comparability Study controls for: gestational age, antenatal steroid exposure, small for gestational age, site, intubated on day 2, SNAP-II score, and surfactant administration* Study controls for any additional factor: see above* Outcome Assessment of outcome: b) record linkage* Was follow-up long enough for outcomes to occur: a) (prior to death or hospital discharge)* Adequacy of follow-up of cohorts: a) complete follow up-all subjects accounted for* **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	moribund neonates, those with major congenital anomalies, and neonates who died before day 3 after birth				Some neonates only required CPAP and did not require intubation at birth. However, some of these neonates subsequently developed respiratory distress syndrome and required intubation on day 2 of life.
Full citation McPherson, C., Neil, J. J., Tjoeng, T. H., Pineda, R., Inder, T. E., A pilot randomized trial of high-dose caffeine therapy in preterm infants, Pediatric Research, 78, 198-204, 2015 **Ref Id** 726674	**Sample size** n= 74 Standard dose= 37; high dose= 37 **Characteristics** Standard dose, n= 37 Birth weight, g, mean (SD)= 949 (245) Gestational age, weeks, mean (SD)= 26.8 (1.8) Antenatal steroids, n (%)= 27 (73)	**Interventions** Standard dose versus high dose caffeine Standard dose: Administered intravenously as 20 mg/kg of caffeine citrate followed by 10 mg/kg 24 hours after the initial dose (30 mg/kg total over 36 hours) High dose: Administered intravenously as an initial loading dose of	**Details** Randomisation: sequence generated by dispensing pharmacist who was not involved in clinical care Allocation concealment: not reported Blinding: Clinical and research team blinded to randomisation until completion of developmental assessment at 2 years of age Attrition: Statistical analysis: Differences across groups were explored using Student's t-tests, Mann Whitney U-tests, and chi-squared analyses. Logistic and linear regression models were employed, relating caffeine group to outcome measures with	**Results** Outcome: Mortality prior to discharge, n (%) Standard-dose= 5/37; High-dose= 7/37 BPD at 36 weeks PMA, n (%) Standard-dose= 19/37; High-dose= 18/37 Outcome: NEC, n (%)	**Limitations** Risk of bias assessing using Cochrane risk of bias tool Random sequence generation: Unclear risk (unclear whether randomisation was computer generated) Allocation concealment: Unclear risk (method of allocation concealment not reported)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out US **Study type** RCT **Aim of the study** The aim of the study was to assess the effect of early high dose versus standard dose caffeine on clinical outcomes and neurdovelopmental outcomes in preterm babies. **Study dates** Not reported **Source of funding** National Institute of Child Health and Development	CRIB score, mean (SD)= 3.9 (3.5) High dose, n= 37 Birth weight, g, mean (SD)= 872 (257) Gestational age, weeks, mean (SD)= 26.3 (1.9) Antenatal steroids, n (%)= 26 (70) CRIB score, mean (SD)= 4.7 (4.1) **Inclusion criteria** • ≤ 30 weeks gestation **Exclusion criteria** • Known congenital anomaly, were moribund and/or in respiratory failure (defined as requiring	40 mg/kg of caffeine citrate followed by 20 mg/kg 12 hours later, then 10 mg/kg at 24 and 36 hours after the initial dose (80 mg/kg total over 36 hours)	adjustment for potential covariates. Follow up: Clinical outcomes measured prior to discharge; neurodevelopmental outcomes were assessed at 2 years Outcomes: PDA, NEC, severe ROP, brain injury, growth, developmental at term equivalent age	Standard-dose= 5/37; High-dose= 6/37	Blinding of participants and personnel: Low risk (Clinical and research team blinded to randomisation until completion of developmental assessment at 2 years of age) Blinding of outcome assessment: Low risk Incomplete outcome data: Low risk Selective reporting: All outcomes stated in Methods reported in Results Other bias: Low risk **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Intellectual and Developmental Disabilities Research Center, Washington University Doris Duke Charitable Foundation	>80% FiO_2 for six hours and/or having more than two inotropic drugs excluding hydrocortisone), or had severe brain injury (grade III–IV IVH) present in the first 24 hours of life				
Full citation Schmidt, B, Anderson, Pj, Doyle, Lw, Dewey, D, Grunau, Re, Asztalos, Ev, Davis, Pg, Tin, W, Moddemann, D, Solimano, A, Ohlsson, A, Barrington, Kj, Roberts, Rs, Survival without disability to age 5 years after neonatal caffeine therapy for apnea of	**Sample size** Follow up study; see Schmidt 2006 (CAP trial 2006) for study details **Characteristics** **Inclusion criteria** **Exclusion criteria**	**Interventions**	**Details** Follow up: 5 years Outcomes: Severe cognitive impairment (Full Scale IQ of less than 70 (2 SD below the mean of 100) on the Wechsler Preschool and Primary Scale of Intelligence III), severe hearing loss (prescription of hearing aids or cochlear implants), bilateral blindness (corrected visual acuity less than 20/200 in the better eye)	**Results** Outcome: Cognitive impairment, n/N Caffeine=38/768; Placebo= 38/750 Outcome: Severe hearing loss, n/N Caffeine=22/798; Placebo= 25/773 Outcome: Bilateral blindness, n/N Caffeine=7/792; Placebo= 7/763	**Limitations** Risk of bias assessed using Cochrane risk of bias tool Blinding of outcome assessment: Low risk Incomplete outcome data: High risk (18% attrition due to incomplete assessments, had vital status only, or were lost to follow up) For all other areas, please see Schmidt 2006

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
prematurity, JAMA, 307, 275-282, 2012 **Ref Id** 636207 **Country/ies where the study was carried out** **Study type** **Aim of the study** **Study dates** **Source of funding**					**Other information**
Full citation Schmidt, B, Roberts, Rs, Davis, P, Doyle, Lw, Barrington, Kj, Ohlsson, A, Solimano, A, Tin, W, Caffeine therapy for	**Sample size** n= 2006 Caffeine= 1006; Placebo= 1000 **Characteristics**	**Interventions** Caffeine versus placebo Caffeine: Intravenous loading dose of 20mg/kg caffeine citrate, daily maintenance dose of	**Details** Randomisation: Computer-generated randomisation Allocation concealment: A pharmacist at each centre received a binder with prespecified sequence of treatment group assignments from the statistician at the coordinating centre who was not involved	**Results** Outcome: Mortality prior to discharge, n/N Caffeine: 52/1006; Placebo: 55/1000	**Limitations** Risk of bias assessing using Cochrane risk of bias tool Random sequence generation: Low risk Allocation

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
apnea of prematurity, New England journal of medicine, 354, 2112-2121, 2006 **Ref Id** 804466 **Country/ies where the study was carried out** Australia and Canada **Study type** Multi-centre RCT **Aim of the study** The aim of the study was to assess short and long term benefits or risks in preterm with very low birth weights receiving methylxanthines. **Study dates** Not reported	Caffeine, n= 1006 Birth weight, g, mean (SD)= 964 (186) Gestational age, weeks, mean (SD)= 27 (2) Apgar score at 5 minutes, median (IQR)= Control, n= 1000 Birth weight, g, mean (SD)= 958 (181) Gestational age, weeks, mean (SD)= 27 (2) Apgar score at 5 minutes, median (IQR)= 8 (7-9) **Inclusion criteria** • Birth weight 500-1250 grams • Considered to be candidates for methylxanthine therapy during the first 10 days of life **Exclusion criteria**	5mg/kg. If apneas persisted, the daily maintenance dose could be increased to a maximum doe of 10mg/kg. Placebo: Intravenous loading dose of 20mg/kg of normal saline, daily maintenance dose of 5mg/kg. Caffeine was discontinued at the discretion of local clinicians. Open-label methylxanthines and use of doxapram were discouraged.	in the trial Blinding: Only the designated pharmacists were aware of treatment allocation Attrition: No attrition Statistical analysis: Logistic-regression models were adjusted for treatment and center. Continuous variables were analysed with the Student's t-test; Fisher's exact test or nonparametric tests were used for assessing the study drug and cointerventions Follow up: after recruitment and during initial hospitalisaion Outcomes: Short-term outcomes of BPD (need for supplemental oxygen at PMA 36 weeks), NEC (diagnosed during surgary, at autopsy, or by a finding of pneumatosis intestinalis, hepatobiliary gas, or free intraperitoneal air on radiography.	Outcome: BPD at 36 weeks PMA, n/N Caffeine: 350/1006; Placebo: 447/1000 Outcome: NEC, n/N Caffeine: 63/1006; Placebo: 67/1000	concealment: Low risk Blinding of participants and personnel: Low risk Blinding of outcome assessment: Low risk (did not state whether investigators were blinded at outcome assessment, but lack of blinding unlikely to affect assessment) Incomplete outcome data: Low risk Selective reporting: Low risk Other bias: high risk (190 (9.5%) of participants received >/= 1 dose of open-label methylxanthines **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding Canadian Institutes of Health Research National Health and Medical Research Council of Australia	• Had dysmorphic features or congenital abnormalities likely to affect life expectancy or neurologic development • Unlikely to be available for long term follow up • Previously treated with methlxanthine				
Full citation Schmidt, B, Roberts, Rs, Davis, P, Doyle, Lw, Barrington, Kj, Ohlsson, A, Solimano, A, Tin, W, Long-term effects of caffeine therapy for apnea of prematurity, New England Journal of Medicine, 357, 1893-1902, 2007	**Sample size** Follow up study; see Schmidt 2006 (CAP trial 2006) for study details **Characteristics** **Inclusion criteria**	**Interventions**	**Details** Follow up: 18-21 months corrected age Outcomes: Cerebral palsy (diagnosed if the child had a nonprogressive motor impairment by abnormal muscle tone and decrease range or control of movements). Cognitive delay (MDI score < 85 on the BSID-II). Severe hearing loss (audiometry was performed to determine the presence or absence of hearing loss). Blindness was defined as corrected visual acuity less than 20/200.	**Results** Outcome: Cerebral palsy, n/N Caffeine= 40/909; Placebo= 66/901 Outcome: Cognitive delay (MDI < 85), n/N Caffeine= 293/867; Placebo= 329/858 Outcome: Severe hearing loss, n/N Caffeine= 17/909; Placebo= 22/905	**Limitations** Risk of bias assessed using Cochrane risk of bias tool Blinding of outcome assessment: Low risk ('Only [the safety monitoring] committee and the selected study pharmacists had access to the prespecified and randomly generated

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ref Id 636208 **Country/ies where the study was carried out** **Study type** **Aim of the study** **Study dates** **Source of funding**	**Exclusion criteria**			Outcome: Bilateral blindness, n/N Caffeine= 6/911; Placebo= 8/905	sequence of treatment-group assignments') Incomplete outcome data: High risk (6.9% attrition due to death or loss to follow up) For all other areas, please see Schmidt 2006 **Other information**
Full citation Schmidt, B., Roberts, R. S., Anderson, P. J., Asztalos, E. V., Costantini, L., Davis, P. G., Dewey, D., D'Ilario, J., Doyle, L. W., Grunau, R. E., Moddemann, D.,	**Sample size** Follow up study; see Schmidt 2006 (CAP trial 2006) for study details **Characteristics**	**Interventions**	**Details** Follow up: 11 years Outcomes: Cerebral palsy (outcome measurement not defined), blindness (a corrected visual acuity of less than 20/200 in the better eye), deafness (prescription of hearing aids or cochlear implants).	**Results** Outcome: Cerebral palsy, n/N Caffeine=21/484; Placebo= 29/484 Outcome: Blindness, n/N Caffeine= 4/484; Placebo= 1/484	**Limitations** Risk of bias assessed using Cochrane risk of bias tool Blinding of outcome assessment: Low risk Incomplete outcome data: High risk (54% attrition due to

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Nelson, H., Ohlsson, A., Solimano, A., Tin, W., Dix, J., Adams, B. A., Warriner, E., Callanan, C., Davis, N., McDonald, M., Duff, J., Kelly, E., Hutchinson, E., Hohn, D., Ayaz, A., Allen, J., Haslam, R., Goodchild, L., Lontis, R. M., Opie, G., Woods, H., Marchant, E., Magrath, E., Williamson, A., Bairam, A., Belanger, S., Fraser, A., Leblanc, M., Synnes, A., Butt, A., Petrie, J., Sauve, R. S., Christianson, H., Anseeuw-Deeks, D., Makarchuk, S., Debooy, V., Granke, N., Bow, J., Nwaesei, C., Ryan, H., Saunders, C., Herlenius, E., Legnevall, L., Bohm, B., Bergstrom, B. M., Stalnacke, S., Sunden-Cullberg, S., Mayes, C.,	**Inclusion criteria** **Exclusion criteria**			Outcome: Deafness, n/N Caffeine= 16/484; Placebo=13/484	incomplete assessment, loss to follow, or refusal) For all other areas, please see Schmidt 2006 **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
McCusker, C., Robinson, U., Embleton, N., Carnell, J., Academic performance, motor function, and behavior 11 years after neonatal caffeine citrate therapy for apnea of prematurity: An 11-year follow-up of the CAP randomized clinical trial, JAMA pediatrics, 171, 564-572, 2017 **Ref Id** 804469 **Country/ies where the study was carried out** **Study type** **Aim of the study** **Study dates**					

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding					
Full citation Steer, P., Flenady, V., Shearman, A., Charles, B., Gray, P. H., Henderson-Smart, D., Bury, G., Fraser, S., Hegarty, J., Rogers, Y., Reid, S., Horton, L., Charlton, M., Jacklin, R., Walsh, A., High dose caffeine citrate for extubation of preterm infants: A randomised controlled trial, Archives of Disease in Childhood: Fetal and Neonatal Edition, 89, F499-F503, 2004 **Ref Id** 668115	**Sample size** n= 234 5mg/kg= 121; 20mg/kg= 113 **Characteristics** 5mg/kg, n= 121 Birth weight, g, mean (SD)= 1010.5 (239.6) Gestational age, weeks, mean (SD)= 27.4 (1.4) Antenatal steroids, n (%)= 106 (88) RDS, n (%)= 110 (91) Exogenous surfactant, n (%) 101 (84) Mechanical ventilation at enrollment, median (IQR)= 4.2 (2.29-12.41) 20 mg/kg, n=113 Birth weight, g, mean (SD)= 1009.2 (255.6) Gestational age, weeks, mean (SD)= 27.1 (1.4)	**Interventions** This periextubation group was part of a larger clinical trial assessing high and low dose caffeine in infants of less than 30 weeks gestation requiring methylxanthine for either periextubation management or treatment of apnoea. The results of the larger trial were reported in Gray 2011 Low dose caffeine versus high dose caffeine 5mg/kg: 20mg/kg loading dose of caffeine citrate followed at 24 hour intervals of a	**Details** Randomisation: Computer-generated list of random numbers Allocation concealment: The caffeine citrate solutions were identical in appearance Blinding: Investigators and clinical staff were blind to treatment allocation Attrition: Some attrition for neurodevelopmental outcomes due to death and attrition due to follow up; intention to treat analysis not reported Statistical analysis: Student t-tests or Mann–Whitney U-tests were performed as appropriate for continuous variables, and X^2 or Fisher's exact test for categorical data. The level of statistical significance was P = 0.05. Follow up: Babies were assessed at 12 months corrected age Outcomes: Neurological development (Griffiths Mental Developmental Scales (severe impairment in cognition 2 SD below the mean (general quotient score of 75)), bilateral blindness (need for hearing aids), failure of extubation (decision by the	**Results** Outcome: Mortality prior to discharge, n/N 5mg/kg=7/121; 20mg/kg=5/113 Outcome: BPD at 28 days of life, n/N* 5mg/kg=80/121; 20mg/kg=64/113 Outcome: BPD, oxygen requirement at 36 weeks PMA, n/N* 5mg/kg=51/121; 20mg/kg=33/113 Outcome: Continuing apnoea, Episodes of apnoea recorded by nursing staff within 7 days of the start of caffeine	**Limitations** Risk of bias assessing using Cochrane risk of bias tool Random sequence generation: Low risk (Computer-generated list of random numbers) Allocation concealment: Low risk (Investigators and clinical staff were blind to treatment allocation) Blinding of participants and personnel: Low risk (Investigators and clinical staff were blind to treatment allocation) Blinding of outcome assessment: Low risk 'The assessments

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out Australia **Study type** Mutli-centre RCT **Aim of the study** The aim of the study was to compare two dosing regimens of caffeine citrate in the periextubation period for neonates in regard to successful extubation and adverse events **Study dates** September 1996 to April 1999 **Source of funding** National Health and Medical Research Council	Antenatal steroids, n (%)= 97 (86) RDS, n (%)= 96 (85) Exogenous surfactant, n (%) 90 (80) Mechanical ventilation at enrollment, median (IQR)= 4.7 (2.5-12.7) **Inclusion criteria** • Gestational age < 30 weeks • Had received or were expected to receive at least 48 hours of mechanical ventilation **Exclusion criteria** • Major congenital abnormality, sepsis, grade III or IV intraventricular haemorrhage,	maintenance dose of 5 mg/kg 20 mg/kg: 80mg/kg loading dose of caffeine citrate followed at 24 hour intervals of a maintenance dose of 20 mg/kg 'Standard neonatal practices were employed in all the collaborating centres. Infants with recurrent episodes of abnormal cardiorespiratory events not responding to the allocated caffeine dosage regimen had additional intervention such as nasal continuous positive airways pressure (NCPAP), doxapram infusion or mechanical ventilation. Decisions on the details of neonatal care were made by the attending physicians. Infants requiring ongoing	attending neonatologist not to attempt extubation based on the clinical condition of the infant) or the use of reintubation or doxapram within seven days of caffeine loading), necrotising enterocolotis (not defined), tachycardia (not defined), death before discharge, bronchopulmonary dysplasia (oxygen dependency at 28 days of postmenstrual age or 36 weeks of postmenstrual age), documented apnoea (episodes of apnoea recorded by nursing staff within 7 days of the start of caffeine treatment)	treatment, median (IQR) 5mg/kg=7 (2-22); 20mg/kg=4 (1-12) P < 0.01 Outcome: Extubation failure, n/N 5mg/kg=36/121; 20mg/kg=17/113 Outcome: Tachycardia, n/N 5mg/kg=1/121; 20mg/kg=4/113 Outcome: Necrotising enterocolitis, n/N 5mg/kg=5/121; 20mg/kg=0/113 *Number extracted for whole sample population, not just survivors	were performed by paediatricians and psychologists in a blinded fashion who were unaware of a child's trial allocation status' Incomplete outcome data: Neurodevelopmental outcomes: high risk (23% attrition from initial sample randomised due to death and loss to follow up) Selective reporting: Moderate risk (neurodevelopmental outcomes were reported as a composite, as opposed to separately) Other bias: Low risk **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Mater Health Services' Private Practice Trust Fund	and previous methylxanthine therapy	treatment with methylxanthines who had been transferred from a tertiary to a regional centre were switched to theophylline.'			
Full citation Steer, P. A., Flenady, V. J., Shearman, A., Lee, T. C., Tudehope, D. I., Charles, B. G., Periextubation caffeine in preterm neonates: a randomized dose response trial, Journal of Paediatrics & Child HealthJ Paediatr Child Health, 39, 511-5, 2003 **Ref Id** 753356	**Sample size** n= 127 3mg/kg=42; 15 mg/kg=40; 30 mg/kg=45 **Characteristics** 3 mg/kg, n=42 Birth weight, g, mean (SD)= 1160 (333) Gestational age, weeks, mean (SD)= 28 (1.8) Antenatal steroids, n (%)= 33 (78) Days of mechanical ventilation, mean (SD)= 3.5 (2.3) 15 mg/kg, n=40 Birth weight, g, mean (SD)= 1230 (324) Gestational age, weeks,	**Interventions** 3mg/kg caffeine versus 15 mg/kg versus 30 mg/kg Loading dose of 2mL/kg caffeine citrate, with either 6, 30, or 60 mg/kg caffeine according to treatment group, administered intravenously or through the orogastric tube if being fed enterally over a 15 minute period. Maintenance dose of 1mL/kg given at 24 hour intervals for the following 6 days, starting 24 hours after the loading dose.	**Details** Randomisation: Computer-generated list of random numbers Allocation concealment: Allocation performed by pharmacist not associated in any other way with the trial Blinding: Investigators, medical and nursing staff were blinded to treatment allocation Attrition: Intention to treat analysis was used Statistical analysis: ANOVA with Bonferroni multiple comparison tests and Wilcoxin rank sum test for continuous variables, chi-square or Fishers exact test for categorical data Follow up: Prior to discharge Outcomes: Primary outcome was failure of extubation from mechanical ventilation, defined as either: (i) an inability to extubate from mechanical ventilation within 48 h of caffeine loading for a planned extubation;	**Results** Outcome: Extubation failure, n/N 3mg/kg: 19/42; 15mg/kg: 10/40; 30mg/kg: 11/45 Outcome: Tachycardia, n/N 3mg/kg: 1/42; 15mg/kg: 5/40; 30mg/kg: 8/45 Outcome: NEC, n/N 3mg/kg: 0/42; 15mg/kg: 2/40; 30mg/kg: 0/45	**Limitations** Risk of bias assessing using Cochrane risk of bias tool Random sequence generation: Low risk Allocation concealment: Low risk Blinding of participants and personnel: Low risk Blinding of outcome assessment: Low risk Incomplete outcome data: Low risk Selective reporting: Moderate risk (Methods section did not state all of the

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out Australia **Study type** Single-centre RCT **Aim of the study** The aim of the study was to compare the effectiveness of three dosing regimens of caffeine for preterm infants in the peri-extubation period **Study dates** September 1993 to November 1995 **Source of funding** Not reported	mean (SD)= 28.4 (1.7) Antenatal steroids, n (%)= 32 (80) Days of mechanical ventilation, mean (SD)= 3.1 (2.2) 30 mg/kg, n=45 Birth weight, g, mean (SD)= 1090 (367) Gestational age, weeks, mean (SD)= 27.8 (1.9) Antenatal steroids, n (%)= 38 (85) Days of mechanical ventilation, mean (SD)= 3.9 (2.7) **Inclusion criteria** • Gestational age < 31 weeks • Received or were anticipated to receive at least 48 hours of mechanical ventilation	Caffeine was administered for a total of 7 days, after which point routine management of apnoae (including theophylline) was started where required. 'Clinical staff were instructed to follow routine management for any single abnormal cardiorespiratory event; initial intervention by stimulation alone, followed by oxygen administration, bag and mask ventilation, and finally intubation and mechanical ventilation. Recurrent episodes of abnormal cardiorespiratory events not responding to the allocated caffeine regimen involved continuation of the caffeine, plus further medical interventions such as	or (ii) the use of reintubation or doxapram within 7 days of commencing caffeine therapy		outcomes that were reported in the Results section) **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Exclusion criteria • Major congenital abnormality, infection, major neurological condition, mechanical ventilation for a period greater than 28 days, previous exposure to methylxanthine therapy	NPCPAP, doxapram infusion, or mechanical ventilation as deemed necessary. The decisions on the timing of extubation, the reinstitution of mechanical ventilation, the duration of NPCPAP (after 24 h post-extubation) and the use of doxapram, were at the discretion of the attending clinician.'			
Full citation Taha, D., Kirkby, S., Nawab, U., Dysart, K. C., Genen, L., Greenspan, J. S., Aghai, Z. H., Early caffeine therapy for prevention of bronchopulmonary dysplasia in preterm infants, Journal of Maternal-Fetal and	**Sample size** n= 2951 Early=1986; Late=965 **Characteristics** Early, n=1986 Birth weight, g, mean (SD)=938 (201) Gestational age, weeks, mean (SD)= 27.5 (2.0) Prenatal steroids, n	**Interventions** Early caffeine administration versus late caffeine administration Early: Received caffeine on days 0-2 of life Late: Received caffeine on days 3-10 of life	**Details** Data collection: This study was a retrospective analysis of the Alere Neonatal Database for infants admitted to the NICU between June 2006 and May 2011. The database is comprised of standardised clinical, socio-demographic and cost-related information pertaining to preterm babies admitted to the NICU in 1000+ hospitals across the US. All demographic data were obtained prospectively from the neonatal chart and entered into the Database.	**Results** Outcome: Mortality prior to discharge, n/N Early= 188/1986; Late= 79/965 Outcome: BPD at 36 weeks PMA, n/N Early=716/1986; Late=451/965 Outcome: NEC, n/N	**Limitations** Risk of bias assessed using the Newcastle-Ottawa Quality Assessment Scale for Cohort Studies Selection Representativeness of the exposed cohort: a) truly representative of the average preterm baby requiring

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Neonatal Medicine, 27, 1698-1702, 2014 **Ref Id** 654378 **Country/ies where the study was carried out** US **Study type** Retrospective cohort study **Aim of the study** The aim of the study was to assess if the early administration of caffeine treatment was associated with improved survival without bronchopulmonary dysplasia (BPD) in preterm babies. **Study dates**	(%)=956 (48.1) 5-minute Apgar score, median (IQR)=8 (1-10) Ventilated any time, n (%)= 1614 (81.3) Surfactant, n (%)= 1349 (67.9) Apnea, n (%)= 1776 (89.4) Late, n=965 Birth weight, g, mean (SD)=899 (216) Gestational age, weeks, mean (SD)= 27.2 (2.1) Prenatal steroids, n (%)= 418 (43.3) 5-minute Apgar score, median (IQR)= 8 (1-10) Ventilated any time, n (%)= 804 (83.3) Surfactant, n (%)= 685 (71.0) Apnea, n (%)= 869 (90.5) **Inclusion criteria** • Admitted to the NICU • ≤ 1250g at birth • Treated with caffeine within		Statistical analysis: Continuous variables were analysed with Student's t-tests and Mann-Whitney U-tests; categorical variables were assessed with chi-square or Fisher's exact tests. Linear and logistic regressions controlled for gestational age, birth weight, centres and the prenatal steroids. A p-value of < 0.05 was considered statistically significant. Follow up: Not reported Outcomes: Death (not defined), bronchopulmonary dysplasia (requiring oxygen or a higher level of respiratory support at 36 weeks post-menstrual age), NEC (if the baby was kept NPO (i.e. fasting), treated with antibiotics and radiographic findings were documented in the chart or infant required surgery for NEC).	Early=144/1986; Late=57/965	respiratory support in the community* Selection of the non exposed cohort: a) drawn from the same community as the exposed cohort* Ascertainment of exposure: a) secure record (hospital record)* Demonstration that outcome of interest was not present at start of study: a) yes* Comparability Study controls for: gestational age, birth weight, centres and the prenatal steroid* Study controls for any additional factor: see above* Outcome Assessment of outcome: b)record linkage* Was follow-up long enough for outcomes to occur: a)yes* Adequacy of follow-

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
June 2006 to May 2011 **Source of funding** Not reported	the first 10 days of life **Exclusion criteria** Not reported				up of cohorts: a) complete follow up* **Other information**
Full citation Lodha, A., Rabi, Y., Soraisham, A., Dobry, J., Lodha, A., Amin, H., Awad, E. A., Tang, S., Sahai, A., Bhandari, V., Does duration of caffeine therapy in preterm infants born </=1250 g at birth influence neurodevelopmental (ND) outcomes at 3 years of age?, Journal of Perinatology, 2018 **Ref Id** 870847	**Sample size** n=448 Stopped caffeine ≤ 14 days after birth= 139 Stopped caffeine 15-30 days after birth= 122 Stopped caffeine > 30 days after birth= 187 **Characteristics** Early cessation of caffeine ≤ 14 days (ECC) Birth weight, g, mean (SD)= 979 (339) Gestational age, weeks, mean (SD)= 27 (3) Gestational age at caffeine stoppage, weeks, mean (SD)= 28(3) Male, n (%)= 79 (56.8)	**Interventions** The loading dose of caffeine base for management of AOP was 10 mg/kg. The maintenance dose was 2.5 mg/kg to 5 mg/kg every 24 h and usually commencing 24 h after the loading dose. Criteria for cessation of caffeine were when babies reached 35 weeks' corrected age and or when infants were free from apnea requiring intervention for 7 days and apnea free for at	**Details** Data collection: The study is a retrospective cohort study of babies admitted to the Foothills Medical Centre NICU. Perinatal and neonatal data were collected according to Canadian Neonatal Network standards. Statistical analysis: Baby and maternal baseline characteristics were compared between the three groups using the Chi-square test for categorical variables and Kruskal–Wallis test for nonnormally distributed continuous variables. Neonatal and 3-year neurodevelopmental outcomes were compared using the Chi-square or Fisher' s exact test. Logistic regression was performed to explore the effect of caffeine duration on 3-year ND outcomes, after adjusting for clinically important neonatal variables. Logistic regressions were run with caffeine duration, gestational age at birth, and maternal smoking as	**Results** BPD at 36 weeks PMA, n/N ECC= 71/122 ICC= 34/92 LCC= 81/165 Cerebral palsy, n/N ECC= 5/138 ICC= 6/140 LCC= 4/149 Moderate cognitive impairment, n/N ECC= 14/130 ICC= 17/133 LCC= 20/139 Severe cognitive impairment, n/N ECC= 2/130 ICC= 7/133 LCC= 1/139 Deafness, n/N ECC=2/134 ICC=3/135	**Limitations** Risk of bias assessed using the Newcastle-Ottawa Quality Assessment Scale for Cohort Studies Selection Representativeness of the exposed cohort: a) truly representative of the average preterm requiring respiratory support in the community* Selection of the non exposed cohort: a) drawn from the same community as the exposed cohort* Ascertainment of exposure: a) secure

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out Canada **Study type** Retrospective cohort study **Aim of the study** The aim of the study was to assess the effect of different durations of caffeine on long-term neurodevelopmental outcomes at 3 corrected age in preterm babies. **Study dates** January 2002 to December 2009 **Source of funding** Not reported	Intermediate cessation of caffeine 15-30 days (ICC) Birth weight, g, mean (SD)= 1010 (210) Gestational age, weeks, mean (SD)= 28 (2) Gestational age at caffeine stoppage, weeks, mean (SD)= 31 (3) Male, n (%)= 54 (44.3) Late cessation of caffeine > 30 days (LCC) Birth weight, g, mean (SD)= 980 (210) Gestational age, weeks, mean (SD)= 27 (2) Gestational age at caffeine stoppage, weeks, mean (SD)= 33 (3) Male, n (%)= 92 (49.2) **Inclusion criteria** All infants weighing ≤ 1250 g at birth who received their first dose of caffeine within the first week of life ,as well as all premature babies born before 30 weeks'	least 5–7 days prior to discharge after discontinuing caffeine. The study population was split into three groups based on when the caffeine was stopped after birth: BPDC	baseline variables, plus each of the neonatal risk factors separately Follow up: 3 years Primary outcomes: The presence of ND impairment (present if any of the following were found: cerebral palsy (CP), borderline or severe cognitive delay (borderline cognitive function was defined as a full scale IQ score of 1– 2 standard deviations (SD) below the mean, and cognitive delay as >2 SD below the mean, on the Wechsler Preschool and Primary Scale of Intelligence, Third Edition (WPPSI-III) or Fourth Edition (WPPSI-IV)), major (bilateral visual impairment) or minor visual impairment (corrected visual acuity <20/60 but >20/200 in the better eye), or hearing impairment or deafness). Secondary outcomes: IVH, NEC, RDS, BPD, ROP	LCC=1/147 Blindness, n/N ECC= 3/137 ICC= 5/141 LCC= 5/148 Necrotising enterocolitis, n/N ECC= 19/139 ICC= 11/122 LCC= 16/286	record (hospital questionnaire)* Demonstration that outcome of interest was not present at start of study: a) yes* Comparability Study controls for: caffeine duration, gestational age at birth, and maternal smoking as baseline variables, plus each of the neonatal risk factors separately* Study controls for any additional factor: a) yes* Outcome Assessment of outcome: b) record linkage* Was follow-up long enough for outcomes to occur: a) yes (3 years)* Adequacy of follow-up of cohorts: a) incomplete follow up - not all babies

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	gestation, birth weight < 1500 g, receiving continuous positive airway pressure (CPAP) from birth, before extubation from the ventilator and for apnoea of prematurity (AOP) **Exclusion criteria** Babies born with congenital abnormalities or chromosomal disorders or those who died				accounted for in results **Other information** Bias from retrospective design of the data collection. 60 babies were excluded due to missing data on their caffeine intake
Full citation Murner-Lavanchy, I. M., Doyle, L. W., Schmidt, B., Roberts, R. S., Asztalos, E. V., Costantini, L., Davis, P. G., Dewey, D., D'Ilario, J., Grunau, R. E., Moddemann, D., Nelson, H., Ohlsson, A.,	**Sample size** Follow up study; see Schmidt 2006 (CAP trial 2006) for study details **Characteristics** **Inclusion criteria**	**Interventions**	**Details** Follow-up: 11-year follow up- follow up was conducted between May 2011 and May 2016 for the year between the child's 11th and 12th birthday. Efforts to locate and examine the children continued beyond this age when necessary. Outcomes: General intelligence was estimated with the full-scale IQ from the 4-subtest version of the Wechsler Abbreviated Scale of Intelligence–II	**Results** General intelligence (Wechsler Abbreviated Scale of Intelligence-II [WASI-II]), Full-scale IQ < 85 Intervention= 76/392 Control= 86/393	**Limitations** Risk of bias assessed using Cochrane risk of bias tool Blinding of outcome assessment: Low risk Incomplete outcome data: High risk (39% attrition due to incomplete

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Solimano, A., Tin, W., Anderson, P. J., Dix, J., Adams, B. A., Warriner, E., Callanan, C., Davis, N., McDonald, M., Duff, J., Kelly, E., Hutchinson, E., Hohn, D., Ayaz, A., Allen, J., Haslam, R., Goodchild, L., Lontis, R. M., Opie, G., Woods, H., Marchant, E., Magrath, E., Williamson, A., Synnes, A., Butt, A., Petrie, J., Sauve, R. S., Christianson, H., Anseeuw-Deeks, D., Makarchuk, S., Debooy, V., Granke, N., Bow, J., Herlenius, E., Legnevall, L., Bohm, B., BergStrom, B. M., Stalnacke, S., Sunden-Cullberg, S., Mayes, C., McCusker, C., Robinson, U., Embleton, N., Carnell, J., Neurobehavioral	**Exclusion criteria**		(WASI-II). Cognitive impairment was defined as a full-scale IQ < 85 (<1 SD relative to the normative mean).		assessments or loss to follow up) For all other areas, please see Schmidt 2006 **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
outcomes 11 years after neonatal caffeine therapy for apnea of prematurity, Pediatrics, 141 (5) (no pagination), 2018 **Ref Id** 870850 **Country/ies where the study was carried out** **Study type** **Aim of the study** **Study dates** **Source of funding**					

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Clinical evidence tables for question 3.8 What is the effectiveness of interventions for closing a patent ductus arteriosus in preterm babies requiring respiratory support?

RCTs

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Aranda, J. V., Clyman, R., Cox, B., Van Overmeire, B., Wozniak, P., Sosenko, I., Carlo, W. A., Ward, R. M., Shalwitz, R., Baggs, G., Seth, A., Darko, L., A randomized, double-blind, placebo-controlled trial on intravenous ibuprofen L-lysine for the early closure of nonsymptomatic patent ductus arteriosus within 72 hours of birth in extremely low-birth-weight infants, American Journal of Perinatology, 26, 235-246, 2009 **Ref Id**	**Sample size** N= 136 n, intervention= 68 n, control= 68 **Characteristics** Intervention group Birthweight (g), mean (SD)= 798.5 (128.7) Gestational age (wk), mean (SD)= 26.1 (1.3) Gender, male, n (%)= 32 (47) Apgar score, 1 minute, median (IQR)= 4.0 (2.0), n=67 Apgar score, 5 minutes, median (IQR)= 7.0 (2.0), n=67 Baseline neurological exam abnormal, n/total (%)= 6/68 (8.8) Baseline apnea, n/total (%)= 15/68 (22) Mechanical ventilation, n/total (%)= 47/68 (69) Control group Birthweight (g), mean (SD)= 797.3 (132.8)	**Interventions** Intervention: 10mg/mL ibuprofen (L-lysine formulation) given intravenously for 10 minutes using a 10mg/kg loading dose followed by 5mg/kg/d on the second and third study day, using an umbilical venous catheter or peripheral IV site Control: normal saline solution given at same intervals as the intervention	**Details** Following echocardiogram confirmation of a PDA, infants were randomised into the 2 treatment groups within 72 hours of birth. The coded vials of study drug or placebo contained indistinguishable colourless solutions dispensed by the blinded research pharmacists of the participating sites. Central randomisation was performed using a dynamic allocation method of biased coin randomisation, balancing within birth weight, within each site, and in the study overall. Intention-to-treat analysis was used.	**Results** Mortality prior to discharge Ibuprofen= 8/68 (11.8%) Placebo= 10/68 (14.7%) O_2 needed at 28 days corrected age Ibuprofen= 58/65 (89.2%) Placebo= 53/65 (81.5%) O_2 needed at 36 weeks corrected age Ibuprofen= 42/46 (91.3%) Placebo= 48/52 (92.3%) Rescued who were ligated Ibuprofen= 8/17 (47.1%) Placebo= 9/33 (27.3%) NEC	**Limitations** The quality assessment was performed using the Cochrane risk of bias tool for RCTs Random sequence generation- Low risk ["Central randomization (ClinPhone Plc., Nottingham, UK) was implemented using a dynamic allocation method of biased coin randomization, balancing within birth weight, within each site, and in the study overall."] Allocation concealment- Low risk ["The coded vials of study drug or placebo contained indistinguishable colorless solutions dispensed by the

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
726115 **Country/ies where the study was carried out** US **Study type** Multi-centre, double-blinded, randomised, placebo-controlled trial **Aim of the study** The aim of this study was the assess the efficacy and safety of intravenous ibuprofen for the early closure of nonsymptomatic PDA within 72 hours of birth in extremely low birth weight infants with evidence of ductal shunting by echocardiogram. **Study dates**	Gestational age (wk), mean (SD)= 26.2 (1.4) Gender, male, n (%)= 37 (54) Apgar score, 1 minute, median (IQR)= 4.0 (2.0), n=67 Apgar score, 5 minutes, median (IQR)= 7.0 (2.0), n=68 Baseline neurological exam abnormal, n/total (%)= 4/68 (5.9) Baseline apnea, n/total (%)= 13/68 (19) Mechanical ventilation, n/total (%)= 46/68 (67) **Inclusion criteria** • All preterm infants born ≤ 30 week's gestation • Admitted to the NICU • Birth weight 500-1000g • < 72 hours postnatal age • Non-symptomatic PDA • Evidence of ductal shunting documented by echocardiogram • Informed consent signed by parent or legal guardian			Ibuprofen= 9/65 (13.8%) Placebo= 9/65 (13.8)	blinded research pharmacists of the participating sites."] Blinding of participants and personnel- Low risk ["Plasma ibuprofen assays by high-pressure liquid chromatography were performed at the conclusion of the clinical trial when blinding was broken."] Blinding of outcome assessment- Low risk Incomplete outcome data- Unclear risk [All stated outcomes were reported; however, not all outcomes were reported with means and SDs] Selective reporting- Low risk Other sources of bias- Low risk **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
March 2002 to March 2005 **Source of funding** National Institutes of Health; Ross Abbott Laboratories	**Exclusion criteria** • Major congenital malformations and/or chromosomal anomalies • Proven congenital bacterial infection • Maternal antenatal nonsteroidal anti-inflammatory exposure < 72 hours before delivery • Treatment with a steroid at anytime since birth • Unremitting shock requiring high doses of vasopressors • Renal failure or oliguria • Platelet count < 75,000mm^3 • Clinical bleeding tendency • Expected survival < 48 hours in the opinion of the attending neonatologist • Participation in other clinical intervention trials • For multiple births, no more than two of the infants could be enrolled				
Full citation	**Sample size**	**Interventions**	**Details**	**Results**	**Limitations**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Bagnoli, F., Rossetti, A., Messina, G., Mori, A., Casucci, M., Tomasini, B., Treatment of patent ductus arteriosus (PDA) using ibuprofen: Renal side-effects in VLBW and ELBW newborns, Journal of Maternal-Fetal and Neonatal Medicine, 26, 423-429, 2013 **Ref Id** 688473 **Country/ies where the study was carried out** Italy **Study type** Randomised, controlled, double-blind, parallel design trial	n=134 Ibuprofen= 67 Placebo= 67 **Characteristics** Intervention group Male, n/total= 36 SGA, n/total= 17 Mean gestational age, weeks, mean (SD)= 27 + 3 (2.5) Mean birth weight, g, mean (SD)= 989 (326) Control group Male, n/total= 39 SGA, n/total= 14 Mean gestational age, weeks, mean (SD)= 27 + 6 (4) Mean birth weight, g, mean (SD)= 1197 (835) **Inclusion criteria** • Gestational age ≤ 32 weeks • Birth weight ≤ 1500g • PDA with evidence of ductal shunting documented by echocardiography • Postnatal age > 72 h	Ibuprofen= Ibuprofen was given intravenously for 10 min using 10 mg/kg loading doses, followed by 5 mg/kg/d on the second and third study days, using an umbilical venous catheter or peripheral IV site Placebo= The treatment course for the control group was not reported	Preterm neonates were randomized to receive either placebo or a 3-day-course (10 mg/kg, 5 mg/kg and 5 mg/kg) of IV ibuprofen. The subjects were stratified into three birth weight categories: 500–750 g (n = 18), 751–1000 g (n = 26), and >1000 g (n = 23), and subdivided into two gestational age categories: ≤26 weeks (n = 32) and >26 weeks (n = 35). Confidence intervals were calculated at 95%. Power analysis was not performed, as the difference was observed at prearranged significance level sets and because the power is appropriately indicated by confidence intervals.	Median creatinine day 7 Ibuprofen= 1mg/dl Placebo= 0.6mg/dl p=0.0003 Median blood urea nitrogen day 7 Ibuprofen= 84mg/dl Placebo= 38mg/dl p= 0.0000002	The quality assessment was performed using the Cochrane risk of bias tool for RCTs Random sequence generation- Unclear risk (Method of randomisation was not specified) Allocation concealment- Unclear risk (Method for allocation concealment was not specified) Blinding of participants and personnel- Low risk (Study did not state how researchers, physicians, or participants were blinded; however, lack of blinding unlikely to affect outcome assessment) Blinding of outcome assessment- Low risk (Study did not state how researchers, physicians, or participants were blinded; however, lack of blinding unlikely to

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study The aim of this study was to assess whether or not treatment of preterm infants with PDA using intravenous ibuprofen can affect renal function **Study dates** January 2006 to December 2010 **Source of funding** Not reported	• Informed consent signed by parent/legal guardian **Exclusion criteria** • Congenital heart malformation, major congenital malformations and or/chromosomal anomalies • Antental renal malformation on fetal ultrasound • Platelet count < 75,000/mm^3 • Clinical bleeding tendency • Renal failure • Congenital bacterial infection • Treatment with a steroid at any time since birth				affect outcome assessment) Incomplete outcome data- Low risk (ITT analysis used) Selective reporting- High risk (Medians were not presented with their IQRs) Other sources of bias- Unclear risk (Source of funding was not reported) **Other information**
Full citation De Carolis, M. P., Romagnoli, C., Polimeni, V., Piersigilli, F., Zecca, E., Papacci, P., Delogu, A. B.,	**Sample size** n= 46 Ibuprofen= 23 Placebo= 23 **Characteristics**	**Interventions** Intervention: Ibuprofen as lysine salt, according to the following therapeutic regime: 10 mg/kg infused over 20 min via peripheral vein and commenced	**Details** Randomisation was carried out at birth by random permuted blocks for both prophylaxis and control groups, envisaging 25	**Results**	**Limitations** The quality assessment was performed using the Cochrane risk of bias tool for RCTs Random sequence

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Tortorolo, G., Prophylactic ibuprofen therapy of patent ductus arteriosus in preterm infants, European Journal of Pediatrics, 159, 364-368, 2000 **Ref Id** 688800 **Country/ies where the study was carried out** Italy **Study type** Placebo-controlled RCT **Aim of the study** The aim of this study was to assess the efficacy of ibuprofen in the prophylaxis of PDA in preterm infants and at detecting side-effects	All infants in the study were ventilated Intervention group (n=23) Gestational age, weeks, mean (SD)= 28.1 (1.1) Birth weight, g, mean (SD)= 934 (288) Small for gestational age, n (%)= 12 (52.2) Male, n (%)= 14 (60.9) Antenatal steroids, n (%)= 13 (56.5) Control group (n=23) Gestational age, weeks, mean (SD)= 28.0 (1.9) Birth weight, g, mean (SD)= 993 (308) Small for gestational age, n (%)= 16 (69.6) Male, n (%)= 12 (52.2) Antenatal steroids, n (%)= 17 (73.9) **Inclusion criteria** • Gestational age <31 weeks • Admitted to the NICU • PDA determined by echocardiographic evaluation	within a period of 2 h following birth. A further two treatments of 5 mg/kg, using the same modality, were administered by infusion at 24 and 48 h after the first dose. Placebo: No placebo was administered to the control group.	neonates in each. Neonates were studied immediately after birth, on the 3rd day of life, and then whenever clinical suspicion of PDA occurred. Diagnosis of PDA was always confirmed by colour-flow Doppler echocardiography and PDA was considered haemodynamically significant when the left atrial aortic root ratio was >1:3. In the presence of significant PDA at the completion of the ibuprofen cycle, treatment with indomethacin (three times 0.2 mg/kg at 12 h intervals, administered by i.v. infusion over 20 min) was carried out. The same treatment was administered to control neonates having significant PDA on the 3rd day of life. Failure to respond to medical treatment was an indication for		generation- Low risk ("Randomisation was carried out at birth by random permuted blocks for both prophylaxis and control groups, envisaging 25 neonates in each.") Allocation concealment- Low risk ("Echocardiographic evaluation was performed by the same investigator who was blinded to the treatment schedule.") Blinding of participants and personnel- Unclear risk (Did not state whether participants and hospital staff were blinded) Blinding of outcome assessment- Unclear risk (Did not state whether participants and hospital staff were blinded) Incomplete outcome data- Unclear risk (Did not state whether intention-to-treat analysis or another

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates April 1996 to July 1997 **Source of funding** Not reported	**Exclusion criteria** • Birth weight < 500g • Antenatal indomethacin administration • Congenital heart defect • Persistent pulmonary hypertension • Severe thrombocytopenia • Major congenital malformations		surgical ligation. Differences between groups were calculated with Mann-Whitney-Wilcoxon test for non-parametric data and with Student's t test for unpaired parametric data. Fisher's Exact test was employed for dichotomous variables. Statistical significance was considered equal to P < 0.05.		method was used to manage drop outs) Selective reporting- Low risk (All stated outcomes were reported with respective ranges for medians and SDs for means) Other sources of bias- High risk ("In the presence of significant PDA at the completion of the ibuprofen cycle, treatment with indomethacin (three times 0.2 mg/kg at 12 h intervals, administered by i.v. infusion over 20 min) was carried out. The same treatment was administered to control neonates having significant PDA on the 3rd day of life. Failure to respond to medical treatment was an indication for surgical ligation.") **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Gournay,V., Roze,J.C., Kuster,A., Daoud,P., Cambonie,G., Hascoet,J.M., Chamboux,C., Blanc,T., Fichtner,C., Savagner,C., Gouyon,J.B., Flurin,V., Thiriez,G., Prophylactic ibuprofen versus placebo in very premature infants: a randomised, double-blind, placebo-controlled trial, Lancet, 364, 1939-1944, 2004 **Ref Id** 259753 **Country/ies where the study was carried out** France	**Sample size** n= 131 Ibuprofen= 65 Placebo= 66 **Characteristics** Intervention group (n=65) Birthweight, g, mean (SD)=844 (181) Gestational age, wk, mean (SD)= 26.3 (0.9) Gender, male, n (%)= 35 (54) Apgar score, 1 minute, mean (SD)=5.7 (3.0) Apgar score, 5 minutes, mean (SD)= 8.4 (1.8) CRIB index, n (%)= 6.6 (3.7) Control group (n=66) Birthweight, g, mean (SD)= 851 (164) Gestational age, wk, mean (SD)= 26.3 (0.9) Gender, male, n (%)= 31 (47) Apgar score, 1 minute, mean (SD)= 5.6 (2.9) Apgar score, 5 minutes, mean (SD)= 8.0 (2.1) CRIB index, n (%)= 6.4 (3.1)	**Interventions** Intervention= 2-mL vials containing 5 g/L intravenous ibuprofen. Loading dose of 10 mg/kg then two maintenance doses of 5 mg/kg at 24-h interval Placebo= 2-mL vials containing 0.9% saline. Equivalent volumes of saline	**Details** The study took place across 11 tertiary neonatal intensive care centres in France. Patients were randomly assigned to receive within 6 h after birth either a prophylactic course of intravenous ibuprofen or equivalent volumes of placebo. After the prophylactic course of ibuprofen or placebo on day 3, an echocardiogram with colour-doppler-flow was done by a trained physician, with a high-frequency 7·5 MHz transducer to check the ductus. The need for an open-label ibuprofen course was then based on the detection of substantial PDA, defined as PDA visible on the echocardiogram. After	**Results** Mortality prior to discharge Ibuprofen, n (%)= 18 (29) Placebo, n (%)= 19 (29) BPD at 36 weeks, n (%) Ibuprofen= 19 (29) Placebo= 15 (23) At least 1 episode of urinary output < 2 mL/kg per h (day 1-3), n (%) Ibuprofen= 37 (57) Placebo= 26 (39) At least episode of serum creatinine > 140 umol/L (day 1-3), n (%) Ibuprofen= 8 (12) Placebo= 1 (2) NEC, n (%) Ibuprofen= 11 (17%) Placebo= 3 (5%) Isolated intestinal perforation, n (%) Ibuprofen= 5 (8) Placebo= 1 (2)	**Limitations** The quality assessment was performed using the Cochrane risk of bias tool for RCTs Random sequence generation- Low risk ("Randomisation was balanced with a one to one ratio and blocks of four treatments.") Allocation concealment- Low risk ("A sealed randomisation envelope was given with each treatment box and kept at the hospital pharmacy. Treatment allocation was within sites, and each study centre was provided with an increasing number of blocks after recruitment of newborn babies.") Blinding of participants and personnel- ("The following study drugs

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study type Multi-centre, double-blind, randomised, placebo-controlled RCT **Aim of the study** The aim of the study was to determine whether ibuprofen could reduce the need for surgical ligation in preterm neonates with PDA **Study dates** March 2001 to December 2001 **Source of funding** Orphan Europe	**Inclusion criteria** • Gestational age < 28 weeks • Postnatal age < 6 hours • Signed parental consent **Exclusion criteria** • Maternal use of nephrotoxic medication within 3 days before delivery • Major congenital malformations • Proven severe congenital maternal-fetal infection • Shock or life threatening infection • Hydrops fetalis • IVH grade 3 or 4 • Apparent neurological dysfunction • Substantial right to left shunt through the ducturs • Clinical bleeding		day 7, if the open-label course of ibuprofen had failed to achieve closure of the ductus arteriosus, the choice of back-up therapy (indomethacin 0·2 mg/kg, then 0·25 mg/kg at 24-h intervals, surgical ligation, or both) was left to the attending neonatologist. All surviving patients were followed up to 36 weeks of postconceptional age, which was generally the time of discharge from the participating centre.		were supplied as blinded prophylactic treatment by Orphan Europe (Paris, France): 2-mL vials containing either 5 g/L intravenous ibuprofen, or 0.9% saline. Boxes containing four treatments (two ibuprofen and two placebo) were provided to the study centres.") Blinding of outcome assessment- Low risk Incomplete outcome data- Low risk ("Thus, we did the per-protocol analysis on 131 preterm newborn babies") Selective reporting- Low risk (All stated outcomes were reported with respective IQRs and SDs reported) Other sources of bias- High risk (Patients received open-label ibuprofen)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					Other information
Full citation Harkin, P., Harma, A., Aikio, O., Valkama, M., Leskinen, M., Saarela, T., Hallman, M., Paracetamol Accelerates Closure of the Ductus Arteriosus after Premature Birth: A Randomized Trial, Journal of Pediatrics., 13, 2016 **Ref Id** 512466 **Country/ies where the study was carried out** Finland **Study type** Single-centre, double-blind, randomised,	**Sample size** n= 48 Paracetamol= 23 Placebo= 25 **Characteristics** Intervention group (n=65) Birth weight, g, mean (SD)= 1220 (430) Gestational age, week, mean (SD)= 28.4 (2.36) Gender, male, n (%)= 13 (57) Apgar score, 1 minute, median (IQR)= 7 (2-9) Apgar score, 5 minutes, median (IQR)= 7 (4-10) Antenatal steroids, n (%)= 20 (87) Control group (n=66) Birth weight, g, mean (SD)= 1120 (340) Gestational age, week, mean (SD)= 28.3 (2.06) Gender, male, n (%)= 14 (56) Apgar score, 1 minute, median (IQR)= 6 (1-9)	**Interventions** Intervention= intravenous paracetamol (ie, Perfalgan 10 mg/mL, or Paracetamol 10 mg/mL solutions for infusion) Placebo= 0.45% saline solution	**Details** A separate team of nurses prepared the study drug in a study pharmacy outside NICU. The first cardiac ultrasound examination was performed before the study drug, and then once a day until 1 day after the study medication period. Afterwards, infants with an open ductus were examined 1-2 times per week, unless otherwise indicated. For continuous variables, the independent samples t-test or the Mann-Whitney U-test, and for categorical values, the X-squared test, were used as appropriate.	**Results** Mortality prior to discharge Paracetamol, n (%)= 0 Placebo, n (%)= 1 (4) BPD supplemental oxygen at 28 days, n (%) Paracetamol= 7 (30) Placebo= 11 (44) BPD supplemental oxygen at 36 weeks after conception, n (%) Paracetamol= 0 Placebo= 1 (4) Postnatal age for ductal closure, > 27 weeks gestation, mean (SD) Paracetamol= 80 (151) Placebo= 322 (514) p= 0.004 Infants < 27 weeks gestation= no	**Limitations** The quality assessment was performed using the Cochrane risk of bias tool for RCTs Random sequence generation- Low risk ("Computer randomization was performed using a 4-block design. To decrease the risk of significant heterogeneity between cases and controls, individual treatment strata were defined by sex and gestational age.") Allocation concealment- Low risk ("The treatment allocation codes were sealed in sequentially labeled opaque envelopes. Both paracetamol and saline

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
placebo-controlled RCT **Aim of the study** The aim of the study was to assess the effect of paracetamol on early closure of PDA and to assess possible adverse effects of the drug **Study dates** Not reported **Source of funding** Alma and KA Snellman Foundation; The Finnish Medical Foundation; The Foundation for Paediatric Research; and Sigrid Juselius Foundation	Apgar score, 5 minutes, median (IQR)= 7 (2-9) Antenatal steroids, n (%)= 25 (100) **Inclusion criteria** • Admitted to NICU • Very low gestational age **Exclusion criteria** • Septic shock • Major malformation • Chromosomal abnormality			statistically significant difference Oliguria (<1 mL/kg/h), n (%) Paracetamol= 5 (22) Placebo= 7 (28) Polyuria (> 5 mL/kg/h), n (%) Paracetamol= 6 (26) Placebo=9 (36) NEC, stage 3 Paracetamol, n (%)= 0 Placebo, n (%)= 1 (4)	solutions appeared equally transparent in the syringe.") Blinding of participants and personnel- Low risk ("All nurses and doctors involved in the treatment and study of the infants were blinded to the study medication. A separate team of nurses prepared the study drug in a study pharmacy outside NICU. The drug was given to the study patient's nurse in a syringe.") Blinding of outcome assessment- Low risk Incomplete outcome data- Low risk ("All outcomes were analyzed by intention to treat") Selective reporting- Low risk Other sources of bias- Low risk

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					Other information
Full citation Kanmaz,G., Erdeve,O., Canpolat,F.E., Oguz,S.S., Uras,N., Altug,N., Greijdanus,B., Dilmen,U., Serum ibuprofen levels of extremely preterm infants treated prophylactically with oral ibuprofen to prevent patent ductus arteriosus, European Journal of Clinical Pharmacology, 69, 1075-1081, 2013 **Ref Id** 323877 **Country/ies where the study was carried out** Turkey	**Sample size** n= 46 Ibuprofen= 23 Control= 23 **Characteristics** Ibuprofen group (n=23) Birth weight, g, mean (SD)= 775 (131) Gestational age, wk, mean (SD)= 25.6 (1.6) Gender, male, n= 13 Duration of intubation, day, median (IQR)= 5 (0-40) Apgar score, 5 minutes, median (IQR)= 7 (3-9) Antenatal steroids, (%)= 60.8 Control group (n=23) Birth weight, g, mean (SD)= 749 (225) Gestational age, wk, mean (SD)= 26.4 (1.7) Gender, male, n= 11 Duration of intubation, day, median (IQR)= 2 (0-15)	**Interventions** Intervention= The intervention group received oral ibuprofen; 10 mg/kg within 12–24 h after birth followed by 5 mg/kg at 24 and 48 h. Oral ibuprofen (312 mOsmol/L and stabilized with propyl parapen, methyl parapen, and sodium benzoate) was given via an orogastric tube, which was flushed with 1 mL of sterile water to ensure delivery of the drug Control= received no treatment	**Details** Before treatment and 72 h after treatment, all infants were evaluated with a complete blood count, renal function tests, bilirubin, pro-brain natriuretic peptide levels, cranial ultrasonography, and echocardiography. Blood samples for serum ibuprofen level determination were collected at 12 h following the last dose of administered ibuprofen. All samples were immediately centrifuged, and the resulting serum was separated and kept frozen pending analysis. Echocardiograms were performed by a cardiologist blinded to group (intervention or	**Results** Mortality prior to discharge Ibuprofen, n (%)= 4/23 (17.3) Control, n (%)= 6/23 (26) BPD Ibuprofen, n (%)= 8/19 (42.1) Control, n (%)= 5/17 (29.4) Day 1, mean (SD) Platelet count (x1000)(mm^3) Ibuprofen= 231 (75) Control= 196 (77) Urea (mg/dL) Ibuprofen= 47 (22) Control= 46.5 (20) Creatinine (mg/dL) Ibuprofen= 0.64 (0.2) Control= 0.72 (0.21) Bilirubin (mg/dL) Ibuprofen= 3.1 (1.4) Control= 3.5 (1.7)	**Limitations** The quality assessment was performed using the Cochrane risk of bias tool for RCTs Random sequence generation- Unclear risk (Randomisation generation was not specified) Allocation concealment- Low risk ("Enrolled preterm infants were randomized either to the intervention (prophylactic oral ibuprofen administration) group or control group using sealed opaque envelops which stratified the infants according to GA and BW.") Blinding of participants and personnel- Unclear

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study type Single-centre, double-blind, randomised, placebo-controlled RCT **Aim of the study** The aim of the study was the assess the effects of early oral ibuprofen administration on the incidence of hemodynamically significant PDA and define the assocation between serum ibuprofen levels and ductal closure **Study dates** July 2011 to November 2011 **Source of funding** Not reported	Apgar score, 5 minutes, median (IQR)= 7 (3-9) Antenatal steroids, (%)= 60.8 **Inclusion criteria** • Gestational age < 28 weeks and/or • Birth weight of < 1000g **Exclusion criteria** • Major congenital abnormalities • Life threatening infection • Grade 3 or 4 IVH • Urine output < 1 mL/kg/h during the preceding 8h • Serum creatinine level of >1.6 mg/dL • Platelet count of <60,000 mm^3 • Tendency to bleed • Hyperbilirubinemia requiring exchange transfusion • Pulmanory hpyertension		control) within 24 h following the last dose of ibuprofen, usually on the fourth day of life.	Day 4, mean (SD) Platelet count (x1000)(mm^3) Ibuprofen= 206 (94) Control= 170 (85) Urea (mg/dL) Ibuprofen= 99.5 (52) Control= 92 (56) Creatinine (mg/dL) Ibuprofen= 1 (0.4) Control= 0.91 (0.5) Bilirubin (mg/dL) Ibuprofen= 5.3 (1.6) Control= 5.6 (2.4) NEC, n (%) Ibuprofen= 2/19 (10.5) Control= 5/17 (29.4)	risk (Did not specify if researchers or nurses were blinded) Blinding of outcome assessment- Low risk"Echocardiograms were performed by a cardiologist blinded to group (intervention or control) within 24 h following the last dose of ibuprofen, usually on the fourth day of life." Incomplete outcome data- Unclear risk (All randomised patients were accounted for in analysis; however, method such as ITT or per-protocol analysis was not reported for managing attrition) Selective reporting- Low risk (All stated outcomes were reported with respective ranges for medians and SDs for means) Other sources of bias- High risk (Study was stopped early, but reason was not stated.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					Power analysis was 72%, when necessary power level calculated was 80%.) **Other information**
Full citation Oncel, M. Y., Eras, Z., Uras, N., Canpolat, F. E., Erdeve, O., Oguz, S. S., Neurodevelopmental Outcomes of Preterm Infants Treated with Oral Paracetamol Versus Ibuprofen for Patent Ductus Arteriosus, American journal of perinatology, 34, 1185-1189, 2017 **Ref Id** 703644	**Sample size** n=61 Ibuprofen= 31 Paracetamol= 30 **Characteristics** Paracetamol group (n=30) Birth weight, g, mean (SD)= 991 (217) Gestational age, wk, mean (SD)= 28 (1.7) Gender, male, n (%)= 20 (66.7) Apgar score, 5 minutes, median (range)= 8 (5-9) Ibuprofen group (n=31) Birth weight, g, mean (SD)= 982 (186) Gestational age, wk, mean (SD)= 27.6 (1.9) Gender, male, n (%)= 14 (45.2)	**Interventions**	**Details** Neurodevelopmental follow-up was conducted by a team consisting of a neonatologist, a developmental pediatrician, an audiologist, and an ophthalmologist. A comprehensive assessment was performed at 18 to 24 months' corrected age by a certified and experienced examiner who was blind to the previous assignment of infants to oral paracetamol or ibuprofen groups. An	**Results** Neurodevelopmental impairment, n (%) Paracetamol= 9 (30) Ibuprofen= 10 (32.3) Moderate to severe cerebral palsy, n (%) Paracetamol= 4 (13.3) Ibuprofen= 2 (6.5) Blindness, n (%) Paracetamol= 0 (0) Ibuprofen= 1 (3.2) Deafness, n (%) Paracetamol= 0 (0) Ibuprofen= 1 (3.2) PDA closure rate (after the first course), n (%) Paracetamol= 26 (86.7) Ibuprofen= 23 (74.2)	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out **Study type** See Oncel 2014 for study details **Aim of the study** **Study dates** **Source of funding**	Apgar score, 5 minutes, median (range)= 8 (5-9) **Inclusion criteria** **Exclusion criteria**		experienced audiologist and ophthalmologist did the hearing and vision screening.	Reopening and closure with 2nd cure, n (%) Paracetamol= 4 (13.3) Ibuprofen= 4 (12.9) Surgical ligation rate, n (%) Paracetamol= 0 (0) Ibuprofen= 2 (6.5) NEC stage ≥ 2 Paracetamol= 1 (3.3) Ibuprofen= 0 (0)	
Full citation Oncel, M. Y., Yurttutan, S., Erdeve, O., Uras, N., Altug, N., Oguz, S. S., Canpolat, F. E., Dilmen, U., Oral paracetamol versus oral ibuprofen in the management of patent ductus	**Sample size** n= 80 Ibuprofen= 40 Paracetamol= 40 **Characteristics** Ibuprofen group (n=65) Birth weight, g, mean (SD)= 973 (224)	**Interventions** Intervention 1= Oral paracetamol at a dose of 15 mg/kg every 6 hours for 3 days Intervention 2= Oral ibuprofen at an initial dose of 10 mg/kg followed by 5 mg/kg at 24 and 48 hours.	**Details** 80 patients completed the study protocol. Both paracetamol and ibuprofen were administered via an orogastric tube, which was flushed with 1-2 mL of sterile water to	**Results** Mortality prior to discharge Ibuprofen, n (%)= 2 (5) Paracetamol, n (%)= 3 (7.5) **Total (< 30 weeks), n/total**	**Limitations** The quality assessment was performed using the Cochrane risk of bias tool for RCTs Random sequence generation- high risk ("The patients were randomly assigned to a treatment group by

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
arteriosus in preterm infants: a randomized controlled trial, Journal of Pediatrics, 164, 510-4.e1, 2014 **Ref Id** 726809 **Country/ies where the study was carried out** Turkey **Study type** RCT **Aim of the study** The aim of the study was to compare the efficacy and safety of oral paracetamol and oral ibuprofen to close PDA in preterm infants. **Study dates** February to December 2012	Gestational age, wk, mean (SD)= 27.3 (2.1) Gender, male, n (%)= 19 (47.5) Apgar score, 1 minute, median (IQR)= 5 (1-7) Apgar score, 5 minutes, median (IQR)= 7 (5-9) Antenatal steroids, n (%)= 30 (75) Placebo group (n=66) Birth weight, g, mean (SD)= 931 (217) Gestational age, wk, mean (SD)= 27.3 (1.7) Gender, male, n (%)= 23 (57.5) Apgar score, 1 minute, median (IQR)= 5 (2-7) Apgar score, 5 minutes, median (IQR)= 8 (5-9) Antenatal steroids, n (%)= 30 (75) **Inclusion criteria** • Gestational age ≤ 30 weeks • Birth weight ≤ 1250g • Postnatal age 48-96 hours • 1 of the following echocardiographic criteria: a duct size >1.5mm, a left atrium to aorta ratio > 1/5. end diastolic reversal of blood flow in the aorta, or		ensure delivery of the drug. An exclusive breast milk diet was attempted for all infants from the first day of life, and all infants continued their current enteral feeding regimen during the study. 1 day after the treatment, an echocardiographic evaluation was performed by a pediatric cardiologist who was blinded to the treatment group to determine the success of the treatment and the need for a second course via the same route. For all patients enrolled in the study, fluid intake was started at 70-80 mL/kg per day and was increased by increments of 10-20 mL/kg each day, to a maximum of 150 mL/kg per day.	PDA closure rate (after 1st course) Ibuprofen= 31/40 Paracetamol=29/40 Reopening and closure with 2nd cure Ibuprofen=5/40 Paracetamol=7/40 Surgical ligation rate Ibuprofen=2/40 Paracetamol=1/40 **< 28 weeks, n (%)** PDA closure rate (after 1st course) Ibuprofen=11/19 Paracetamol=17/23 Reopening and closure with 2nd cure Ibuprofen=4/19 Paracetamol=7/23 Surgical ligation rate Ibuprofen=2/19 Paracetamol=1/23 **≤ 26 weeks, n (%)** PDA closure rate (after 1st course) Ibuprofen=9/16 Paracetamol=10/23	cards in sequentially numbered sealed opaque envelopes, and 80 patients completed the study protocol.") Allocation concealment- unclear risk (Study did not discuss methods of allocation) Blinding of participants and personnel- Unclear risk (Study did not discuss whether parents, nurses, other physicians, or researchers were blinded) Blinding of outcome assessment- Low risk ("One day after the treatment, an echocardiographic evaluation was performed by a pediatric cardiologist who was blinded to the treatment group to determine the success of the treatment and the need for a second course via the same route.")

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding Not reported	poor cardia function in addition to clinical signs of PDA **Exclusion criteria** • Presence of major congenital abnormalities, right to left ductal shunting, life threatening infection, grade 3 or 4 IVH, urine output less than 1 mL/kg/h during the preceding 8 hours, serum creatinine level > 1.6 mg/dL, platelet count <60,000/mm^3, liver failure, hyperbilirubinemia requiring exchange transfusion, persistent pulmonary hypertension			Reopening and closure with 2nd cure Ibuprofen=4/16 Paracetamol=6/23 Surgical ligation rate Ibuprofen=2/16 Paracetamol=1/23 BUN (mg/dL), mean (SD) Ibuprofen pre-treatment= 60.3 (21.5) Ibuprofen post-treatment= 60.9 (29.6) Paracetamol pre-treatment= 62.1 (25.7) Paracetamol post-treatment= 55.1 (22.8) Serum creatinine (mg/dL), mean (SD) Ibuprofen pre-treatment= 0.66 (0.22) Ibuprofen post-treatment= 0.72 (0.24)	Incomplete outcome data- Unclear risk (Study did not discuss the methods for managing attrition, such as using intention to treat analysis or per protocol analysis) Selective reporting- Low risk (All stated outcomes were reported) Other sources of bias- Low risk **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Paracetamol pre-treatment= 0.77 (0.21) Paracetamol post-treatment= 0.75 (0.23) Urine output (mL/kg/h), mean (SD) Ibuprofen pre-treatment= 2.4 (0.87) Ibuprofen post-treatment= 2.3 (0.93) Paracetamol pre-treatment= 2.72 (0.76) Paracetamol post-treatment= 2.31 (0.68) NEC Ibuprofen, n (%)= 10 (25) Paracetamol, n (%)= 12 (30) Gastrointestinal bleeding Ibuprofen, n (%)= 1 (2.5) Paracetamol, n (%)= 0	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Overmeire, B, Allegaert, K, Casaer, A, Debauche, C, Decaluwé, W, Jespers, A, Weyler, J, Harrewijn, I, Langhendries, Jp, Prophylactic ibuprofen in premature infants: a multicentre, randomised, double-blind, placebo-controlled trial, Lancet (london, england), 364, 1945-1949, 2004 **Ref Id** 726831 **Country/ies where the study was carried out** Belgium **Study type**	**Sample size** n= 415 Ibuprofen= 205 Placebo= 210 **Characteristics** Ibuprofen group (n=205) Birth weight, g, mean (SD)= 1048 (315) Gestational age, wk, mean (SD)= 28.1 (1.7) Gender, male, n (%)=19 (47.5) Clinical chorioamnionitis, n (%)= 42 (20) Prolonged rupture of membranes, n (%)=72 (35) Antenatal steroids, n (%)= 169 (82) Placebo group (n=210) Birth weight, g, mean (SD)=1065 (324) Gestational age, wk, mean (SD)=28.1 (1.6) Gender, male, n (%)=23 (57.5) Clinical chorioamnionitis, n (%)=54 (21) Prolonged rupture of membranes, n (%)=69 (33) Antenatal steroids, n (%)= 180 (86)	**Interventions** Intervention= Intravenous 3 doses of ibuprofen lysine as an initial dose of 10 mg/kg within the first 6 h of life, followed by two doses of 5 mg/kg after 24 h and 48 h Control= 3 doses of saline as an initial dose of 1 mL/kg, followed by 0.5 mL/kg after 24 h and 48 h	**Details** Randomisation was performed independently by the chief pharmacist at each hospital in a 1-1 ratio between ibuprofen and placebo, in blocks of 10. The study preparations were delivered in 2mL glass vials containing either 20 mg ibuprofen with 14 mg lysine in water or normal saline. Fluid was given according to standard guidelines.	**Results** Mortality prior to discharge Ibuprofen, n (%)= 23 (11) Placebo, n (%)= 25 (12) BPD Ibuprofen, n (%)= 103 (50) Placebo, n (%)= 97 (46) Closed on day 3, n/total Ibuprofen=172/205 Placebo=126/210 24-26 weeks, n/total Ibuprofen=39/50 Placebo=25/51 27-28 weeks, n/total Ibuprofen=65/80 Placebo=50/84 29-30 weeks, n/total Ibuprofen=68/75 Placebo=51/75 Reopened after closure on day 3, n/total Ibuprofen=5/205 Placebo=7/210	**Limitations** The quality assessment was performed using the Cochrane risk of bias tool for RCTs Random sequence generation- Low risk ("Randomisation was done independently by the chief pharmacist at each hospital in a 1 to 1 ratio between ibuprofen and placebo, in blocks of ten.") Allocation concealment- Low risk ("The attending and consulting physicians, nurses, study collaborators, and parents were unaware of treatment allocation.") Blinding of participants and personnel- Low risk ("The attending and consulting physicians, nurses, study collaborators,

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Multi-centre, placebo-controlled, double-blinded trial **Aim of the study** The aim of the study was to assess the efficacy of early ibuprofen in reducing severe IVH and PDA. **Study dates** February 1999 - September 2001 **Source of funding** Not reported	**Inclusion criteria** • Gestational age 24-30 weeks • Written informed consent signed by parents **Exclusion criteria** • Major congenital malformation or chromosomal anomaly, intraventricular haemorrhage higher than grade 1 already detected during baseline cranial ultrasonography, an Apgar score at 5 minutes of less than 5, signs of congenital infection or life-threatening septicaemia, uncontrolled hypotension, or contraindications for administration of ibuprofen (eg, serum creatinine greater than 115 µmol/L or serum bilirubin more than 85			Rescue treatment, n/total Ibuprofen=13/205 Placebo=42/210 Ligated, n/total Ibuprofen=5/205 Placebo=10/210 Urine production (ml/kg/h), mean (SD) Day 1 Ibuprofen=1.4 (1.1) Placebo=2.3 (1.4) Day 3 Ibuprofen=3.8 (1.7) Placebo=4.0 (1.6) Oliguria < 0.5 mL/kg/h on days 1 to 3, n (%) Ibuprofen=45 (22) Placebo=30 (14) Serum creatinine (µmol/L), mean (SD) Day 1 Ibuprofen=72 (19) Placebo=69 (16) Day 3 Ibuprofen=101 (25) Placebo=88 (19) NEC stage 3 Ibuprofen, n (%)= 6 (3) Placebo, n (%)= 12 (6)	and parents were unaware of treatment allocation.") Blinding of outcome assessment- Unclear risk (blinding of outcome assessment not described) Incomplete outcome data- Low risk ("Data were analysed by intention to treat.") Selective reporting- Low risk (All stated outcomes were reported with ranges and SDs) Other sources of bias- Low risk **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	μmol/L, platelet count less than 60"109/L, tendency to bleed as revealed by haematuria, blood in the endotracheal or gastric aspirate or stools, or oozing from puncture sites)				
Full citation Sosenko,I.R., Fajardo,M.F., Claure,N., Bancalari,E., Timing of patent ductus arteriosus treatment and respiratory outcome in premature infants: a double-blind randomized controlled trial, Journal of Pediatrics, 160, 929-935, 2012 **Ref Id** 199166 **Country/ies where the study was carried out**	**Sample size** n= 105 Ibuprofen= 54 Placebo= 51 **Characteristics** Ibuprofen group (n=205) Birth weight, g, mean (SD)=854 (204) Gestational age, wk, median (IQR)=26 (23-28) Gender, female, n (%)=29 (54) Surfactant administration, n (%)=39 (72) Apgar score, 5 minutes, median (IQR)=7 (5-9) Antenatal steroids, n (%)= 46 (85) Placebo group (n=210) Birth weight, g, mean (SD)=842 (203)	**Interventions** Intervention: Ibuprofen lysine; initial dose of 10mg/kg, 2 doses of 5 mg/kg each, every 24 hours, by slow intravenous infusion Control: Placebo involved equivalent volumes of dextrose by slow intravenous infusion on the same schedule as the intervention group	**Details** After 24 hours of age, but not after 14 days of age, eligible infants were observed for the presence of early, mild symptoms of a PDA and when the initial echocardiogram results were negative for PDA, the enrolled infants were observed until 14 days of age, and a repeat echocardiogram was conducted when PDA symptoms developed. When the results of this repeat echocardiogram were positive, the baby was then randomised to one	**Results** Death or O_2 dependency at 36 weeks PMA All infants Ibuprofen, n (%)= 4 (7) Placebo, n (%)= 6 (12) **Repeat course of blinded study drug, first 28 days** All infants Ibuprofen, n (%)= 9/54 (17) Placebo, n (%)= 24/51 (47) **Open-label ibuprofen, first 28 days** Ibuprofen, n (%)= 7/54 (13)	**Limitations** The quality assessment was performed using the Cochrane risk of bias tool for RCTs Random sequence generation- Low risk ("randomized (via sealed envelopes prepared by using a random number table) to one of two study groups") Allocation concealment- Low risk ("Clinicians, investigators and nursing staff were blinded to the study group to which the baby was assigned

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
US **Study type** Single-centre, placebo-controlled, double-blinded, randomised trial **Aim of the study** The aim of the study was to assess whether early ibuprofen treatment, at the outset of PDA symptoms, would improve respiratory outcomes in premature infants **Study dates** January 2008 to August 2010 **Source of funding** Ovation Pharmaceuticals; University of Miami	Gestational age, wk, median (IQR)=25 (24-29) Gender, female, n (%)=21 (41) Surfactant administration, n (%)=38 (75) Apgar score, 5 minutes, median (IQR)=7 (4-9) Antenatal steroids, n (%)= 45 (88) **Inclusion criteria** • Birth weight 500-1250g • Gestational age 23-32 weeks • >24 hours old but ≤ 14 days old **Exclusion criteria** • severely small for gestational age (>3 SD less than the mean birth weight for gestational age) or had major congenital malformations, proven sepsis (positive blood culture results), serum creatinine level >1.7, oliguria		of the two study groups. The two study groups were: 1) ‘‘Early’’ treatment (blinded ibuprofen); or 2) ‘‘Expectant’’ treatment (blinded placebo).	Placebo, n (%)= 10/51 (20) **NEC (requiring surgery)** All infants Ibuprofen (n=54), n (%)= 5 (9) Placebo (n=51), n (%)= 2 (4) **Spontaneous intestinal perforation** All infants Ibuprofen, n (%)= 2/54 (4) Placebo, n (%)= 4/51 (8)	and the medication the baby was receiving. Only the neonatal pharmacists were aware of the study group of each baby and were responsible for preparing the ‘‘blinded’’ ibuprofen or ‘‘blinded’’ placebo study drug.") Blinding of participants and personnel- Low risk ("Clinicians, investigators and nursing staff were blinded to the study group to which the baby was assigned and the medication the baby was receiving. Only the neonatal pharmacists were aware of the study group of each baby and were responsible for preparing the ‘‘blinded’’ ibuprofen or ‘‘blinded’’ placebo study drug.") Blinding of outcome assessment- Low risk Incomplete outcome

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	(urine output <1 cc/kg/hr), pulmonary hypertension (with right-to-left PDA shunt), abdominal pathology (abdominal distension, discoloration, abnormal abdominal radiograph), bleeding diathesis, terminal condition (intractable respiratory failure, intractable hypotension, no expectation of survival beyond 48 hours) • Infants with symptoms of a HS PDA				data- Low risk ("Data analyses were conducted on an intention-to-treat basis.") Selective reporting- Low risk (All stated outcomes were reported with ranges and SDs) Other sources of bias- High risk ("For both groups, treatment with ibuprofen (open label) was initiated only when symptoms of a HS PDA developed and a PDA was confirmed with echocardiography.") **Other information**

1

1 **Observational studies**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Laughon,M., Bose,C., Clark,R., Treatment strategies to prevent or close a patent ductus arteriosus in preterm infants and outcomes, Journal of Perinatology, 27, 164-170, 2007 **Ref Id** 254263 **Country/ies where the study was carried out** US **Study type** Retrospective cohort study **Aim of the study** The aim of the study was to describe the treatments used to prevent or treat PDA in preterm infants.	**Sample size** n= 4587 Ligation only= 701 PDA without treatment= 3886 **Characteristics** Ligation only (n=701) Gestational age, wk, median (IQR)=25 (24-27) Birth weight, g, median (IQR)=730 (624-895) Female, n (%)=313 (45) Apgar score, 1 minute, median (IQR)=5 (2-6) Apgar score, 1 minutes, median (IQR)=7 (6-8) Exposure to neonatal dexamethasone, n/total= 287/701 PDA without treatment (n=3882) Gestational age, wk, median (IQR)=27 (26-29) Birth weight, g, median (IQR)=970 (750-1220) Female, n (%)=1685 (43) Apgar score, 1 minute, median (IQR)=6 (3-7)	**Interventions** Ligation only= ligation of the PDA was performed and in whom there was no report of prior use of indomethacin PDA without treatment= diagnosis of PDA and win whom there was no report of treatment (i.e. indomethacin or ligation)	**Details** The study examined the cohorts in terms of demographic characteristics, mortality and common neonatal morbidities, including CLD, NEC, intestinal perforation, retinopathy of prematurity (ROP) and IVH. CLD was defined as treatment with oxygen at discharge or at 36 weeks postmenstrual age, whichever occurred first. The authors used the Vermont-Oxford Network operational definitions for other morbidities, which were confirmed during periodic audits.	**Results** **Critical outcomes** **Mortality before discharge** Mortality, n/total Ligation only=98/701 PDA without treatment=566/3886 Mortality among survivors > 2 days, n/total Ligation only=96/688 PDA without treatment=406/3647 Mortality among survivors ≥ 7 days Ligation only=82/667 PDA without treatment=286/3463 **Bronchpulmonary dysplasia (Oxygen dependency at 36 weeks corrected gestation or 28 days of age)**	**Limitations** **Selection** **Representativeness of the exposed cohort** a) truly representative * **Selection of the non exposed cohort** a) drawn from the same community as the exposed cohort* **Ascertainment of exposure** a) secure record* **Demonstration that outcome of interest was not present at start of study** a) no **Comparability** **Study controls for**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates 1997-2004 **Source of funding** The researchers stated that there was no financial disclosure to report	Apgar score, 1 minutes, median (IQR)=8 (7-9) Exposure to neonatal dexamethasone, n/total=1046/3882 **Inclusion criteria** • Born 23-30 weeks gestation • Cared for in NICUs managed by the Pediatrix Medical Group • Discharged from the unit **Exclusion criteria** Not reported			N/A **Neurodevelopmental outcomes at >18 months** N/A **Important outcomes** **Failure of patent ductus arteriosus closure** N/A **Renal impairment** N/A **Gastrointestinal complications** NEC Ligation only, n (%)= 86 (13) PDA without treatment, n (%)= 271 (7) Intestinal perforation	unclear **Study controls for any additional factor** unclear **Outcome** **Assessment of outcome** record linkage* **Was follow-up long enough for outcomes to occur** a) yes* **Adequacy of follow up of cohorts** a) complete follow up* **Other information** "The de-identified data set does not include data on how the diagnosis of a PDA was made or the echocardiographic findings in patients with a diagnosis. Similarly, there are no data on how the

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Ligation only, n (%)= 43 (6) PDA without treatment, n (%)= 66 (2)	clinician made the decision to treat a PDA when it was first diagnosed. Because of the way data is recorded on medication use, we only evaluated the first course of therapy and were unable to obtain information on dose. We did not evaluate the outcome of neonates exposed to multiple courses of indomethacin."
Full citation Madan, J. C., Kendrick, D., Hagadorn, J. I., Frantz, I. D., 3rd, National Institute of Child, Health, Human Development Neonatal Research, Network, Patent ductus arteriosus therapy: impact on neonatal and 18-month outcome, Pediatrics, 123, 674-81, 2009 **Ref Id**	**Sample size** n= 538 Primary surgery= 135 No treatment= 403 **Characteristics** Primary surgery (n=135) Gestational age, wk, mean (SD)=25.1 (1.4) Birth weight, g, mean (SD)=726 (133) Male, n (%)=77 (57) Antenatal steroids, n (%)=101 (75)	**Interventions** Intervention= primary surgical closure Control= Supportive treatment (Met clinical criteria for significant PDA and who received no indomethacin treatment or surgical ligation for PDA. Some patients who received supportive treatment received	**Details** We performed a cohort study using multicenter data prospectively collected for the NRN GDB. Inclusion of infants in the NRN GDB was approved by the institutional review board for each of the sites. Demographic details and clinical information related to presence of, and treatment for, PDA, as well as outcomes, were collected. Information was	**Results** **Critical outcomes** **Mortality before discharge** Mortality, n (%) Primary surgery= 40/135 (30) No treatment= 140/403 (35)	**Limitations** **Selection** **Representativeness of the exposed cohort** a) truly representative* **Selection of the non exposed cohort**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
727840 **Country/ies where the study was carried out** US **Study type** Retrospective cohort study **Aim of the study** The aim of the study was to assess different treatments for PDA as a risk factor for death or neurodevelopmental impairment at 18 or 22 months, BPD, or NEC in extremely low birth weight infants. **Study dates** 2000-2004 **Source of funding** The study reported that there were no financial	Indomethacin within 24hr, n (%)=17 (13) No treatment (n=403) Gestational age, wk, mean (SD)=25.6 (1.5) Birth weight, g, mean (SD)=758 (148) Male, n (%)=211 (52) Antenatal steroids, n (%)=304 (76) Indomethacin within 24hr, n (%)=119 (30) **Inclusion criteria** • Survived > 72 hours • Developed clinically significant PDA • Had 18 to 22 month neurodevelopmental follow up before October 27, 2006 **Exclusion criteria**	prophylactic indomethacin before the diagnosis of PDA)	collected regarding indomethacin administration within the first 24 hours of life, whether for PDA or IVH prophylaxis. Details regarding clinicians' choice of therapy, several complications of prematurity, and therapy for PDA other than indomethacin or surgery were not available. Illness severity scores were unavailable; therefore, the presence of RDS and the number of doses of surfactant were used as markers of illness severity.	**Bronchpulmonary dysplasia (Oxygen dependency at 36 weeks corrected gestation or 28 days of age)** N/A **Neurodevelopmental outcomes at >18 months** N/A **Important outcomes** **Failure of patent ductus arteriosus closure** N/A **Renal impairment** N/A **Gastrointestinal complications** N/A	a) drawn from the same community as the exposed cohort* **Ascertainment of exposure** a) secure record* **Demonstration that outcome of interest was not present at start of study** b) no **Comparability** **Study controls for** GA, gender* **Study controls for any additional factor** Center, birth weight, RDS, prophylactic indomethacin* **Outcome** **Assessment of outcome** b) record linkage*

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
relationships relevant to disclose	• Congenital heart disease or chromosomal abnormalities • Insufficient follow-up data to determine outcome at 18 or 22 months				**Was follow-up long enough for outcomes to occur** a) yes (18 to 22 months)* **Adequacy of follow up of cohorts** a) complete follow up* **Other information** "Some patients who received supportive treatment received prophylactic indomethacin before the diagnosis of PDA." "Details regarding clinicians' choice of therapy, several complications of prematurity, and therapy for PDA other than indomethacin or surgery were not available. Illness severity scores were unavailable; therefore, the presence of RDS and the number of doses of surfactant were used as markers of illness severity."

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Mirea, L., Sankaran, K., Seshia, M., Ohlsson, A., Allen, A. C., Aziz, K., Lee, S. K., Shah, P. S., Treatment of patent ductus arteriosus and neonatal mortality/morbidities: adjustment for treatment selection bias, J PediatrThe Journal of pediatrics, 161, 689-94.e1, 2012 **Ref Id** 744951 **Country/ies where the study was carried out** Canada **Study type** Retrospective cohort study	**Sample size** n= 904 Ligation only= 327 Conservative= 577 **Characteristics** Ligation only (n=327) Gestational age, wk, mean (SD)=26.0 (2.3) Female, n (%)=142 (43) Apgar score, 5 minutes, ≤ 5, n (%)=68 (22) Antenatal corticosteroid, n (%) None=56 (19) Partial=101 (35) Complete=134 (46) Conservative (n=577) Gestational age, wk, mean (SD)=28.3 (2.3) Female, n (%)=256 (44) Apgar score, 5 minutes, ≤ 5, n (%)=64 (11) Antenatal corticosteroid, n (%) None=103 (18) Partial=232 (42)	**Interventions** Conservative management alone= including fluid restriction and/or diuretics, without medical or surgical intervention) Surgical ligation only= performed in infants with PDA unresponsive to medical treatment or with contraindications to medical treatment	**Details** Secondary data analysis of data from 22 NICUs gathered in the Canadian Neonatal Network. Data were collected by trained abstractors at each site until each patient was discharged from the NICU according to a standard manual of protocols and definitions, and were entered directly from patient charts (recorded at each site) into computers using a customized data entry program with built-in error checking algorithms. Diagnosis of PDA was made clinically and/or echocardiographically.	**Results** **Critical outcomes** **Mortality before discharge** Ligation only, n (%)= 35 (10.7) Conservative, n (%= 72 (12.5) p value= 0.22 **Bronchpulmonary dysplasia (Oxygen dependency at 36 weeks corrected gestation or 28 days of age)** Ligation only, n (%)= 199 (66.3) Conservative, n (%)= 138 (27.1) p value < 0.0001	**Limitations** **Selection** **Representativeness of the exposed cohort** a) truly representative* **Selection of the non exposed cohort** a) drawn from the same community* **Ascertainment of exposure** a) secure record* **Demonstration that outcome of interest was not present at start of study** b) no **Comparability** **Study controls for**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study The aim of the study was to assess the association between treatment of PDA and neonatal outcomes in preterm infants. **Study dates** 2004 to 2008 **Source of funding** Not reported	Complete=222 (40) **Inclusion criteria** • Infants born between 2004-2008 • GA ≤ 32 weeks • Diagnosed with PDA from 22 NICUs in Canada **Exclusion criteria** • Infants with prophylactic treatment of indomethacin, who received indomethacin within the first 24 hours after birth • Died within 72 hours after birth • Congenital heart defects			**Neurodevelopmental outcomes at >18 months** N/A **Important outcomes** **Failure of patent ductus arteriosus closure** N/A **Renal impairment** N/A **Gastrointestinal complications** NEC stages 2 or 3 Ligation only, n (%)= 70 (34.3) Conservative, n (%)= 34 (6.0) p value < 0.0001	Sex, GA* **Study controls for any additional factor** Site, year of birth, cesarean birth, inborn/outborn* **Outcome** **Assessment of outcome** b) record linkage* **Was follow-up long enough for outcomes to occur** a) yes* **Adequacy of follow up of cohorts** a) complete follow up* **Other information** "Surgical ligation was performed in infants with PDA unresponsive to medical treatment or with contraindications to medical treatment. It is possible that infants were

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					initially provided with conservative treatment, and if this failed, infants were subsequently treated with indomethacin or ligation, or with indomethacin followed by ligation." "We note that some infants classified as conservatively treated could have received prophylactic indomethacin, thereby contaminating the control group, and reducing the observed impact of indomethacin treatment administered specifically for PDA; however, data regarding prophylactic indomethacin use were not available for adjustment."

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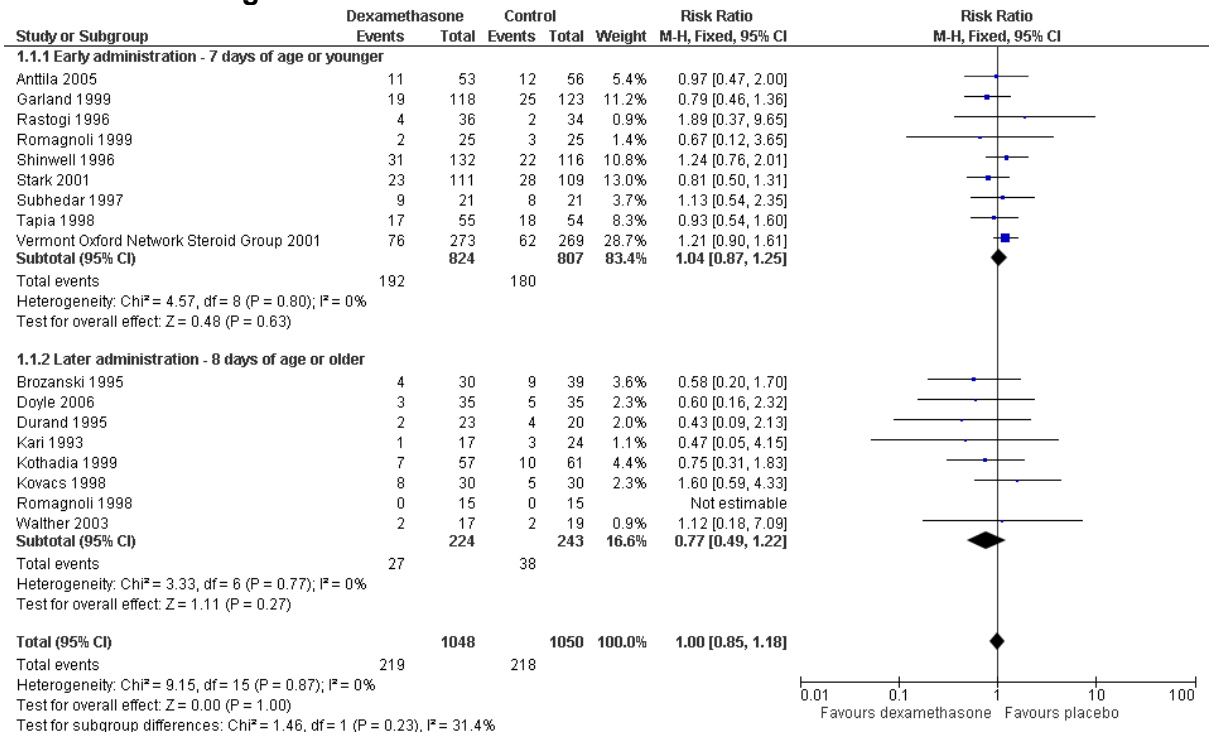
Appendix E – Forest plots

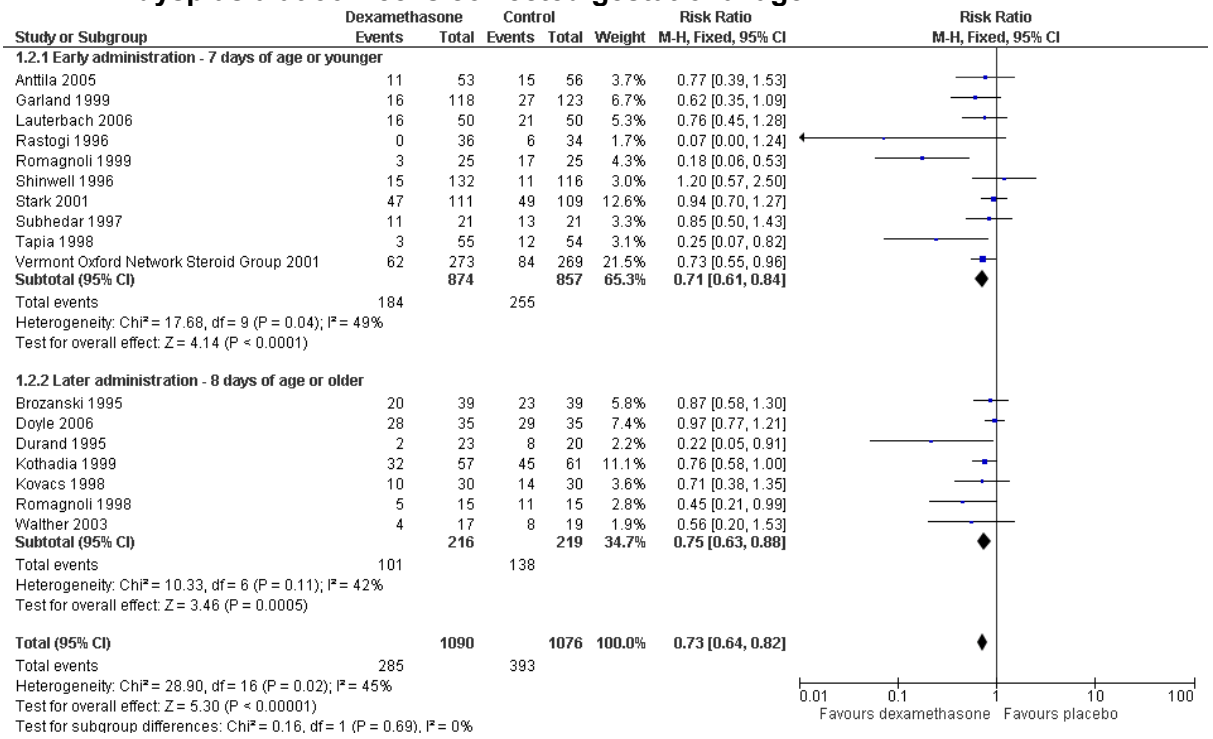
Forest plots for question 3.4 What is the effectiveness of corticosteroids in preterm babies requiring respiratory support?

Figure 1: Comparison 1.1. Dexamethasone versus placebo – mortality prior to discharge



CI: confidence interval; MD: mean difference; M-H: Mantel-Haenszel; RR: risk ratio

Figure 2: Comparison 1.1. Dexamethasone versus placebo – bronchopulmonary dysplasia at 36 weeks corrected gestational age



CI: confidence interval; MD: mean difference; M-H: Mantel-Haenszel; RR: risk ratio

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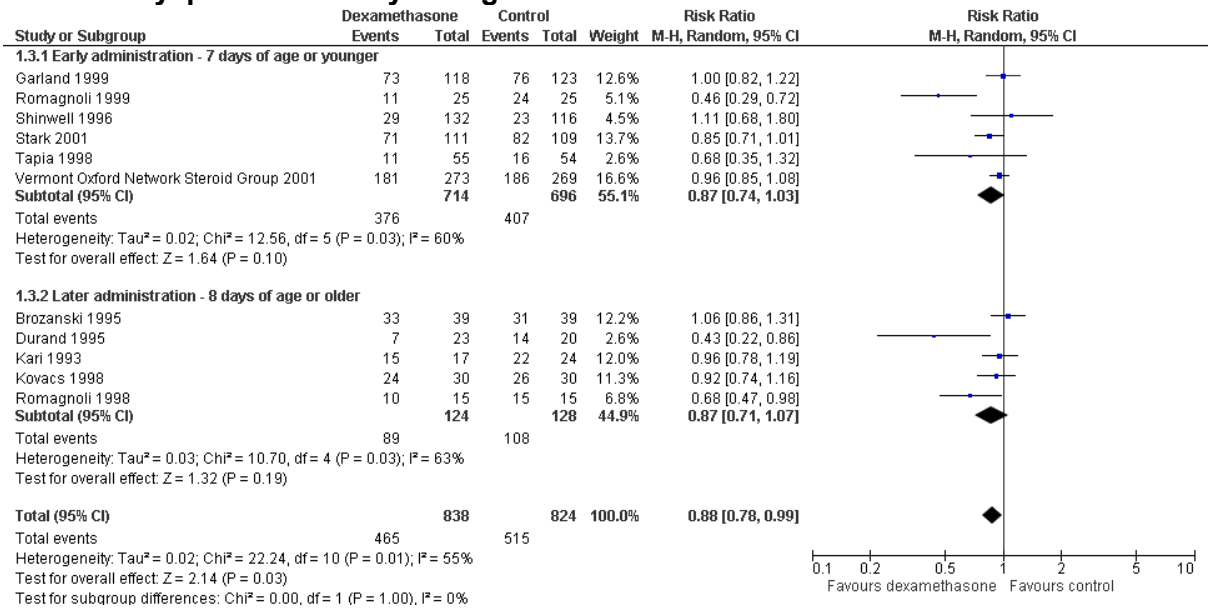
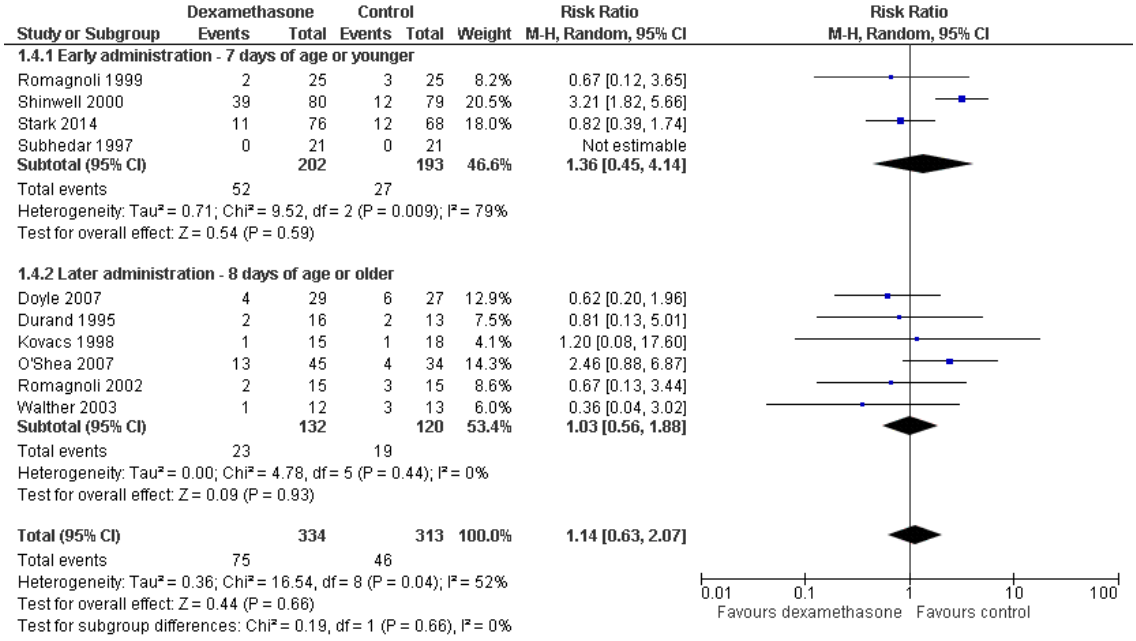
Figure 3: Comparison 1.1. Dexamethasone versus placebo– bronchopulmonary dysplasia at 28 days of age



CI: confidence interval; MD: mean difference; M-H: Mantel-Haenszel; RR: risk ratio

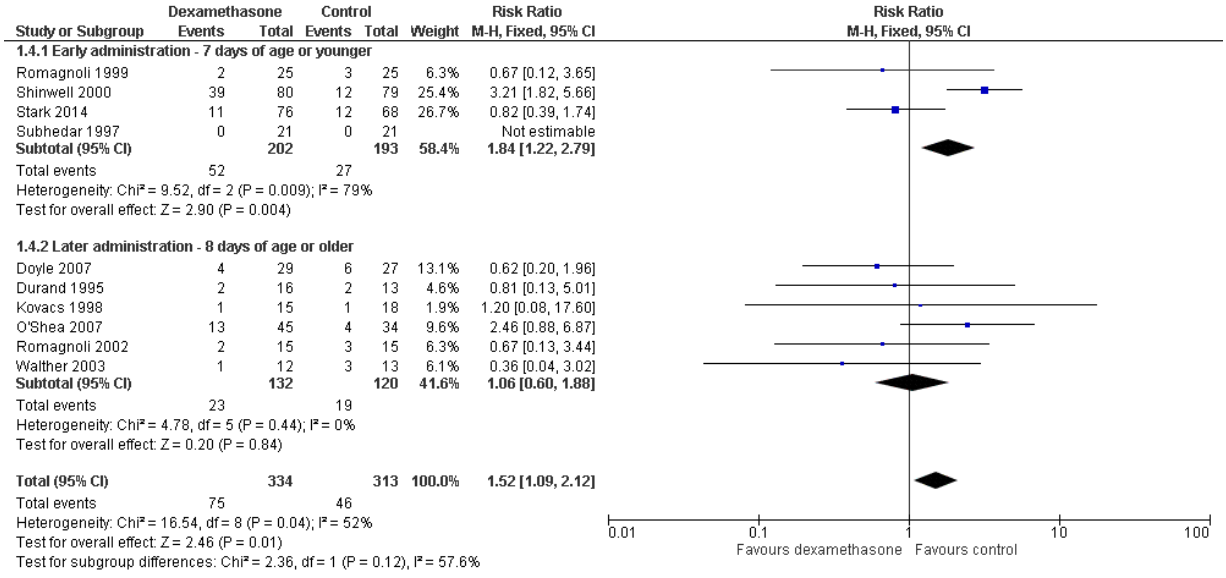
2

Figure 4: Comparison 1.1. Dexamethasone versus placebo – Neurodevelopmental outcomes: cerebral palsy at 18 months of age or older (random effects meta-analysis)



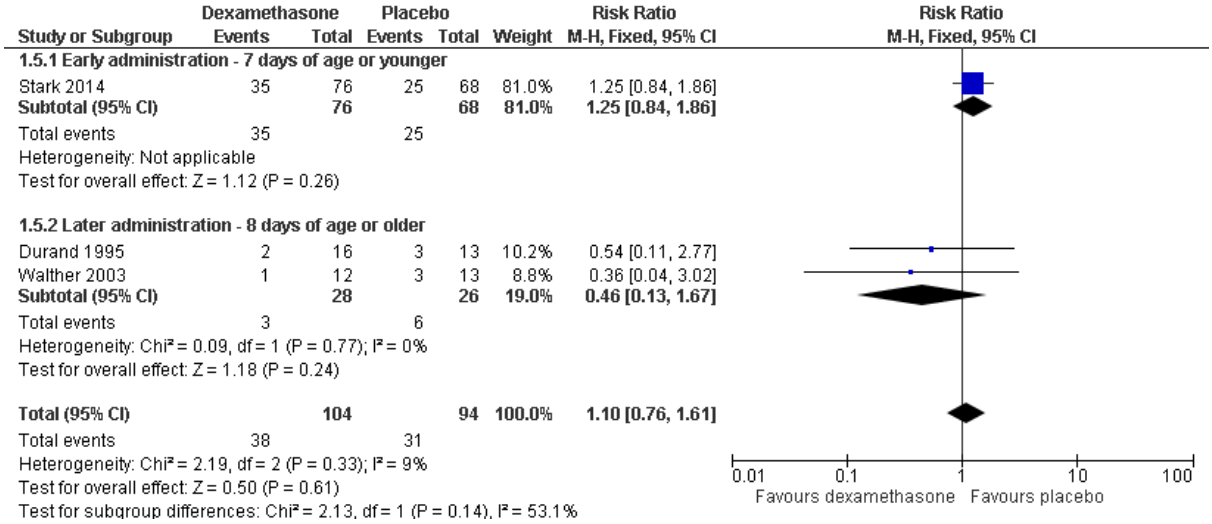
CI: confidence interval; MD: mean difference; M-H: Mantel-Haenszel; RR: risk ratio

Figure 5: Comparison 1.1. Dexamethasone versus placebo – Neurodevelopmental outcomes: cerebral palsy at 18 months of age or older (fixed effects meta-analysis)



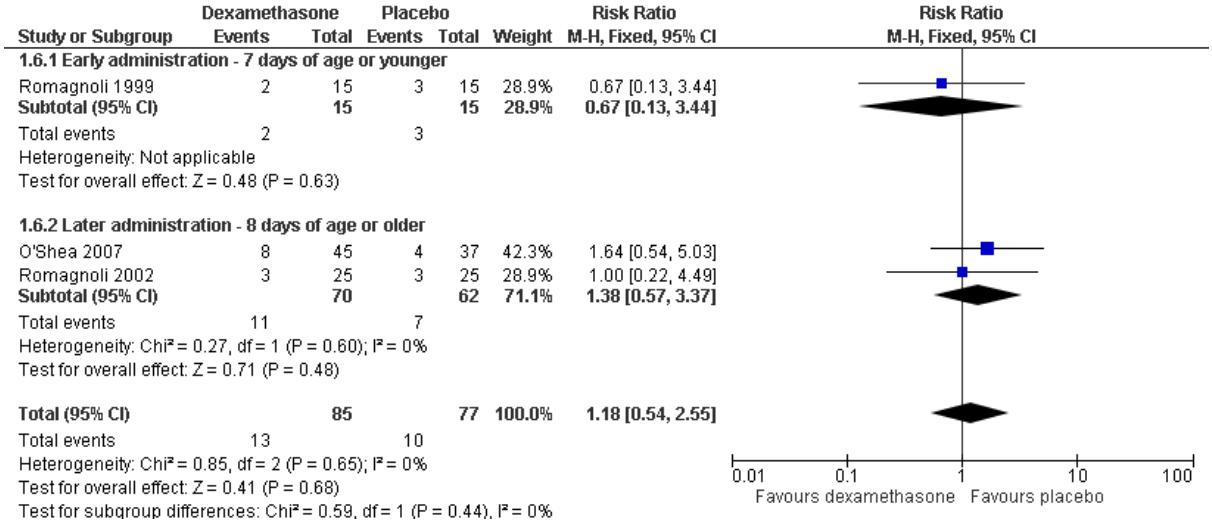
CI: confidence interval; MD: mean difference; M-H: Mantel-Haenszel; RR: risk ratio

Figure 6: Comparison 1.1. Dexamethasone versus placebo – Neurodevelopmental outcomes: severe cognitive impairment at 18 months of age or older



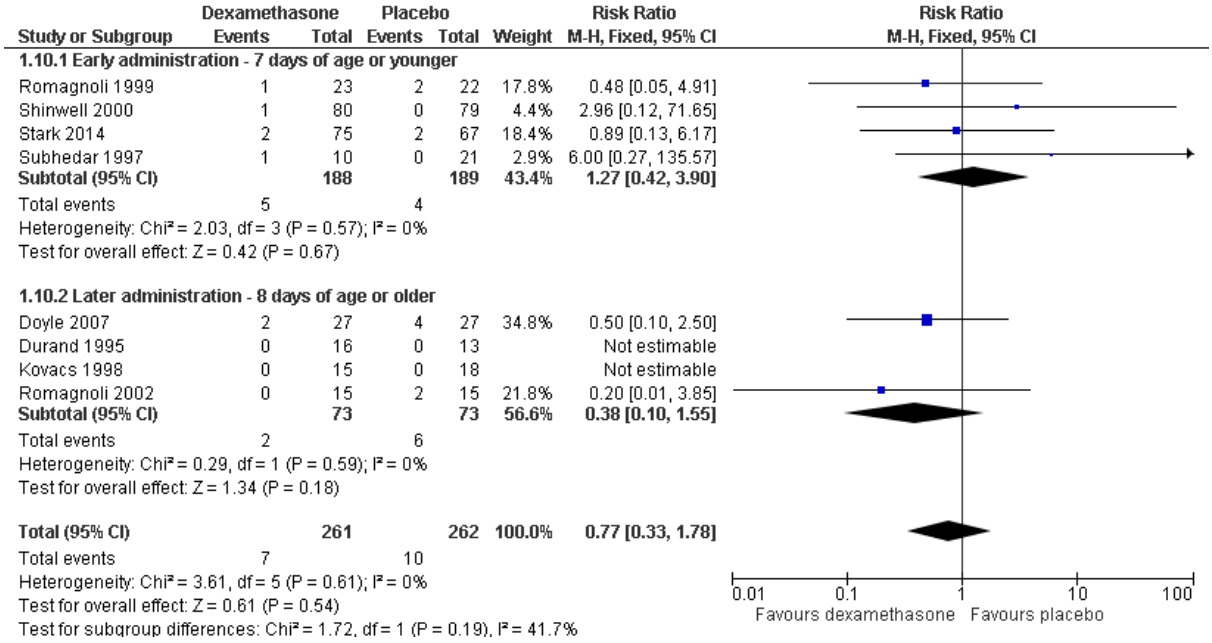
CI: confidence interval; MD: mean difference; M-H: Mantel-Haenszel; RR: risk ratio

Figure 7: Comparison 1.1. Dexamethasone versus placebo – Neurodevelopmental outcomes: severe intellectual impairment (IQ <70) at 18months of age or older



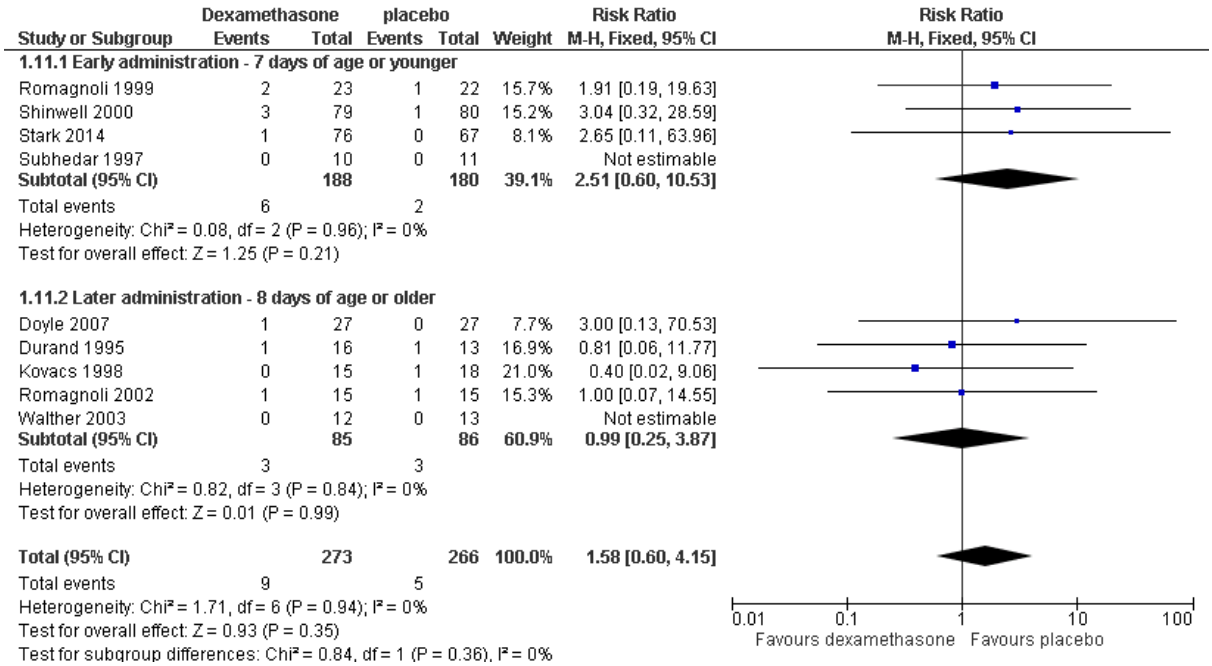
CI: confidence interval; MD: mean difference; M-H: Mantel-Haenszel; RR: risk ratio

Figure 8: Comparison 1.1. Dexamethasone versus placebo – Neurodevelopmental outcomes: severe blindness at 18 months of age or older



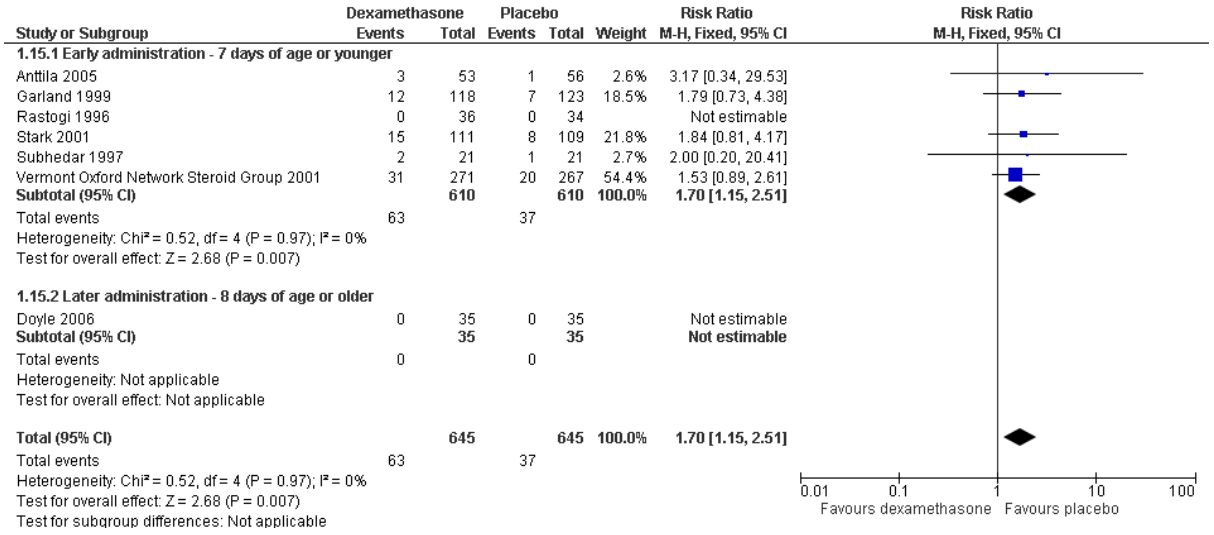
CI: confidence interval; MD: mean difference; M-H: Mantel-Haenszel; RR: risk ratio

Figure 9: Comparison 1.1. Dexamethasone versus placebo – Neurodevelopmental outcomes: severe deafness at 18 months of age or older



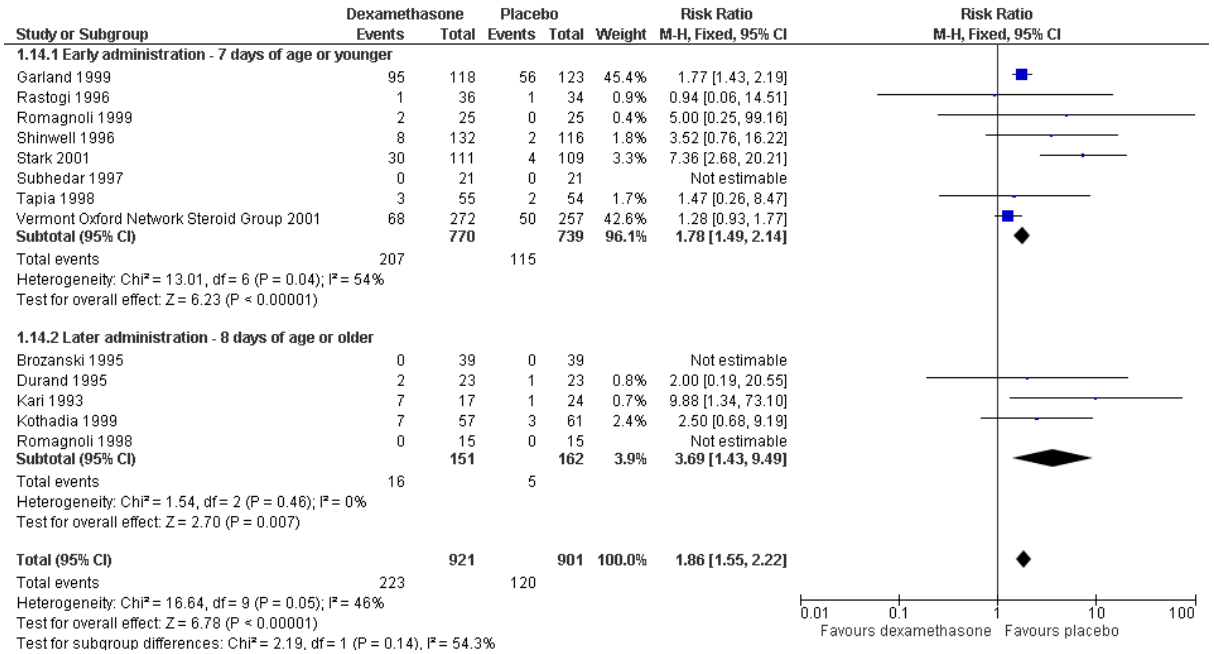
CI: confidence interval; MD: mean difference; M-H: Mantel-Haenszel; RR: risk ratio

Figure 10: Comparison 1.1. Dexamethasone versus placebo – gastro-intestinal perforation



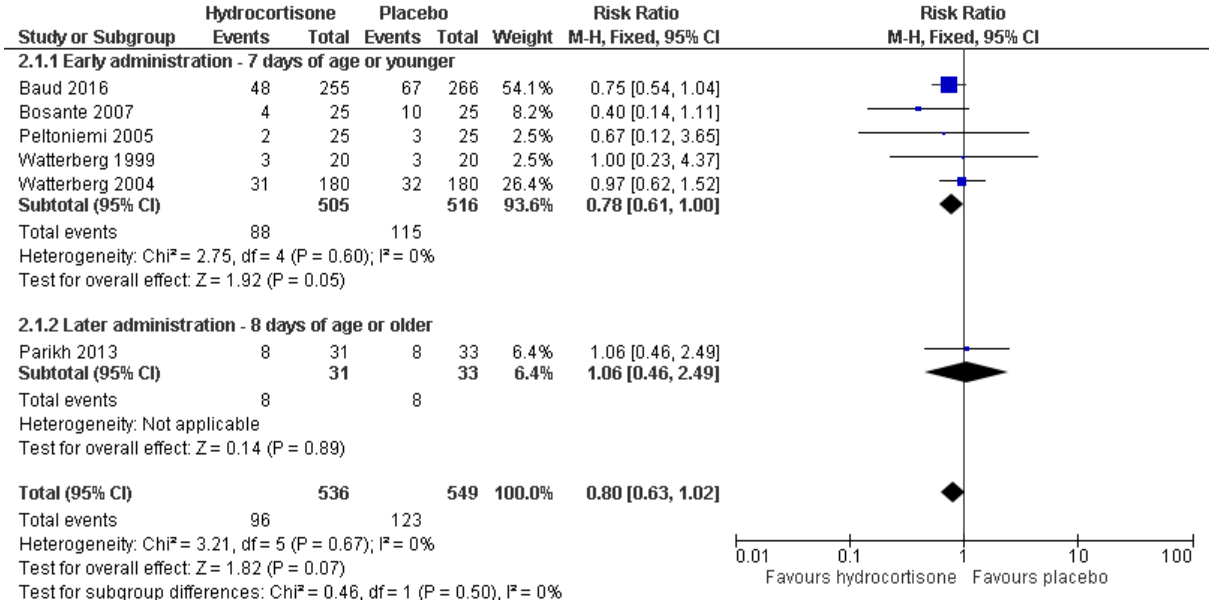
CI: confidence interval; MD: mean difference; M-H: Mantel-Haenszel; RR: risk ratio

Figure 11: Comparison 1.1. Dexamethasone versus placebo – hypertension



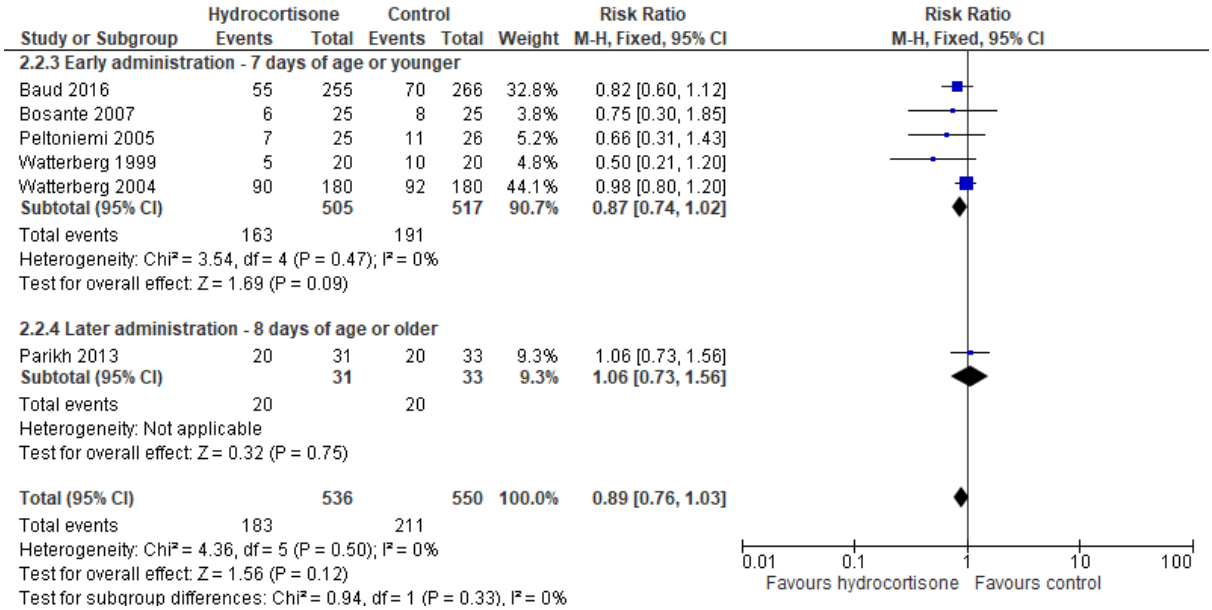
CI: confidence interval; MD: mean difference; M-H: Mantel-Haenszel; RR: risk ratio

Figure 12: Comparison 1.2. Hydrocortisone versus placebo – mortality prior to discharge



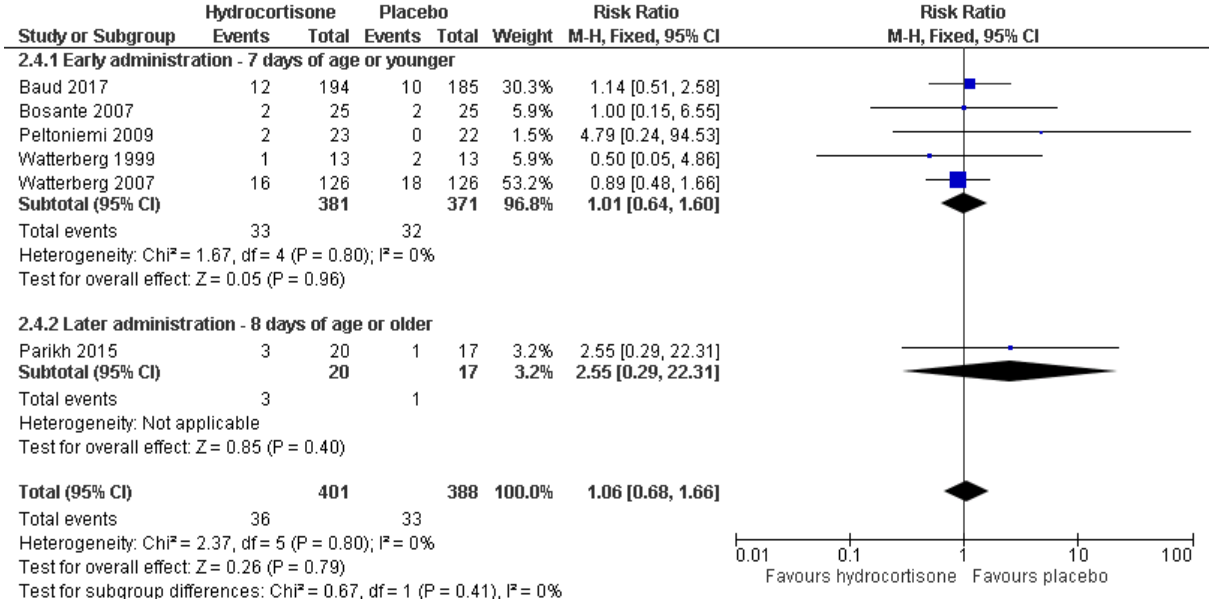
CI: confidence interval; MD: mean difference; M-H: Mantel-Haenszel; RR: risk ratio

Figure 13: Comparison 1.2. Hydrocortisone versus placebo – bronchopulmonary dysplasia at 36 weeks corrected gestational age



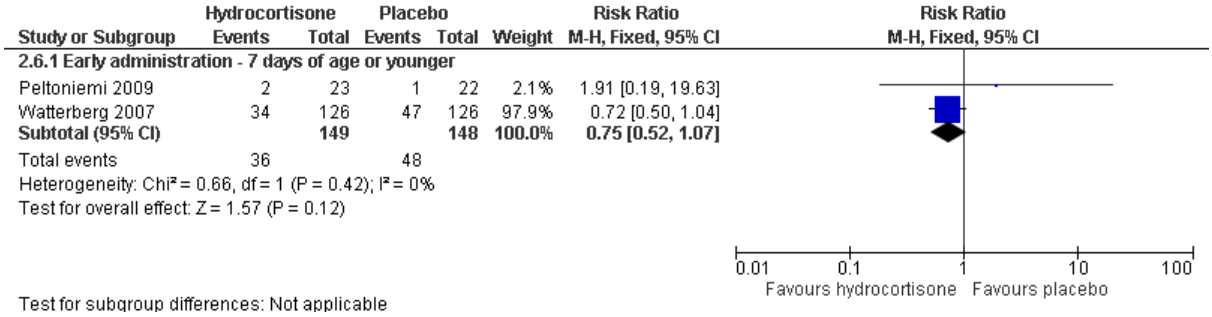
CI: confidence interval; MD: mean difference; M-H: Mantel-Haenszel; RR: risk ratio

Figure 14: Comparison 1.2. Hydrocortisone versus placebo – Neurodevelopmental



CI: confidence interval; MD: mean difference; M-H: Mantel-Haenszel; RR: risk ratio

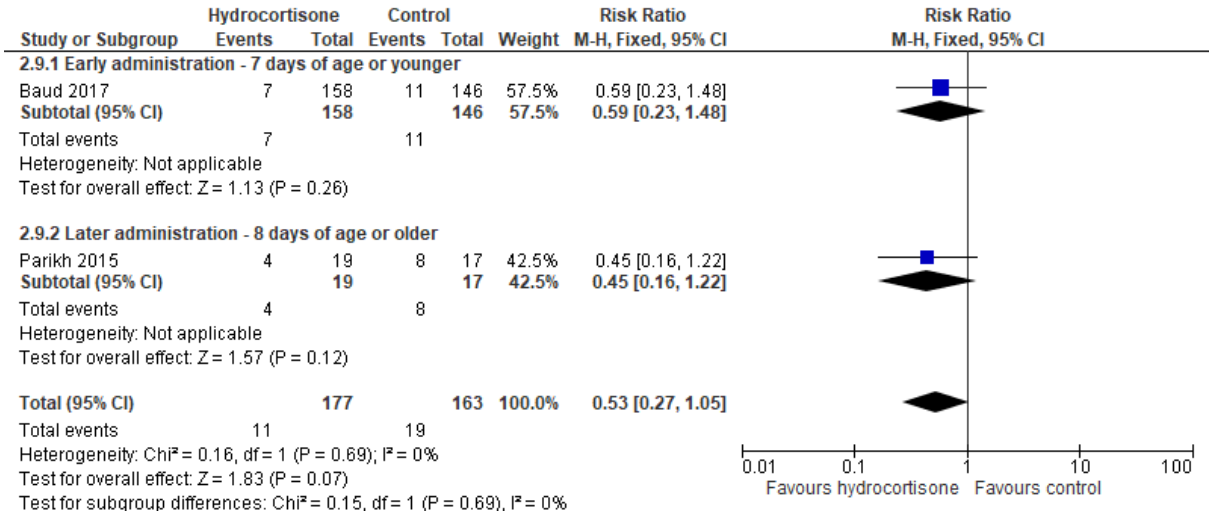
Figure 15: Comparison 1.2. Hydrocortisone versus placebo – severe cognitive impairment at 18 months of age or older



Test for subgroup differences: Not applicable

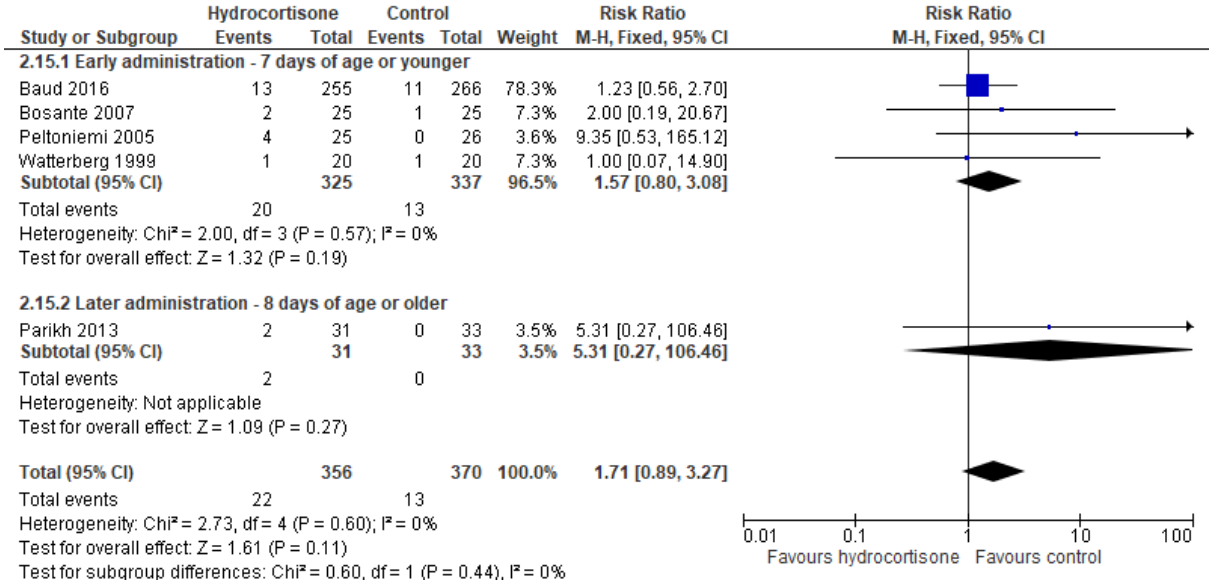
CI: confidence interval; MD: mean difference; M-H: Mantel-Haenszel; RR: risk ratio

Figure 16: Comparison 1.2. Hydrocortisone versus placebo – moderate or severe cognitive impairment at 18 months of age or older



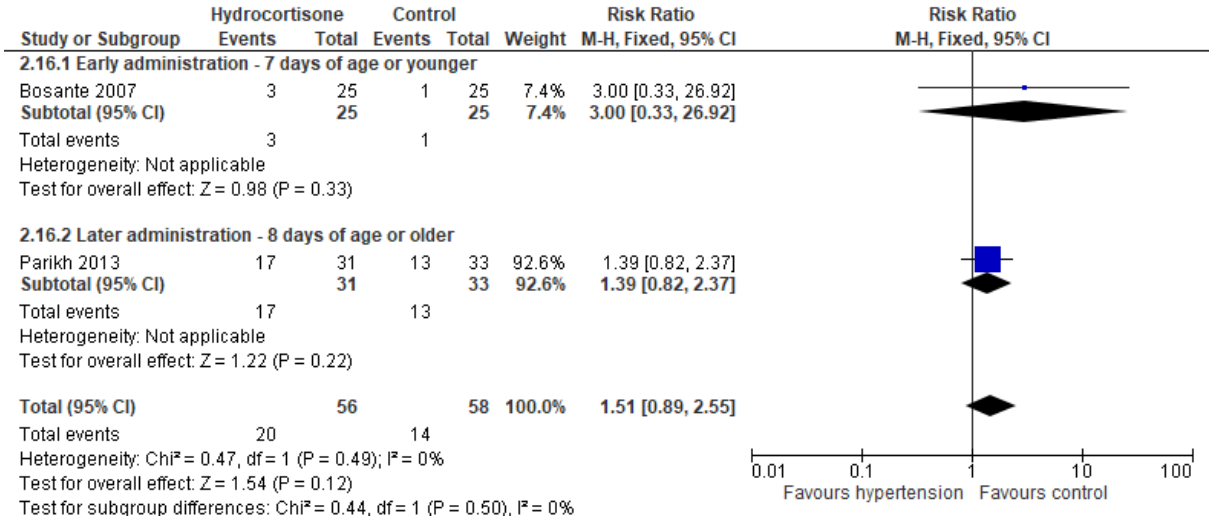
1 CI: confidence interval; MD: mean difference; M-H: Mantel-Haenszel; RR: risk ratio

Figure 17: Comparison 1.2. Hydrocortisone versus placebo – gastro-intestinal perforation



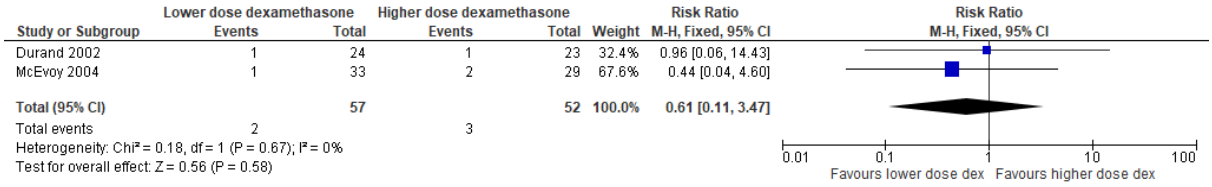
CI: confidence interval; MD: mean difference; M-H: Mantel-Haenszel; RR: risk ratio

Figure 18: Comparison 1.2. Hydrocortisone versus placebo – hypertension



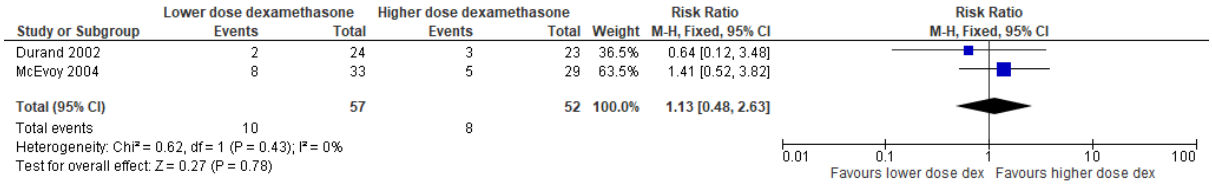
CI: confidence interval; MD: mean difference; M-H: Mantel-Haenszel; RR: risk ratio

Figure 19: Comparison 3.1. Lower cumulative dose of dexamethasone versus higher cumulative dose of dexamethasone – mortality prior to discharge



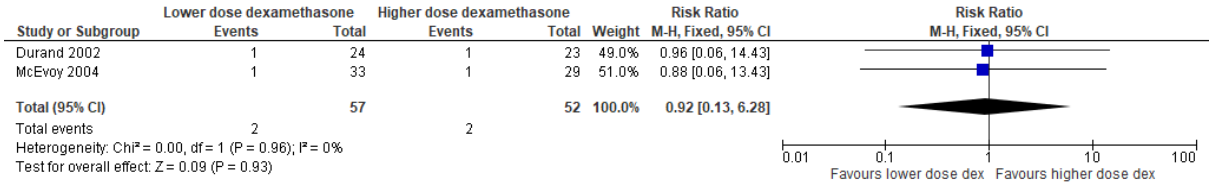
CI: confidence interval; Dex: dexamethasone; MD: mean difference; M-H: Mantel-Haenszel; RR: risk ratio

Figure 20: Comparison 3.1. Lower cumulative dose of dexamethasone versus higher cumulative dose of dexamethasone – bronchopulmonary dysplasia at 36 weeks corrected gestational age



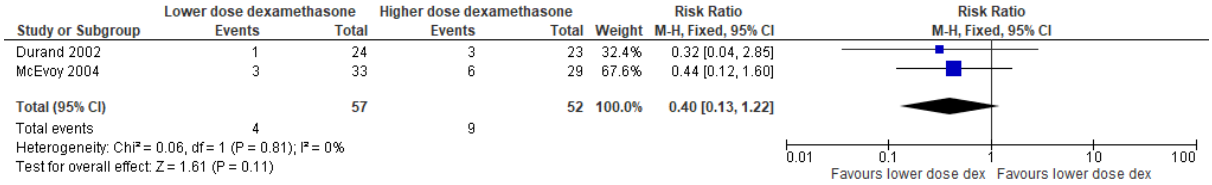
CI: confidence interval; Dex: dexamethasone; MD: mean difference; M-H: Mantel-Haenszel; RR: risk ratio

Figure 21: Comparison 3.1. Lower cumulative dose of dexamethasone versus higher cumulative dose of dexamethasone – gastro-intestinal perforation



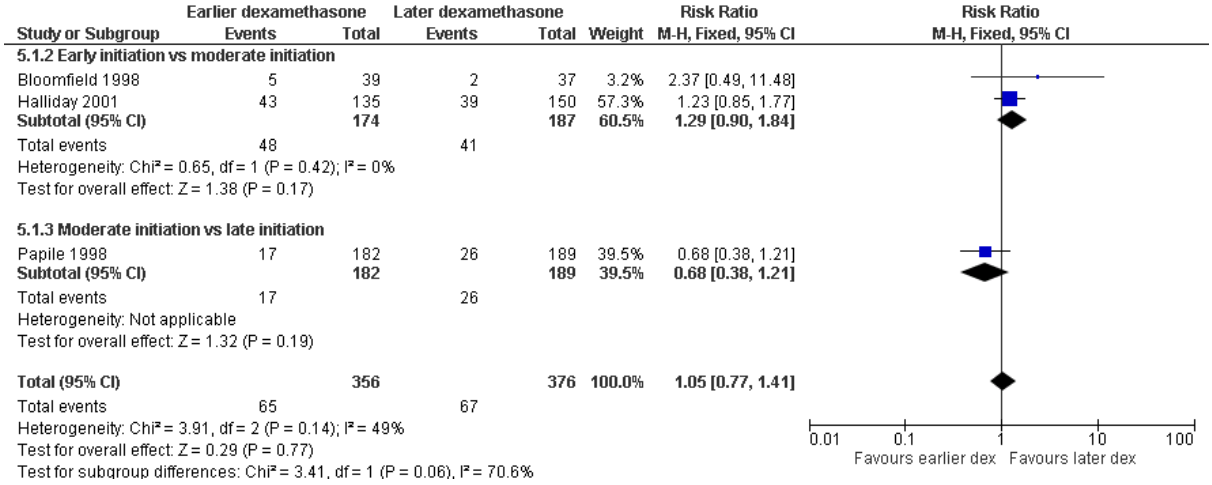
CI: confidence interval; Dex: dexamethasone; MD: mean difference; M-H: Mantel-Haenszel; RR: risk ratio

Figure 22: Comparison 3.1. Lower cumulative dose of dexamethasone versus higher cumulative dose of dexamethasone - hypertension



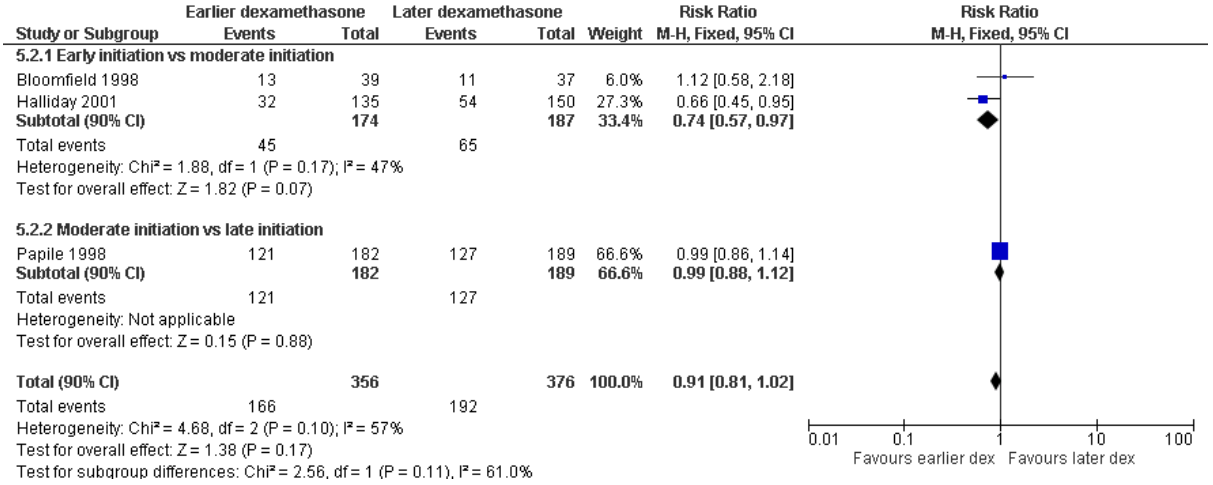
CI: confidence interval; Dex: dexamethasone; MD: mean difference; M-H: Mantel-Haenszel; RR: risk ratio

Figure 23: Comparison 4.1. Earlier initiation dexamethasone versus later initiation dexamethasone – mortality prior to discharge



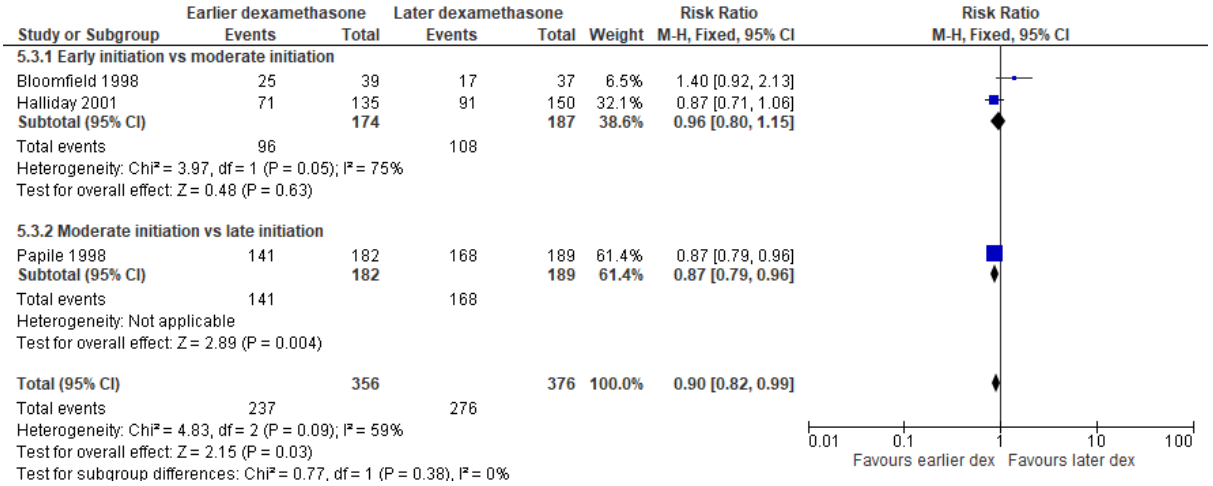
CI: confidence interval; Dex: dexamethasone; MD: mean difference; M-H: Mantel-Haenszel; RR: risk ratio

Figure 24: Comparison 4.1. Earlier initiation dexamethasone versus later initiation dexamethasone – bronchopulmonary dysplasia at 36 weeks corrected gestational age



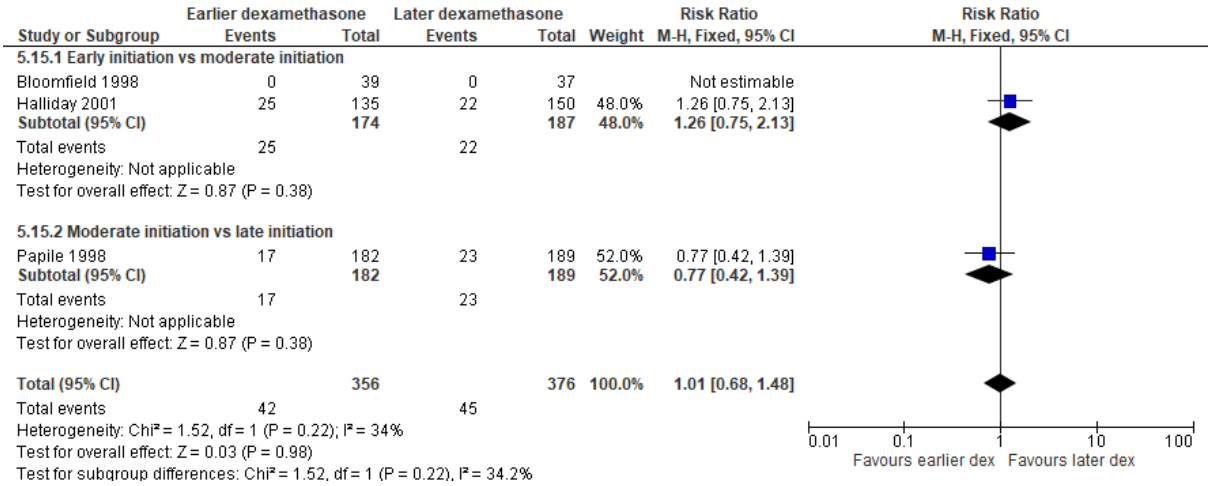
CI: confidence interval; Dex: dexamethasone; MD: mean difference; M-H: Mantel-Haenszel; RR: risk ratio

Figure 25: Comparison 4.1. Earlier initiation dexamethasone versus later initiation dexamethasone – bronchopulmonary dysplasia at 28 days of age



CI: confidence interval; Dex: dexamethasone; MD: mean difference; M-H: Mantel-Haenszel; RR: risk ratio

Figure 26: Comparison 4.1. Earlier initiation dexamethasone versus later initiation dexamethasone – hypertension



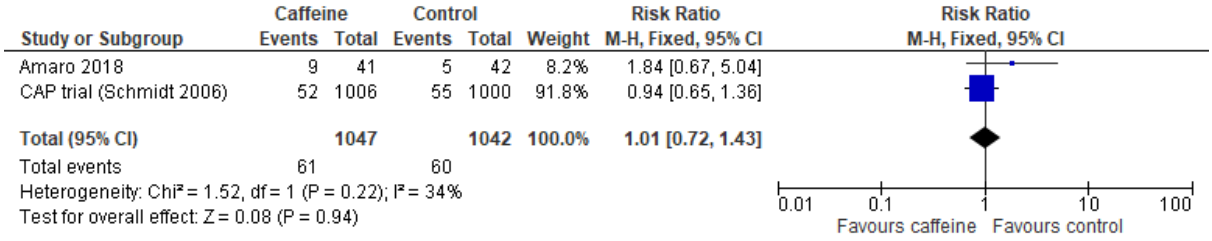
CI: confidence interval; Dex: dexamethasone; MD: mean difference; M-H: Mantel-Haenszel; RR: risk ratio

Forest plots for question 3.5 What is the safety and effectiveness of diuretics in preterm babies on respiratory support?

No meta-analyses were conducted for this review.

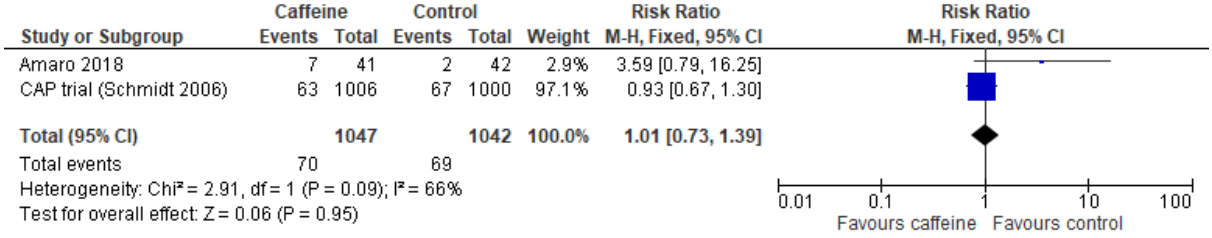
Forest plots for question 3.6 What is the effectiveness of caffeine in preterm babies requiring respiratory support?

Figure 27: Comparison 1: Caffeine versus placebo – Mortality prior to discharge



CI: confidence interval; M-H: Mantel-Haenszel

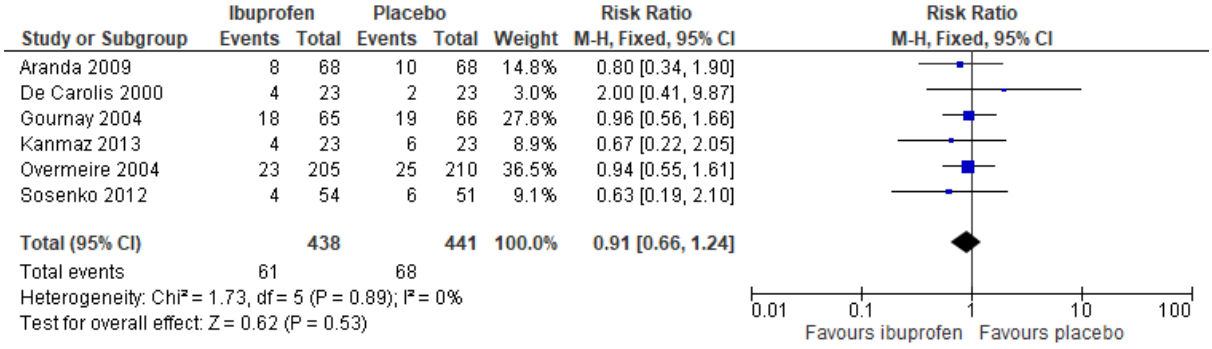
Figure 28: Comparison 1: Caffeine versus placebo – Necrotising enterocolitis



CI: confidence interval; M-H: Mantel-Haenszel

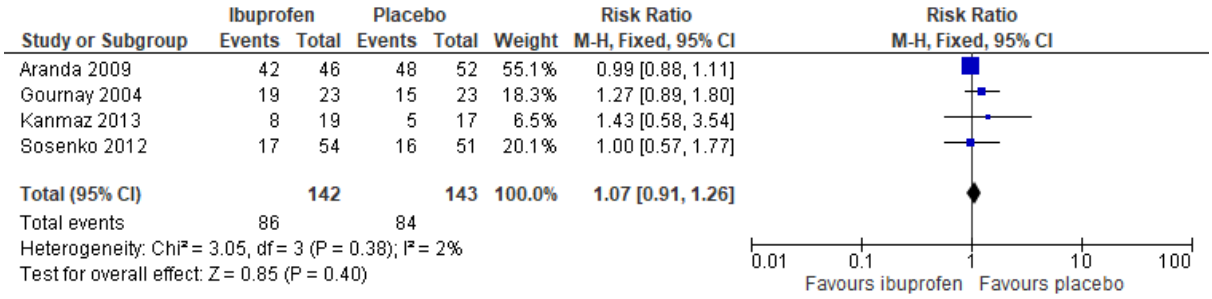
Forest plots for question 3.8 What is the effectiveness of interventions for closing a patent ductus arteriosus in preterm babies requiring respiratory support?

Figure 29: Comparison 1.1 Ibuprofen versus placebo – Mortality prior to discharge



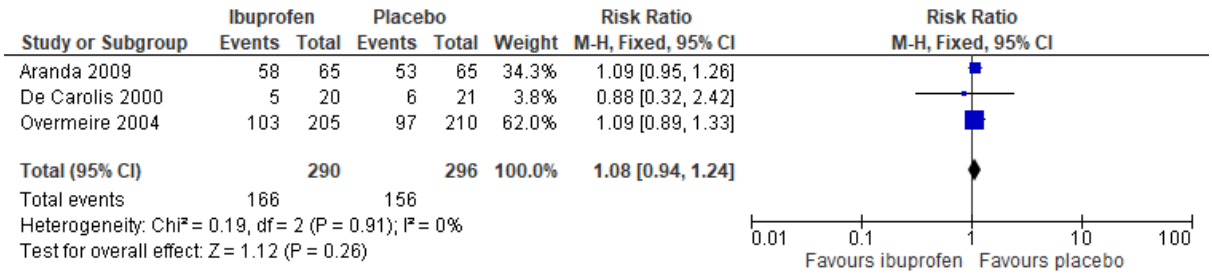
CI: confidence interval; M-H: Mantel-Haenszel

Figure 30: Comparison 1.1 Ibuprofen versus placebo – BPD at 36 weeks postmenstrual age



BPD: bronchopulmonary dysplasia; CI: confidence interval; M-H: Mantel-Haenszel

Figure 31: Comparison 1.1 Ibuprofen versus placebo – BPD at 28 days of life

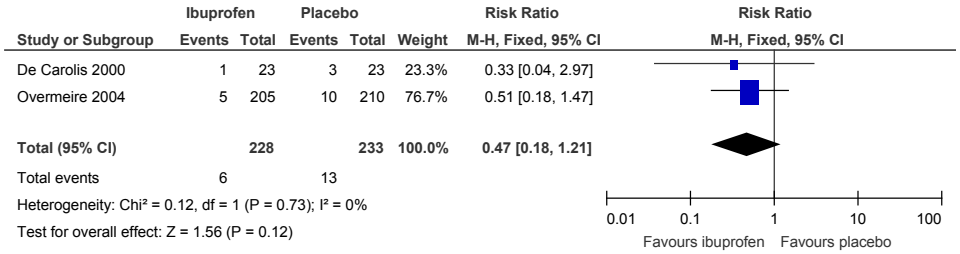


BPD: bronchopulmonary dysplasia; CI: confidence interval; M-H: Mantel-Haenszel

Figure 32: Comparison 1.1 Ibuprofen versus placebo – PDA required back-up treatment with indomethacin

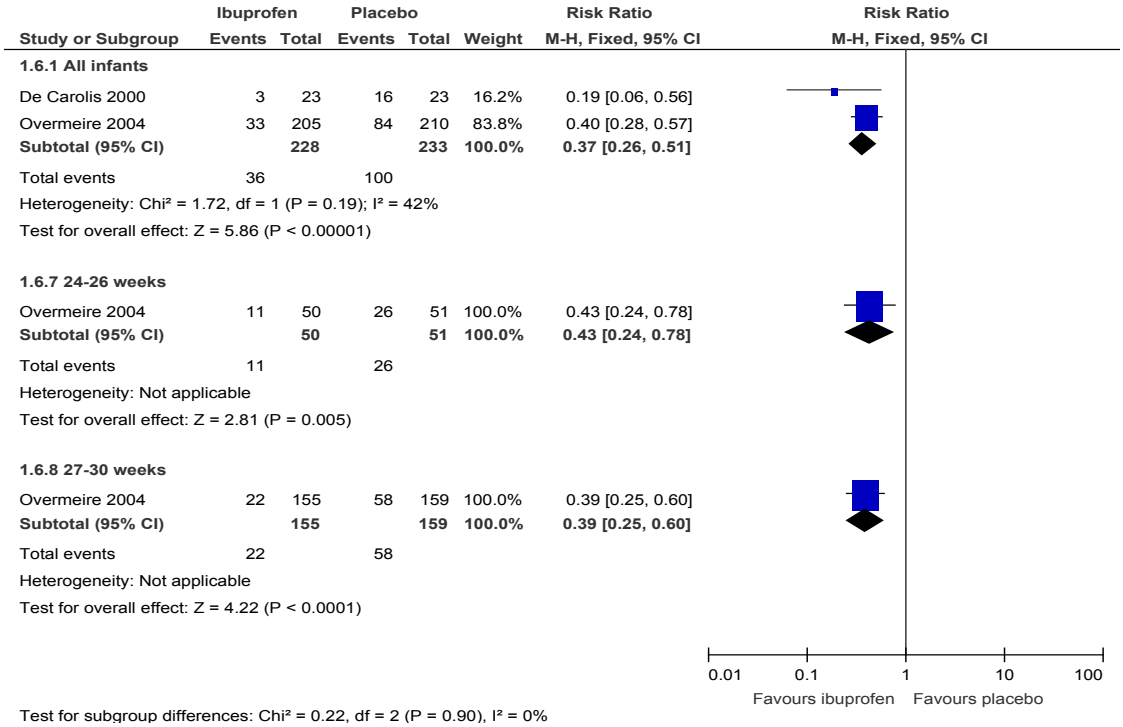
CI: confidence interval; M-H: Mantel-Haenszel

Figure 33: Comparison 1.1 Ibuprofen versus placebo – PDA required surgical ligation



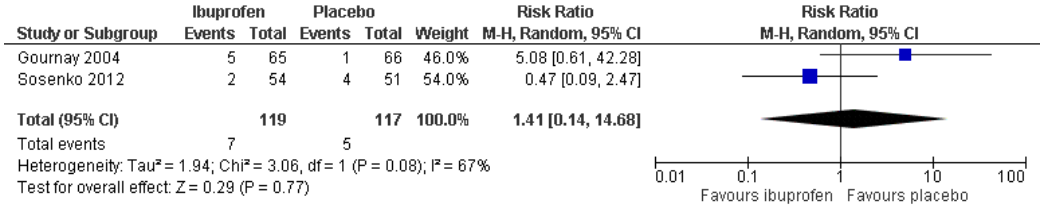
CI: confidence interval; M-H: Mantel-Haenszel

Figure 34: Comparison 1.1 Ibuprofen versus placebo – PDA failed to close on day 3



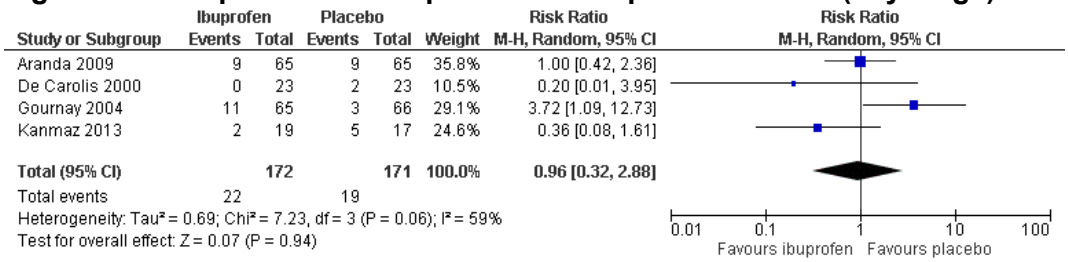
CI: confidence interval; M-H: Mantel-Haenszel

Figure 35: Comparison 1.1 Ibuprofen versus placebo – Intestinal perforation



CI: confidence interval; M-H: Mantel-Haenszel

Figure 36: Comparison 1.1 Ibuprofen versus placebo – NEC (any stage)



CI: confidence interval; M-H: Mantel-Haenszel; NEC: necrotising enterocolitis

1

1 Appendix F – GRADE tables

GRADE tables for Question 3.4 What is the effectiveness of corticosteroids in preterm babies requiring respiratory support?

3 Table 11: Clinical evidence profile: Comparison 1.1. Dexamethasone versus placebo

Quality assessment							Number of babies		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dexamethasone	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Mortality prior to discharge												
17	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	219/1048 (20.9%)	218/1050 (20.8%)	RR 1 (0.85 to 1.18)	0 fewer per 1000 (from 31 fewer to 37 more)	HIGH	CRITICAL
Mortality prior to discharge - Early administration - 7 days of age or younger												
9	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	192/824 (23.3%)	180/807 (22.3%)	RR 1.04 (0.87 to 1.25)	9 more per 1000 (from 29 fewer to 56 more)	HIGH	CRITICAL
Mortality prior to discharge - Later administration - 8 days of age or older												
8	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	27/224 (12.1%)	38/243 (15.6%)	RR 0.77 (0.49 to 1.22)	36 fewer per 1000 (from 80 fewer to 34 more)	MODERATE	CRITICAL
Bronchopulmonary dysplasia at 36 weeks corrected gestational age												
17	randomised trials	no seriou	no serious inconsistency	no serious indirectness	serious[1]	none	285/1090 (26.1%)	393/1076 (36.5%)	RR 0.73 (0.64 to 0.82)	99 fewer per 1000	MODERATE	CRITICAL

Quality assessment							Number of babies		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dexamethasone	Placebo	Relative (95% CI)	Absolute	Quality	Importance
		s risk of bias								(from 66 fewer to 131 fewer)		
Bronchopulmonary dysplasia at 36 weeks corrected gestational age - Early administration - 7 days of age or younger												
10	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	184/874 (21.1%)	255/857 (29.8%)	RR 0.71 (0.61 to 0.84)	86 fewer per 1000 (from 48 fewer to 116 fewer)	MODERATE	CRITICAL
Bronchopulmonary dysplasia at 36 weeks corrected gestational age - Later administration - 8 days of age or older												
7	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	101/216 (46.8%)	138/219 (63%)	RR 0.75 (0.63 to 0.88)	158 fewer per 1000 (from 76 fewer to 233 fewer)	MODERATE	CRITICAL
Bronchopulmonary dysplasia at 28 days of age												
11	randomised trials	no serious risk of bias	serious	no serious indirectness	serious[1]	none	465/838 (55.5%)	515/824 (62.5%)	RR 0.88(0.78 to 0.99)	75 fewer per 1000 (from 6 fewer to 138 fewer)	LOW	CRITICAL
Bronchopulmonary dysplasia at 28 days of age - Early administration - 7 days of age or younger												
6	randomised trials	no serious risk of bias	serious	no serious indirectness	serious[1]	none	376/714 (52.7%)	407/696 (58.5%)	RR 0.87 (0.74 to 1.03)	76 fewer per 1000 (from 152 fewer to 18 more)	LOW	CRITICAL

Quality assessment							Number of babies		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Dexamethasone**	**Placebo**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Bronchopulmonary dysplasia at 28 days of age - Later administration - 8 days of age or older												
5	randomised trials	no serious risk of bias	serious	no serious indirectness	serious[1]	none	89/124 (71.8%)	108/128 (84.4%)	RR 0.87 (0.71 to 1.07)	110 fewer per 1000 (from 245 fewer to 59 more)	LOW	CRITICAL
Cerebral Palsy at 18 months or older of age												
10	randomised trials	no serious risk of bias	serious[2]	serious[3]	very serious[4]	none	75/334 (22.5%)	46/313 (14.7%)	RR 1.14 (0.63to 2.07)	21 more per 1000 (from 245 fewer to 59 more)	VERY LOW	CRITICAL
Cerebral Palsy at 18 months or older of age - Early administration - 7 days of age or younger												
4	randomised trials	no serious risk of bias	serious[2]	serious[3]	very serious[4]	none	52/202 (25.7%)	27/193 (14%)	RR 1.36 (0.45 to 4.14)	50 more per 1000 (from 77 fewer to 439 more)	VERY LOW	CRITICAL
Cerebral Palsy at 18 months or older of age - Later administration - 8 days of age or older												
6	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	very serious[4]	none	23/132 (17.4%)	19/120 (15.8%)	RR 1.03 (0.56 to 1.88)	5 more per 1000 (from 70 fewer to 139 more)	VERY LOW	CRITICAL
Severe cognitive impairment (Bayley MDI <70 or <-2SD on other validated scales)												

Quality assessment							Number of babies		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Dexamethasone**	**Placebo**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	38/104 (36.5%)	31/94 (33%)	RR 1.1 (0.76 to 1.61)	33 more per 1000 (from 79 fewer to 201 more)	LOW	CRITICAL
Severe cognitive impairment (Bayley MDI <70 or <-2SD on other validated scales) - Early administration - 7 days of age or younger												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	35/76 (46.1%)	25/68 (36.8%)	RR 1.25 (0.84 to 1.86)	92 more per 1000 (from 59 fewer to 316 more)	MODERATE	CRITICAL
Severe cognitive impairment (Bayley MDI <70 or <-2SD on other validated scales) - Later administration - 8 days of age or older												
2	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	very serious[4]	none	3/28 (10.7%)	6/26 (23.1%)	RR 0.46 (0.13 to 1.67)	125 fewer per 1000 (from 201 fewer to 155 more)	VERY LOW	CRITICAL
Severe intellectual impairment (IQ <70 on validated scales)												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	13/85 (15.3%)	10/77 (13%)	RR 1.18 (0.54 to 2.55)	23 more per 1000 (from 60 fewer to 201 more)	LOW	CRITICAL
Severe intellectual impairment (IQ <70 on validated scales) - Early administration - 7 days of age or younger												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	very serious[4]	none	2/15 (13.3%)	3/15 (20%)	RR 0.67 (0.13 to 3.44)	66 fewer per 1000 (from	VERY LOW	CRITICAL

Quality assessment							Number of babies		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dexamethasone	Placebo	Relative (95% CI)	Absolute	Quality	Importance
										174 fewer to 488 more)		
Severe intellectual impairment (IQ <70 on validated scales) - Later administration - 8 days of age or older												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	11/70 (15.7%)	7/62 (11.3%)	RR 1.38 (0.57 to 3.37)	43 more per 1000 (from 49 fewer to 268 more)	LOW	CRITICAL
Severe psychomotor impairment (Bayley PSI <70 or <-2SD on other validated scales) - Early administration - 7 days of age or younger												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	21/74 (28.4%)	22/62 (35.5%)	RR 0.8 (0.49 to 1.31)	71 fewer per 1000 (from 181 fewer to 110 more)	LOW	CRITICAL
Moderate or severe cognitive impairment (Bayley MDI <85 or <-SD on validated scale) - Later administration - 8 days of age or older												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	16/27 (59.3%)	12/24 (50%)	RR 1.19 (0.71 to 1.97)	95 more per 1000 (from 145 fewer to 485 more)	LOW	CRITICAL
Severe deafness												
8	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	very serious[4]	none	7/261 (2.7%)	10/262 (3.8%)	RR 0.77 (0.33 to 1.78)	9 fewer per 1000 (from 26 fewer to 30 more)	VERY LOW	CRITICAL

Quality assessment							Number of babies		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Dexamethasone**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Severe deafness - Early administration - 7 days of age or younger												
4	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	very serious[4]	none	5/188 (2.7%)	4/189 (2.1%)	RR 1.27 (0.42 to 3.9)	6 more per 1000 (from 12 fewer to 61 more)	VERY LOW	CRITICAL
Severe deafness - Later administration - 8 days of age or older												
4	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	very serious[4]	none	2/73 (2.7%)	6/73 (8.2%)	RR 0.38 (0.1 to 1.55)	51 fewer per 1000 (from 74 fewer to 45 more)	VERY LOW	CRITICAL
Severe blindness												
9	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	very serious[4]	none	9/273 (3.3%)	5/266 (1.9%)	RR 1.58 (0.6 to 4.15)	11 more per 1000 (from 8 fewer to 59 more)	VERY LOW	CRITICAL
Severe blindness - Early administration - 7 days of age or younger												
4	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	very serious[4]	none	6/188 (3.2%)	2/180 (1.1%)	RR 2.51 (0.6 to 10.53)	17 more per 1000 (from 4 fewer to 106 more)	VERY LOW	CRITICAL
Severe blindness - Later administration - 8 days of age or older												
5	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	very serious[4]	none	3/85 (3.5%)	3/86 (3.5%)	RR 0.99 (0.25 to 3.87)	0 fewer per 1000 (from 26 fewer to	VERY LOW	CRITICAL

Quality assessment							Number of babies		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dexamethasone	Placebo	Relative (95% CI)	Absolute	Quality	Importance
										100 more)		
Days on invasive ventilation - Early administration - 7 days of age or younger (Garland 1999) (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	n= 118 Median (range) 27 days (2 to 120)	n=123 Median (range) 30 days (3 to 69)		Median 3 days less (p=0.20)	MODERATE	IMPORTANT
Days on invasive ventilation - Early administration - 7 days of age or younger (Romagnoli 1999) (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	25	25	-	MD 18.1 lower (27.68 to 8.52 lower)	MODERATE	IMPORTANT
Days on invasive ventilation - Early administration - 7 days or younger (Shinwell 19996) (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	132	116	-	MD 2 lower (2.27 to 1.73 lower)	HIGH	IMPORTANT
Days on invasive ventilation - Early administration - 7 days or younger (Subhedar 1997) (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	n=21 Median=23 Range= 6-44	n=21 Median= 13 Range=5 -39	-	Median 10 days more (p-not reported)	MODERATE	IMPORTANT
Days on invasive ventilation - Early administration - 7 days or younger (Tapia 1998) (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	55	54	-	MD 5 lower (8.7 to 1.3 lower)	MODERATE	IMPORTANT
Days on invasive ventilation - Early administration - 7 days of age or younger (Vermont Oxford Network Steroid Group 2001) (Better indicated by lower values)												
1	randomised trials	no seriou	no serious inconsistency	no serious indirectness	no serious imprecision	none	273	269	-	MD 5.5 lower (5.82 to	HIGH	IMPORTANT

Quality assessment							Number of babies		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dexamethasone	Placebo	Relative (95% CI)	Absolute	Quality	Importance
		s risk of bias								5.18 lower)		
Days on invasive ventilation - Later administration - 8 days of age or older (Durand 1995) (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	n=23 Median (range) 20 days Range=17-33	n=20 Median (range) 35 days Range=25-75	-	Median 15 days less (p < 0.01)	MODERATE	IMPORTANT
Days on invasive ventilation - Later administration - 8 days or older (Kari 1993) (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	n=17 Median (range) 24 days Range=20-40	n=24 Median (range) 40 days Range= 22-50	-	Median 0 days less (p-not significant)	MODERATE	IMPORTANT
Days on invasive ventilation - Later administration - 8 days or older (Kothadia 1999) (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	n=57 Median (range) 13 days (1 to 64)	n=61 Median (range) 25 days (6 to 104)	-	Median 12 days less (p= 0.005)	MODERATE	IMPORTANT
Days on invasive ventilation - Later administration - 8 days or older (Walther 2003) (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	17	19	-	MD 10 lower (32.56 lower to 12.56 higher)	MODERATE	IMPORTANT
Gastro-intestinal perforation												
7	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	63/645 (9.8%)	37/645 (5.7%)	RR 1.7 (1.15 to 2.51)	40 more per 1000 (from 9 more to 87 more)	MODERATE	IMPORTANT

Quality assessment							Number of babies		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dexamethasone	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Gastro-intestinal perforation - Early administration - 7 days of age or younger												
6	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	63/610 (10.3%)	37/610 (6.1%)	RR 1.7 (1.15 to 2.51)	42 more per 1000 (from 9 more to 92 more)	MODERATE	IMPORTANT
Gastro-intestinal perforation - Later administration - 8 days of age or older												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[6]	none	0/35 (0%)	0/35 (0%)	RD 0.0 (-0.05 to 0.05)	0 more per 1000 (from 50 fewer to 50 more)	LOW	IMPORTANT
Hypertension												
13	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	223/921 (24.2%)	120/901 (13.3%)	RR 1.86 (1.55 to 2.22)	115 more per 1000 (from 73 more to 162 more)	HIGH	IMPORTANT
Hypertension - Early administration - 7 days of age or younger												
8	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	207/770 (26.9%)	115/739 (15.6%)	RR 1.78 (1.49 to 2.14)	121 more per 1000 (from 76 more to 177 more)	HIGH	IMPORTANT
Hypertension - Later administration - 8 days of age or older												
5	randomised trials	no seriou	no serious inconsistency	no serious indirectness	no serious imprecision	none	16/151 (10.6%)	5/162 (3.1%)	RR 3.69 (1.43 to 9.49)	83 more per 1000	HIGH	IMPORTANT

Quality assessment							Number of babies		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dexamethasone	Placebo	Relative (95% CI)	Absolute		
		s risk of bias								(from 13 more to 262 more)		

CI: confidence interval; IQ: intelligence quotient; MD: mean difference; MDI; mental development index; PDI: psychomotor development index; RD: risk difference; RR: relative risk; SD: standard deviation

[1] The quality of the evidence was downgraded by 1 as the 95% CI crosses 1 MID

[2] The quality of evidence was downgraded by 1 because of of heterogeneity (I2=52% for the overall analysis); random effects model used; subgroup analysis done according to early versus late administration but heterogeneity remained in the early administration group (I2=79%)

[3] The quality of the evidence was downgraded by 1 as there was uncertainty around the timeframe for outcome assessment (follow-up papers were not available for assessment and precise timeframes were not documented in the systematic reviews by Doyle 2014a and 2014b)

[4] The quality of evidence was downgraded by 2 as the 95% CI crosses 2 MIDs

[5] The quality of evidence was downgraded by 1 as imprecision was not calculable because the data were reported as medians available

[6] Downgraded by 2 as the confidence interval of the risk difference includes appreciable harm and benefit

[7] The quality of evidence was downgraded by 1 because of of heterogeneity (I2=55% for the overall analysis); random effects model used; subgroup analysis done according to early versus late administration but heterogeneity remained: (I2=60% for early and I2=63% for late administration).

Table 12: Clinical evidence profile: Comparison 1.2. Hydrocortisone versus placebo

Quality assessment							Number of babies		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hydrocortisone	Placebo	Relative (95% CI)	Absolute		
Mortality prior to discharge												
6	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	96/536 (17.9%)	123/549 (22.4%)	RR 0.80 (0.63 to 1.02)	45 fewer per 1000 (from 83 fewer to 4 more)	MODERATE	CRITICAL
Mortality prior to discharge - Early administration - 7 days of age or younger												

Quality assessment							Number of babies		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Hydrocortisone**	**Placebo**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	88/505 (17.4%)	115/516 (22.3%)	0.78 (0.61 to 1)	49 fewer per 1000 (from 87 fewer to 0 more)	MODERATE	CRITICAL
Mortality prior to discharge - Later administration - 8 days of age or older												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	8/31 (25.8%)	8/33 (24.2%)	1.06 (0.46 to 2.49)	15 more per 1000 (from 131 fewer to 361 more)	LOW	CRITICAL
Bronchopulmonary dysplasia at 36 weeks corrected gestational age												
6	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	183/536 (34.1%)	211/550 (38.4%)	RR 0.89 (0.76 to 1.03)	42 fewer per 1000 (from 92 fewer to 12 more)	MODERATE	CRITICAL
Bronchopulmonary dysplasia at 36 weeks corrected gestational age - Early administration - 7 days of age or younger												
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	163/505 (32.3%)	191/517 (36.9%)	RR 0.87 (0.74 to 1.02)	48 fewer per 1000 (from 96 fewer to 7 more)	MODERATE	CRITICAL
Bronchopulmonary dysplasia at 36 weeks corrected gestational age - Later administration - 8 days of age or older												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	20/31 (64.5%)	20/33 (60.6%)	RR 1.06 (0.73 to 1.56)	36 more per 1000 (from 164 fewer to 339 more)	LOW	CRITICAL
Cerebral Palsy at 18 months of age or older												
6	randomised trials	no serious	no serious inconsistency	no serious indirectness	very serious[2]	none	36/401 (9%)	33/388 (8.5%)	RR 1.06 (0.68 to 1.66)	5 more per 1000 (from 27	LOW	CRITICAL

Quality assessment							Number of babies		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hydrocortisone	Placebo	Relative (95% CI)	Absolute	Quality	Importance
		risk of bias								fewer to 56 more)		
Cerebral Palsy at 18 months of age or older - Early administration - 7 days of age or younger												
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	33/381 (8.7%)	32/371 (8.6%)	RR 1.01 (0.64 to 1.6)	1 more per 1000 (from 31 fewer to 52 more)	LOW	CRITICAL
Cerebral Palsy at 18 months of age or older - Later administration - 8 days of age or older												
1	randomised trials	serious3	no serious inconsistency	no serious indirectness	very serious[2]	none	3/20 (15%)	1/17 (5.9%)	RR 2.55 (0.29 to 22.31)	91 more per 1000 (from 42 fewer to 1000 more)	VERY LOW	CRITICAL
Severe cognitive impairment (Bayley MDI <70 or <-2SD on other validated scales) - Early administration - 7 days of age or younger												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	36/149 (24.2%)	48/148 (32.4%)	RR 0.75 (0.52 to 1.07)	81 fewer per 1000 (from 156 fewer to 23 more)	MODERATE	CRITICAL
Severe intellectual impairment (IQ <70 on validated scales) - Early administration - 7 days of age or younger												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	2/17 (11.8%)	1/17 (5.9%)	RR 2.00 (0.2 to 20.04)	59 more per 1000 (from 47 fewer to 1000 more)	LOW	CRITICAL
Severe psychomotor impairment (Bayley PSI <70 or <-2SD on other validated scales) - Early administration - 7 days of age or younger												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	33/126 (26.2%)	29/126 (23%)	RR 1.14 (0.74 to 1.76)	32 more per 1000 (from 60 fewer to 175 more)	LOW	CRITICAL

Quality assessment							Number of babies		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hydrocortisone	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Moderate or severe cognitive impairment (Bayley MDI <85 or <-SD on validated scale)												
2	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[1]	none	11/177 (6.2%)	19/163 (11.7%)	RR 0.53 (0.27 to 1.05)	55 fewer per 1000 (from 85 fewer to 6 more)	LOW	CRITICAL
Moderate or severe cognitive impairment (Bayley MDI <85 or <-SD on validated scale) - Early administration - 7 days of age or younger												
1	randomised trials	Serious[4]	no serious inconsistency	no serious indirectness	very serious[2]	none	7/158 (4.4%)	11/146 (7.5%)	RR 0.59 (0.23 to 1.48)	31 fewer per 1000 (from 58 fewer to 36 more)	VERY LOW	CRITICAL
Moderate or severe cognitive impairment (Bayley MDI <85 or <-SD on validated scale) - Later administration - 8 days of age or older												
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[1]	none	4/19 (21.1%)	8/17 (47.1%)	RR 0.45 (0.16 to 1.22)	259 fewer per 1000 (from 395 fewer to 104 more)	LOW	CRITICAL
Moderate or severe language impairment (Bayley LDI <85 or <-SD on validated scale) - Later administration - 8 days of age or older												
1	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	very serious[2]	none	9/18 (50%)	10/17 (58.8%)	RR 0.85 (0.46 to 1.56)	88 fewer per 1000 (from 318 fewer to 329 more)	VERY LOW	CRITICAL
Moderate cognitive impairment (Bayley MDI 70-84 or -1 to -2SD on other validated scales) - Early administration - 7 days of age or younger												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	5/23 (21.7%)	1/22 (4.5%)	RR 4.78 (0.61 to 37.75)	172 more per 1000 (from 18 fewer to 1000 more)	LOW	CRITICAL

Quality assessment							Number of babies		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hydrocortisone	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Severe deafness - Early administration - 7 days of age or younger												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/204 (0%)	0/193 (0%)	RD 0.00 (-0.01 to 0.01)	0 more per 1000 (from 10 fewer to 10 more)	HIGH	CRITICAL
Severe blindness												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/224 (0%)	0/210 (0%)	RD 0.00 (-0.02 to 0.02)	0 more per 1000 (from 20 fewer to 20 more)	HIGH	CRITICAL
Severe blindness - Early administration - 7 days of age or younger												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/204 (0%)	0/193 (0%)	RD 0.00 (-0.01 to 0.01)	0 more per 1000 (from 10 fewer to 10 more)	HIGH	CRITICAL
Severe blindness - Later administration - 8 days of age or older												
1	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/20 (0%)	0/17 (0%)	RD 0.00 (-0.01 to 0.01)	0 more per 1000 (from 10 fewer to 10 more)	HIGH	CRITICAL
Days on invasive ventilation - Early administration - 7 days of age or younger (Bosante 2007) (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[9]	none	n=25 Median (IQR) 4 days (2 to 21)	n=25 Median (IQR) 15 days (2 to 27)	-	Median 0 days difference (p- not significant)	MODERATE	IMPORTANT
Days on invasive ventilation - Early administration - 7 days or younger (Watterberg 1999) (Better indicated by lower values)												
1	randomised trials	no serious	no serious inconsistency	no serious indirectness	serious[9]	none	n=17 Median (IQR) 25 days (14 to 34)	n=17	-	Median 0 days differenc	MODERATE	IMPORTANT

Quality assessment							Number of babies		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Hydrocortisone**	**Placebo**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
		risk of bias						Median (IQR) 32 days (11 to 45)		e (p=0.03)		
Days on invasive ventilation - Early administration - 7 days of age or younger (Watterberg 2004) (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[9]	none	n=149 Median (IQR) 32 days (13 to 54)	n= 148 Median (IQR) 35 days (17 to 47)	-	Median 3 days less (p=0.86)	MODERATE	IMPORTANT
Days on invasive ventilation - Later administration - 8 days of age or older (Parikh 2013) (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	Serious[10]	no serious imprecision	none	31	33	-	MD 2.8 higher (5.04 lower to 10.64 higher)	MODERATE	IMPORTANT
Gastro-intestinal perforation												
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	22/356 (6.2%)	13/370 (3.5%)	RR 1.71 (0.89 to 3.27)	25 more per 1000 (from 4 fewer to 80 more)	MODERATE	IMPORTANT
Gastro-intestinal perforation - Early administration - 7 days of age or younger												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	20/325 (6.2%)	13/337 (3.9%)	RR 1.57 (0.8 to 3.08)	22 more per 1000 (from 8 fewer to 80 more)	MODERATE	IMPORTANT
Gastro-intestinal perforation - Later administration - 8 days of age or older												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	2/31 (6.5%)	0/33 (0%)	RR 5.31 (0.27 to 106.46)	-	LOW	IMPORTANT

Quality assessment							Number of babies		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hydrocortisone	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Hypertension												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	20/56 (35.7%)	14/58 (24.1%)	RR 1.51 (0.89 to 2.55)	123 more per 1000 (from 27 fewer to 374 more)	MODERATE	IMPORTANT
Hypertension - Early administration - 7 days of age or younger												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	3/25 (12%)	1/25 (4%)	RR 3 (0.33 to 26.92)	80 more per 1000 (from 27 fewer to 1000 more)	LOW	IMPORTANT
Hypertension - Later administration - 8 days of age or older												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	17/31 (54.8%)	13/33 (39.4%)	RR 1.39 (0.82 to 2.37)	154 more per 1000 (from 71 fewer to 540 more)	MODERATE	IMPORTANT

CI: confidence interval; IQ: intelligence quotient; LDI: language development index; MD: mean difference; MDI; mental development index; PDI: psychomotor development index; RD: risk difference; RR: relative risk; SD: standard deviation

[1] The quality of evidence was downgraded by 1 as the 95% CI crosses 1 MID

[2] The quality of the evidence was downgraded by 2 as the 95% CI crosses 2 MIDs

[3] The quality of the evidence was downgraded by 1 as only 65% of the infants were followed-up for cerebral palsy assessment

[4] The quality of evidence was downgraded by 1 because only 76% and 73% of infants were followed-up in the hydrocortisone and placebo group, respectively for cognitive assessment with RBL tool in Baud 2017, and only 63% infants were followed-up for cognitive assessment in Parikh 2015

[5] The quality of evidence was downgraded by 1 because only 63% infants were followed-up for cognitive assessment

[6] The quality of evidence was downgraded by 1 because only 61% of infants were followed-up for language assessment

[7] Imprecision was not calculable because there were zero events in both intervention groups

[8] The quality of evidence was downgraded by 1 because there was uncertainty around how many infants were followed up for visual assessments

[9] The quality of evidence was downgraded by 1 as imprecision was not calculable because the data were reported as medians

[10] The quality of evidence was downgraded by 1 as the days on ventilation included invasive and non-invasive ventilation

Table 13: Clinical evidence profile: Comparison 1.3. Budesonide versus placebo

Quality assessment							Number of babies		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Budesonide	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Bronchopulmonary dysplasia at 36 weeks corrected gestational age												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	8/13 (61.5%)	11/14 (78.6%)	RR 0.78 (0.47 to 1.3)	173 fewer per 1000 (from 416 fewer to 236 more)	VERY LOW	CRITICAL
Bronchopulmonary dysplasia at 28 days of age												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	13/13 (100%)	14/14 (100%)	RR 1 (0.87 to 1.15)	0 fewer per 1000 (from 130 fewer to 150 more)	MODERATE	CRITICAL
Total days on invasive ventilation (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	n=13 Median (range) 11 days (1 to 40)	n=14 Median (range) 14 days (1 to 38)	-	Median 1 day less (p not significant)	LOW	IMPORTANT

CI: confidence interval; RR: relative risk; SD: standard deviation

[1] The quality of evidence was downgraded by 1 due to unclear randomisation and allocation concealment.
[2] The quality of evidence was downgraded by 2 as the 95% CI crosses 2 MID
[3] The quality of evidence was downgraded by 1 as imprecision was not calculable because data were reported as medians

Table 14: Clinical evidence profile: Comparison 3.1. Lower cumulative dose dexamethasone versus higher cumulative dose dexamethasone

Quality assessment							Number of babies		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lower dose dexamethasone	Higher dose dexamethasone	Relative (95% CI)	Absolute	Quality	Importance
Mortality prior to discharge												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	2/57 (3.5%)	3/52 (5.8%)	RR 0.61 (0.11 to 3.47)	22 fewer per 1000 (from 51 fewer to 142 more)	LOW	CRITICAL
Bronchopulmonary dysplasia at 36 weeks corrected gestational age												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	10/57 (17.5%)	8/52 (15.4%)	RR 1.13 (0.48 to 2.63)	20 more per 1000 (from 80 fewer to 251 more)	LOW	CRITICAL
Cerebral Palsy at 18 months of age or older												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	very serious[1]	none	2/18 (11.1%)	2/18 (11.1%)	RR 1 (0.16 to 6.35)	0 fewer per 1000 (from 93 fewer to 594 more)	VERY LOW	CRITICAL
Severe cognitive impairment (Bayley MDI <70 or <-2SD on other validated scales)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	very serious[1]	none	3/24 (12.5%)	4/23 (17.4%)	RR 0.72 (0.18 to 2.87)	49 fewer per 1000 (from 143 fewer to	VERY LOW	CRITICAL

Quality assessment							Number of babies		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Lower dose dexamethasone**	**Higher dose dexamethasone**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
										325 more)		
Severe blindness												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	very serious[2]	none	0/24 (0%)	1/23 (4.3%)	RR 0.32 (0.01 to 6.1)	30 fewer per 1000 (from 43 fewer to 222 more)	VERY LOW	CRITICAL
Days on invasive ventilation (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	33	29	-	MD 1.1 lower (14.2 lower to 12 higher)	LOW	IMPORTANT
Gastro-intestinal perforation												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	2/57 (3.5%)	2/52 (3.8%)	RR 0.92 (0.13 to 6.28)	3 fewer per 1000 (from 33 fewer to 203 more)	LOW	IMPORTANT
Hypertension												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	4/57 (7%)	9/52 (17.3%)	RR 0.4 (0.13 to 1.22)	104 fewer per 1000 (from 151 fewer to 38 more)	MODERATE	IMPORTANT

1 *CI: confidence interval; MD: mean difference; MDI; mental development index; RR: relative risk*

[1] *The quality of the evidence was downgraded by 2 as the 95% CI crosses 2 MIDs*
[2] *The quality of evidence was downgraded by 1 as there was uncertainty around the timeframe of cerebral palsy assessment*
[3] *The quality of evidence was downgraded by 1 as the 95% CI crosses 1 MID*

Table 15: Clinical evidence profile: Comparison 3.2. Individual tailored course dexamethasone versus continuous tapered course dexamethasone

Quality assessment							Number of babies		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Individual tailored dexamethasone	Continuous tapered dexamethasone	Relative (95% CI)	Absolute	Quality	Importance
Mortality prior to discharge												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious1	none	5/17 (29.4%)	4/16 (25%)	RR 1.18 (0.38 to 3.62)	45 more per 1000 (from 155 fewer to 655 more)	LOW	CRITICAL
Bronchopulmonary dysplasia at 36 weeks corrected gestational age												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious1	none	9/17 (52.9%)	8/16 (50%)	RR 1.06 (0.55 to 2.06)	30 more per 1000 (from 225 fewer to 530 more)	LOW	CRITICAL
Bronchopulmonary dysplasia at 28 days of age												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious2	none	14/17 (82.4%)	15/16 (93.8%)	RR 0.88 (0.68 to 1.13)	113 fewer per 1000 (from 300 fewer to 122 more)	MODERATE	CRITICAL
Days on invasive ventilation (Better indicated by lower values)												

Quality assessment							Number of babies		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Individual tailored dexamethasone**	**Continuous tapered dexamethasone**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious2	none	17	16	-	MD 7.5 higher (2.2 to 12.8 higher)	MODERATE	IMPORTANT
Gastro-intestinal perforation												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious1	none	9/17 (52.9%)	8/16 (50%)	RR 1.06 (0.55 to 2.06)	30 more per 1000 (from 225 fewer to 530 more)	LOW	IMPORTANT
Hypertension												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious1	none	9/17 (52.9%)	8/16 (50%)	RR 1.06 (0.55 to 2.06)	30 more per 1000 (from 225 fewer to 530 more)	LOW	IMPORTANT

CI: confidence interval; MD: mean difference; RR: relative risk
[1] The quality of the evidence was downgraded by 2 as the 95% CI crosses 2 MIDs
[2] The quality of the evidence was downgraded by 1 as the 95% CI crosses 1 MID

Table 16: Clinical evidence profile: Comparison 4.1. Earlier initiation dexamethasone versus later initiation dexamethasone

Quality assessment							Number of babies		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Earlier administration dexamethasone**	**Later administration dexamethasone**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Mortality prior to discharge												

Quality assessment							Number of babies		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Earlier administration dexamethasone	Later administration dexamethasone	Relative (95% CI)	Absolute	Quality	Importance
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious1	none	65/356 (18.3%)	67/376 (17.8%)	RR 1.05 (0.77 to 1.41)	9 more per 1000 (from 41 fewer to 73 more)	LOW	CRITICAL
Mortality prior to discharge - Early initiation vs moderate initiation												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious2	none	48/174 (27.6%)	41/187 (21.9%)	RR 1.29 (0.9 to 1.84)	64 more per 1000 (from 22 fewer to 184 more)	MODERATE	CRITICAL
Mortality prior to discharge - Moderate initiation vs late initiation												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious2	none	17/182 (9.3%)	26/189 (13.8%)	RR 0.68 (0.38 to 1.21)	44 fewer per 1000 (from 85 fewer to 29 more)	MODERATE	CRITICAL
Bronchopulmonary dysplasia at 36 weeks corrected gestational age - Early initiation vs moderate initiation												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious2	none	45/174 (25.9%)	65/187 (34.8%)	0.74 (0.57 to 0.97)	90 fewer per 1000 (from 10 fewer to 149 fewer)	MODERATE	CRITICAL
Bronchopulmonary dysplasia at 36 weeks corrected gestational age - Moderate initiation vs late initiation												
1	randomised trials	no seriou	no serious inconsistency	no serious indirectness	no serious imprecision	none	121/182 (66.5%)	127/189 (67.2%)	0.99 (0.88 to 1.12)	7 fewer per 1000	HIGH	CRITICAL

Quality assessment							Number of babies		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Earlier administration dexamethasone	Later administration dexamethasone	Relative (95% CI)	Absolute	Quality	Importance
		s risk of bias								(from 81 fewer to 81 more)		
Bronchopulmonary dysplasia at 28 days of age												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	237/356 (66.6%)	276/376 (73.4%)	RR 0.9 (0.82 to 0.99)	73 fewer per 1000 (from 7 fewer to 132 fewer)	HIGH	CRITICAL
Bronchopulmonary dysplasia at 28 days of age - Early initiation vs moderate initiation												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	96/174 (55.2%)	108/187 (57.8%)	RR 0.96 (0.8 to 1.15)	23 fewer per 1000 (from 116 fewer to 87 more)	HIGH	CRITICAL
Bronchopulmonary dysplasia at 28 days of age - Moderate initiation vs late initiation												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious2	none	141/182 (77.5%)	168/189 (88.9%)	RR 0.87 (0.79 to 0.96)	116 fewer per 1000 (from 36 fewer to 187 fewer)	MODERATE	CRITICAL
Cerebral Palsy at 18 months of age or older - Early initiation vs moderate initiation												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious1	none	2/22 (9.1%)	6/34 (17.6%)	RR 0.52 (0.11 to 2.33)	85 fewer per 1000	LOW	CRITICAL

Quality assessment							Number of babies		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Earlier administration dexamethasone	Later administration dexamethasone	Relative (95% CI)	Absolute	Quality	Importance
										(from 157 fewer to 235 more)		
Severe cognitive impairment (Bayley MDI <70 or <-2SD on other validated scales) - Early initiation vs moderate initiation												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious1	none	2/24 (8.3%)	4/37 (10.8%)	RR 0.77 (0.15 to 3.89)	25 fewer per 1000 (from 92 fewer to 312 more)	LOW	CRITICAL
Moderate cognitive impairment (Bayley MDI 70-84 or -1 to -2SD on other validated scales) - Early initiation vs moderate initiation												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	1/24 (4.2%)	1/37 (2.7%)	RR 1.54 (0.1 to 23.49)	15 more per 1000 (from 24 fewer to 608 more)	LOW	CRITICAL
Severe deafness - Early initiations vs moderate initiation												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	0/24 (0%)	0/37 (0%)	RD 0.00 (-0.07 to 0.07)	0 more per 1000 (from 70 fewer to 70 more)	HIGH	CRITICAL
Severe blindness - Early initiation vs moderate initiation												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	0/24 (0%)	0/37 (0%)	RD 0.00 (-0.07 to 0.07)	0 more per 1000 (from 70 fewer to	HIGH	CRITICAL

Quality assessment							Number of babies		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Earlier administration dexamethasone	Later administration dexamethasone	Relative (95% CI)	Absolute	Quality	Importance
										70 more)		
Gastro-intestinal perforation - Early initiation vs moderate initiation												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	6/135 (4.4%)	5/150 (3.3%)	RR 1.33 (0.42 to 4.27)	11 more per 1000 (from 19 fewer to 109 more)	LOW	IMPORTANT
Hypertension												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	42/356 (11.8%)	45/376 (12%)	RR 1.01 (0.68 to 1.48)	1 more per 1000 (from 38 fewer to 57 more)	LOW	IMPORTANT
Hypertension - Early initiation vs moderate initiation												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	25/174 (14.4%)	22/187 (11.8%)	RR 1.26 (0.75 to 2.13)	31 more per 1000 (from 29 fewer to 133 more)	LOW	CRITICAL
Hypertension - Moderate initiation vs late initiation												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	17/182 (9.3%)	23/189 (12.2%)	RR 0.77 (0.42 to 1.39)	28 fewer per 1000 (from 71 fewer to 47 more)	LOW	IMPORTANT

1 *CI: confidence interval; MDI; mental development index; RD risk difference; RR: relative risk*

[1] *[1] The quality of evidence was downgraded by 2 because the 95% CI crosses 2 MIDs*
[2] *[2] The quality of evidence was downgraded by 1 because the 95% CI crosses 1 MID*
[3] *[3] The quality of evidence was downgraded by 2 because the 95% CI of the absolute effect includes appreciable benefit and harm*

GRADE tables for Question 3.5 What is the safety and effectiveness of diuretics in preterm babies on respiratory support?

Table 17: Clinical evidence profile: Comparison 1.1 Chlorothiazide plus spironolactone versus placebo

Quality assessment							Number of babies		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Chlorothiazide plus Spironolactone**	**Placebo**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Nephrocalcinosis (1 year PMA)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	7/22 (31.8%)	5/21 (23.8%)	RR 1.34 (0.5 to 3.56)	81 more per 1000 (from 119 fewer to 610 more)	VERY LOW	IMPORTANT
Hearing loss (1 year PMA)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious3	none	2/22 (9.1%)	1/21 (4.8%)	RR 1.91 (0.19 to 19.52)	43 more per 1000 (from 39 fewer to 882 more)	VERY LOW	IMPORTANT
Supplemental electrolytes												
1	randomised trials	serious[1]	no serious inconsistency	very serious[4]	very serious[3]	none	2/22 (9.1%)	0/21 (0%)	RR 4.78 (0.24 to 94.12)	-	VERY LOW	IMPORTANT

CI: confidence interval; MID: minimal important difference; PMA: Post-menstrual age; RR: Relative risk;

1 The quality of the evidence was downgraded by 1 because of incomplete outcome data, and it was unclear if there was any bias in the random sequence generation, allocation concealment, and blinding of participants or personnel.
2 The quality of the evidence was downgraded by 1 because the study period was from June 1989 to June 1992
3 The quality of evidence was downgraded by 2 because the 95% CI crosses 2 default MIDs
4 The quality of the evidence was downgraded by 2 because the study period was from June 1989 to June 1992 and supplemental electrolytes may include sodium or potassium

Table 18: Clinial evidence profile: comparison 2.1 Furosemide versus other diuretic(s)

Quality assessment							Number of babies		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Furosemide	Other diuretics	Relative (95% CI)	Absolute	Quality	Importance
Hyponatraemia – rate per 1000 infant days (measured with: < 125 mmol/L; Better indicated by lower values)												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	36759	2598	-	MD 1.1 lower per 1000 infant days (CI not reported)	VERY LOW	IMPORTANT
Severe hyponatraemia – rate per 1000 infant days (measured with: < 115 mmol/L; Better indicated by lower values)												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	36759	2598	-	MD 0 lower per 1000 infant days (CI not reported)	VERY LOW	IMPORTANT

CI: confidence interval; MD: mean difference; PMA: Post-menstrual age; RR: Relative risk;
1 Baseline differences between furosemide group and other diuretics group not controlled for in the analysis
2 Not possible to assess imprecision as SDs or P-values were not reported

Table 19: Clinical evidence profile: comparison 3.1 Chlorothiazide plus spironolactone versus chlorothiazide

Quality assessment							Number of babies		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Chlorothiazide plus Spironolactone	Chlorothiazide	Relative (95% CI)	Absolute	Quality	Importance
Hyponatraemia (sodium supplementation required)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	11/17 (64.7%)	7/16 (43.8%)	RR 1.48 (0.77 to 2.85)	210 more per 1000 (from 101 fewer to	LOW	IMPORTANT

Quality assessment							Number of babies		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Chlorothiazide plus Spironolactone	Chlorothiazide	Relative (95% CI)	Absolute		
										809 more)		

1 *CI: confidence interval; MID: minimal important difference; RR: Relative risk*
2 *1 The quality of evidence was downgraded by 2 because the 95% CI crosses 2 default MIDs*
3

GRADE tables for Question 3.6 What is the effectiveness of caffeine in preterm babies requiring respiratory support?

5 **Table 20: Clinical evidence profile: Comparison 1 – Caffeine versus placebo**

Quality assessment							Number of babies		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Caffeine	Placebo	Relative (95% CI)	Absolute		
Mortality prior to discharge, Infants 23-30^{+6} weeks												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	61/1047 (5.8%)	60/1042 (5.8%)	RR 1.01 (0.72 to 1.43)	1 more per 1000 (from 16 fewer to 25 more)	LOW	CRITICAL
Bronchopulmonary dysplasia at 36 weeks post-menstrual age or 28 days of life, Infants 23-30 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	15/41 (36.6%)	20/42 (47.6%)	RR 0.77 (0.46 to 1.28)	110 fewer per 1000 (from 257 fewer to 133 more)	LOW	CRITICAL
Bronchopulmonary dysplasia at 36 weeks post-menstrual age, Infants < 31 weeks												
1	randomised trials	no serious	no serious inconsistency	no serious indirectness	serious[2]	none	350/1006 (34.8%)	447/1000 (44.7%)	RR 0.78 (0.7 to 0.87)	98 fewer per 1000 (from 58	MODERATE	CRITICAL

Quality assessment							Number of babies		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Caffeine	Placebo	Relative (95% CI)	Absolute	Quality	Importance
		risk of bias								fewer to 134 fewer)		
Cerebral palsy, Infants < 31 weeks - 18-21 months follow up, All infants												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	40/909 (4.4%)	66/901 (7.3%)	RR 0.6 (0.41 to 0.88)	29 fewer per 1000 (from 9 fewer to 43 fewer)	MODERATE	CRITICAL
Cerebral palsy - 18-21 months follow up, Respiratory indications - Pre-extubation, Infants < 31 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	19/305 (6.2%)	39/339 (11.5%)	RR 0.54 (0.32 to 0.92)	53 fewer per 1000 (from 9 fewer to 78 fewer)	MODERATE	CRITICAL
Cerebral palsy - 18-21 months follow up, Respiratory indications - Apnoea treatment, Infants < 31 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	11/388 (2.8%)	18/361 (5%)	RR 0.57 (0.27 to 1.19)	21 fewer per 1000 (from 36 fewer to 9 more)	MODERATE	CRITICAL
Cerebral palsy - 18-21 months follow up, Respiratory indications - Apnoea prophylaxis, Infants < 31 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	10/215 (4.7%)	9/200 (4.5%)	RR 1.03 (0.43 to 2.49)	1 more per 1000 (from 26 fewer to 67 more)	LOW	CRITICAL
Cerebral palsy - 18-21 months follow up, Respiratory support - No PPV, Infants < 31 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	3/168 (1.8%)	4/138 (2.9%)	RR 0.62 (0.14 to 2.71)	11 fewer per 1000 (from 25 fewer to 50 more)	LOW	CRITICAL
Cerebral palsy - 18-21 months follow up, Respiratory support - Non-invasive ventilation, Infants < 31 weeks												

Quality assessment							Number of babies		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Caffeine	Placebo	Relative (95% CI)	Absolute		
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	8/273 (2.9%)	12/274 (4.4%)	RR 0.67 (0.28 to 1.61)	14 fewer per 1000 (from 32 fewer to 27 more)	LOW	CRITICAL
Cerebral palsy - 18-21 months follow up, Respiratory support - Endotracheal tube, Infants < 31 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	29/468 (6.2%)	49/488 (10%)	RR 0.62 (0.4 to 0.96)	38 fewer per 1000 (from 4 fewer to 60 fewer)	MODERATE	CRITICAL
Cerebral palsy - 5 year follow up, Infants < 31 weeks												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[1]	none	28/735 (3.8%)	34/698 (4.9%)	RR 0.78 (0.48 to 1.28)	11 fewer per 1000 (from 25 fewer to 14 more)	VERY LOW	CRITICAL
Cerebral palsy - 11 year follow up, Infants < 31 weeks												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[1]	none	21/484 (4.3%)	29/484 (6%)	RR 0.72 (0.42 to 1.25)	17 fewer per 1000 (from 35 fewer to 15 more)	VERY LOW	CRITICAL
Severe cognitive impairment - 18-21 months follow up, MDI score < 85 on the BSID-II, All infants												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	293/867 (33.8%)	329/858 (38.3%)	RR 0.88 (0.78 to 1)	46 fewer per 1000 (from 84 fewer to 0 more)	MODERATE	CRITICAL
Severe cognitive impairment - 18-21 months follow up, MDI score < 85 on the BSID-II (Respiratory indications - Pre-extubation) , Infants < 31 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	105/285 (36.8%)	145/327 (44.3%)	RR 0.83 (0.68 to 1.01)	75 fewer per 1000 (from 142	MODERATE	CRITICAL

Quality assessment							Number of babies		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Caffeine**	**Placebo**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
										fewer to 4 more)		
Severe cognitive impairment - 18-21 months follow up, MDI score < 85 on the BSID-II (Respiratory indications - Apnoea treatment) , Infants < 31 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	110/374 (29.4%)	117/341 (34.3%)	RR 0.86 (0.69 to 1.06)	48 fewer per 1000 (from 106 fewer to 21 more)	MODERATE	CRITICAL
Severe cognitive impairment - 18-21 months follow up, MDI score < 85 on the BSID-II (Respiratory indications - Apnoea prophylaxis) , Infants < 31 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	78/207 (37.7%)	66/189 (34.9%)	RR 1.08 (0.83 to 1.4)	28 more per 1000 (from 59 fewer to 140 more)	MODERATE	CRITICAL
Severe cognitive impairment - 18-21 months follow up, MDI score < 85 on the BSID-II (Respiratory support - No PPV), Infants < 31 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	55/162 (34%)	33/129 (25.6%)	RR 1.33 (0.92 to 1.91)	84 more per 1000 (from 20 fewer to 233 more)	MODERATE	CRITICAL
Severe cognitive impairment - 18-21 months follow up, MDI score < 85 on the BSID-II (Respiratory support - Non-invasive ventilation), Infants < 31 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	77/263 (29.3%)	91/260 (35%)	RR 0.84 (0.65 to 1.07)	56 fewer per 1000 (from 123 fewer to 25 more)	MODERATE	CRITICAL
Severe cognitive impairment - 18-21 months follow up, MDI score < 85 on the BSID-II (Respiratory support - Endotracheal tube), Infants < 31 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	161/442 (36.4%)	204/468 (43.6%)	RR 0.84 (0.71 to 0.98)	70 fewer per 1000 (from 9 fewer to 126 fewer)	MODERATE	CRITICAL
Severe cognitive impairment - 5 year follow up - Full Scale IQ < 70 on Wechsler Preschool and Primary Scale of Intelligence III, Infants < 31 weeks												

Quality assessment							Number of babies		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Caffeine**	**Placebo**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[1]	none	38/768 (4.9%)	38/750 (5.1%)	RR 0.98 (0.63 to 1.51)	1 fewer per 1000 (from 19 fewer to 26 more)	VERY LOW	CRITICAL
Severe cognitive impairment - 11 year follow up - Full scale IQ < 85 Wechsler Abbreviated Scale of Intelligence-II, Infants < 31 weeks												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	76/392 (19.4%)	86/393 (21.9%)	RR 0.89 (0.67 to 1.17)	24 fewer per 100 (from 72 fewer to 37 more)	LOW	CRITICAL
Deafness - 18-21 months follow up, Infants < 31 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	17/909 (1.9%)	22/905 (2.4%)	RR 0.77 (0.41 to 1.44)	6 fewer per 1000 (from 14 fewer to 11 more)	LOW	CRITICAL
Deafness - 5 years follow up, Infants < 31 weeks												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[1]	none	22/798 (2.8%)	25/773 (3.2%)	RR 0.85 (0.48 to 1.5)	5 fewer per 1000 (from 17 fewer to 16 more)	VERY LOW	CRITICAL
Deafness - 11 years follow up, Infants < 31 weeks												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[1]	none	16/484 (3.3%)	13/484 (2.7%)	RR 1.23 (0.6 to 2.53)	6 more per 1000 (from 11 fewer to 41 more)	VERY LOW	CRITICAL
Blindness - 18-21 months follow up, Infants < 31 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	6/911 (0.66%)	8/905 (0.88%)	RR 0.75 (0.26 to 2.14)	2 fewer per 1000 (from 7	LOW	CRITICAL

Quality assessment							Number of babies		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Caffeine	Placebo	Relative (95% CI)	Absolute	Quality	Importance
										fewer to 10 more)		
Blindness - 5 years follow up, Infants < 31 weeks												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[1]	none	7/792 (0.88%)	7/763 (0.92%)	RR 0.96 (0.34 to 2.73)	0 fewer per 1000 (from 6 fewer to 16 more)	VERY LOW	CRITICAL
Blindness - 11 years follow up, Infants < 31 weeks												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	4/484 (0.83%)	13/484 (2.7%)	RR 0.31 (0.1 to 0.94)	19 fewer per 1000 (from 2 fewer to 24 fewer)	LOW	CRITICAL
Extubation failure, Infants 23-30 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	8/41 (19.5%)	8/42 (19%)	RR 1.02 (0.42 to 2.47)	4 more per 1000 (from 110 fewer to 280 more)	LOW	IMPORTANT
Necrotising enterocolitis, Infants 23-30+6 weeks												
2	randomised trials	no serious risk of bias	serious[4]	no serious indirectness	very serious[1]	none	70/1047 (6.7%)	69/1042 (6.6%)	RR 1.01 (0.73 to 1.39)	1 more per 1000 (from 18 fewer to 26 more)	VERY LOW	CRITICAL

1 *BSID-II: Bayley Scales of Infant Development-II; IQ: Intelligence Quotient; MDI: Mental Development Index; PPV: positive pressure ventilation; RR: risk ratio*

2 [1] The quality of evidence was downgraded by 2 because the CI crosses 2 MIDs
3 [2] The quality of evidence was downgraded by 1 because the CI crosses 1 MID
4 [3] The quality of evidence was downgraded by 1 because of high attrition at 5-year follow-up (29%) and 11- year follow-up (54%)
5 [4] The quality of evidence was downgraded by 1 due to suspected heterogeneity (I-squared=66%)

Table 21: Clinical evidence profile: Comparison 2 – Lower dose caffeine versus higher dose caffeine

Quality assessment							Number of babies		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lower dose caffeine	Higher dose caffeine	Relative (95% CI)	Absolute	Quality	Importance
Mortality prior to discharge - 5mg/kg versus 20 mg/kg (All respiratory indications), Infants < 30 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	7/126 (5.6%)	5/120 (4.2%)	RR 1.33 (0.44 to 4.09)	14 more per 1000 (from 23 fewer to 129 more)	LOW	CRITICAL
Mortality prior to discharge - 5mg/kg versus 20 mg/kg (Respiratory indication - Peri-extubation), Infants < 30 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	7/121 (5.8%)	5/113 (4.4%)	RR 1.31 (0.43 to 4)	14 more per 1000 (from 25 fewer to 133 more)	LOW	CRITICAL
Mortality prior to discharge - 20mg/kg versus 80mg/kg, Infants ≤ 30 weeks												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	5/37 (13.5%)	7/37 (18.9%)	RR 0.71 (0.25 to 2.05)	55 fewer per 1000 (from 142 fewer to 199 more)	VERY LOW	CRITICAL
Bronchopulmonary dysplasia at 36 weeks post-menstrual age - 5mg/kg versus 20mg/kg - (Respiratory indication - peri-extubation), Infants < 30 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	51/121 (42.1%)	33/113 (29.2%)	RR 1.44 (1.01 to 2.06)	128 more per 1000 (from 3 more to 310 more)	MODERATE	CRITICAL
Bronchopulmonary dysplasia at 36 weeks post-menstrual age - 5mg/kg versus 20mg/kg - (All respiratory indications), Infants < 30 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	52/126 (41.3%)	35/120 (29.2%)	RR 1.41 (1 to 2)	120 more per 1000 (from 0 more to 292 more)	MODERATE	CRITICAL
Bronchopulmonary dysplasia at 36 weeks post-menstrual age - 20mg/kg versus 80mg/kg - Infants ≤ 30 weeks												

Quality assessment							Number of babies		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lower dose caffeine	Higher dose caffeine	Relative (95% CI)	Absolute	Quality	Importance
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	19/37 (51.4%)	18/37 (48.6%)	RR 1.06 (0.67 to 1.67)	29 more per 1000 (from 161 fewer to 326 more)	VERY LOW	CRITICAL
Bronchopulmonary dysplasia at 28 days of age- 5mg/kg versus 20mg/kg - (Respiratory indication- peri-extubation), Infants < 30 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	80/121 (66.1%)	64/113 (56.6%)	RR 1.17 (0.95 to 1.43)	96 more per 1000 (from 28 fewer to 244 more)	MODERATE	CRITICAL
Continued apnoea (number of documented periods) - 5mg/kg versus 20mg/kg (All respiratory indications), Infants < 30 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	N=126 Median (IQR) 6 periods (2 to 20)	N=120 Median (IQR) 4 periods (1 to 12)	-	Median 2 more periods (p=0.05)	MODERATE	IMPORTANT
Continued apnoea (number of documented periods) - 5mg/kg versus 20 mg/kg (Respiratory indication - Peri-extubation), Infants < 30 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	N=121 Median (IQR) 7 periods (2 to 22)	N=113 Median (IQR) 4 periods (1 to 12)	-	Median 3 more periods (p<0.01)	MODERATE	IMPORTANT
Extubation failure - 3mg/kg versus 15mg/kg, Infants < 32 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	19/42 (45.2%)	10/40 (25%)	RR 1.81 (0.96 to 3.4)	202 more per 1000 (from 10 fewer to 600 more)	MODERATE	IMPORTANT
Extubation failure - 3mg/kg versus 30mg/k, Infants < 32 weeks												

Quality assessment							Number of babies		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lower dose caffeine	Higher dose caffeine	Relative (95% CI)	Absolute	Quality	Importance
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	19/42 (45.2%)	11/45 (24.4%)	RR 1.85 (1 to 3.41)	208 more per 1000 (from 0 more to 589 more)	MODERATE	IMPORTANT
Extubation failure - 15mg/kg versus 30mg/kg, Infants < 32 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	10/40 (25%)	11/45 (24.4%)	RR 1.02 (0.49 to 2.15)	5 more per 1000 (from 125 fewer to 281 more)	LOW	IMPORTANT
Extubation failure - 5mg/kg versus 20mg/kg (Respiratory indication - peri-extubation), Infants < 30 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	36/121 (29.8%)	17/113 (15%)	RR 1.98 (1.18 to 3.32)	147 more per 1000 (from 27 more to 349 more)	MODERATE	IMPORTANT
Tachycardia - 3mg/kg versus 15mg/kg, Infants < 32 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	1/42 (2.4%)	5/40 (12.5%)	RR 0.19 (0.02 to 1.56)	101 fewer per 1000 (from 123 fewer to 70 more)	LOW	IMPORTANT
Tachycardia - 3mg/kg versus 30mg/kg, Infants < 32 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	2/42 (4.8%)	8/45 (17.8%)	RR 0.27 (0.06 to 1.19)	130 fewer per 1000 (from 167 fewer to 34 more)	MODERATE	IMPORTANT
Tachycardia - 15mg/kg versus 30mg/kg, Infants < 32 weeks												

Quality assessment							Number of babies		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lower dose caffeine	Higher dose caffeine	Relative (95% CI)	Absolute		
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	5/40 (12.5%)	8/45 (17.8%)	RR 0.7 (0.25 to 1.98)	53 fewer per 1000 (from 133 fewer to 174 more)	LOW	IMPORTANT
Tachycardia - 5mg/kg versus 20mg/kg (Respiratory indication - peri-extubation), Infants < 30 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	1/121 (0.83%)	4/113 (3.5%)	RR 0.23 (0.03 to 2.06)	27 fewer per 1000 (from 34 fewer to 38 more)	LOW	IMPORTANT
Necrotising enterocolitis - 3mg/kg versus 15mg/kg, Infants < 32 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	0/42 (0%)	2/40 (5%)	RR 0.19 (0.01 to 3.85)	41 fewer per 1000 (from 49 fewer to 142 more)	LOW	IMPORTANT
Necrotising enterocolitis - 3mg/kg versus 30mg/kg, Infants < 32 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	0/42 (0%)	0/45 (0%)	RD 0.0 (-0.04 to 0.04)	0 more per 1000 (from 40 fewer to 40 more)	LOW	IMPORTANT
Necrotising enterocolitis - 15mg/kg versus 30mg/kg, Infants < 32 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	2/40 (5%)	0/45 (0%)	RR 5.61 (0.28 to 113.47)	23 more per 1000 (from 4 fewer to 562 more)[6]	LOW	IMPORTANT
Necrotising enterocolitis - 5mg/kg versus 20mg/kg (Respiratory indication - peri-extubation), Infants < 30 weeks												
1	randomised trials	no serious	no serious inconsistency	no serious indirectness	very serious[1]	none	5/121 (4.1%)	0/113 (0%)	RR 10.28	46 more per 1000	LOW	IMPORTANT

Quality assessment							Number of babies		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lower dose caffeine	Higher dose caffeine	Relative (95% CI)	Absolute	Quality	Importance
		risk of bias							(0.57 to 183.8)	(from 2 fewer to 914 more)[6]		
Necrotising enterocolitis - 20mg/kg versus 80mg/kg, Infants ≤ 30 weeks												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	5/37 (13.5%)	6/37 (16.2%)	RR 0.83 (0.28 to 2.49)	28 fewer per 1000 (from 117 fewer to 242 more)	VERY LOW	IMPORTANT

1 *IQR: interquartile range; RR: risk ratio*

2 [1] The quality of evidence was downgraded by 2 because the CI crosses 2 MIDs
3 [2] The quality of evidence was downgraded by 1 due to unclear random sequence generation and allocation concealment
4 [3] The quality of evidence was downgraded by 1 because the CI crosses 1 MID
5 [4] The quality of evidence was downgraded by 1 – imprecision was not assessable due to results being presented as medians
6 [5] Not assessable due to 0 events in both treatment arms
7 [6] Control event rate was 0% so absolute values were calculated using an assumed baseline risk of 0.5%.

8 **Table 22: Clinical evidence profile: Comparison 3 – Earlier administration of caffeine versus later administration of caffeine**

Quality assessment							Number of babies		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Early administration of caffeine	Later administration of caffeine	Relative (95% CI)	Absolute	Quality	Importance
Mortality prior to discharge - Administration at < 2 days versus ≥ 2 days, Infants ≤ 32 weeks												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	12/143 (8.4%)	12/143 (8.4%)	RR 1 (0.46 to 2.15)	0 fewer per 1000 (from 45	VERY LOW	CRITICAL

Quality assessment							Number of babies		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Early administration of caffeine	Later administration of caffeine	Relative (95% CI)	Absolute	Quality	Importance
										fewer to 97 more)		
Mortality prior to discharge - Administration at < 3 days versus ≥ 3 days												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	659/14535 (4.5%)	542/14535 (3.7%)	RR 1.22 (1.09 to 1.36)	8 more per 1000 (from 3 more to 13 more)	VERY LOW	CRITICAL
Mortality prior to discharge - Administration at < 3 days versus ≥ 3 days, Infants < 31 weeks												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	217/3806 (5.7%)	75/1295 (5.8%)	RR 0.98 (0.76 to 1.27)	1 fewer per 1000 (from 14 fewer to 16 more)	VERY LOW	CRITICAL
Mortality prior to discharge - Administration at < 3 days versus ≥ 3 days												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	188/1986 (9.5%)	79/965 (8.2%)	RR 1.16 (0.9 to 1.49)	13 more per 1000 (from 8 fewer to 40 more)	VERY LOW	IMPORTANT
Bronchopulmonary dysplasia at 36 weeks post-menstrual age - Administration at < 2 days versus ≥ 2 days, Infants ≤ 32 weeks												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	43/143 (30.1%)	49/143 (34.3%)	RR 0.88 (0.63 to 1.23)	41 fewer per 1000 (from 127 fewer to 79 more)	VERY LOW	CRITICAL
Bronchopulmonary dysplasia at 36 weeks post-menstrual age - Administration at < 3 days versus ≥ 3 days, Infants < 31 weeks												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	999/3806 (26.2%)	340/1295 (26.3%)	RR 1 (0.9 to 1.11)	0 fewer per 1000 (from 26 fewer to 29 more)	LOW	CRITICAL

Quality assessment							Number of babies		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Early administration of caffeine	Later administration of caffeine	Relative (95% CI)	Absolute	Quality	Importance
Bronchopulmonary dysplasia at 36 weeks post-menstrual age - Administration at < 3 days versus ≥ 3 days												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	716/1986 (36.1%)	451/965 (46.7%)	RR 0.77 (0.71 to 0.84)	107 fewer per 1000 (from 75 fewer to 136 fewer)	VERY LOW	CRITICAL
Bronchopulmonary dysplasia at 36 weeks post-menstrual age or 28 days of age - Administration at < 3 days versus ≥ 3 days												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	3070/14535 (21.1%)	4154/14535 (28.6%)	RR 0.74 (0.71 to 0.77)	74 fewer per 1000 (from 66 fewer to 83 fewer)	LOW	CRITICAL
Bronchopulmonary dysplasia at 28 days of age - Administration at < 3 days versus ≥ 3 days, Infants < 31 weeks												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1535/3806 (40.3%)	502/1295 (38.8%)	RR 1.04 (0.96 to 1.13)	16 more per 1000 (from 16 fewer to 50 more)	LOW	IMPORTANT
Necrotising enterocolitis - NEC any stage												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1219/14535 (8.4%)	1187/14535 (8.2%)	RR 1.03 (0.95 to 1.11)	2 more per 1000 (from 4 fewer to 9 more)	LOW	IMPORTANT
Necrotising enterocolitis - NEC any stage												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious2	none	144/1986 (7.3%)	57/965 (5.9%)	RR 1.23 (0.91 to 1.65)	14 more per 1000 (from 5 fewer to 38 more)	VERY LOW	IMPORTANT

Quality assessment							Number of babies		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Early administration of caffeine**	**Later administration of caffeine**	**Relative (95% CI)**	**Absolute**		
Necrotising enterocolitis - NEC stage ≥ 2, Infants < 31 weeks												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious2	none	240/3806 (6.3%)	78/1295 (6%)	RR 1.05 (0.82 to 1.34)	3 more per 1000 (from 11 fewer to 20 more)	VERY LOW	IMPORTANT

1 *NEC: necrotising enterocolitis; RR: risk ratio*

2 [1] The quality of evidence was downgraded by 2 because the CI crosses 2 MIDs
3 [2] The quality of evidence was downgraded by 1 because the CI crosses 1 MID

4 **Table 23: Clinical evidence profile: Comparison 4 – Shorter duration caffeine versus longer duration caffeine**

Quality assessment							Number of babies		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Shorter duration**	**Longer duration**	**Relative (95% CI)**	**Absolute**		
Bronchopulmonary dysplasia at 36 weeks post-menstrual age, Infants < 30 weeks - ECC versus ICC												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	71/122 (58.2%)	34/92 (37%)	RR 1.57 (1.16 to 2.14)	211 more per 1000 (from 59 more to 421 more)	VERY LOW	CRITICAL
Bronchopulmonary dysplasia at 36 weeks post-menstrual age, Infants < 30 weeks - ECC versus LCC												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	71/122 (58.2%)	81/165 (49.1%)	RR 1.19 (0.95 to 1.47)	93 more per 1000 (from 25 fewer to 231 more)	VERY LOW	CRITICAL
Bronchopulmonary dysplasia at 36 weeks post-menstrual age, Infants < 30 weeks - ICC versus LCC												

Quality assessment							Number of babies		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Shorter duration**	**Longer duration**	**Relative (95% CI)**	**Absolute**		
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	34/92 (37%)	82/165 (49.7%)	RR 0.74 (0.55 to 1.01)	129 fewer per 1000 (from 224 fewer to 5 more)	VERY LOW	CRITICAL
Cerebral palsy, 3 year follow up - Infants < 30 weeks - ECC versus ICC												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	5/138 (3.6%)	6/140 (4.3%)	RR 0.85 (0.26 to 2.71)	6 fewer per 1000 (from 32 fewer to 73 more)	VERY LOW	CRITICAL
Cerebral palsy, 3 year follow up - Infants < 30 weeks - ECC versus LCC												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	5/138 (3.6%)	4/149 (2.7%)	RR 1.35 (0.37 to 4.92)	9 more per 1000 (from 17 fewer to 105 more)	VERY LOW	CRITICAL
Cerebral palsy, 3 year follow up - Infants < 30 weeks - ICC versus LCC												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	6/140 (4.3%)	4/149 (2.7%)	RR 1.6 (0.46 to 5.54)	16 more per 1000 (from 14 fewer to 122 more)	VERY LOW	CRITICAL
Moderate cognitive impairment, 3 year follow up - Full scale IQ 1-2 SD below the mean, Infants < 30 weeks - ECC versus ICC												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	14/130 (10.8%)	17/133 (12.8%)	RR 0.84 (0.43 to 1.64)	20 fewer per 1000 (from 73 fewer to 82 more)	VERY LOW	CRITICAL
Moderate cognitive impairment, 3 year follow up - Full scale IQ 1-2 SD below the mean, Infants < 30 weeks - ECC versus LCC												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	14/130 (10.8%)	20/139 (14.4%)	RR 0.75 (0.39 to 1.42)	36 fewer per 1000 (from 88 fewer to 60 more)	VERY LOW	CRITICAL
Moderate cognitive impairment, 3 year follow up - Full scale IQ 1-2 SD below the mean, Infants < 30 weeks - ICC versus LCC												

Quality assessment							Number of babies		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Shorter duration	Longer duration	Relative (95% CI)	Absolute		
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	17/133 (12.8%)	20/139 (14.4%)	RR 0.89 (0.49 to 1.62)	16 fewer per 1000 (from 73 fewer to 89 more)	VERY LOW	CRITICAL
Severe cognitive impairment, 3 year follow up - Full scale IQ > 2 SD below the mean, Infants < 30 weeks - ECC versus ICC												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/130 (1.5%)	7/133 (5.3%)	RR 0.29 (0.06 to 1.38)	37 fewer per 1000 (from 49 fewer to 20 more)	VERY LOW	CRITICAL
Severe cognitive impairment, 3 year follow up - Full scale IQ > 2 SD below the mean, Infants < 30 weeks - ECC versus LCC												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/130 (1.5%)	1/139 (0.72%)	RR 2.14 (0.2 to 23.3)	8 more per 1000 (from 6 fewer to 160 more)	VERY LOW	CRITICAL
Severe cognitive impairment, 3 year follow up - Full scale IQ > 2 SD below the mean, Infants < 30 weeks - ICC versus LCC												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	7/133 (5.3%)	1/139 (0.72%)	RR 7.32 (0.91 to 58.66)	45 more per 1000 (from 1 fewer to 415 more)	VERY LOW	CRITICAL
Deafness, 3 year follow up - Infants < 30 weeks - ECC versus ICC												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/134 (1.5%)	3/135 (2.2%)	RR 0.67 (0.11 to 3.96)	7 fewer per 1000 (from 20 fewer to 66 more)	VERY LOW	CRITICAL
Deafness, 3 year follow up - Infants < 30 weeks - ECC versus LCC												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/134 (1.5%)	1/147 (0.68%)	RR 2.19 (0.2 to 23.92)	8 more per 1000 (from 5 fewer to 156 more)	VERY LOW	CRITICAL
Deafness, 3 year follow up - Infants < 30 weeks - ICC versus LCC												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	3/135 (2.2%)	1/147 (0.68%)	RR 3.27 (0.34 to 31.03)	15 more per 1000 (from	VERY LOW	CRITICAL

Quality assessment							Number of babies		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Shorter duration	Longer duration	Relative (95% CI)	Absolute		
										4 fewer to 204 more)		
Blindness, 3 year follow up - Infants < 30 weeks - ECC versus ICC												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	3/137 (2.2%)	5/141 (3.5%)	RR 0.62 (0.15 to 2.53)	13 fewer per 1000 (from 30 fewer to 54 more)	VERY LOW	CRITICAL
Blindness, 3 year follow up - Infants < 30 weeks - ECC versus LCC												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	3/137 (2.2%)	5/148 (3.4%)	RR 0.65 (0.16 to 2.66)	12 fewer per 1000 (from 28 fewer to 56 more)	VERY LOW	CRITICAL
Blindness, 3 year follow up - Infants < 30 weeks - ICC versus LCC												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	5/141 (3.5%)	5/148 (3.4%)	RR 1.05 (0.31 to 3.55)	2 more per 1000 (from 23 fewer to 86 more)	VERY LOW	CRITICAL
Necrotising enterocolitis, Infants < 30 weeks - ECC versus ICC												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	19/139 (13.7%)	11/122 (9%)	RR 1.52 (0.75 to 3.06)	47 more per 1000 (from 23 fewer to 186 more)	VERY LOW	IMPORTANT
Necrotising enterocolitis, Infants < 30 weeks - ECC versus LCC												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	19/139 (13.7%)	16/286 (5.6%)	RR 2.44 (1.3 to 4.6)	81 more per 1000 (from 17 more to 201 more)	VERY LOW	IMPORTANT
Necrotising enterocolitis, Infants < 30 weeks - ICC versus LCC												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	11/122 (9%)	16/286 (5.6%)	RR 1.61 (0.77 to 3.37)	34 more per 1000 (from 13 fewer to 133 more)	VERY LOW	IMPORTANT

1 *ECC: early cessation of caffeine; ICC: intermediate cessation of caffeine; LCC: late cessation of caffeine; NEC: necrotising enterocolitis; RR: risk ratio*

2 [1] The quality of the evidence was downgraded by 1 due incomplete follow up (Lodha 2018)
3 [2] The quality of evidence was downgraded by 1 because the CI crosses 1 MID
4 [3] The quality of evidence was downgraded by 2 because the CI crosses 2 MIDs
5

6 GRADE tables for Question 3.8 What is the effectiveness of interventions for closing a patent ductus arteriosus in preterm 7 babies requiring respiratory support?

8 **Table 24: Clinical evidence profile – Comparison 1.1 Ibuprofen versus placebo**

Quality assessment							Number of babies		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ibuprofen	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Mortality prior to discharge												
6	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	61/438 (13.9%)	68/441 (15.4%)	RR 0.91 (0.66 to 1.24)	14 fewer per 1000 (from 52 fewer to 37 more)	LOW	CRITICAL
BPD at 36 weeks PMA												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	86/142 (60.6%)	84/143 (58.7%)	RR 1.07 (0.91 to 1.26)	41 more per 1000 (from 53 fewer to 153 more)	MODERATE	CRITICAL
BPD at 28 days of life												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	166/290 (57.2%)	156/296 (52.7%)	RR 1.08 (0.94 to 1.24)	42 more per 1000 (from 32 fewer to 126 more)	HIGH	CRITICAL
PDA required back-up treatment with indomethacin												

Quality assessment							Number of babies		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Ibuprofen**	**Placebo**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	16/228 (7%)	58/233 (24.9%)	RR 0.28 (0.17 to 0.47)	179 fewer per 1000 (from 132 fewer to 207 fewer)	HIGH	IMPORTANT
PDA required surgical ligation												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	6/228 (2.6%)	13/233 (5.6%)	RR 0.47 (0.18 to 1.21)	30 fewer per 1000 (from 46 fewer to 12 more)	MODERATE	IMPORTANT
PDA failed to close on day 3 - All infants												
2	randomised trials	no serious risk of bias	serious[3]	no serious indirectness	no serious imprecision	none	36/228 (15.8%)	100/233 (42.9%)	RR 0.37 (0.26 to 0.51)	270 fewer per 1000 (from 210 fewer to 318 fewer)	MODERATE	IMPORTANT
PDA failed to close on day 3 - 24-26 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	11/50 (22%)	26/51 (51%)	RR 0.43 (0.24 to 0.78)	291 fewer per 1000 (from 112 fewer to 387 fewer)	HIGH	IMPORTANT
PDA failed to close on day 3 - 27-30 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	22/155 (14.2%)	58/159 (36.5%)	RR 0.39 (0.25 to 0.6)	223 fewer per 1000 (from 146 fewer to 274 fewer)	HIGH	IMPORTANT
PDA reopened after closure on day 3												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	5/205 (2.4%)	7/210 (3.3%)	RR 0.73 (0.24 to 2.27)	9 fewer per 1000 (from 25	LOW	IMPORTANT

Quality assessment							Number of babies		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Ibuprofen**	**Placebo**	**Relative (95% CI)**	**Absolute**		
										fewer to 42 more)		
Repeated course of blinded study drug, first 28 days												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	9/54 (16.7%)	24/51 (47.1%)	RR 0.35 (0.18 to 0.69)	306 fewer per 1000 (from 146 fewer to 386 fewer)	HIGH	IMPORTANT
Open-label ibuprofen, first 28 days												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	7/54 (13%)	10/51 (19.6%)	RR 0.66 (0.27 to 1.6)	67 fewer per 1000 (from 143 fewer to 118 more)	LOW	IMPORTANT
At least 1 episode of serum creatinine > 140 umol/L (Day 1-3)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	8/65 (12.3%)	1/66 (1.5%)	RR 8.12 (1.05 to 63.13)	108 more per 1000 (from 1 more to 941 more)	MODERATE	IMPORTANT
Serum creatinine (mg/dL) - Day 1 (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	23	23	-	MD 0.08 lower (0.2 lower to 0.04 higher)	MODERATE	IMPORTANT
Serum creatinine (mg/dL) - Day 4 (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	23	23	-	MD 0.09 higher (0.17 lower to 0.35 higher)	MODERATE	IMPORTANT

Quality assessment							Number of babies		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Ibuprofen**	**Placebo**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Serum creatinine (µmol/L) - Day 1 (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	205	210	-	MD 3 higher (0.38 lower to 6.38 higher)	HIGH	IMPORTANT
Serum creatinine (µmol/L) - Day 3 (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	205	210	-	MD 13 higher (8.72 to 17.28 higher)	HIGH	IMPORTANT
Median creatinine (mg/dl) - day 7												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[6]	none	n=67 Median (IQR) 1 mg/dl (NR)	n=67 Median (IQR) 0.6 mg/dl (NR)		Median 0.3 mg/dl less (p=0.0003)	LOW	IMPORTANT
At least 1 episode of urinary output < 2 ml/kg/h (Day 1-3)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	37/65 (56.9%)	26/66 (39.4%)	RR 1.44 (1 to 2.08)	173 more per 1000 (from 0 more to 425 more)	MODERATE	IMPORTANT
Urine production (ml/kg/h) - Day 1 (Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	205	210	-	MD 0.9 lower (1.14 to 0.66 lower)	HIGH	IMPORTANT
Urine production (ml/kg/h) - Day 3 (Better indicated by higher values)												

Quality assessment							Number of babies		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Ibuprofen**	**Placebo**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	205	210	-	MD 0.2 lower (0.52 lower to 0.12 higher)	MODERATE	IMPORTANT
Median blood urea nitrogen (mg/dl) - day 7												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[6]	none	n=67 Median (IQR) 84 mg/dl (NR)	n=67 Median (IQR) 38 mg/dl (NR)		Median 46 mg/dl more (p= 0.0000002)	LOW	IMPORTANT
Urea (mg/dL) - Day 1 (Better indicated by lower values)												
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	23	23	-	MD 0.5 higher (11.65 lower to 12.65 higher)	MODERATE	IMPORTANT
Urea (mg/dL) - Day 4 (Better indicated by lower values)												
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[2]	none	23	23	-	MD 7.5 higher (23.73 lower to 38.73 higher)	LOW	IMPORTANT
Oliguria < 0.5 ml/kg/h (Days 1-3)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	45/205 (22%)	30/210 (14.3%)	RR 1.54 (1.01 to 2.34)	77 more per 1000 (from 1 more to 191 more)	MODERATE	IMPORTANT
Intestinal perforation												

Quality assessment							Number of babies		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Ibuprofen**	**Placebo**	**Relative (95% CI)**	**Absolute**		
2	randomised trials	no serious risk of bias	serious[3]	no serious indirectness	very serious[1]	none	7/119 (5.9%)	5/117 (4.3%)	RR 1.41 (0.14 to 14.68)	16 more per 1000 (from 24 fewer to 135 more)	VERY LOW	IMPORTANT
NEC (requiring surgery)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	5/54 (9.3%)	2/51 (3.9%)	RR 2.36 (0.48 to 11.63)	53 more per 1000 (from 20 fewer to 417 more)	LOW	IMPORTANT
NEC (stage 3)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	6/205 (2.9%)	12/210 (5.7%)	RR 0.51 (0.2 to 1.34)	28 fewer per 1000 (from 46 fewer to 19 more)	LOW	IMPORTANT
NEC (any stage)												
4	randomised trials	no serious risk of bias	serious[3]	no serious indirectness	very serious[1]	none	22/172 (12.8%)	19/171 (11.1%)	RR 0.96 (0.32 to 2.88)	16 more per 1000 (from 40 fewer to 112 more)	VERY LOW	IMPORTANT

BPD: bronchopulmanory dysplasia; CI: confidence interval; NEC: necrotising enterocolitis; NR: not reported; PMA: post menstrual age; RR: risk ratio

[1] The quality of evidence was downgraded by 2 because the 95% CI crosses 2 MIDs

[2] The quality of evidence was downgraded by 1 because the 95% CI crosses 1 MID

[3] The quality of evidence was downgraded by 1 due to potential moderate inconsistency in results (PDA failed to close on day 3 - All infants I^2= 42%; Intestinal perforation I^2= 67%; NEC (any stage) I^2= 59%); no source of heterogeneity identified for NEC; subgroup analysis not possible for the other outcomes as there were only 2 trials; random effects model used

[4] The quality of evidence was downgraded by 1 because the method of randomisation and allocation was not specified and medians were presented without IQRs (Bagnoli 2013)

[5] The quality of evidence was downgraded by 1 because the method of randomisation and managing attrition was unclear and as recruitment stopped earlier than intended, the study was underpowered (Kanmaz 2012)

[6] The quality of evidence was downgraded by 1: imprecision was not calculable because the results were reported as medians

Table 25: Evidence profile: Comparison 1.2 Paracetamol versus placebo

Quality assessment							Number of babies		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Paracetamol	Placebo	Relative (95% CI)	Absolute		
Mortality prior to discharge												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	0/23 (0%)	1/25 (4%)	RR 0.36 (0.02 to 8.45)	26 fewer per 1000 (from 39 fewer to 298 more)	LOW	CRITICAL
BPD at 36 weeks PMA												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	0/23 (0%)	1/25 (4%)	RR 0.36 (0.02 to 8.45)	26 fewer per 1000 (from 39 fewer to 298 more)	LOW	CRITICAL
Oliguria (< 1 mL/kg/h)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	5/23 (21.7%)	7/25 (28%)	RR 0.78 (0.29 to 2.11)	62 fewer per 1000 (from 199 fewer to 311 more)	LOW	IMPORTANT
Polyuria (> 5 mL/kg/h)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	6/23 (26.1%)	9/25 (36%)	RR 0.72 (0.31 to 1.72)	101 fewer per 1000 (from 248 fewer to 259 more)	LOW	IMPORTANT
NEC (stage 3)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	0/23 (0%)	1/25 (4%)	RR 0.36 (0.02 to 8.45)	26 fewer per 1000 (from 39 fewer to 298 more)	LOW	IMPORTANT

BPD: bronchopulmanory dysplasia; CI: confidence interval; NEC: necrotising enterocolitis; PMA: postmenstrual age; RR: risk ratio

[1] The quality of evidence was downgraded by 2 because the 95% CI crosses 2 MIDs

Table 26: Clinical evidence profile – Comparison 2. Surgery versus no surgery

Quality assessment							Number of babies		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surgery	Placebo	Relative (95% CI)	Absolute		
Mortality prior to discharge												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	98/701 (14%)	566/3886 (14.6%)	RR 0.96 (0.79 to 1.17)	6 fewer per 1000 (from 31 fewer to 25 more)	VERY LOW	CRITICAL
Mortality prior to discharge												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	40/135 (29.6%)	140/403 (34.7%)	RR 0.85 (0.64 to 1.14)	52 fewer per 1000 (from 125 fewer to 49 more)	VERY LOW	CRITICAL
Intestinal perforation												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	43/701 (6.1%)	66/3886 (1.7%)	RR 3.61 (2.48 to 5.26)	44 more per 1000 (from 25 more to 72 more)	VERY LOW	IMPORTANT
NEC												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	86/701 (12.3%)	271/3886 (7%)	RR 1.76 (1.4 to 2.21)	53 more per 1000 (from 28 more to 84 more)	VERY LOW	IMPORTANT

CI: confidence interval; NEC: necrotising enterocolitis; RR: risk ratio

[1] The quality of evidence was downgraded by 1 because patients in both arms may have received prophylactic indomethacin (Laughon 2007; Madan 2009)

[2] The quality of evidence was downgraded by 1 because the 95% CI crosses 1 MID

Table 27: Clinical evidence profile – Comparison 3. Surgery versus fluid restriction

Quality assessment							Number of babies		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surgery	Fluid restriction	Relative (95% CI)	Absolute		
Mortality prior to discharge												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	35/327 (10.7%)	72/577 (12.5%)	RR 0.86 (0.59 to 1.25)	17 fewer per 1000 (from 51 fewer to 31 more)	VERY LOW	CRITICAL
BPD at 36 weeks PMA												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	199/327 (60.9%)	138/577 (23.9%)	RR 2.54 (2.15 to 3.01)	368 more per 1000 (from 275 more to 481 more)	VERY LOW	CRITICAL
NEC stages 2 or 3												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	70/327 (21.4%)	34/577 (5.9%)	RR 3.63 (2.47 to 5.35)	155 more per 1000 (from 87 more to 256 more)	VERY LOW	IMPORTANT

BPD: bronchopulmanory dysplasia; CI: confidence interval; NEC: necrotising enterocolitis; PMA: postmenstrual age; RR: risk ratio
[1] The quality of evidence was downgraded by 1 because patients in both arms may have received prophylactic indomethacin (Mirea 2012)
[2] The quality of evidence was downgraded by 1 because the 95% CI crosses 1 MID

Table 28: Clinical evidence profile – Comparison 4. Ibuprofen versus paracetamol

Quality assessment							Number of babies		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ibuprofen	Paracetamol	Relative (95% CI)	Absolute		
Mortality prior to discharge												

Quality assessment							Number of babies		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Ibuprofen**	**Paracetamol**	**Relative (95% CI)**	**Absolute**		
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/40 (5%)	3/40 (7.5%)	RR 0.67 (0.12 to 3.78)	25 fewer per 1000 (from 66 fewer to 209 more)	VERY LOW	CRITICAL
Neurodevelopmental impairment												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	10/31 (32.3%)	9/30 (30%)	RR 1.08 (0.51 to 2.27)	24 more per 1000 (from 147 fewer to 381 more)	VERY LOW	CRITICAL
Moderate to severe cerebral palsy												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/31 (6.5%)	4/30 (13.3%)	RR 0.48 (0.1 to 2.45)	69 fewer per 1000 (from 120 fewer to 193 more)	VERY LOW	CRITICAL
Blindness												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/31 (3.2%)	0/30 (0%)	RR 2.91 (0.12 to 68.66)	-	VERY LOW	CRITICAL
Deafness												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/31 (3.2%)	0/30 (0%)	RR 2.91 (0.12 to 68.66)	-	VERY LOW	CRITICAL
PDA closure after first course of study drug - ≤ 30 weeks												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	31/40 (77.5%)	29/40 (72.5%)	RR 1.07 (0.83 to 1.38)	51 more per 1000 (from 123 fewer to 275 more)	LOW	IMPORTANT
PDA closure after first course of study drug - < 28 weeks												

Quality assessment							Number of babies		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Ibuprofen**	**Paracetamol**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	11/19 (57.9%)	17/23 (73.9%)	RR 0.78 (0.5 to 1.23)	163 fewer per 1000 (from 370 fewer to 170 more)	LOW	IMPORTANT
PDA closure after first course of study drug - ≤ 26 weeks												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	9/16 (56.3%)	10/23 (43.5%)	RR 1.29 (0.69 to 2.44)	126 more per 1000 (from 135 fewer to 626 more)	VERY LOW	IMPORTANT
PDA reopening and closure with second cure - ≤ 30 weeks												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	5/40 (12.5%)	7/40 (17.5%)	RR 0.71 (0.25 to 2.06)	51 fewer per 1000 (from 131 fewer to 185 more)	VERY LOW	IMPORTANT
PDA reopening and closure with second cure - < 28 weeks												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/19 (21.1%)	7/23 (30.4%)	RR 0.69 (0.24 to 2.01)	94 fewer per 1000 (from 231 fewer to 307 more)	VERY LOW	
PDA reopening and closure with second cure - ≤ 26 weeks												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/16 (25%)	6/23 (26.1%)	RR 0.96 (0.32 to 2.86)	10 fewer per 1000 (from 177 fewer to 485 more)	VERY LOW	IMPORTANT
PDA surgical ligation rate - ≤ 30 weeks												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/40 (5.0%)	1/40 (2.5%)	RR 2.00 (0.19 to 21.18)	25 more per 1000 (from 20	VERY LOW	IMPORTANT

Quality assessment							Number of babies		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ibuprofen	Paracetamol	Relative (95% CI)	Absolute		
										fewer to 505 more)		
PDA surgical ligation rate - < 28 weeks												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/19 (10.5%)	1/23 (4.3%)	RR 2.42 (0.24 to 24.69)	62 more per 1000 (from 33 fewer to 1000 more)	VERY LOW	IMPORTANT
PDA surgical ligation rate - ≤ 26 weeks												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/16 (12.5%)	1/23 (4.3%)	RR 2.88 (0.28 to 29.08)	82 more per 1000 (from 31 fewer to 1000 more)	VERY LOW	IMPORTANT
Change in BUN (mg/dL) from pre-treatment to post-treatment (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	40	40	-	MD 7.6 higher (0.25 to 14.95 higher)	LOW	IMPORTANT
Change in serum creatinine (mg/dL) from pre-treatment to post-treatment (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	40	40	-	MD 0.08 higher (0.01 to 0.15 higher)	LOW	IMPORTANT
Change in urine output (mL/kg/h) from pre-treatment to post-treatment (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	40	40	-	MD 0.31 higher (0.06 to 0.56 higher)	LOW	IMPORTANT

Quality assessment							Number of babies		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ibuprofen	Paracetamol	Relative (95% CI)	Absolute		
NEC (any stage)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	10/40 (25%)	12/40 (30%)	RR 0.83 (0.41 to 1.7)	51 fewer per 1000 (from 177 fewer to 210 more)	VERY LOW	IMPORTANT
NEC (NEC stage ≥ 2)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/31 (0%)	1/30 (3.3%)	RR 0.32 (0.01 to 7.63)	23 fewer per 1000 (from 33 fewer to 221 more)	VERY LOW	IMPORTANT
Gastrointestinal bleeding												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/40 (2.5%)	0/40 (0%)	RR 3 (0.13 to 71.51)	-	VERY LOW	IMPORTANT

BUN: blood urea nitrogen; CI: confidence interval; NEC: necrotising enterocolitis; PDA: patent ductus arteriosus; RR: risk ratio

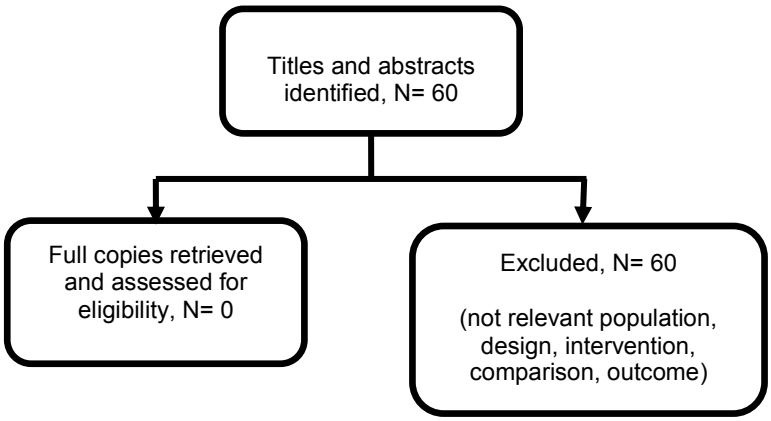
[1] The quality of evidence was downgraded by 1 because of lack of computer-generated randomisation and patient attrition for follow-up neurodevelopmental outcomes (Oncel 2014; Oncel 2017)

[2] The quality of evidence was downgraded by 2 because the 95% CI crosses 2 MIDs

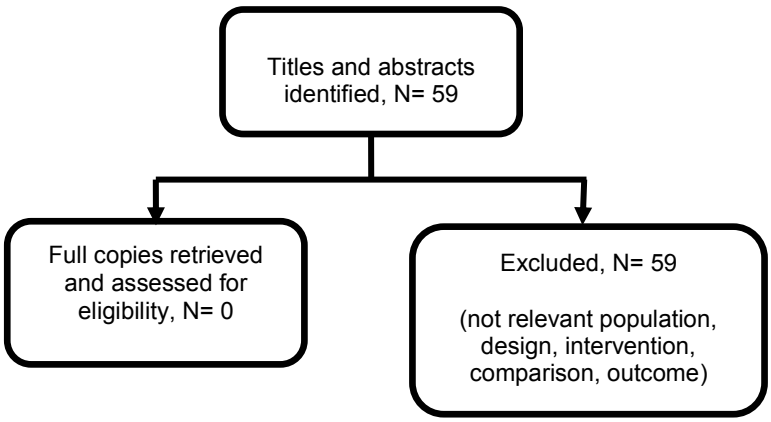
[3] The quality of evidence was downgraded by 1 because the 95% CI crosses 1 MID

Appendix G – Economic evidence study selection

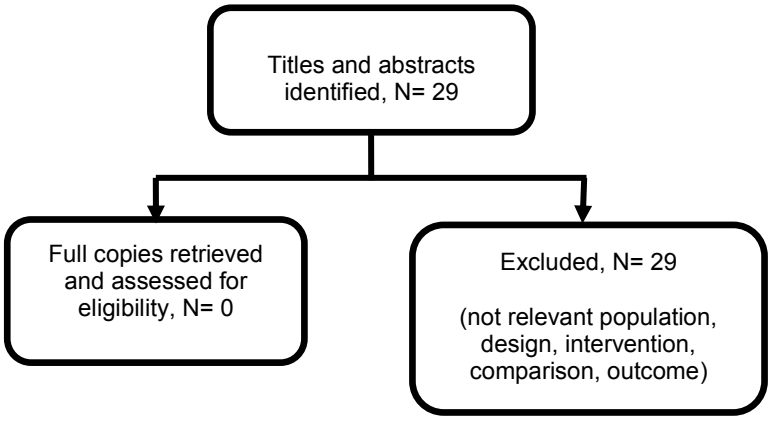
Economic evidence selection for question 3.4 What is the effectiveness of corticosteroids in preterm babies requiring respiratory support?



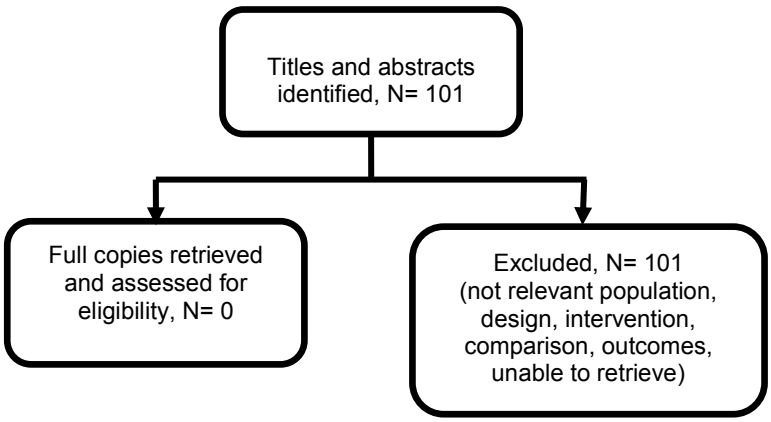
Economic evidence selection for question 3.5 What is the safety and effectiveness of diuretics in preterm babies on respiratory support?



Economic evidence selection for question 3.6 What is the effectiveness of caffeine in preterm babies requiring respiratory support?



Economic evidence selection for question 3.8 What is the effectiveness of interventions for closing a patent ductus arteriosus in preterm babies requiring respiratory support?



Appendix H – Economic evidence tables

Economic evidence tables for question 3.4 What is the effectiveness of corticosteroids in preterm babies requiring respiratory support?

No economic evidence was identified for this review.

Economic evidence tables for question 3.5 What is the safety and effectiveness of diuretics in preterm babies on respiratory support?

No economic evidence was identified for this review.

Economic evidence tables for question 3.6 What is the effectiveness of caffeine in preterm babies requiring respiratory support?

No economic evidence was identified for this review.

Economic evidence tables for question 3.8 What is the effectiveness of interventions for closing a patent ductus arteriosus in preterm babies requiring respiratory support?

No economic evidence was identified for this review.

Appendix I – Economic evidence profiles

Economic evidence profiles for question 3.4 What is the effectiveness of corticosteroids in preterm babies requiring respiratory support?

No economic evidence was identified for this review.

Economic evidence profiles for question 3.5 What is the safety and effectiveness of diuretics in preterm babies on respiratory support?

No economic evidence was identified for this review.

Economic evidence profiles for question 3.6 What is the effectiveness of caffeine in preterm babies requiring respiratory support?

No economic evidence was identified for this review.

Economic evidence profiles for question 3.8 What is the effectiveness of interventions for closing a patent ductus arteriosus in preterm babies requiring respiratory support?

No economic evidence was identified for this review.

Appendix J – Economic analysis

Economic analysis for question 3.4 What is the effectiveness of corticosteroids in preterm babies requiring respiratory support?

No economic analysis was undertaken for this review.

Economic analysis for question 3.5 What is the safety and effectiveness of diuretics in preterm babies on respiratory support?

No economic analysis was undertaken for this review.

Economic analysis for question 3.6 What is the effectiveness of caffeine in preterm babies requiring respiratory support?

No economic analysis was undertaken for this review.

Economic analysis for question 3.8 What is the effectiveness of interventions for closing a patent ductus arteriosus in preterm babies requiring respiratory support?

No economic analysis was undertaken for this review.

Appendix K – Excluded studies

Excluded studies for question 3.4 What is the effectiveness of corticosteroids in preterm babies requiring respiratory support?

Clinical studies

Study	Reason for Exclusion
Dexamethasone therapy in neonatal chronic lung disease: an international placebo-controlled trial. Collaborative Dexamethasone Trial Group, Pediatrics, 88, 421-427, 1991	Recruitment dates do not meet the inclusion criteria for the review: 1986-1989
Anonymous,, Early treatment of premature infants with steroids: neurological sequelae, Prescrire International, 16, 108-9, 2007	Study design not of interest for review: narrative review
Arias-Camison, J M, Lau, J, Cole, C H, Frantz, I D, Meta-analysis of dexamethasone therapy started in the first 15 days of life for prevention of chronic lung disease in premature infants (Structured abstract), Pediatric Pulmonology, 28, 167-174, 1999	Superseded by recent Cochrane systematic review by Doyle 2014
Arnon, S., Grigg, J., Silverman, M., Effectiveness of budesonide aerosol in ventilator-dependent preterm babies: A preliminary report, Pediatric Pulmonology, 21, 231-235, 1996	Participants in each arm do not meet the inclusion criteria for review: <15 participants in each arm.
Bassler, D, Halliday, Hl, Plavka, R, Hallman, M, Shinwell, Es, Jarreau, Ph, Carnielli, V, Anker, J, Schwab, M, Poets, Cf, The Neonatal European Study of Inhaled Steroids (NEUROSIS): an eu-funded international randomised controlled trial in preterm infants, Neonatology, 97, 52-5, 2010	Study design not of interest for review: Protocol for NEUROSIS trial
Bassler, D., Plavka, R., Shinwell, E. S., Hallman, M., Jarreau, P. H., Carnielli, V., Van den Anker, J. N., Meisner, C., Engel, C., Schwab, M., Halliday, H. L., Poets, C. F., Neurosis Trial Group, Early Inhaled Budesonide for the Prevention of Bronchopulmonary Dysplasia, The New England journal of medicine, 373, 1497-506, 2015	Intervention not of interest for review: budesonide MDI not nebules
Bloomfield,F.H., Knight,D.B., Breier,B.H., Harding,J.E., Growth restriction in dexamethasone-treated preterm infants may be mediated by reduced IGF-I and IGFBP-3 plasma concentrations, Clinical Endocrinology, 54, 235-242, 2001	No outcomes of interest for review: growth outcomes
Carlo, Wa, Stark, Ar, Bauer, C, Donovan, E, Oh, W, Papile, L, Shankaran, S, Tyson, Je, Wright, Ll, Temprosa, E, Poole, K, Effects of minimal ventilation in a multicenter randomized controlled trial of ventilator support and early corticosteroid therapy in	Insufficient data to extract for review: conference abstract

Study	Reason for Exclusion
extremely low birth weight infants, Pediatrics, 104, 738-9, 1999	
Carlo,W.A., Stark,A.R., Wright,L.L., Tyson,J.E., Papile,L.A., Shankaran,S., Donovan,E.F., Oh,W., Bauer,C.R., Saha,S., Poole,W.K., Stoll,B., Minimal ventilation to prevent bronchopulmonary dysplasia in extremely-low-birth-weight infants, Journal of Pediatrics, 141, 370-374, 2002	Results reported elsewhere for inclusion in review: 2 x 2 factorial design, dexamethasone intervention reported in Stark et al 2001
Cole, C. H., Colton, T., Shah, B. L., Abbasi, S., Mackinnon, B. L., Demissie, S., Frantz, Iii I. D., Early inhaled glucocorticoid therapy to prevent bronchopulmonary dysplasia, New England Journal of Medicine, 340, 1005-1010, 1999	Intervention not of interest for review: Inhaled beclomethasone
Couser,R.J., Ferrara,T.B., Falde,B., Johnson,K., Schilling,C.G., Hoekstra,R.E., Effectiveness of dexamethasone in preventing extubation failure in preterm infants at increased risk for airway edema, Journal of Pediatrics, 121, 591-596, 1992	No outcomes of interest for review: pulmonary resistance
de Oliveira Peixoto, F. A., Costa, P. S., Reviewing the use of corticosteroids in bronchopulmonary dysplasia, Jornal de Pediatria, 92, 122-8, 2016	Study design not of interest for review: narrative review
DeCastro,M., El-Khoury,N., Parton,L., Ballabh,P., LaGamma,E.F., Postnatal betamethasone vs dexamethasone in premature infants with bronchopulmonary dysplasia: A pilot study, Journal of Perinatology, 29, 297-304, 2009	Intervention is betamethasone and not of interest
Delara, M., Chauhan, B. F., Le, M. L., Abou-Setta, A. M., Zarychanski, R., tJong, G. W., Efficacy and safety of pulmonary application of corticosteroids in preterm infants with respiratory distress syndrome: a systematic review and meta-analysis, Archives of disease in childhood. Fetal and neonatal edition, 2018	Insufficient data to extract for review: conference abstract
Denjean,A., Paris-Llado,J., Zupan,V., Debillon,T., Kieffer,F., Magny,J.F., Desfreres,L., Llanas,B., Guimaraes,H., Moriette,G., Voyer,M., Dehan,M., Breart,G., Inhaled salbutamol and beclomethasone for preventing broncho-pulmonary dysplasia: a randomised double-blind study, European Journal of Pediatrics, 157, 926-931, 1998	Intervention not of interest for review: beclomethasone
Doyle, L. W., Ehrenkranz, R. A., Halliday, H. L., Dexamethasone treatment after the first week of life for bronchopulmonary dysplasia in preterm infants: a systematic review, Neonatology, 98, 289-96, 2010	Superseded by Cochrane review Doyle 2014
Doyle, L. W., Halliday, H. L., Ehrenkranz, R. A., Davis, P. G., Sinclair, J. C., An update on the impact of postnatal systemic	Comparison not of interest for review: assessment of relationship between cerebral palsy or death with BPD

Study	Reason for Exclusion
corticosteroids on mortality and cerebral palsy in preterm infants: effect modification by risk of bronchopulmonary dysplasia, Journal of Pediatrics, 165, 1258-60, 2014	
Doyle, Lex W., Cheong, Jeanie L., Ehrenkranz, Richard A., Halliday, Henry L., Early (< 8 days) systemic postnatal corticosteroids for prevention of bronchopulmonary dysplasia in preterm infants, Cochrane Database of Systematic Reviews, 2017	Systematic review identified at re-runs stage: systematic review does not include any additional studies to the review
Doyle, Lex W., Cheong, Jeanie L., Ehrenkranz, Richard A., Halliday, Henry L., Late (> 7 days) systemic postnatal corticosteroids for prevention of bronchopulmonary dysplasia in preterm infants, Cochrane Database of Systematic Reviews, 2017	Systematic review identified at re-runs stage: Systematic review does not include any additional studies to the review
Doyle, Lw, Davis, Pg, Morley, Cj, McPhee, A, Carlin, J, Low Dose Dexamethasone Facilitates Extubation in Chronically Ventilator-Dependent Infants A Multicentre International Randomized Controlled Trial. The DART Study Investigators, Pediatric Academic Societies Annual Meeting; 2005 May 14-17; Washington DC, United States, 2005	Insufficient data to extract for review: conference abstract
Doyle,L.W., Davis,P.G., Postnatal corticosteroids in preterm infants: Systematic review of effects on mortality and motor function, Journal of Paediatrics and Child Health, 36, 101-107, 2000	No additional RCTs that are not captured in Doyle et al 2014 cochrane systematic review
Doyle,L.W., Ehrenkranz,R.A., Halliday,H.L., Postnatal hydrocortisone for preventing or treating bronchopulmonary dysplasia in preterm infants: a systematic review, Neonatology, 98, 111-117, 2010	Superseded by Cochrane review Doyle 2014
Ferguson, K. N., Roberts, C. T., Manley, B. J., Davis, P. G., Interventions to improve rates of successful extubation in preterm infants a systematic review and meta-analysis, JAMA Pediatrics, 171, 165-174, 2017	Intervention not of interest for review: mode of ventilation
Gupta, Sachin, Prasanth, Kaninghat, Chen, Chung-Ming, Yeh, Tsu F., Postnatal Corticosteroids for Prevention and Treatment of Chronic Lung Disease in the Preterm Newborn, International Journal of Pediatrics, 2012, 315642, 2012	Study design not of interest for review: narrative review
Halliday, H. L., Ehrenkranz, R. A., Doyle, L. W., Delayed (>3 weeks) postnatal corticosteroids for chronic lung disease in preterm infants, Cochrane Database of Systematic Reviews, CD001145, 2003	Superseded by Doyle 2014 Cochrane review (Late > 7 days postnatal corticosteroids for chronic lung disease in preterm infants).

Study	Reason for Exclusion
Halliday, H. L., Ehrenkranz, R. A., Doyle, L. W., Late (>7 days) postnatal corticosteroids for chronic lung disease in preterm infants, Cochrane Database of Systematic Reviews, (1), 2009	Updated in 2014 by Doyle et al.
Halliday, H. L., Ehrenkranz, R. A., Doyle, L. W., Early postnatal (<96 hours) corticosteroids for preventing chronic lung disease in preterm infants, Cochrane Database of Systematic Reviews, CD001146, 2003	Superseded by Doyle 2014 Cochrane review (Early < 8 days postnatal corticosteroids for preventing chronic lung disease in preterm infants).
Halliday,H.L., Ehrenkranz,R.A., Doyle,L.W., Moderately early (7-14 days) postnatal corticosteroids for preventing chronic lung disease in preterm infants, Cochrane database of systematic reviews (Online), 2003. Date of Publication, -, 2003	No additional RCTs that are not included in cohrane systematic review by Doyle et al 2014
Halliday,H.L., Ehrenkranz,R.A., Doyle,L.W., Early (< 8 days) postnatal corticosteroids for preventing chronic lung disease in preterm infants, Cochrane Database of Systematic Reviews, 2009. Article Number, -, 2009	Updated in 2014 by Doyle et al.
Harrold, J., Ali, S., Oleszczuk, M., Lacaze-Masmonteil, T., Hartling, L., Corticosteroids for the prevention of bronchopulmonary dysplasia in preterm infants: An overview of Cochrane reviews, Evidence-Based Child Health, 8, 2063-2075, 2013	Study design not of interest for review: narrative review
Inwald, D. P., Trivedi, K., Murch, S. H., Costeloe, K., The effect of early inhaled budesonide on pulmonary inflammation in infants with respiratory distress syndrome, European Journal of Pediatrics, 158, 815-6, 1999	Study design not of interest for review: longitudinal study
Jones, R. A., Randomized, controlled trial of dexamethasone in neonatal chronic lung disease: 13- to 17-year follow-up study: II. Respiratory status, growth, and blood pressure, Pediatrics, 116, 379-384, 2005	Recruitment dates do not meet the inclusion criteria for the review: 1986-1989
Jones, R. A. K., Randomized, controlled trial of dexamethasone in neonatal chronic lung disease: 13- to 17-year follow-up study: I. Neurologic, psychological, and educational outcomes, Pediatrics, 116, 370-378, 2005	Recruitment dates do not meet the inclusion criteria for the review: 1986-1989
Jones,R., Wincott,E., Elbourne,D., Grant,A., Controlled trial of dexamethasone in neonatal chronic lung disease: a 3-year follow-up, Pediatrics, 96, 897-906, 1995	Recruitment dates do not meet the inclusion criteria for the review: 1986-1989
Ke, H, Li, Z-K, Yu, X-P, Guo, J-Z, Efficacy of different preparations of budesonide combined with pulmonary surfactant in the treatment of neonatal respiratory distress syndrome: A comparative analysis. [Chinese],	Language not of interest for review: Article written in Chinese

Study	Reason for Exclusion
Chinese Journal of Contemporary Pediatrics, 18, 400-4, 2016	
Kopelman,A.E., Moise,A.A., Holbert,D., Hegemier,S.E., A single very early dexamethasone dose improves respiratory and cardiovascular adaptation in preterm infants, Journal of Pediatrics, 135, 345-350, 1999	Duration of corticosteroid course does not meet inclusion criteria: single dose of dexamethasone
Kothadia, Jm, O'Shea, Tm, Roberts, D, Dillard, Rg, Randomized double-blind placebo-controlled trial of dexamethasone to decrease the duration of ventilator dependency in very low birth weight infants, Pediatric Research, 39, 223a, 1996	Insufficient data to extract for review: conference abstract
Kumar,P., Effect of decreased use of postnatal corticosteroids on morbidity in extremely low birthweight infants, American Journal of Perinatology, 22, 77-81, 2005	Study design not of interest for review: Retrospective review
Lin,Y.J., Yeh,T.F., Hsieh,W.S., Chi,Y.C., Lin,H.C., Lin,C.H., Prevention of chronic lung disease in preterm infants by early postnatal dexamethasone therapy, Pediatric Pulmonology, 27, 21-26, 1999	Country not of interest for review: Taiwan
Lister, P., Iles, R., Shaw, B., Ducharme, F., Inhaled steroids for neonatal chronic lung disease, Cochrane database of systematic reviews (Online), CD002311, 2000	Superseded by Onland 2012 Cochrane review (Late > 7 days inhalation corticosteroids to reduce bronchopulmonary dysplasia in preterm infants)
Merz, U., Kusenbach, G., Hausler, M., Peschgens, T., Hornchen, H., Inhaled budesonide in ventilator-dependent preterm infants: A randomized, double-blind pilot study, Biology of the Neonate, 75, 46-53, 1999	Participants in each arm do not meet the inclusion criteria for review: <15 participants in each arm.
Mieskonen,S., Eronen,M., Malmberg,L.P., Turpeinen,M., Kari,M.A., Hallman,M., Controlled trial of dexamethasone in neonatal chronic lung disease: an 8-year follow-up of cardiopulmonary function and growth, Acta Paediatrica, 92, 896-904, 2003	Participants in each arm do not meet the inclusion criteria for review: <15 participants in each arm.
Morales,P., Rastogi,A., Bez,M.L., Akintorin,S.M., Pyati,S., Andes,S.M., Pildes,R.S., Effect of dexamethasone therapy on the neonatal ductus arteriosus, Pediatric Cardiology, 19, 225-229, 1998	Participants in each arm do not meet the inclusion criteria for review: <15 participants in each arm.
Ng, Pc, Lee, Ch, Bnur, Fl, Chan, Ih, Lee, Aw, Wong, E, Chan, Hb, Lam, Cw, Lee, Bs, Fok, Tf, A double-blind, randomized, controlled study of a "stress dose" of hydrocortisone for rescue treatment of refractory hypotension in preterm infants, Pediatrics, 117, 367-75, 2006	Country not of interest for review: Hong Kong
Onland, W, Offringa, M, Kaam, A, Late (≥7 days) inhalation corticosteroids to reduce bronchopulmonary dysplasia in preterm	Systematic review does not include any additional studies to the review

Study	Reason for Exclusion
infants, Cochrane database of systematic reviews (online), 2017, 2017	
Onland, W., de Jaegere, A. P., van de Loo, M., van Kaam, A. H., Postnatal corticosteroids for the prevention of bronchopulmonary dysplasia, Netherlands Journal of Critical Care, 18, 8-14, 2014	Study design not of interest for review: narrative review
Onland, W., Offringa, M., Cools, F., De Jaegere, A. P., Rademaker, K., Blom, H., Cavatorta, E., Debeer, A., Dijk, P. H., van Heijst, A. F., Kramer, B. W., Kroon, A. A., Mohns, T., van Straaten, H. L., te Pas, A. B., Theyskens, C., van Weissenbruch, M. M., van Kaam, A. H., Systemic Hydrocortisone To Prevent Bronchopulmonary Dysplasia in preterm infants (the SToP-BPD study); a multicenter randomized placebo controlled trial, BMC Pediatrics, 11, 102, 2011	Study design not of interest for review: protocol
Onland, W., Offringa, M., Jaegere, A. P. D., Van Kaam, A. H., Finding the optimal postnatal dexamethasone regimen for preterm infants at risk of bronchopulmonary dysplasia: A systematic review of placebo-controlled trials, Pediatrics, 123, 367-377, 2009	Superseded by Doyle 2014
Onland, W., Offringa, M., van Kaam, A., Late (> 7 days) inhalation corticosteroids to reduce bronchopulmonary dysplasia in preterm infants, Cochrane database of systematic reviews (Online), 4, CD002311, 2012	Only contains one RCT that meets inclusion criteria of review, data extracted from original paper
O'Shea, T. M., Kothadia, J. M., Klinepeter, K. L., Goldstein, D. J., Jackson, B. G., Weaver, Iii R. G., Dillard, R. G., Randomized placebo-controlled trial of a 42-day tapering course of dexamethasone to reduce the duration of ventilator dependency in very low birth weight infants: Outcome of study participants at 1-year adjusted age, Pediatrics, 104, 15-21, 1999	Timeframe around neurodevelopmental outcomes not of interest for review: 1 year
Papile, L, Stoll, B, Donovan, E, Tyson, J, Bauer, C, Wright, L, Krause-Steinrauf, H, Verter, J, Dexamethasone therapy in infants at risk for chronic lung disease (CLD): a multi-center, randomized, double-masked trial, Pediatric Research, 39, 236a, 1996	Insufficient data to extract for review: conference abstract
Pappagallo, M, Bhutani, V, Abbasi, S, Nebulised steroid trial in ventilator-dependent preterm infants, Pediatric Research, 29, 327a, 1991	Insufficient data to extract for review: conference abstract
Rademaker, K. J., Uiterwaal, C. S., Groenendaal, F., Venema, M. M., van Bel, F., Beek, F. J., van Haastert, I. C., Grobbee, D. E., de Vries, L. S., Neonatal hydrocortisone treatment: neurodevelopmental outcome and	Study design not of interest for review: Cohort study

Study	Reason for Exclusion
MRI at school age in preterm-born children, Journal of Pediatrics, 150, 351-7, 2007	
Romagnoli,C., Zecca,E., Vento,G., Maggio,L., Papacci,P., Tortorolo,G., Effect on growth of two different dexamethasone courses for preterm infants at risk of chronic lung disease. A randomized trial, Pharmacology, 59, 266-274, 1999	No outcomes of interest for review: growth outcomes
Sanders,R.J., Cox,C., Phelps,D.L., Sinkin,R.A., Two doses of early intravenous dexamethasone for the prevention of bronchopulmonary dysplasia in babies with respiratory distress syndrome, Pediatric Research, 36, 122-128, 1994	Duration of corticosteroid course does not meet inclusion criteria: two doses of dexamethasone
Shah, S. S., Ohlsson, A., Halliday, H., Shah, V. S., Inhaled versus systemic corticosteroids for the treatment of chronic lung disease in ventilated very low birth weight preterm infants, Cochrane Database of Systematic Reviews, (4) (no pagination), 2007	Superseded by Shah et al 2012
Shah, Sachin S, Ohlsson, Arne, Halliday, Henry L, Shah, Vibhuti S, Inhaled versus systemic corticosteroids for the treatment of bronchopulmonary dysplasia in ventilated very low birth weight preterm infants, Cochrane Database of Systematic Reviews, 2017	No additional studies to 2012
Shah, Sachin S, Ohlsson, Arne, Halliday, Henry L, Shah, Vibhuti S, Inhaled versus systemic corticosteroids for the treatment of chronic lung disease in ventilated very low birth weight preterm infants, Cochrane Database of Systematic Reviews, 2012	Only contains one RCT that meets inclusion criteria of review, data extracted from original paper
Shah, V. S., Ohlsson, A., Halliday, H. L., Dunn, M., Early administration of inhaled corticosteroids for preventing chronic lung disease in very low birth weight preterm neonates, Cochrane Database of Systematic Reviews, 2017 (1) (no pagination), 2017	Only contains one RCT that meets inclusion criteria of review, data extracted from original paper
Shinwell, E. S., Portnov, I., Meerpohl, J. J., Karen, T., Bassler, D., Inhaled corticosteroids for bronchopulmonary dysplasia: A meta-analysis, Pediatrics, 138 (6) (no pagination), 2016	No additional RCTs to cochrane review by Shah et al 2017
Shipalana, N., Cooper, P. A., Strahlendorff, C., Early postnatal steroids for non-ventilated infants weighing less than 1000 g at birth - A randomised trial, Pediatric Reviews and Communications, 8, 29-33, 1994	Country not of interest for review: South Africa
Sinkin, R. A., Dweck, H. S., Horgan, M. J., Gallaher, K. J., Cox, C., Maniscalco, W. M., Chess, P. R., D'Angio, C. T., Guillet, R., Kendig, J. W., Ryan, R. M., Phelps, D. L., Early dexamethasone - Attempting to prevent	Duration of corticosteroid course does not meet inclusion criteria: Dexamethasone given for 2 doses

Study	Reason for Exclusion
chronic lung disease, Pediatrics, 105, 542-548, 2000	
Stark, Ar, Carlo, W, Bauer, C, Donovan, E, Oh, W, Papile, L, Shankaran, S, Tyson, Je, Wright, Ll, Temprosa, M, Poole, K, Complications of early steroid therapy in a randomized controlled trial, Pediatrics, 104, 739, 1999	Insufficient data to extract for review: conference abstract
Suchomski, S. J., Cummings, J. J., A randomized trial of inhaled versus intravenous steroids in ventilator-dependent preterm infants, Journal of Perinatology, 22, 196-203, 2002	Intervention not of interest for review: Inhaled beclomethasone
Victorian Infant, Collaborative, Postnatal corticosteroids and sensorineural outcome at 5 years of age, Journal of Paediatrics & Child Health, 36, 256-61, 2000	Study design not of interest for review: Cohort study
Wang, J. Y., Yeh, T. F., Lin, Y. C., Miyamura, K., Holmskov, U., Reid, K. B. M., Measurement of pulmonary status and surfactant protein levels during dexamethasone treatment of neonatal respiratory distress syndrome, Thorax, 51, 907-913, 1996	Country not of interest for review: Taiwan
Washburn,L.K., Nixon,P.A., O'Shea,T.M., Follow-up of a randomized, placebo-controlled trial of postnatal dexamethasone: blood pressure and anthropometric measurements at school age, Pediatrics, 118, 1592-1599, 2006	No outcomes of interest for review: blood pressure and anthropometrics measurements at school age
Yates, H. L., Newell, S. J., Postnatal intravenous steroids and long-term neurological outcome: Recommendations from meta-analyses, Archives of Disease in Childhood: Fetal and Neonatal Edition, 97, F299-F303, 2012	Clinical recommendations based on a meta-analysis
Yeh,T.F., Prevention of chronic lung disease (CLD) in premature infants with early dexamethasone therapy, Pediatric Pulmonology - Supplement, 16, 35-36, 1997	Insufficient data to extract for review: conference abstract
Yeh,T.F., Lin,Y.J., Huang,C.C., Chen,Y.J., Lin,C.H., Lin,H.C., Hsieh,W.S., Lien,Y.J., Early dexamethasone therapy in preterm infants: a follow-up study, Pediatrics, 101, E7-, 1998	Country not of interest for review: Taiwan
Yeh,T.F., Lin,Y.J., Lin,H.C., Huang,C.C., Hsieh,W.S., Lin,C.H., Tsai,C.H., Outcomes at school age after postnatal dexamethasone therapy for lung disease of prematurity, New England Journal of Medicine, 350, 1304-1313, 2004	Country not of interest for review: Taiwan
Yeh,T.F., Torre,J.A., Rastogi,A., Anyebuno,M.A., Pildes,R.S., Early postnatal dexamethasone therapy in premature infants	Recruitment dates do not meet the inclusion criteria for the review:June-November 1988

Study	Reason for Exclusion
with severe respiratory distress syndrome: a double-blind, controlled study, Journal of Pediatrics, 117, 273-282, 1990	
Yeh,T.F., Lin,Y.J., Hsieh,W.S., Lin,H.C., Lin,C.H., Chen,J.Y., Kao,H.A., Chien,C.H., Early postnatal dexamethasone therapy for the prevention of chronic lung disease in preterm infants with respiratory distress syndrome: a multicenter clinical trial, Pediatrics, 100, E3-, 1997	Country not of interest for review: Taiwan
Zeng, L., Tian, J., Song, F., Li, W., Jiang, L., Gui, G., Zhang, Y., Ge, L., Shi, J., Sun, X., Mu, D., Zhang, L., Corticosteroids for the prevention of bronchopulmonary dysplasia in preterm infants: a network meta-analysis, Archives of disease in childhood. Fetal and neonatal edition, 2018	Systematic review does not include any additional studies to the review
Zhang, Z. Q., Zhong, Y., Huang, X. M., Du, L. Z., Airway administration of corticosteroids for prevention of bronchopulmonary dysplasia in premature infants: a meta-analysis with trial sequential analysis, BMC Pulmonary Medicine, 17, 207, 2017	Systematic review does not include any additional studies to the review

1

2 **Economic studies**

3 All economic studies were excluded at the initial title and abstract screening stage.
4

Excluded studies for question 3.5 What is the safety and effectiveness of diuretics in preterm babies on respiratory support?

Clinical studies

Systematic reviews and RCTs:

Study	Reason for Exclusion
Brion, L. P., Primhak, R. A., Intravenous or enteral loop diuretics for preterm infants with (or developing) chronic lung disease, Cochrane database of systematic reviews (Online), CD001453, 2002	Superseded by Stewart 2011
Brion, L. P., Primhak, R. A., Ambrosio-Perez, I., Diuretics acting on the distal renal tubule for preterm infants with (or developing) chronic lung disease, Cochrane database of systematic reviews (Online), CD001817, 2002	Superseded by Stewart 2011
Brion, L. P., Soll, R. F., Diuretics for respiratory distress syndrome in preterm infants, Cochrane database of systematic reviews (Online), CD001454, 2001	Superseded by Brion 2008
Brion, L.P., Soll,R.F., Diuretics for respiratory distress syndrome in preterm infants, Cochrane Database of Systematic Reviews, 2008. Article Number, -, 2008	Superseded by Stewart 2011
Cotton, R., Suarez, S., Reese, J., Unexpected extra-renal effects of loop diuretics in the preterm neonate, Acta PaediatricaActa Paediatr, 101, 835-45, 2012	Literature review
Hoffman, Dj, Abbasi, S, Cnaan, A, Gerdes, Js, Effect of spironolactone on pulmonary function and electrolyte balance in infants with chronic lung disease, Pediatric Research, 35, 337a, 1994	Abstract
Hoffman, Dj, Abbasi, S, Sivieri, Em, Deuber, C, Bhutani, Vk, Gerdes, Js, Pulmonary function and electrolyte balance following spironolactone treatment in preterm infants with chronic lung disease, Pediatric Research, 41, 56a, 1997	Abstract
Reiter, P. D., Makhlouf, R., Stiles, A. D., Comparison of 6-hour infusion versus bolus furosemide in premature infants, Pharmacotherapy, 18, 63-68, 1998	Comparison not of interest for review: 6hr infusion vs bolus furosemide
Rush, M. G., Engelhardt, B., Parker, R. A., Hazinski, T. A., Double-blind placebo-controlled trial of alternate-day furosemide therapy in infants with chronic bronchopulmonary dysplasia, Journal of Pediatrics, 117, 112-118, 1990	Study dates pre-1990
Segar, J. L., Chemtob, S., Bell, E. F., Changes in body water compartments with diuretic therapy in infants with chronic lung disease, Early Human Development, 48, 99-107, 1997	No outcomes of interest for review: changes in body water compartments and electrolyte intake

Study	Reason for Exclusion
Stewart, A., Brion, L. P., Intravenous or enteral loop diuretics for preterm infants with (or developing) chronic lung disease, Cochrane database of systematic reviews (Online), 9, CD001453, 2011	No RCTs that meet inclusion criteria of review, RCTs excluded based on study dates pre-1990 or no outcomes of interest for review.
Stewart, A., Brion, L. P., Ambrosio-Perez, I., Diuretics acting on the distal renal tubule for preterm infants with (or developing) chronic lung disease, Cochrane database of systematic reviews (Online), 9, CD001817, 2011	Only 2 RCTs that meet inclusion criteria of review - Kao 1994 and Hoffman 2000 (both included and extracted from original RCT). Other RCTs excluded based on study dates pre-1990 or no outcomes of interest for review.
Stewart, A., Brion, L. P., Soll, R., Diuretics for respiratory distress syndrome in preterm infants, Cochrane database of systematic reviews (Online), 12, CD001454, 2011	No RCTs that meet inclusion criteria of review, RCTs excluded based on study dates pre-1990, intervention not of interest for review, or no outcomes of interest for review.

1 Observational studies:

Study	Reason for Exclusion
Blaisdell, C. J., Troendle, J., Zajicek, A., Prematurity,, Respiratory Outcomes, Program, Acute Responses to Diuretic Therapy in very preterm Results from the Prematurity and Respiratory Outcomes Program Cohort Study, Journal of PediatricsJ Pediatr, 20, 20, 2018	Has no outcomes that meet criteria. A prognostic study, not interventional.
Downing, G. J., Egelhoff, J. C., Daily, D. K., Alon, U., Furosemide-related renal calcifications in the premature infant: A longitudinal ultrasonographic study, Pediatric Radiology, 21, 563-565, 1991	Study design not of interest for review: longitudinal study of a clinical group with no comparison group
Downing, G. J., Egelhoff, J. C., Daily, D. K., Thomas, M. K., Alon, U., Kidney function in very low birth weight infants with furosemide-related renal calcifications at ages 1 to 2 years, Journal of Pediatrics, 120, 599-604, 1992	No outcomes of interest for review: kidney function at 1-2 years of age (not including nephrocalcinosis)
Orth, L. E., O'Mara, K. L., Impact of Early Versus Late Diuretic Exposure on Metabolic Bone Disease and Growth in Premature Neonates, Journal of Pediatric Pharmacology and Therapeutics, 23, 26-33, 2018	No outcomes of interest for review
Wise, R. T., Moffett, B. S., Akcan-Arikan, A., Galati, M., Afonso, N., Checchia, P. A., Enhancement of diuresis with metolazone in infant paediatric cardiac intensive care patients, Cardiology in the Young, 28, 27-31, 2018	population not of interest for review: paediatrics

2

Economic studies

4 All economic studies were excluded at the initial title and abstract screening stage.
5

Excluded studies for question 3.6 What is the effectiveness of caffeine in preterm babies requiring respiratory support?

Clinical studies

Study	Reason for Exclusion
Abbasi, S., Aden, U., Allan, W., Bada, H., Barks, J., Bauer, C., Bizzarro, M., Carlo, W., Chen, X., Cummings, J., Ehrenkranz, R., Eyal, F., Faix, R., Fuller, J., Hopper, A., Inder, T., Kaiser, J., Karpen, H., Lifton, R., Maller, Kesselman, Ment, L., O'Shea, T., Poindexter, B., Pourcyrous, M., Sayman, K., Shankaran, S., Vohr, B., Yoder, B., Zhang, H., Early caffeine is associated with decreased IVH in very low birth weight neonates, Annals of neurology, 14), S89, 2010	Conference abstract
Adzikah, S., Maletzki, J., Ruegger, C., Bassler, D., Association of early versus late caffeine administration on neonatal outcomes in very preterm neonates, Acta paediatrica, international journal of paediatrics, 106, 518, 2017	Commentary on another trial
Al Hazzani, F., Survival without Disability to Age 5 years After Neonatal Caffeine Therapy for Apnea of Prematurity, Journal of Clinical Neonatology, 1, 64-6, 2012	Same outcomes and follow up period reported in Schmidt 2012
Armanian, A. M., Iranpour, R., Faghihian, E., Salehimehr, N., Caffeine Administration to Prevent Apnea in Very Premature Infants, Pediatrics and Neonatology, 57, 408-412, 2016	Non-OECD country - Iran
Bajaj, N., Use of methylxanthines in preterm neonates, Perinatology, 18, 72-76, 2017	Narrative review
Bancalari, E., Caffeine reduces the rate of bronchopulmonary dysplasia in very low birth weight infants, Journal of pediatrics, 149, 727-728, 2006	Commentary
Benitz, W. E., Use of caffeine for apnea of prematurity also has long-term neurodevelopmental benefits, Journal of pediatrics, 152, 740-741, 2008	Commentary
Bucher, Hu, Duc, G, Does caffeine prevent hypoxaemic episodes in premature infants? A randomized controlled trial, European journal of pediatrics, 147, 288-291, 1988	Study date pre-1990
Charles, B. G., Townsend, S. R., Steer, P. A., Flenady, V. J., Gray, P. H., Shearman, A., Caffeine citrate treatment for extremely premature infants with apnea: population pharmacokinetics, absolute bioavailability, and implications for therapeutic drug monitoring, Therapeutic drug monitoring, 30, 709-16, 2008	Outcomes not relevant
Comer, A. M., Perry, C. M., Figgitt, D. P., Caffeine citrate: A review of its use in apnoea of prematurity, Paediatric Drugs, 3, 61-79, 2001	Narrative review
Corvaglia, L., Aceti, A., In preterm infants with recurrent apnoea, methylxanthine reduces the	Non Cochrane systematic review- comparisons not relevant, studies assessed individually

Study	Reason for Exclusion
number of episodes and the use of mechanical ventilation in the short term; caffeine is also associated with improved longer term outcomes, Evidence Based Medicine, 16, 120-1, 2011	
Dekker, J., Hooper, S. B., Van Vonderen, J. J., Witlox, R. S. G. M., Lopriore, E., Te Pas, A. B., Caffeine to improve breathing effort of preterm infants at birth: A randomized controlled trial, Pediatric research, 82, 290-296, 2017	Outcomes not relevant
Demauro, S. B., Roberts, R. S., Davis, P., Alvaro, R., Bairam, A., Schmidt, B., Impact of delivery room resuscitation on outcomes up to 18 months in very low birth weight infants, Journal of Pediatrics, 159, 546-550.e1, 2011	Subgroups not relevant
Doyle, L. W., Cheong, J., Hunt, R. W., Lee, K. J., Thompson, D. K., Davis, P. G., Rees, S., Anderson, P. J., Inder, T. E., Caffeine and brain development in very preterm infants, Annals of neurology, 68, 734-742, 2010	Subgroup not relevant to review - Australian babies in the CAP trial (2006)
Erenberg, A, Leff, R, Wynne, Ba, Ludden, T, Results of the first double blind placebo (PL) controlled study of caffeine citrate (CC) for the treatment of apnea of prematurity (AOP), Pediatrics, 102, 756-757, 1998	Conference abstract
Erenberg, A., Leff, R. D., Haack, D. G., Mosdell, K. W., Hicks, G. M., Wynne, B. A., Caffeine citrate for the treatment of apnea of prematurity: A double- blind, placebo-controlled study, Pharmacotherapy, 20, 644-652, 2000	Population not relevant - babies did not require respiratory support
Gupte, A. S., Gupta, D., Ravichandran, S., Michelle Ma, M., Chouthai, N. S., Effect of early caffeine on neurodevelopmental outcome of very low-birth weight newborns, Journal of Maternal-Fetal and Neonatal Medicine, 29, 1233-1237, 2016	Results reported in Davis 2010
Hand, I., Zaghloul, N., Barash, L., Parris, R., Aden, U., Li, H. L., Timing of Caffeine Therapy and Neonatal Outcomes in Preterm Infants: A Retrospective Study, International Journal of Pediatrics, 2016, 9478204, 2016	Fewer than 100 participants in each arm
Henderson-Smart, D. J., Davis, P. G., Prophylactic methylxanthines for extubation in preterm infants, Cochrane Database of Systematic Reviews, (4) (no pagination), 2009	Cochrane review out of date
Henderson-Smart, David J, De, Paoli Antonio G, Prophylactic methylxanthine for prevention of apnoea in preterm infants, Cochrane Database of Systematic Reviews, 2010	Cochrane review with additional included studies relevant to review and outcomes included
Henderson-Smart, David J, De, Paoli Antonio G, Methylxanthine treatment for apnoea in preterm infants, Cochrane Database of Systematic Reviews, 2010	Individual studies reported separately in review
Katheria, A. C., Sauberan, J. B., Akotia, D., Rich, W., Durham, J., Finer, N. N., A Pilot	Fewer than 15 participants in each arm

Study	Reason for Exclusion
Randomized Controlled Trial of Early versus Routine Caffeine in Extremely Premature Infants, American Journal of Perinatology, 32, 879-86, 2015	
Kua, K. P., Lee, S. W. H., Systematic review and meta-analysis of clinical outcomes of early caffeine therapy in preterm neonates, British Journal of Clinical Pharmacology, 83, 180-191, 2017	Non Cochrane systematic review, all studies assessed individually
Mohammed, S., Nour, I., Shabaan, A. E., Shouman, B., Abdel-Hady, H., Nasef, N., High versus low-dose caffeine for apnea of prematurity: a randomized controlled trial, European journal of pediatrics, 174, 949-956, 2015	Non OECD country - Egypt
Pakvasa, M. A., Saroha, V., Patel, R. M., Optimizing Caffeine Use and Risk of Bronchopulmonary Dysplasia in Preterm Infants: A Systematic Review, Meta-analysis, and Application of Grading of Recommendations Assessment, Development, and Evaluation Methodology, Clinics in Perinatology, 45, 273-291, 2018	Non-Cochrane systematic review; articles already assessed individually
Park, H. W., Lim, G., Chung, S. H., Chung, S., Kim, K. S., Kim, S. N., Early Caffeine Use in Very Low Birth Weight Infants and Neonatal Outcomes: A Systematic Review and Meta-Analysis, Journal of Korean medical science, 30, 1828-1835, 2015	Non Cochrane systematic review; all studies assessed individually
Patel, R. M., Leong, T., Carlton, D. P., Vyas-Read, S., Early caffeine therapy and clinical outcomes in extremely preterm infants, Journal of Perinatology, 33, 134-40, 2013	Fewer than 15 participants in each arm
Rhein, L. M., Dobson, N. R., Darnall, R. A., Corwin, M. J., Heeren, T. C., Poets, C. F., McEntire, B. L., Hunt, C. E., Effects of caffeine on intermittent hypoxia in infants born prematurely: A randomized clinical trial, JAMA pediatrics, 168, 250-257, 2014	Outcomes not relevant - hypoxia
Romagnoli, C., De Carolis, M. P., Muzii, U., Zecca, E., Tortorolo, G., Chiarotti, M., De Giovanni, N., Carnevale, A., Effectiveness and side effects of two different doses of caffeine in preventing apnea in premature infants, Therapeutic Drug MonitoringTher Drug Monit, 14, 14-9, 1992	Fewer than 15 participants in each arm
Saeidi, R., Maghrebi, S., Comparison of the early and late caffeine therapy on clinical outcomes in preterm neonates, Giornale italiano di ostetricia e ginecologia, 36, 568-570, 2014	Conference abstract
Schmidt, B, Anderson, Pj, Doyle, Lw, Dewey, D, Grunau, R, Asztalos, E, Davis, Pg, Tin, W, Moddemann, D, Solimano, A, Ohlsson, A, Barrington, K, Roberts, Rs, Investigator, Cap, The caffeine for apnea of prematurity (CAP) trial:	Conference abstract

Study	Reason for Exclusion
outcomes at 5 years, Paediatrics and child health., 16, 11a, 2011	
Shenk, E. E., Bondi, D. S., Pellerite, M. M., Sriram, S., Evaluation of Timing and Dosing of Caffeine Citrate in Preterm Neonates for the Prevention of Bronchopulmonary Dysplasia, The Journal of Pediatric Pharmacology & TherapeuticsJ, 23, 139-145, 2018	Cohort study; < 100 participants in each arm
Srinivasan, P, Katz, S, DeCristofaro, J, Increased caffeine levels do not reduce the frequency of clinical cardiopulmonary events in neonates with apnea of prematurity following repeat bolus therapy. A randomized placebo controlled study, Pediatric research, 51, 420a, 2002	Citation
Tabacaru, C. R., Jang, S. Y., Patel, M., Davalian, F., Zanelli, S., Fairchild, K. D., Impact of Caffeine Boluses and Caffeine Discontinuation on Apnea and Hypoxemia in Preterm Infants, Journal of Caffeine Research, 7, 103-110, 2017	Cohort study- interventions not relevant
Urtiaga Urrestizala, A., Lopez de Heredia y Goya, J., Arranz Cerezo, C., Santesteban Otazu, E., Valls-i-Soler, A., Efficacy of caffeine in extubation of newborns under 32 weeks of age. Systematic revision and observational study, Revista Espanola de Pediatria, 71, 19-27, 2015	Paper unavailable - written in Spanish
Vliegenthart, R., Miedema, M., Hutten, G. J., van Kaam, A. H., Onland, W., High versus standard dose caffeine for apnoea: a systematic review, Archives of Disease in Childhood Fetal & Neonatal EditionArch Dis Child Fetal Neonatal Ed, 07, 07, 2018	Non Cochrane systematic review; studies assessed individually
Zhao, Y, Tian, X, Liu, G, Clinical effectiveness of different doses of caffeine for primary apnea in preterm infants, Zhonghua ER ke za zhi = chinese journal of pediatrics, 54, 33-36, 2016	Non OECD country - China

1 *OECD: Organisation for Economic Co-operation and Development*

Economic studies

3 All economic studies were excluded at the initial title and abstract screening stage.
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Excluded studies for question 3.8 What is the effectiveness of interventions for closing a patent ductus arteriosus in preterm babies requiring respiratory support?

Clinical studies

Systematic reviews and RCTs:

Study	Reason for Exclusion
Outcome after selective early closure of ductus arteriosus in extremely preterm babies (Baby-OSCAR trial) (Project record), Health Technology Assessment Database, 2014	Protocol for a trial
Amoozgar, H., Ghodstehrani, M., Pishva, N., Oral ibuprofen and ductus arteriosus closure in full-term neonates: A prospective case-control study, Pediatric Cardiology, 31, 40-43, 2010	Infants were not preterm
Aranda, J. V., Thomas, R., Systematic review: intravenous Ibuprofen in preterm newborns, Seminars in Perinatology, 30, 114-20, 2006	Not a systematic review
Bagheri, M. M., Niknafs, P., Sabsevari, F., Torabi, M. H., Bahman Bijari, B., Noroozi, E., Mossavi, H., Comparison of Oral Acetaminophen Versus Ibuprofen in Premature Infants With Patent Ductus Arteriosus, Iranian Journal of Pediatrics, 26, e3975, 2016	Not an OECD country
Bell, E. F., Acarregui, M. J., Restricted versus liberal water intake for preventing morbidity and mortality in preterm infants, Cochrane Database of Systematic Reviews, 12, CD000503, 2014	Studies did not match date criteria; comparisons were not relevant- 2 different fluid regimens
Dang, D., Wang, D., Zhang, C., Zhou, W., Zhou, Q., Wu, H., Comparison of oral paracetamol versus ibuprofen in premature infants with patent ductus arteriosus: a randomized controlled trial, PLoS ONE [Electronic Resource]PLoS ONE, 8, e77888, 2013	Not an OECD country
Dani, C., Poggi, C., Mosca, F., Schena, F., Lista, G., Ramenghi, L., Romagnoli, C., Salvatori, E., Rosignoli, M. T., Lipone, P., Comandini, A., Efficacy and safety of intravenous paracetamol in comparison to ibuprofen for the treatment of patent ductus arteriosus in preterm infants: study protocol for a randomized control trial, Trials [Electronic Resource]Trials, 17, 182, 2016	Protocol for a trial
Dani, C., Vangi, V., Bertini, G., Pratesi, S., Lori, I., Favelli, F., Ciuti, R., Bandinelli, A., Martano, C., Murru, P., Messner, H., Schena, F., Mosca, F., High-dose ibuprofen for patent ductus arteriosus in extremely preterm infants: A randomized controlled study, Clinical Pharmacology and Therapeutics, 91, 590-596, 2012	No intervention of interest - compared 2 doses of ibuprofen
Das, R. R., Arora, K., Naik, S. S., Efficacy and safety of paracetamol versus ibuprofen for treating patent ductus arteriosus in preterm	Individual studies assessed

Study	Reason for Exclusion
infants: A meta-analysis, Journal of Clinical Neonatology, 3, 183-190, 2014	
El-Mashad, Ae-R, El-Mahdy, H, Amrousy, D, Elgendy, M, Comparative study of the efficacy and safety of paracetamol, ibuprofen, and indomethacin in closure of patent ductus arteriosus in preterm neonates, European Journal of Pediatrics, 1-8, 2016	Not an OECD country
Hammerman,C., Kaplan,M., Prophylactic ibuprofen in premature infants: a multicentre, randomised, double-blind, placebo-controlled trial, Journal of Pediatrics, 146, 709-710, 2005	Conference abstract
Hochwald, O., Mainzer, G., Borenstein-Levin, L., Jubran, H., Dinur, G., Zucker, M., Mor, M., Khoury, A., Kugelman, A., Adding Paracetamol to Ibuprofen for the Treatment of Patent Ductus Arteriosus in Preterm Infants: A Double-Blind, Randomized, Placebo-Controlled Pilot Study, American Journal of Perinatology., 21, 2018	< 15 babies in each arm
Huang, X., Wang, F., Wang, K., Paracetamol versus ibuprofen for the treatment of patent ductus arteriosus in preterm neonates: a meta-analysis of randomized controlled trials, Journal of Maternal-Fetal & Neonatal MedicineJ Matern Fetal Neonatal Med, 1-7, 2017	Studies assessed independently
Jung, P, Rickards, Ed, Deming, D, Patent ductus arteriosus and associated outcomes in extremely preterm infants, Journal of investigative medicine. Conference: 2018 western medical research conference, WMRC 2018. United states, 66, 89, 2018	Conference abstract
Kluckow, M. R., Carlisle, H., Broom, M., Woods, P., Jeffery, M., Desai, D., Evans, N. J., A randomised blinded placebo controlled trial of paracetamol to treat later PDA, Journal of Paediatrics and Child Health, 52, 100, 2016	Conference abstract
Knight, D. B., The treatment of patent ductus arteriosus in preterm infants. A review and overview of randomized trials, Seminars in Neonatology, 6, 63-73, 2001	Studies did not meet inclusion criteria i.e. date range or intervention
Lotfy, W, Badrawi, N, Ghawas, M, Ehsan, E, Aly, H, Oral ibuprofen solution (O) is efficacious for the treatment of patent ductus arteriosus (PDA) in premature infants: a randomized controlled trial, Pedaitric academic societies annual meeting, 2005	Conference abstract
Mitra, S., Florez, I. D., Tamayo, M. E., Mbuagbaw, L., Vanniyasingam, T., Veroniki, A. A., Zea, A. M., Zhang, Y., Sadeghirad, B., Thabane, L., Association of placebo, indomethacin, ibuprofen, and acetaminophen with closure of hemodynamically significant patent ductus arteriosus in preterm infants a systematic review and meta-analysis, JAMA -	Systematic review included indomethacin as a comparison; individual studies already assessed

Study	Reason for Exclusion
Journal of the American Medical Association, 319, 1221-1238, 2018	
Mosalli, R., Alfaleh, K., Prophylactic surgical ligation of patent ductus arteriosus for prevention of mortality and morbidity in extremely low birth weight infants, Cochrane Database of Systematic Reviews, CD006181, 2008	Only 1 study included in review, did not meet date criteria
Nct,, Paracetamol in the treatment of patent ductus arteriosus in the premature neonate, Clinicaltrials.gov/show/nct01291654, 2013	Full text not available
Nct,, Adding paracetamol to ibuprofen for treatment of patent ductus arteriosus in preterm infants, Clinicaltrials.gov/show/nct02002741, 2013	Study not yet completed
Ohlsson, A., Shah, S. S., Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants, Cochrane Database of Systematic Reviews, CD004213, 2011	Studies assessed individually - reported independently
Ohlsson, Arne, Shah, Prakeshkumar S, Paracetamol (acetaminophen) for patent ductus arteriosus in preterm or low birth weight infants, Cochrane Database of Systematic Reviews, 2018	Cochrane review published after original NGA review was done; all relevant studies included, no additional outcomes reported
Ohlsson, Arne, Shah, Prakeshkumar S, Paracetamol (acetaminophen) for patent ductus arteriosus in preterm or low-birth-weight infants, Cochrane Database of Systematic Reviews, 2015	Studies were assessed individually - reported separately
Oncel, M. Y., Yurttutan, S., Uras, N., Altug, N., Ozdemir, R., Ekmen, S., Erdeve, O., Dilmen, U., An alternative drug (paracetamol) in the management of patent ductus arteriosus in ibuprofen-resistant or contraindicated preterm infants, Archives of Disease in Childhood Fetal & Neonatal EditionArch Dis Child Fetal Neonatal Ed, 98, F94, 2013	Conference abstract
Overmeire, B, Langhendries, Jp, Vanhaesebrouck, P, Lecoutere, D, Broek, H, Ibuprofen for early treatment of patent ductus arteriosus, a randomized multicenter trial, Pediatric Research, 43, 200a, 1998	Conference abstract
Pacifici,G.M., Clinical pharmacology of the loop diuretics furosemide and bumetanide in neonates and infants, Paediatric Drugs, 14, 233-246, 2012	Not a systematic review
Patel, J, Marks, Ka, Roberts, I, Azzopardi, D, Edwards, Ad, Ibuprofen treatment of patent ductus arteriosus, Lancet, 346, 255, 1995	Conference abstract
Raychaudhuri, H., Bahadur, A., Alam, M., Nayak, S., Ali, I., Closing the ductus arteriosus in preterm infants. a review of present treatment strategies and developing a disease staging	Conference abstract

Study	Reason for Exclusion
protocol, Archives of Disease in Childhood, 103 (Supplement 1), A101-A102, 2018	
Rubaltelli, F, Bertini, G, Reali, Mf, Vangi, V, Dani, C, Does early closure of PDA with ibuprofen reduce the severity of RDS in premature infants?, Pediatric Research, 43, 296a, 1998	Conference abstract
Salama, H, Alsisi, A, Al-Rifai, H, Shaddad, A, Samawal, L, Habboub, L, A randomized controlled trial on the use of oral ibuprofen to close patent ductus arteriosus in premature infants, Journal of Neonatal-Perinatal Medicine, 1, 153-158, 2008	Not an OECD country
Schmidt, B., Wright, L. L., Davis, P., Solimano, A., Roberts, R. S., Indomethacin Prophylaxis in Preterms, Investigators, Ibuprofen prophylaxis in preterm neonates, Lancet, 360, 492, 2002	Conference abstract
Stewart, C. D., Morris, B. H., Huseby, V., Kennedy, K. A., Moya, F. R., Randomized trial of sterile water by gavage drip in the fluid management of extremely low birth weight infants, Journal of perinatology, 29, 26-32, 2009	Population did not have PDA before start of study
Terrin, G., Conte, F., Oncel, M. Y., Scipione, A., McNamara, P. J., Simons, S., Sinha, R., Erdeve, O., Tekgunduz, K. S., Dogan, M., Kessel, I., Hammerman, C., Nadir, E., Yurttutan, S., Jasani, B., Alan, S., Manguso, F., De Curtis, M., Paracetamol for the treatment of patent ductus arteriosus in preterm neonates: a systematic review and meta-analysis, Archives of Disease in Childhood Fetal & Neonatal EditionArch Dis Child Fetal Neonatal Ed, 101, F127-36, 2016	Studies assessed individually - reported independently
Van Overmeire, B., Allegaert, K., Casaer, A., Debauche, C., Decaluwe, W., Jespers, A., Weyler, J., Harrewijn, I., Langhendries, J. P., Prophylactic ibuprofen in premature infants: A multicentre, randomised, double-blind, placebo-controlled trial, Lancet, 364, 1945-1949, 2004	Duplicate
Yang, B., Gao, X., Ren, Y., Wang, Y., Zhang, Q., Oral paracetamol vs. oral ibuprofen in the treatment of symptomatic patent ductus arteriosus in premature infants: A randomized controlled trial, Experimental and Therapeutic Medicine, 12, 2531-2536, 2016	Not an OECD country

1 *OECD: Organisation for Economic Co-operation and Development*

2 Observational studies:

Study	Reason for Exclusion
Alexander,F., Chiu,L., Kroh,M., Hammel,J., Moore,J., Analysis of outcome in 298 extremely low-birth-weight infants with patent ductus arteriosus, Journal of Pediatric Surgery, 44, 112-117, 2009	Fewer than 100 patients in each arm;
De Buyst, J., Rakza, T., Pennaforte, T., Johansson, A. B., Storme, L., Hemodynamic effects of fluid restriction in preterm infants with	Fewer than 100 patients in each arm; not comparative

Study	Reason for Exclusion
significant patent ductus arteriosus, Journal of Pediatrics, 161, 404-8, 2012	
Heuchan,A.M., Hunter,L., Young,D., Outcomes following the surgical ligation of the patent ductus arteriosus in premature infants in Scotland, Archives of Disease in Childhood Fetal and Neonatal Edition, 97, F39-F44, 2012	Fewer than 100 patients in each arm
Kabra, N. S., Schmidt, B., Roberts, R. S., Doyle, L. W., Papile, L., Fanaroff, A., Trial of Indomethacin Prophylaxis in Preterms, Investigators, Neurosensory impairment after surgical closure of patent ductus arteriosus in extremely low birth weight infants: results from the Trial of Indomethacin Prophylaxis in Preterms, Journal of Pediatrics, 150, 229-34, 234.e1, 2007	The total rates of exposure to indomethacin between birth and discharge from the study centre were identical in the 2 groups: 89% of infants in both groups received doses of randomly assigned prophylactic indomethacin, open-label therapeutic indomethacin, or both.
Letshwiti, J. B., Semberova, J., Pichova, K., Dempsey, E. M., Franklin, O. M., Miletin, J., A conservative treatment of patent ductus arteriosus in very low birth weight infants, Early Human Development, 104, 45-49, 2017	Comparators not relevant - received same interventions at different time points
Mandhan, P., Brown, S., Kukkady, A., Samarakkody, U., Surgical closure of patent ductus arteriosus in preterm low birth weight infants, Congenital Heart Disease, 4, 34-7, 2009	Not comparative
Natarajan,G., Chawla,S., Aggarwal,S., Short-term outcomes of patent ductus arteriosus ligation in preterm neonates: reason for concern?, American Journal of Perinatology, 27, 431-437, 2010	Comparison not relevant - immediate ligation vs delayed ligation
Niinikoski, H., Alanen, M., Parvinen, T., Aantaa, R., Ekblad, H., Kero, P., Surgical closure of patent ductus arteriosus in very-low-birth-weight infants, Pediatric Surgery International, 17, 338-41, 2001	Not comparative
Raval,M.V., Laughon,M.M., Bose,C.L., Phillips,J.D., Patent ductus arteriosus ligation in premature infants: who really benefits and at what cost?, Journal of Pediatric Surgery, 42, 69-75, 2007	Not comparative
Rheinlaender, C., Helfenstein, D., Pees, C., Walch, E., Czernik, C., Obladen, M., Koehne, P., Neurodevelopmental outcome after COX inhibitor treatment for patent ductus arteriosus, Early Human Development, 86, 87-92, 2010	In the comparison arm < 2/3 of infants were on ibuprofen
Stephens, B. E., Gargus, R. A., Walden, R. V., Mance, M., Nye, J., McKinley, L., Tucker, R., Vohr, B. R., Fluid regimens in the first week of life may increase risk of patent ductus arteriosus in extremely low birth weight infants, Journal of Perinatology, 28, 123-8, 2008	Comparator not relevant - compared three courses of fluid regimen
Tashiro, J., Wang, B., Sola, J. E., Hogan, A. R., Neville, H. L., Perez, E. A., Patent ductus arteriosus ligation in premature infants in the	Did not specify the proportion of patients in the control arm who received indomethacin versus ibuprofen

Study	Reason for Exclusion
United States, Journal of Surgical ResearchJ Surg Res, 190, 613-22, 2014	
Tsui,I., Ebani,E., Rosenberg,J.B., Lin,J., Angert,R.M., Mian,U., Patent ductus arteriosus and indomethacin treatment as independent risk factors for plus disease in retinopathy of prematurity, Journal of Pediatric Ophthalmology and Strabismus, 50, 88-92, 2013	Fewer than 100 patients in each arm
Weisz, D. E., Martins, F. F., Nield, L. E., El-Khuffash, A., Jain, A., McNamara, P. J., Acetaminophen to avoid surgical ligation in extremely low gestational age neonates with persistent hemodynamically significant patent ductus arteriosus, Journal of Perinatology, 36, 649-653, 2016	Not comparative
Weisz, D. E., Mirea, L., Rosenberg, E., Jang, M., Ly, L., Church, P. T., Kelly, E., Kim, S. J., Jain, A., McNamara, P. J., Shah, P. S., Association of Patent Ductus Arteriosus Ligation With Death or Neurodevelopmental Impairment Between Extremely Preterm Infants, JAMA Pediatrics, 171, 443-449, 2017	Comparison arm did not specify which portion received indomethacin vs ibuprofen
Weisz, D. E., More, K., McNamara, P. J., Shah, P. S., PDA ligation and health outcomes: a meta-analysis, Pediatrics, 133, e1024-1046, 2014	Not a Cochrane systematic review, studies assessed individually
Youn, Y. A., Moon, C. J., Kim, S. Y., Lee, J. Y., Sung, I. K., Outcomes of primary ligation of patent ductus arteriosus compared with secondary ligation after pharmacologic failure in very-low-birth-weight infants, Pediatric Cardiology, 35, 793-7, 2014	Fewer than 100 patients in each arm

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Economic studies

3 All economic studies were excluded at the initial title and abstract screening stage.

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Appendix L – Research recommendations

Research recommendations for question 3.4 What is the effectiveness of corticosteroids in preterm babies requiring respiratory support?

What is the comparative efficacy of hydrocortisone compared with dexamethasone for preventing bronchopulmonary dysplasia in preterm babies requiring respiratory support?

Why this is important

Bronchopulmonary dysplasia (BPD) can cause significant morbidity and mortality in preterm babies. Lung inflammation is an important risk factor for development of BPD, and treatment with corticosteroids with their strong anti-inflammatory properties can decrease or ameliorate BPD. However, use of corticosteroids in treatment or prevention of BPD is controversial, and although there is some evidence to support the use of dexamethasone in the prevention of BPD there is little evidence for hydrocortisone and so it is difficult to recommend the most effective steroid agent. Corticosteroids can also have significant short and long term adverse effects including an impact on neurodevelopmental outcomes, and these risks may differ between different drugs, and might outweigh the beneficial effects of corticosteroids.

Table 29: Research recommendation rationale

Research question	What is the comparative efficacy of hydrocortisone compared with dexamethasone for preventing BPD in preterm babies requiring respiratory support?
Importance to 'patients' or the population	BPD is a serious complication of prematurity. Advances in care now result in better survival of preterm babies, however these babies are highly vulnerable and at high risk for BPD. Most babies with BPD get better in time however they have significant respiratory vulnerability, are prone to chest infections, may require home oxygen and there is also an impact on long term neurodevelopmental outcome. Use of an effective steroid with minimal adverse effects could greatly improve outcomes in these babies.
Relevance to NICE guidance	Although there was some evidence from the NICE evidence review that dexamethasone decreases BPD, no studies were identified that directly examined the comparative safety or effectiveness of dexamethasone versus hydrocortisone. There is currently no consensus on the need, choice, dose or timing of postnatal steroids in the UK.
Relevance to the NHS	The results of the proposed research would standardise the clinical practice across neonatal units across NHS, improve patient care and potentially reduce length of stay and reduce adverse effects, which may lead to a reduction in NHS costs.
National priorities	To decrease morbidity and mortality related to prematurity
Current evidence base	From the NICE evidence review there was no robust evidence on which l steroid to use and when it should be used
Equality	Preterm neonates have an equal right to safe and effective treatment to prevent BPD, thus reducing future complication and improving their quality of life.
Feasibility	There are always ethical issues in conducting studies in vulnerable populations, and these would require careful consideration, but could be overcome. The numbers of children affected are also (fortunately) small, however a well conducted multicentre study would be likely to be adequately powered

Table 30: Research recommendation modified PICO table

Criterion	Explanation
Population	Preterm infants requiring respiratory support after 7 days of age
Intervention	Hydrocortisone (IV/Oral)
Comparator	Dexamethasone (IV/Oral)
Outcome	**Critical:** • Mortality prior to discharge • Bronchopulmonary dysplasia • Neurodevelopmental outcomes at 2 years of age **Important:** • Adverse effects of corticosteroids
Study design	Double blinded randomised controlled trial
Timeframe	2 years follow-up

Is nebulised budesonide effective versus placebo in preventing bronchopulmonary dysplasia in preterm babies requiring respiratory support?

Why this is important

Bronchopulmonary dysplasia (BPD) can cause significant morbidity and mortality in preterm babies. Lung inflammation is an important risk factor for development of BPD, and treatment with corticosteroids with their strong anti-inflammatory properties can decrease or ameliorate BPD. However, use of corticosteroids in treatment or prevention of BPD is controversial, and although there is some evidence to support the use of dexamethasone in the prevention of BPD there is little evidence for nebulised budesonide and so it is difficult to recommend the most effective steroid agent. Corticosteroids can also have significant short and long term adverse effects including an impact on neurodevelopmental outcomes, and these risks may differ between different drugs, and might outweigh the beneficial effects of corticosteroids.

Table 31: Research recommendation rationale

Research question	Is nebulised budesonide effective versus placebo in preventing BPD in preterm babies requiring respiratory support?
Importance to 'patients' or the population	BPD is a serious complication of prematurity. Advances in care now result in better survival of preterm babies, however these babies are highly vulnerable and at high risk for BPD. Most babies with BPD get better in time however they have significant respiratory vulnerability, are prone to chest infections, may require home oxygen and also impact on long term neurodevelopmental outcome. Use of an effective steroid with minimal adverse effects could greatly improve outcomes in these babies. Systemic corticosteroids may have benefits in decreasing BPD but can have significant adverse effects on growth and neurodevelopment. Inhaled corticosteroids may offer clinical efficacy without systemic adverse effects.
Relevance to NICE guidance	In the NICE evidence review there was a lack of evidence on use of inhaled corticosteroids for prevention of BPD. Only 1 very low quality RCT was identified and only short term outcomes were captured. There is currently no consensus on the need, choice, dose or timing of postnatal steroids in the UK
Relevance to the NHS	The results of the proposed research would standardise the clinical practice across neonatal units across NHS, improve patient care and potentially reduce length of stay and reduce adverse effects, which may lead to a reduction in NHS costs.
National priorities	To decrease morbidity and mortality related to prematurity

Research question	Is nebulised budesonide effective versus placebo in preventing BPD in preterm babies requiring respiratory support?
Current evidence base	In the NICE evidence review, no o robust evidence on which postnatal steroid to use and when it should be used was identified.
Equality	Preterm neonates have an equal right to safe and effective treatment to prevent BPD, thus reducing future complication and improving their quality of life.
Feasibility	There are always ethical issues in conducting studies in vulnerable populations, and these would require careful consideration, but could be overcome. The numbers of children affected are also (fortunately) small, however a well conducted multicentre study would be likely to be adequately powered

Table 32: Research recommendation modified PICO table

Criterion	Explanation
Population	Preterm infants requiring respiratory support
Intervention	Inhaled budesonide
Comparator (without the risk factor)	Placebo
Outcome	**Critical:** Mortality prior to discharge • Bronchopulmonary dysplasia • Neurodevelopmental outcomes at 2 years of age **Important:** • Adverse effects of inhaled budesonide
Study design	Double blinded randomised controlled trial
Timeframe	2 years follow-up

Research recommendations for question 3.5 What is the safety and effectiveness of diuretics in preterm babies on respiratory support?

What is the effectiveness of diuretics compared with placebo in preventing bronchopulmonary dysplasia (BPD) in preterm babies on respiratory support?

Why this is important

BPD can cause significant morbidity and mortality in preterm babies. Diuretics have been used to prevent lung oedema and hence ameliorate BPD. However there is limited knowledge regarding the impact of diuretic treatment on both short and long term outcomes in preterm babies. Currently there is no evidence to support the use of diuretics to prevent BPD, nor information on the choice of diuretic, dose, timing, frequency and duration of treatment. Diuretics can also have significant short term and long term adverse effects and these risks might outweigh the beneficial effects of diuretics. Further research is therefore required to determine the place of diuretics in the prevention of BPD.

Table 33: Research recommendation rationale

Research question	What is the effectiveness of diuretics compared with placebo in preventing bronchopulmonary dysplasia (BPD) in preterm babies on respiratory support?
Importance to 'patients' or the population	BPD is a significant complication of prematurity. Advances in care now result in better survival of preterm babies but these babies are highly vulnerable and at high risk for BPD, which can lead to significant respiratory vulnerability, leave babies prone to chest infections, requiring home oxygen and can also impact on long term neurodevelopmental outcomes.
Relevance to NICE guidance	In the NICE evidence review there was no evidence that diuretics prevent or reduce BPD, nor is there evidence of benefit on long term outcomes such as mortality and neurodevelopmental outcomes.
Relevance to the NHS	The results of the proposed research would standardise the clinical practice across neonatal units across NHS, improve patient care and potentially reduce length of stay and reduce adverse effects, which may lead to a reduction in NHS costs.
National priorities	To decrease morbidity and mortality related to prematurity
Current evidence base	In the NICE evidence review, there was no robust evidence on whether diuretics are beneficial, which diuretic to use and when it should be used
Equality	Preterm babies have an equal right to safe and effective treatment to prevent BPD, thus reducing future complications and improving their quality of life.
Feasibility	There are always ethical issues in conducting studies in vulnerable populations and these would require careful consideration, but could be overcome. The numbers of children affected are also (fortunately) small, however a well conducted multicentre study would be likely to be adequately powered

Table 34: Research recommendation modified PICO table

Criterion	Explanation
Population	Preterm babies requiring respiratory support
Intervention	Diuretics (IV/oral)
Comparator	Placebo
Outcome	**Critical:** BPD at 36 weeks gestation • Mortality prior to discharge • Neurodevelopmental outcomes at 2 years of age **Important:** • Adverse effects of diuretics
Study design	Double blinded randomised control trial
Timeframe	2 2 years follow-up

What is the effectiveness of diuretics compared with placebo in the treatment of bronchopulmonary dysplasia (BPD) in preterm babies on respiratory support?

Why this is important

BPD can cause significant morbidity and mortality in preterm babies. Diuretics have been used to decrease lung oedema and treat BPD. However there is limited knowledge on their impact on both short and long term outcomes in preterm babies and currently there is no evidence to support the use of diuretics in the treatment of BPD, nor information on the

choice of diuretic, dose, timing, frequency and duration of treatment. Diuretics can also have significant short term and long term adverse effects and these risks might outweigh the beneficial effects of diuretics. Further research is therefore required to determine the place of diuretics in the treatment of BPD.

Table 35: Research recommendation rationale

Research question	What is the effectiveness of diuretics compared with placebo in the treatment of bronchopulmonary dysplasia (BPD) in preterm babies on respiratory support?
Importance to 'patients' or the population	BPD is a significant complication of prematurity. Advances in care now result in better survival of preterm babies but these babies are highly vulnerable and at high risk for BPD, which can lead to significant respiratory vulnerability, leave babies prone to chest infections, requiring home oxygen and also impact on long term neurodevelopmental outcomes.
Relevance to NICE guidance	In the NICE evidence review, there was no evidence for the effectiveness of diuretics to treat BPD or evidence of benefit on long term outcomes such as mortality and neurodevelopmental outcomes.
Relevance to the NHS	The results of the proposed research would standardise the clinical practice across neonatal units across NHS, improve patient care and potentially reduce length of stay and reduce adverse effects, which may lead to a reduction in NHS costs.
National priorities	To decrease morbidity and mortality related to prematurity
Current evidence base	In the NICE evidence review there was no robust evidence on whether diuretics are beneficial, which diuretic to use and when it should be used
Equality	Preterm neonates have an equal right to safe and effective treatment for BPD, thus reducing future complications and improving their quality of life.
Feasibility	There are always ethical issues in conducting studies in vulnerable populations and these would require careful consideration, but could be overcome. The numbers of children affected are also (fortunately) small, however a well conducted multicentre study would be likely to be adequately powered

Table 36: Research recommendation modified PICO table

Criterion	Explanation
Population	Preterm babies requiring respiratory support at 36 weeks gestation
Intervention	Diuretics (IV/oral)
Comparator	Placebo
Outcome	**Critical:** • Mortality prior to discharge • Respiratory support including oxygen prior to discharge • Neurodevelopmental outcomes at 2 years of age **Important:** • Adverse effects of diuretics
Study design	Double blinded randomised control trial
Timeframe	2 years follow-up

Research recommendations for question 3.6 What is the effectiveness of caffeine and safety of caffeine in preterm babies requiring respiratory support?

What is the optimal maintenance dose of caffeine citrate in order to optimise neurodevelopmental outcomes in preterm babies?

Why this is important

Caffeine citrate is used in the management of apnoeas of prematurity and to reduce extubation failure rates. A maintenance dose up to 10mg/kg/day has been shown to reduce the incidence of BPD, cerebral palsy and severe cognitive impairment. There is evidence that higher maintenance doses of 20-30mg/kg/day (following high loading doses) are associated with reduced apnoeas, extubation failure and BPD when compared with maintenance doses of 3-5 mg/kg/day. However long term neurodevelopmental outcomes with higher maintenance dosing have not been assessed, and the higher dose may be associated with increased side effects, and require blood monitoring.

Table 37: Research recommendation rationale

Research question	What is the optimal maintenance dose of caffeine citrate in order to optimise neurodevelopmental outcomes in preterm babies?
Importance to 'patients' or the population	Preterm babies are at a high risk of severe and debilitating life-long complications. BPD is an important complication of prematurity. Advances in care now result in better survival of preterm infants however these infants are highly vulnerable and at high risk for BPD. Most babies with BPD get better in time however they have significant respiratory vulnerability, prone to chest infections, may require home oxygen and there is also an impact on long term neurodevelopmental outcome.
Relevance to NICE guidance	High priority: Published evidence identified for the NICE evidence review did not provide any information on long-term neurodevelopmental outcomes with higher doses of caffeine citrate, so it was not possible to provide guidance on the most optimal and effective maintenance dose of caffeine citrate that will provide better neurodevelopmental outcomes for preterm babies.
Relevance to the NHS	The results of the proposed research would standardise clinical practice across neonatal units across NHS, improve patient care and potentially reduce length of stay and reduce adverse effects, which may lead to a reduction in NHS costs.
National priorities	To decrease morbidity and mortality related to prematurity.
Current evidence base	There was insufficient evidence in the NICE evidence review on the most optimal and effective maintenance dose of caffeine citrate that will provide better neurodevelopmental outcomes for preterm babies.
Equality	Pre-term babies are at higher risk of long-term health complications due the nature of their prematurity. They have an equal right as older babies to have better health and Quality of Life outcomes

Table 38: Research recommendation modified PICO table

Criterion	Explanation
Population	Infants <30 weeks or <1.5Kg. Analysis by gestational age (or weight), and type of respiratory support cohorts.
Intervention	Caffeine citrate: intravenous or oral

Criterion	Explanation
	Loading dose = 20mg/kg Maintenance dose = 5mg/kg/day starting 24 hours after the loading dose
Comparator	Caffeine citrate: intravenous or oral Loading dose = 20mg/kg Maintenance doses = 10mg/kg/day; 20mg/kg/day or 30mg/kg/day starting 24 hours after the loading dose
Outcome	**Critical:** Neurodevelopmental outcomes at ≥18 months: Cerebral palsy (reported as presence or absence of condition, not severity of condition) Neurodevelopmental delay (reported as dichotomous outcomes, not continuous outcomes such as mean change in score) Severe (score of >2 SD below normal on validated assessment scales, or on Bayley's assessment scale of mental developmental index (MDI) or psychomotor developmental index (PDI) <70 or complete inability to assign score due to CP or severe cognitive delay) Moderate (Score of 1-2 SD below normal on validated assessment scales, or on Bayley's assessment scale of MDI or PDI 70-84) Neurosensory impairment (reported as presence or absence of condition, not severity of condition) Severe hearing impairment (e.g. deaf) Severe visual impairment (e.g. blind) **Important:** Apnoea of prematurity Extubation failure Days on invasive ventilation BPD Retinopathy of prematurity Adverse effects including tachycardia, gastrointestinal side-effects Combination of above-disease free survival-primary outcome
Study design	Multicentre randomised controlled trial with longitudinal follow-up
Timeframe	5-6 years to ensure a sufficient number of babies are enrolled and followed up for a minimum of 2 years

Research recommendations for question 3.8 What is the effectiveness of interventions for closing a patent ductus arteriosis in preterm babies requiring respiratory support.

Are any echocardiographic parameters able to improve the predictive course of PDA and therefore suggest a group of babies who would benefit from PDA treatment?

Why this is important

Patent ductus arteriosus (PDA) is a common clinical condition in preterm babies. Preterm babies with PDA are at greater risk for several morbidities, including higher rates of bronchopulmonary dysplasia (BPD), necrotising enterocolitis, and mortality. Several treatment approaches have been investigated including prophylactic treatment shortly after birth irrespective of the size of the PDA, presymptomatic treatment using echocardiography

at variable postnatal ages to select babies for treatment prior to the duct becoming clinically significant, and symptomatic treatment once the PDA becomes clinically apparent or hemodynamically significant. Despite there being good evidence that medical treatments lead to increased rates of ductal closure, trials have failed to show improved outcomes for babies.

Appropriately designed randomized controlled trials (RCTs) are therefore needed to enable the selection of babies who require closure, using available clinical and echocardiographic parameters of a haemodynamically significant PDA.

Table 39: Research recommendation rationale

Research question	Are any echocardiographic parameters able to improve the predictive course of PDA and therefore suggest a group of babies who would benefit from PDA treatment?
Importance to 'patients' or the population	Patent ductus arteriosus is an important clinical condition in preterm babies, which leads to more respiratory instability and increased risk for several morbidities and mortality. Identifying babies who might benefit from treatment is difficult. An ongoing study (BabyOscar) uses the same echocardiographic parameters regardless of age or size.
Relevance to NICE guidance	Published evidence in the NICE evidence review was insufficient to suggest any particular group of babies who would benefit from this treatment.
Relevance to the NHS	Simple interventions at an early stage in a baby's life would standardise clinical practice across neonatal units across the NHS. This may substantially affect their hospital stay; reducing length of stay and also reducing long-term respiratory admissions and improve later health, which may lead to a reduction in NHS costs..
National priorities	To decrease morbidity and mortality related to prematurity.
Current evidence base	Evidence identified in the NICE evidence review has shown increased rates of ductal closure with a number of interventions but has not shown any other clear clinical benefits.
Equality	As there is equipoise in this area all babies should be automatically enrolled into this study in units taking part. Preterm babies have an equal right to safe and effective treatment to prevent BPD and other morbidities of prematurity, thus improving their quality of life.

Table 40: Research recommendation modified PICO table

Criterion	Explanation
Population	Babies <30 weeks or <1.5Kg, with gestation/unit cohorting
Intervention	Paracetamol or ibuprofen
Prognostic or risk factor	Predefined clinical and or echocardiographic parameters (adjusted for gestation or weight of baby) which suggest an increased significance of PDA.
Comparator	Placebo

Outcome	**Critical:**
	• Bronchopulmonary dysplasia at 36 weeks,
	• Mortality prior to discharge
	•
	• Neurodevelopmental outcomes at ≥18 months:
	  ○ Cerebral Palsy (reported as presence or absence of condition, not severity of condition)
	  ○ Neurodevelopmental delay (reported as dichotomous outcomes, not continuous outcomes such as mean change in score)

Criterion	Explanation
	- Severe (score of >2 SD below normal on validated assessment scales, **or** on Bayley's assessment scale of mental developmental index (MDI) or psychomotor developmental index (PDI) <70 or complete inability to assign score due to CP or severe cognitive delay) - Moderate (Score of 1-2 SD below normal on validated assessment scales, or on Bayley's assessment scale of MDI or PDI 70-84) o Neurosensory impairment (reported as presence or absence of condition, not severity of condition) o Severe hearing impairment (e.g. deaf) o Severe visual impairment (e.g. blind) **Important** • Days on ventilator, • Length of hospital stay • NEC • Combination of above-disease free survival-primary outcome • Cost analysis
Study design	Multicentre RCT with longitudinal follow-up
Timeframe	5-6 years to ensure a sufficient number of babies are enrolled and followed up for a minimum of 18 months

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