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Specialist neonatal respiratory care for babies born preterm

[B] Evidence reviews for respiratory support

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Evidence reviews

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Final

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

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Respiratory support

This evidence report contains information on 5 reviews relating to respiratory support.

- Review question 1.1 What respiratory support (excluding resuscitation) is the most effective for preterm babies before admission to the neonatal unit?
- Review question 3.3 What is the most effective way of using surfactant in managing respiratory distress syndrome?
- Review question 3.1 What is the most effective way to administer oxygen during respiratory support?
- Review question 3.2 What is the effectiveness and safety of the different assisted ventilation techniques in preterm babies?
- Review question 3.7 What is the effectiveness of nitric oxide in preterm babies requiring invasive ventilation?

Review question 1.1 What respiratory support (excluding resuscitation) is the most effective for preterm babies before admission to the neonatal unit?

Introduction

The type of care a preterm baby receives within the first few hours of life can have a significant impact on their long-term outcome. The phrase “golden hour,” first used in trauma patients, has been adopted to refer to neonatal care at this crucial time.

Early delivery room respiratory support in preterm infants has been extensively investigated and may make a significant contribution to reducing the risk of long-term lung damage, other morbidities and even death. One of the difficult choices in the current era is to determine whether or not to intubate a preterm baby in order to give surfactant very soon after birth. Many babies can be supported by non-invasive methods of delivering oxygen, such as continuous positive airways pressure (CPAP), which avoid intubation. There is evidence that surfactant can be administered to these non-intubated babies using less invasive administration techniques that may reduce the risk of morbidity associated with intubation. At present it is not clear which is the best strategy.

This review aims to explore which delivery room respiratory support techniques are likely to give optimal disease-free survival in preterm infants. We have compared early invasive intubation and surfactant administration techniques, with less invasive surfactant administration techniques and non-invasive respiratory support techniques.

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 before admission to the neonatal unit **Exclusions:** • Preterm babies with any congenital abnormalities except patent ductus arteriosus
Intervention	**Assisted ventilation techniques:** **Non-invasive ventilation techniques:** • Hi Flow (HF)/ Hi flow nasal cannula (HFNC)/ Humidified hi flow nasal cannula (HHFNC)/ Heated, humidified, hi flow nasal cannula (HHHFNC) – delivered at equal to or more than 5L/min • Continuous positive airway pressure therapy (CPAP) **Invasive ventilation techniques:** • Invasive ventilation (all types) delivered following intubation **Surfactant administration:** • Minimally invasive techniques: o Minimally invasive surfactant therapy (MIST) o Less invasive surfactant administration (LISA) o Avoidance of mechanical ventilation (AMV) • Surfactant administered via endotracheal tube : o Early extubation administration:

	- Intubate surfactant extubate (InSuRE) - Intubate surfactant extubate (ISX) - Take care method ○ -Conventional endotracheal administration
Comparison	**<u>Assisted ventilation technique comparisons</u>** **Non-invasive ventilation versus no assisted ventilation comparisons:** 1. CPAP versus no assisted ventilation 2. Hi Flow versus no assisted ventilation **Non-invasive ventilation technique comparisons:** 1. CPAP versus Hi Flow **Invasive versus non-invasive ventilation technique comparisons:** 1. CPAP versus invasive ventilation **(***both ventilation techniques received surfactant)* 2. Hi Flow versus invasive ventilation **(***both ventilation techniques received surfactant)* **<u>Ventilation versus surfactant comparisons</u>** **Non-invasive ventilation technique with or without surfactant comparisons:** 1. CPAP with surfactant versus CPAP alone 2. Hi Flow with surfactant administrations versus Hi Flow alone **Invasive ventilation with surfactant versus non-invasive ventilation without surfactant comparison:** 1. CPAP alone versus invasive ventilation with surfactant 2. Hi Flow alone versus invasive ventilation with surfactant
Outcome	**Critical outcomes:** • Mortality prior to discharge • Bronchopulmonary dysplasia (BPD) (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) ○ 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:** • Failed non-invasive ventilation (reported as requiring intubation) • Pneumothorax • Severe intraventricular haemorrhage (grade 3 or 4)

AMV: avoidance of mechanical ventilation; BPD: bronchopulmonary dysplasia; CP: cerebral palsy; CPAP: continuous positive airways pressure; HF: hi flow; HFNC: hi flow nasal cannula; HHFN: humidified hi flow nasal cannula; HHHFNC: heated humidified hi flow nasal canula; InSuRE: intubate surfactant rapidly extubate; ISX: intubate surfactant extubate; LISA: Less invasive surfactant administration ; MDI: mental development index; MIST: minimally invasive surfactant therapy; 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 receiving respiratory support (excluding resuscitation) before admission to the neonatal unit, 1 Cochrane Systematic Review (Subramaniam 2016) and 5 randomised controlled trials (RCTs) were included in this review (Dunn 2011; Finer 2010; Morley 2008; Sandri 2004; Sandri 2010). One additional publication with long term neurodevelopmental outcomes of an RCT was identified (Vaucher 2012 [*Finer 2010*]).

One RCT compared non-invasive ventilation versus no assisted ventilation (Sandri 2004). No studies compared different non-invasive ventilation techniques. One RCT compared non-invasive ventilation with surfactant versus invasive ventilation with surfactant (Dunn 2011). 2 RCTs compared non-invasive ventilation with surfactant versus non-invasive ventilation alone (Dunn 2011; Sandri 2010). Four publications compared non-invasive ventilation alone versus invasive ventilation with surfactant (Dunn 2011; Finer 2010; Morley 2008; Vaucher 2012 [Finer 2010]).

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 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 review				
Subramaniam 2016	• Preterm infants < 32 weeks gestation or < 1500g • Studies where > 80% met above criteria	Prophylactic nCPAP versus other forms of treatment	Mortality prior to discharge Bronchopulmonary dysplasia at 36 weeks PMA	

Study and setting	Population	Intervention/ comparison	Outcomes	Comments
			Need for assisted ventilation Pneumothorax Severe IVH (grade 3 or 4)	
RCTs included in the Cochrane systematic review				
Dunn 2011 US (Subramaniam 2016)	n= 648 • If parent was considered at high risk of having a preterm delivery at 26^{+0} - 29^{+6} week's gestation	Prophylactic surfactant + invasive ventilation versus ISX + nCPAP versus nCPAP	Mortality prior to discharge Bronchopulmonary dysplasia at 36 weeks PMA Failed non-invasive ventilation *(for ISX and nCPAP arm)* Pneumothorax Severe IVH (grade 3 or 4)	3-arm RCT
Finer 2010 US (Subramaniam 2016)	n= 1316 • GA 24^{+0} to 27^{+6} weeks • No congenital malformations • Decision had been made to provide full resuscitation	nCPAP versus nCPAP + surfactant	Mortality prior to discharge Bronchopulmonary dysplasia at 36 weeks PMA Pneumothorax Severe IVH (grade 3 or 4)	Cross over was allowed for infants in the CPAP group for ethical concerns
Morley 2008 Australia (Subramaniam 2016)	n= 610 • GA 25^{+0} to 28^{+6} weeks • No congenital malformations • Birth in a hospital participating in the trial • Ability to breathe at 5 mins after birth, but needing respiratory support	nCPAP versus invasive ventilation + surfactant	Mortality prior to discharge Bronchopulmonary dysplasia at 36 weeks PMA Failed non-invasive ventilation *(for nCPAP arm)* Pneumothorax Severe IVH (grade 3 or 4)	
Sandri 2004	n=230	Prophylactic surfactant + nCPAP	Mortality prior to discharge	

Study and setting	Population	Intervention/ comparison	Outcomes	Comments
Italy (Subramaniam 2016)	• GA 28-31 weeks • No congenital malformations • Birth in hospital	versus rescue surfactant + nCPAP	Bronchopulmonary dysplasia at 36 weeks PMA Failed non-invasive ventilation *(for prophylactic arm)* Pneumothorax Severe IVH (grade 3 or 4)	
RCTs				
Sandri 2010 Italy	n= 208 • GA 25^{+0} to 28^{+6} weeks	Prophylactic surfactant + nCPAP versus nCPAP	Mortality prior to discharge BPD (oxygen dependency at 36 weeks corrected gestation or 28 days of age Failed non-invasive ventilation Pneumothorax Severe IVH (grade 3 or 4)	"During stabilization and transport to the NICU, any CPAP device was allowed according to the practice of each investigative site"
Vaucher 2012 US	n= 990 • 18-22 months corrected age • Surviving from Finer 2010 RCT	Please see Finer 2010	Neurodevelopmental outcomes at ≥18 months	Cross over was allowed for infants in the CPAP group for ethical concerns

BPD: bronchopulmonary dysplasia; CPAP: continuous positive airway pressure; GA: gestational age; ISX: intubate-surfactant-extubate; IVH: intraventricular haemorrhage; nCPAP: nasal continuous positive airway pressure; NICU: neonatal intensive care unit; PMA: postmenstrual age

See appendix D for clinical evidence tables.

Quality assessment of clinical studies included in the evidence review

See appendix F for GRADE tables.

Economic evidence

No economic evidence on the cost effectiveness of respiratory support (excluding resuscitation) in preterm babies before admission to the neonatal unit 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. Non-invasive ventilation versus no assisted ventilation

Comparison 1.1 CPAP versus no assisted ventilation

Critical outcomes

Mortality prior to discharge

- Low quality evidence from 1 RCT (n=230) showed no clinically significant difference in mortality prior to discharge among preterm babies who received CPAP compared to no assisted ventilation.

Bronchopulmonary dysplasia (BPD) at 36 weeks post-menstrual age (PMA)

- Low quality evidence from 1 RCT (n=230) showed no clinically significant difference in BPD at 36 weeks PMA among preterm babies who received CPAP compared to no assisted ventilation.

Neurodevelopmental outcomes at ≥ 18 months

- No studies reported on this critical outcome

Important outcomes

Failed non-invasive ventilation

- Evidence from 1 RCT (n=230, low risk of bias) among preterm babies showed that 14 out of 115 (12%) who were randomised to CPAP failed non-invasive ventilation requiring intubation. The outcome was not relevant for preterm babies on no assisted ventilation, therefore, the 2 interventions could not be compared and imprecision could not be assessed.

Pneumothorax

- Low quality evidence from 1 RCT (n=230) showed no clinically significant difference in pneumothorax among preterm babies who received CPAP compared to no assisted ventilation.

Severe IVH (grade 3 or 4)

- Low quality evidence from 1 RCT (n=230) showed no clinically significant difference in severe IVH (grade 3 or 4) among preterm babies who received CPAP compared to no assisted ventilation.

Comparison 1.2 Hi flow versus no assisted ventilation

- No studies reported on this comparison

Comparison 2. Non-invasive ventilation technique A versus non-invasive ventilation technique B

- No studies reported on this comparison

Comparison 3. Non-invasive ventilation versus invasive ventilation (both ventilation techniques received surfactant)

Comparison 3.1 CPAP versus invasive ventilation (both ventilation techniques received surfactant)

Critical outcomes

Mortality prior to discharge

- Very low quality evidence from 1 RCT (n=425) showed no clinically significant difference in mortality prior to discharge among preterm babies who received CPAP compared to invasive ventilation (both ventilation techniques received surfactant).

BPD at 36 weeks PMA

- Low quality evidence from 1 RCT (n=425) showed no clinically significant difference in BPD at 36 weeks PMA among preterm babies who received CPAP compared to invasive ventilation (both ventilation techniques received surfactant).

Neurodevelopmental outcomes at ≥ 18 months

- No studies reported on this critical outcome

Important outcomes

Failed non-invasive ventilation

- Evidence from 1 RCT (n=425, high risk of bias) among preterm babies showed that 128 out of 216 (59%) who were randomised to CPAP with surfactant failed non-invasive ventilation and required invasive ventilation. The outcome was not relevant for preterm babies on invasive ventilation with surfactant, therefore, the 2 interventions could not be compared and imprecision could not be assessed.

Pneumothorax

- Very low quality evidence from 1 RCT (n=425) showed no clinically significant difference in pneumothorax among preterm babies who received CPAP compared to invasive ventilation (both ventilation techniques received surfactant).

Severe IVH (grade 3 or 4)

- Very low quality evidence from 1 RCT (n=425) showed no clinically significant difference in severe IVH (grade 3 or 4) among preterm babies who received CPAP compared to invasive ventilation (both ventilation techniques received surfactant).

Comparison 3.2 Hi flow versus invasive ventilation (both ventilation techniques received surfactant)

- No studies reported on this comparison

Comparison 4. Non-invasive ventilation with surfactant versus non-invasive ventilation

Comparison 4.1 CPAP with surfactant versus CPAP alone

Critical outcomes

Mortality prior to discharge

- Low quality evidence from 2 RCTs (n=647) showed no clinically significant difference in mortality prior to discharge among preterm babies who received CPAP with surfactant compared to CPAP alone.

BPD at 36 weeks PMA

- Moderate quality evidence from 2 RCTs (n=647) showed no clinically significant difference in BPD at 36 weeks PMA among preterm babies who received CPAP with surfactant compared to CPAP alone.

Neurodevelopmental outcomes at ≥ 18 months

- No studies reported on this critical outcome

Important outcomes

Failed non-invasive ventilation

- Very low quality evidence from 2 RCTs (n=647) showed no clinically significant difference in failed non-invasive ventilation requiring intubation among preterm babies who received CPAP with surfactant compared to CPAP alone

Pneumothorax

- Very low quality evidence from 2 RCTs (n=647) showed no clinically significant difference in pneumothorax among preterm babies who received CPAP with surfactant compared to CPAP alone.

Severe IVH (grade 3 or 4)

- Low quality evidence from 2 RCTs (n=647) showed no clinically significant difference in severe IVH (grade 3 or 4) among preterm babies who received CPAP with surfactant compared to CPAP alone.

Comparison 4.2 Hi flow with surfactant versus Hi flow alone

- No studies reported on this comparison

Comparison 5. Non-invasive ventilation versus invasive ventilation with surfactant

Comparison 5.1 CPAP alone versus invasive ventilation with surfactant

Critical outcomes

Mortality prior to discharge

- Moderate quality evidence from 3 RCTs (n=2,358) showed that there may be a clinically significant decrease in mortality prior to discharge among preterm babies who received CPAP alone compared to invasive ventilation with surfactant, however there is uncertainty around this estimate.

BPD at 36 weeks PMA

- High quality evidence from 3 RCTs (n=2,358) showed that there may be a clinically significant improvement in BPD at 36 weeks PMA among preterm babies who received CPAP alone compared to invasive ventilation with surfactant, however there is uncertainty around this estimate.

Neurodevelopmental outcomes at ≥18 months: Moderate or severe cerebral palsy at 18 months or older of age

- Low quality evidence from 1 RCT (n=990) showed no clinically significant difference in moderate or severe cerebral palsy at 18-22 months of age among preterm babies who received CPAP alone compared to invasive ventilation with surfactant.

Neurodevelopmental outcomes at ≥18 months: Severe cognitive impairment at 18 months or older of age

- Low quality evidence from 1 RCT (n=990) showed no clinically significant difference in severe cognitive impairment at 18-22 months of age (defined as BSID-III [Bayley scales of infant and toddler development, 3rd edition] cognitive score <70) among preterm babies who received CPAP alone compared to invasive ventilation with surfactant.

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

- Very low quality evidence from 1 RCT (n=990) showed no clinically significant difference in bilateral blindness at 18-22 months of age among preterm babies who received CPAP alone compared to invasive ventilation with surfactant.

Neurodevelopmental outcomes at ≥18 months: Hearing impairment at 18 months or older of age

- Low quality evidence from 1 RCT (n=990) showed no clinically significant difference in hearing impairment at 18-22 months of age among preterm babies who received CPAP alone compared to invasive ventilation with surfactant.

Important outcomes

Failed non-invasive ventilation

- Evidence from 1 RCT (n=432, high risk of bias) among preterm babies showed that 116 out of 223 (52%) who were randomised to CPAP alone failed non-invasive ventilation and required invasive ventilation. The outcome was not relevant for preterm babies on invasive ventilation, therefore, the 2 interventions could not be compared and imprecision could not be assessed.

- Evidence from 1 RCT (n=610, high risk of bias) among preterm babies showed that 141 out of 307 (46%) who were randomised to CPAP alone failed non-invasive ventilation and required invasive ventilation. The outcome was not relevant for preterm babies on invasive ventilation, therefore, the 2 interventions could not be compared and imprecision could not be assessed.

Pneumothorax

- Very low quality evidence from 3 RCTs (n=2,358) showed no clinically significant difference in pneumothorax among preterm babies who received CPAP alone compared to invasive ventilation with surfactant.

Severe IVH (grade 3 or 4)

- Low quality evidence from 3 RCTs (n=2,358) showed no clinically significant difference in severe IVH (grade 3 or 4) among preterm babies who received CPAP alone compared to invasive ventilation with surfactant.

Comparison 5.2. Hi flow versus invasive ventilation with surfactant

- No studies reported on this comparison

See appendix E for Forest plots.

Economic evidence statements

- No economic evidence on the cost effectiveness of respiratory support (excluding resuscitation) in preterm babies before admission to the neonatal unit was available.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee agreed that respiratory support in the delivery room primarily aims to reduce the rate of mortality and BPD, and therefore these were considered the critical outcomes for decision making. However, the committee also agreed that neurodevelopmental outcomes were important as these could have a life-long impact on the baby and their parents or carers, and the committee were concerned with the absence of evidence on neurodevelopmental outcomes for this evidence review.

Failed non-invasive ventilation requiring intubation, which may itself increase the risk of BPD, was considered an important outcome. Additionally pneumothorax, a possible adverse event associated with surfactant administration was also considered as an important outcome in decision making and in considering the balance of benefits and harms. Finally, severe intraventricular haemorrhage can occur in preterm babies, and may be associated with respiratory difficulties, so this was also chosen as an important outcome to balance the risks and benefits of early respiratory support.

The quality of the evidence

There was little evidence for several comparisons of interest. There was no evidence for several important comparisons such as Hi flow versus no assisted ventilation, Hi flow versus invasive ventilation with surfactant, Hi flow versus invasive ventilation (both with surfactant), Hi flow with surfactant versus Hi flow alone, or comparing different types of invasive ventilation. There was also no evidence for neurodevelopmental outcomes at 18 months or more. This limited the ability of the committee to make recommendations on several types of practice.

The evidence in the pairwise comparisons was assessed using the GRADE methodology. The quality of evidence in this review ranged from very low to high quality. The evidence on CPAP alone compared to invasive ventilation with surfactant was of high or moderate quality for the critical outcomes (except neurodevelopmental outcomes), whereas the evidence for the important outcomes was of low or very low quality.

The quality of evidence was most often downgraded because of the uncertainty around the risk, which was primarily because of the low event rate, or because of a lack of blinding. The lack of blinding was especially pertinent for subjective outcomes with poorly defined criteria such as criteria for intubation and neurodevelopmental outcomes. However, the committee agreed that this was inevitable as blinding was difficult with different ventilation options.

Benefits and harms

This review looks at balancing the benefits and risks of different approaches to providing respiratory support in the delivery room. The committee was aware that the evidence regarding CPAP versus invasive ventilation showed no difference, but was low quality. While the evidence supported CPAP as the preferred intervention, this should not be taken that there is an absence of negative consequences related to CPAP. However, given that the quality of the evidence was high for mortality and BPD, which were designated as critical outcomes, it was decided that a strong recommendation was suitable.

In preterm babies before admission to the neonatal unit, the committee decided that CPAP should be used as the ventilation technique of choice in the delivery room during and after stabilisation, unless there is a clinical need for invasive ventilation.

The evidence demonstrated that there was no clinical difference between CPAP alone and invasive ventilation with surfactant for any of the outcomes prioritised. However, there was a trend for a reduction in mortality prior to discharge and BPD at 36 weeks PMA in preterm babies who were administered CPAP alone compared to invasive ventilation with surfactant in the delivery room. Furthermore, when the confidence intervals were adjusted from 95% to 90% for all variables, the reduction in mortality prior to discharge and BPD at 36 weeks PMA with CPAP alone compared to invasive ventilation with surfactant became clinically significant, while for the other variables it did not. Although the evidence did not show a clear benefit of CPAP alone over invasive ventilation with surfactant, the committee agreed that one of the main benefits of CPAP alone was its non-invasive nature, therefore opting for CPAP alone in the delivery room would eliminate the risks associated with invasive ventilation. Although there was evidence that some babies may fail non-invasive ventilation and later require invasive ventilation the committee still thought this was a positive result, as a number of babies would still avoid the risks of invasive ventilaton completely. Because of the potential for positive benefits, and the avoidance of harms of invasive ventilation, with no other negative consequence, the committee agreed to recommend strongly that non-invasive ventilation using CPAP should be tried first. Nonetheless, if there is a clear indication for invasive ventilation from the outset, for example a preterm baby who is initially placed on non-invasive ventilation, but is not breathing adequately after a period of support, has an unstable heart rate, or whose oxygen saturations are not improving despite high oxygen levels, the committee emphasised that CPAP alone should not be prioritised over the more clinically appropriate invasive ventilation with surfactant. The committee also highlighted that the Newborn Life Support guidelines should also be followed in the minutes after birth.

The majority of the studies comparing CPAP alone and invasive ventilation with surfactant were in preterm babies at ≥25^{+0} weeks gestation. The committee highlighted that babies younger than 25 weeks gestation were probably not mature enough to be stabilised on CPAP alone, which would most likely fail. Nonetheless, the committee could not agree on a set gestational age for whom CPAP alone was appropriate as it is dependent on the baby and emphasised that clinical judgement should be used when deciding whether to commence CPAP or invasive ventilation. The committee highlighted that it may be more practical to use invasive ventilation with surfactant in the delivery room for very immature preterm babies.

The committee discussed whether the use of CPAP in the delivery room should be alone or in combination with surfactant. There was a prominent but non-significant trend for CPAP with surfactant over CPAP alone to reduce the rate of BPD at 36 weeks PMA. The committee agreed that the evidence wasn't strong enough to make a recommendation on the combination of CPAP with surfactant. However the committee were concerned about the risk of implying that standard practice should be no surfactant. In view of this, the committee prioritised recommending further research on the comparison of CPAP with surfactant and CPAP alone in the delivery room.

Cost effectiveness and resource use

There was no economic evidence assessing the cost-effectiveness of respiratory support strategies in preterm babies at birth and before transfer to the neonatal unit.

The committee discussed that the clinical evidence generally showed no difference between invasive and non-invasive techniques, and in some comparisons was trending in favour of non-invasive techniques (that is, CPAP).

The committee expressed the view that non-invasive ventilation (that is, CPAP) is associated with lower costs when compared with invasive-ventilation techniques and as a result it is likely to be the most cost-effective strategy in babies who need it at birth and before transfer to the neonatal unit.

Other factors the committee took into account

When reviewing the evidence, the committee also noted that local factors such as the distance from the labour ward to the neonatal unit and method of moving a baby (e.g. resuscitaire, transport incubator) will also influence early care and the choice of ventilation method that might be required before admission to the neonatal unit.

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Review question 3.3 What is the most effective way of using surfactant in managing respiratory distress syndrome?

Introduction

Respiratory distress syndrome (RDS) in preterm babies is caused by a deficiency of lung surfactant. The risk of RDS increases with decreasing gestational age, and is almost inevitable in babies born at less than 28 weeks gestation. Without surfactant the lungs become stiff and the alveoli collapse at end-expiration, and untreated RDS is a major cause of morbidity and mortality in preterm infants.

Surfactant is a naturally produced surface-active lipoprotein complex mixed with proteins, which reduces the surface tension at the alveolar liquid surface. Surfactant allows alveoli to stay open in expiration and substantially reduces the work of breathing. It also reduces shearing forces on immature alveolar membrane, preventing membrane rupture and protein leak into the alveolar space with resulting lung damage. RDS in preterm babies can be prevented by administration of exogenous animal derived surfactant therapy, and this substantially reduces mortality and respiratory morbidity for this population, including improved survival without bronchopulmonary dysplasia (BPD) at 28 days.

However, the optimal dose (including the use of single or multiple administration) and mode of administration of surfactant remains controversial and may make a significant contribution to the chances of long term lung damage, other morbidities or death. The various techniques of administration can be grouped into three categories:

- conventional endotracheal intubation (where the baby is intubated, surfactant is administered and the baby then continues on mechanical ventilation)
- endotracheal intubation and surfactant administration followed by immediate extubation (also called Intubate, Surfactant, Rapid Extubation, and known as InSuRE or ISX)
- surfactant administration without endotracheal intubation via a thin endotracheal catheter during spontaneous breathing or with continuous positive airways pressure (CPAP) (known as Minimally Invasive Surfactant Therapy, MIST or Less Invasive Surfactant Administration, LISA, or Avoidance of Mechanical Ventilation, AMV).

This review aims to explore which administration technique and dosing regimen is likely to give optimal outcomes in preterm infants.

Summary of the protocol

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

Table 3: Summary of the protocol (PICO table)

Population	Preterm babies receiving surfactant: **Exclusions:** • Preterm babies with any congenital abnormalities except patent ductus arteriosus • Studies where 50% or less of the mothers of preterm babies have not received antenatal steroids
Intervention	**Surfactants available in the UK:** • Porcactant (Curosurf) • Beractant (Survanta)

	Administration techniques of surfactant: • Minimally invasive techniques: - Minimally invasive surfactant therapy (MIST) - Less invasive surfactant administration (LISA) - Avoidance of mechanical ventilation (AMV) - Take care method • Laryngeal mask airway (LMA) • Endotracheal tube administration of surfactant - Early extubation administration: ○ Intubate, surfactant, extubate (InSuRE) ○ Intubate, surfactant, extubate (ISX) - Conventional endotracheal administration
Comparison	**Administration techniques of surfactant:** • Early extubation following administration of surfactant (INSURE/ISX) versus conventional endotracheal administration of surfactant with mechanical ventilation • Minimally invasive techniques (MIST/LISA/AMV) versus endotracheal tube administration of surfactant • Laryngeal mask airway versus endotracheal tube administration of surfactant Minimally invasive techniques (MIST/LISA/AMV) versus laryngeal mask airway **Surfactant dosing regimens:** • Single dose 100mg/kg surfactant A administration versus single dose 200mg/kg surfactant A administration • Multiple dose surfactant A versus single dose surfactant A
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 (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 Bayley 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 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 • Severe intraventricular haemorrhage (grade 3 or 4) • Pneumothorax • Pulmonary haemorrhage

AMV: avoidance of mechanical ventilation; CP: cerebral palsy; InSuRE: intubate, surfactant, rapidly extubate; ISX: intubate, surfactant, extubate; LMA: laryngeal mask airway; LISA: less invasive surfactant administration; MDI: mental development index; MIST: minimally invasive surfactant therapy; PDI: psychomotor developmental index; RCT: randomised controlled trial; SD: standard deviation

Clinical evidence

Included studies

For preterm babies receiving surfactant, 7 randomised controlled trials (RCTs) were identified (Dani 2004; Dunn 2011; Gopel 2011; Kanmaz 2013; Kribs 2015; Pinheiro 2016; Speer 1992).

Two RCTs compared early extubation following administration of surfactant to conventional endotracheal administration of surfactant with mechanical ventilation (Dani 2004; Dunn 2011).

Three RCTs compared minimally invasive surfactant administration techniques to endotracheal tube administration of surfactant (Gopel 2011; Kanmaz 2013; Kribs 2015).

Note: The committee discussed the ambiguity in the description of endotracheal administration of surfactant in one paper, Gopel 2011. Based on the methods described in the paper, the committee agreed that the administration method was conventional endotracheal administration rather than early extubation after administration of surfactant. Thus, rather than having a separate sub-group ('InSuRE or conventional') in the minimally invasive surfactant administration techniques analyses, the data from Gopel 2011 were analysed together with other conventional administration techniques. However, it was noted that there is some uncertainty to this grouping as the authors did not explicitly define their endotracheal administration technique.

One RCT compared laryngeal mask administration (LMA) of surfactant to endotracheal tube administration of surfactant (Pinheiro 2016)

One RCT compared multiple dose surfactant to single dose surfactant (Speer 1992). 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 4 provides a brief summary of the included studies.

Table 4: Summary of included studies

Study and setting	Population	Intervention/ comparison	Outcomes	Comments
Dani 2004 RCT Italy	n=27 Inborn infants of 0-6 hours of age and <30 weeks gestation with respiratory distress syndrome	Early extubation following administration of surfactant followed by CPAP versus conventional endotracheal administration	• Mortality prior to discharge • BPD at 36 weeks PMA • Days on invasive ventilation • Pneumothorax	

Study and setting	Population	Intervention/ comparison	Outcomes	Comments
		of surfactant with mechanical ventilation		
Dunn 2011 RCT US	n=656 Preterm babies 26-30 weeks gestation	Early extubation following administration of surfactant followed by CPAP versus conventional endotracheal administration of surfactant with mechanical ventilation	• Mortality prior to discharge • BPD at 36 weeks PMA • Days on invasive ventilation • Pneumothorax • Pulmonary haemorrhage	
Gopel 2011 RCT Germany	n=220 Preterm infants with a gestational age 26-28^{+6} and birthweight less than 1.5kg, enrolled within 12 hours of birth FiO_2 criteria for surfactant administration: - $\geq$0.3 for less minimally invasive surfactant administration group - 0.3-0.6 for intubation group	Minimally invasive surfactant administration versus endotracheal tube administration of surfactant	• Mortality prior to discharge • Bronchopulmonary dysplasia at 36 weeks PMA • Days on invasive ventilation • Severe IVH (grade 3 or 4) • Pneumothorax • Pulmonary haemorrhage	Not all babies received surfactant in either group Although authors don't explicitly state InSuRE or conventional endotracheal administration of surfactant, the methods described were more aligned with conventional endotracheal administration.
Kanmaz 2013 RCT Turkey	n=200 Inborn preterm infants <32 weeks gestation and who suffered from respiratory distress syndrome FiO_2 criteria for surfactant administration: $\geq$0.4	Minimally invasive surfactant administration versus early extubation following surfactant administration (InSuRE protocol)	• Mortality prior to discharge • BPD at 36 weeks PMA • Days on invasive ventilation • Severe IVH (grade 3 or 4) • Pneumothorax • Pulmonary haemorrhage	
Kribs 2015 RCT Germany	n=211 Infants with a gestational age 23-26^{+6}, spontaneous breathing, age 10-	Minimally invasive surfactant administration versus conventional	• Mortality prior to discharge • BPD at 36 weeks PMA	

Study and setting	Population	Intervention/ comparison	Outcomes	Comments
	120 min, signs of respiratory distress. FiO_2 criteria for surfactant administration: ≥0.3	endotracheal administration of surfactant with mechanical ventilation	• Days on invasive ventilation • Severe IVH (grade 3 or 4) • Pneumothorax • Pulmonary haemorrhage	
Pinheiro 2016 RCT US	n=61 29-36^{+6} gestational age, diagnosis of respiratory distress syndrome between 4 and 48 hours of age. FiO_2 criteria for surfactant administration: 0.3-0.6	Laryngeal mask administration versus early extubation following surfactant administration (InSuRE protocol)	• Mortality prior to discharge • BPD at 36 weeks PMA or 28 days of age • Pneumothorax	
Speer 1992 RCT Europe	n=357 Premature infants with a birthweight 700-200g, respiratory distress syndrome, assisted ventilation, supplemental oxygen equal or greater to 60%, age 2-15 hours	Single dose versus three doses of Curosurf	• Mortality prior to discharge • BPD at 28 days of age • Severe IVH (grade 3 or 4) • Pneumothorax • Pulmonary haemorrhage	No study dates reported in the RCT

BPD: bronchopulmonary dysplasia; CPAP: continuous positive airways pressure; FiO_2: fraction of inspired oxygen; InSuRE: intubate, surfactant, extubate; IVH: intraventricular haemorrhage; 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 different ways of administering surfactant 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. Early extubation following administration of surfactant versus conventional endotracheal administration of surfactant

Critical outcomes

Mortality prior to discharge

- Very low quality evidence from 2 RCTs (n=452) showed no clinically significant difference in mortality prior to discharge among preterm babies with a gestational age of ≤30 weeks who underwent early extubation following administration of surfactant compared to those who underwent conventional endotracheal administration of surfactant.

Bronchopulmonary dysplasia at 36 weeks post-menstrual age (PMA)

- Low quality evidence from 2 RCTs (n=452) showed a clinically significant reduction in bronchopulmonary dysplasia at 36 weeks PMA among preterm babies with a gestational age of ≤30 weeks who underwent early extubation following administration of surfactant compared to conventional endotracheal administration of surfactant.

Neurodevelopmental outcomes at ≥18 months

- No studies reported on this critical outcome

Important outcomes

Days on invasive ventilation

- Moderate quality evidence from 1 RCT (n=27) showed a clinically significant reduction in days on invasive ventilation among preterm babies with a gestational age of ≤30 weeks who underwent early extubation following administration of surfactant compared to conventional endotracheal administration of surfactant.
- Moderate quality evidence from 1 RCT (n=432) showed no clinically significant difference in days on invasive ventilation among preterm babies with a gestational age of ≤30 weeks who underwent early extubation following administration of surfactant compared to conventional endotracheal administration of surfactant.

Severe intraventricular haemorrhage (grade 3 or 4)

- No studies reported on this important outcome

Pneumothorax

- Very low quality evidence from 2 RCTs (n=452) showed no clinically significant difference in pneumothorax among preterm babies with a gestational age of ≤30 weeks who underwent early extubation following administration of surfactant compared to conventional endotracheal administration of surfactant.

Pulmonary haemorrhage

- Very low quality evidence from 1 RCT (n=425) showed no clinically significant difference in pulmonary haemorrhage among preterm babies with a gestational age of ≤30 weeks who underwent early extubation following administration of surfactant compared to conventional endotracheal administration of surfactant.

Comparison 2. Minimally invasive surfactant administration techniques versus endotracheal administration of surfactant

Critical outcomes

Mortality prior to discharge

Minimally invasive surfactant administration versus all endotracheal administration techniques of surfactant

- Low quality evidence from 3 RCTs (n=631) showed no clinically significant difference in mortality prior to discharge among preterm babies with a gestational age of <32 weeks who underwent minimally invasive surfactant administration compared to endotracheal administration of surfactant.

Minimally invasive surfactant administration versus InSuRE

- Low quality evidence from 1 RCT (n=200) showed no clinically significant difference in mortality prior to discharge among preterm babies with a gestational age of <32 weeks who underwent minimally invasive surfactant administration compared to InSuRE.

Minimally invasive surfactant administration versus conventional endotracheal administration of surfactant

- Very low quality evidence from 2 RCTs (n=431) showed no clinically significant difference in mortality prior to discharge among preterm babies with a gestational age of <29 weeks who underwent minimally invasive surfactant administration compared to conventional endotracheal administration of surfactant.

Bronchopulmonary dysplasia at 36 weeks PMA

Minimally invasive surfactant administration versus all endotracheal administration techniques of surfactant

- Moderate quality evidence from 3 RCTs (n=631) showed a clinically significant reduction in bronchopulmonary dysplasia at 36 weeks PMA among preterm babies with a gestational age of <32 weeks who underwent minimally invasive surfactant administration compared to endotracheal administration of surfactant.

Minimally invasive surfactant administration versus InSuRE

- Moderate quality evidence from 1 RCT (n=200) showed that there may be a clinically significant reduction in bronchopulmonary dysplasia at 36 weeks PMA among preterm babies with a gestational age of <32 weeks who underwent minimally invasive surfactant administration compared to InSuRE, however there is uncertainty around this estimate.

Minimally invasive surfactant administration versus conventional endotracheal administration of surfactant

- Very low quality evidence from 2 RCTs (n=431) showed no clinically significant difference in bronchopulmonary dysplasia at 36 weeks PMA among preterm babies with a gestational age of <29 weeks who underwent minimally invasive surfactant administration compared to conventional endotracheal administration of surfactant.

Neurodevelopmental outcomes at ≥18 months

- No studies reported on this critical outcome

Important outcomes

Days on invasive ventilation

Minimally invasive surfactant administration versus InSuRE

- Moderate quality evidence from 1 RCT (n=200, low risk of bias) showed a clinically significant reduction in total hours of ventilation among preterm babies with a gestational age of <32 weeks who underwent minimally invasive surfactant administration compared to InSuRE.

Minimally invasive surfactant administration versus conventional endotracheal administration of surfactant

- Moderate quality evidence from 1 RCT (n=211) showed a clinically significant reduction in total days of ventilation among preterm babies with a gestational age 23-26^{+6} weeks who underwent minimally invasive surfactant administration compared to conventional endotracheal administration of surfactant, however there is uncertainty around this estimate.
- Very low quality evidence from 1 RCT (n=220) showed a clinically significant reduction in total days of ventilation among preterm babies with a gestational age 26-28^{+6} weeks who underwent minimally invasive surfactant administration compared to conventional endotracheal administration of surfactant, however there is uncertainty around this estimate.

Severe intraventricular haemorrhage (grade 3 or 4)

Minimally invasive surfactant administration versus conventional endotracheal administration techniques of surfactant

- Very low quality evidence from 2 RCTs (n=431) showed no clinically significant difference in severe intraventricular haemorrhage (IVH) among preterm babies with a gestational age of <29 weeks who underwent minimally invasive surfactant administration compared to endotracheal administration of surfactant.

Pneumothorax

Minimally invasive surfactant administration versus all endotracheal administration techniques of surfactant

- Moderate quality evidence from 3 RCTs (n=631) showed a clinically significant reduction in pneumothorax among preterm babies with a gestational age of <32 weeks who underwent minimally invasive surfactant administration compared to endotracheal administration of surfactant.

Minimally invasive surfactant administration versus InSuRE

- Low quality evidence from 1 RCT (n=200) showed no clinically significant difference in pneumothorax among preterm babies with a gestational age of <32 weeks who underwent minimally invasive surfactant administration compared to InSuRE.

Minimally invasive surfactant administration versus conventional endotracheal administration of surfactant

- Very low quality evidence from 2 RCTs (n=431) showed a clinically significant difference in pneumothorax among preterm babies with a gestational age of <29 weeks who underwent minimally invasive surfactant administration compared to conventional endotracheal administration of surfactant, however there is uncertainty around this estimate.

Pulmonary haemorrhage

Minimally invasive surfactant administration versus all endotracheal administration techniques of surfactant

- Moderate quality evidence from 3 RCTs (n=631) showed no clinically significant difference in pulmonary haemorrhage among preterm babies with a gestational age of <32 weeks

who underwent minimally invasive surfactant administration compared to endotracheal administration of surfactant.

Minimally invasive surfactant administration versus InSuRE

- Low quality evidence from 1 RCT (n=200) showed no clinically significant difference in pulmonary haemorrhage among preterm babies with a gestational age of <32 weeks who underwent minimally invasive surfactant administration compared to InSuRE.

Minimally invasive surfactant administration versus conventional endotracheal administration of surfactant

- Low quality evidence from 2 RCTs (n=431) showed no clinically significant difference in pulmonary haemorrhage among preterm babies with a gestational age of <29 weeks who underwent minimally invasive surfactant administration compared to conventional endotracheal administration of surfactant.

Comparison 3. Laryngeal mask airway versus endotracheal administration of surfactant

Critical outcomes

Mortality prior to discharge

- Evidence from 1 RCT (n=30, low risk of bias) showed no difference in mortality prior to discharge in both the laryngeal mark airway (LMA) arm and InSuRE arm among preterm babies with a gestational age of 29-36^{+6} weeks.

Bronchopulmonary dysplasia at 28 days of age or 36 weeks PMA

- Low quality evidence from 1 RCT (n=30) showed no clinically significant difference in bronchopulmonary dysplasia at 28 days of age or 36 weeks PMA among preterm babies age 29-36^{+6} weeks PMA who underwent LMA compared to InSuRE.

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

Severe intraventricular haemorrhage (grade 3 or 4)

- No studies reported on this important outcome

Pneumothorax

- Low quality evidence from 1 RCT (n=30) showed no clinically significant difference in pneumothorax among preterm babies with a gestational age of 29-36^{+6} weeks who underwent LMA compared to InSuRE.

Pulmonary haemorrhage

- No studies reported on this important outcome

Comparison 4. Minimally invasive techniques versus laryngeal mask airway

- No studies reported on this comparison

Comparison 5. Single dose 100mg/kg surfactant A administration versus single dose 200mg/kg surfactant A administration

- No studies reported on this comparison

Comparison 6. Multiple dose surfactant A administration versus single dose surfactant A administration

Critical outcomes

Mortality prior to discharge

- Low quality evidence from 1 RCT (n=343) showed that there may be a clinically significant reduction in mortality prior to discharge among preterm babies who received multiple dose surfactant compared to those who received single dose surfactant.

Bronchopulmonary dysplasia at 28 days of age

- Very low quality evidence from 1 RCT (n=343) showed no clinically significant difference in bronchopulmonary dysplasia at 28 days of age among preterm babies who received multiple dose surfactant compared to those who received single dose surfactant.

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

Severe intraventricular haemorrhage (grade 3 or 4)

- Very low quality evidence from 1 RCT (n=343) showed no clinically significant difference in severe IVH among preterm babies who received multiple dose surfactant compared to those who received single dose surfactant.

Pneumothorax

- Low quality evidence from 1 RCT (n=343) showed a clinically significant reduction in pneumothorax among preterm babies who received multiple dose surfactant compared to those who received single dose surfactant.

Pulmonary haemorrhage

- Very low quality evidence from 1 RCT (n=343) showed no clinically significant difference in pulmonary haemorrhage among preterm babies who received multiple dose surfactant compared to those who received single dose surfactant.

See appendix E for Forest plots.

Economic evidence statements

- No economic evidence on the cost effectiveness of different ways of administering surfactant in preterm babies requiring respiratory support was available.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee agreed that the use of minimally invasive surfactant administration techniques compared to endotracheal administration in preterm babies may reduce the incidence of mortality and BPD, and therefore these outcomes were considered the critical outcomes for decision making. However, the committee also agreed that neurodevelopmental outcomes were important as these could have a life-long impact on the affected individual and their

parents or carers, and the committee were concerned with the absence of evidence on neurodevelopmental outcomes for this evidence review.

Total days on invasive ventilation, which may itself increase the risk of BPD, was considered an important outcome. Additionally pneumothorax, a possible adverse event associated with surfactant administration and positive pressure ventilation was also considered as an important outcome in decision making and in considering the balance of benefits and harms.

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 moderate to very low quality. Most of the evidence on minimally invasive surfactant administration techniques compared to all endotracheal methods of administering surfactant was of moderate quality. The evidence on minimally invasive surfactant administration techniques compared to early extubation following surfactant administration (InSuRE/ISX) or conventional endotracheal administration of surfactant was of low or very low quality.

The quality of evidence was most often downgraded because of uncertainty around the risk estimate, criteria for surfactant administration, and because not all babies were treated with surfactant in both arms of studies.

As discussed in the clinical evidence section, the committee discussed the ambiguity in the description of endotracheal administration of surfactant in Gopel 2011. The paper was interpreted to be conventional endotracheal administration rather than a minimally invasive surfactant administration technique, but there is some uncertainty to this grouping. The committee did not want to ignore important research data, but this potential wrong grouping may be considered detrimental to the quality of the evidence.

Considerable heterogeneity was observed in the studies assessing the number of days on invasive ventilation, for the analysis of early extubation following surfactant administration (InSuRE/ISX) compared to conventional endotracheal administration of surfactant. This was attributed to the wide range and inclusive invasive ventilation techniques included in Dani 2004 and very narrow high frequency oscillatory ventilation technique included in Dunn 2011. The studies varied over such a broad range of variables (techniques, age, number of days treated) that meta-analyses or subgroup analyses would not have been useful or reasonable to conduct. In view of this, studies were not meta-analysed, but rather assessed separately. For all other comparisons, where number of days on invasive ventilation were reported, the studies did not report the number of days on invasive ventilation as means, but rather as medians due to a skewed distribution, and so imprecision could not be assessed for these studies.

No evidence was found on the use of 100mg/kg dose versus the 200mg/kg dose of surfactant. The committee prioritised making a research recommendation for a comparative study on the optimal surfactant regime in preterm babies requiring surfactant.

Single RCTs were identified for the use of laryngeal mask airways compared to minimally invasive techniques and multiple doses compared to single doses of surfactant, both of which were of very low quality. The committee highlighted the need for more evidence on the use of multiple versus single doses and prioritised this for a research recommendation.

Benefits and harms

It is established clinical practice in the UK to administer surfactant in preterm babies requiring invasive ventilation, therefore the committee decided not to prioritise the comparison of surfactant administration to no surfactant administration with invasive ventilation in preterm babies. Nonetheless, the committee agreed that a recommendation to explicitly give surfactant with invasive ventilation in preterm babies requiring invasive ventilation should be made to avoid the misunderstanding that an absence of a recommendation equates to not recommending using surfactant alongside invasive ventilation.

In preterm babies that do not require invasive ventilation, the committee decided that if surfactant was indicated then minimally invasive surfactant administration techniques should be considered. The evidence showed that overall minimally invasive surfactant administration techniques reduced the incidence of BPD at 36 weeks PMA and pneumothorax, compared to endotracheal administration of surfactant. Overall, studies showed an improvement in days on invasive ventilation, although these studies all reported medians and thus could not be meta-analysed. However, the committee agreed that the statistically significant improvement with minimally invasive surfactant administration techniques seemed clinically important and biologically plausible. The committee agreed that one of the main benefits of minimally invasive surfactant administration was that babies would not be put on invasive ventilation at all, as once ventilated it can take hours or days for them to be weaned off successfully.

There were no clinically important differences in mortality prior to discharge, intraventricular haemorrhage, or pulmonary haemorrhage. No clinical evidence was found for the effect of minimally invasive surfactant administration techniques compared to endotracheal administration of surfactant on neurodevelopmental outcomes at ≥18 months of age. The committee discussed the absence of clinical evidence for the effect of minimally invasive surfactant techniques compared to endotracheal administration of surfactant on neurodevelopmental outcomes. In view of the potential life-long impact of neurodevelopmental impairment on the affected individual and their parents or carers, the committee agreed that they could not make a firm recommendation offering minimally invasive surfactant administration techniques in all babies. The inconsistent improvements in BPD at 36 weeks PMA and pneumothorax for minimally invasive surfactant administration techniques against specific groups of endotracheal administered surfactant was an additional consideration in the decision not to make a firm recommendation for all babies, as the committee recognised that important clinical differences existed between early extubation and conventional endotracheal administration methods. Furthermore, the improvements in BPD at 36 weeks PMA and pneumothorax were not seen in individual comparisons against early extubation following surfactant administration (InSuRE/ ISX) nor conventional endotracheal administration of surfactant, but rather minimally invasive techniques against overall endotracheal administration of surfactant.

The committee discussed that not all neonatal units and healthcare professionals have the facilities or have been adequately trained to use minimally invasive surfactant administration techniques. Therefore the committee highlighted the need for alternative surfactant administration techniques. The committee agreed that early extubation following surfactant administration (InSuRE/ISX) should be considered as an alternative, as the evidence showed that early extubation following surfactant administration (InSuRE/ISX) led to a reduced incidence of BPD at 36 weeks PMA compared to conventional endotracheal administration.

The committee did not make any recommendations on laryngeal mask airway due to the paucity of evidence identified. The committee highlighted that although there was lack of evidence on laryngeal mask airway, that this may provide an important clinical option for preterm babies. In view of this, the committee wrote a research recommendation on the optimal minimally invasive surfactant administration technique.

No recommendations were made by the committee on surfactant dosing regimens due to the lack of evidence and relevance to current clinical practice, given that the only study included in the review was from the late 1980's to early 1990's. The committee agreed that a research recommendation on the optimal surfactant dosing regime was appropriate.

Cost effectiveness and resource use

There was no evidence on the cost-effectiveness of different ways of administering surfactant in preterm babies requiring respiratory support. The committee explained that not using surfactant is not an option and the expense will be incurred anyway irrespective of the regimen used to administer it. The committee further explained that this question is only

looking at subtle differences in the regimens. Minimally invasive surfactant administration techniques showed a clinical benefit using BPD at 36 weeks PMA, days on mechanical ventilation, and incidence of pneumothorax outcomes. The committee discussed intervention costs associated with different ways of administering surfactant in preterm babies and it was noted that minimally invasive surfactant administration techniques have lower intervention costs when compared with other administration techniques including conventional endotracheal administration as it does not require the use of a ventilator, ventilator tubing or such high intensity nursing. Based on the above, the committee concluded that since minimally invasive surfactant administration has lower intervention costs and more favourable outcomes when compared with other administration techniques it is also likely to be a cost-effective option (that is, a dominant administration technique).

Other factors the committee took into account

The committee discussed the fact that all the evidence presented in this review was for babies <32 weeks PMA, but decided not to limit their recommendations to this age group, as the benefits of surfactant administration are likely to be similar in babies of all gestational ages. The committee agreed the recommendation could therefore be extrapolated to all preterm babies.

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Review question 3.1 What is the most effective way to administer oxygen during respiratory support?

Introduction

Low flow oxygen is frequently used in neonatal units, as an integral part of respiratory support in preterm babies. The goal of oxygen therapy is to achieve adequate delivery of oxygen to the tissues without causing oxygen toxicity.

In addition to delivering oxygen via a ventilator or CPAP circuit, there are several different methods of low-flow oxygen administration: head box oxygen, incubator, facemask, nasal prongs, nasal cannula and nasopharyngeal catheter. Oxygen can be delivered humidified or non-humidified, and the method of titration can be automated or manual. It is important to know, the efficacy, potential risks, and the impact on lung function of the different methods when used in preterm babies.

The aim of this review is to determine the optimal type of oxygen delivered, method of administration and method of titration in preterm babies requiring respiratory support.

Summary of the protocol

See Table 5 for a summary of the population, intervention, comparison and outcome (PICO) characteristics of this review.

Table 5: 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	**Type of low-flow oxygen delivered at ≤1L/min**
	- Humidified
	- Non-humidified
	Method of oxygen administration:
	- Low-flow systems
	  ○ Nasal cannula
	  ○ Incubator
	Method of oxygen titration:
	- Automated
	- Manual

Comparison	**1. Type of low-flow oxygen delivered at ≤1L/min:** - Humidified oxygen vs non-humidified oxygen **2. Method of oxygen administration:** - Nasal cannula vs incubator **3. Method of oxygen titration:** - Automated vs. manual
Outcome	**Critical outcomes:** - Bronchopulmonary dysplasia at 36 weeks postmenstrual age or 28 days of age

	- Days of oxygen - Time spent within optimal target saturation limits **Important outcomes:** - Retinopathy of prematurity - Nasal trauma - Comfort score/ pain score - Number of manual adjustments of titration

RCT: randomised control trial

For full details see review protocol in appendix A.

Clinical evidence

Included studies

In total, 6 study reports were included in this review (Claure 2009; Claure 2011; Hallenberger 2014; Kaam 2015; Travers 2018; Van Zanten 2017).

Five were randomised crossover trials (RCTs) (Claure 2009; Claure 2011; Hallenberger 2014; Kaam 2015; Travers 2018) and 1 was a retrospective cohort study (Van Zanten 2017).

One RCT (Travers 2018) compared nasal cannula to incubator.

Four RCTs (Claure 2009; Claure 2011; Hallenberger 2014; Kaam 2015) and 1 retrospective cohort study (Van Zanten 2017) compared automated to manual titration.

No studies compared humidified oxygen to non-humidified oxygen.

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 6 provides a brief summary of the included studies.

Table 6: Summary of included studies

Study and setting	Population	Intervention/ comparison	Outcomes	Comments
Randomised crossover trials				
Claure 2009 US	n= 16 Preterm babies receiving supplemental oxygen from mechanical ventilation, and who had had eight or more episodes of hypoxemia in 4 hours.	Automated versus manual titration. Babies underwent 4hrs under each condition consecutively Target oxygen saturation range: 88-95% Intervention: FiO_2 was adjusted by an automated system,	• Time spent within optimal target saturation	

Study and setting	Population	Intervention/ comparison	Outcomes	Comments
		which measured arterial oxygen saturation once per second Control: FiO_2 was adjusted manually by clinical staff members		
Claure 2011 US	n= 32 Preterm infants who needed mechanical ventilation of supplemental oxygen due to frequent episodes of decreased blood oxygen saturation	Automated versus manual titration. Babies underwent 24hrs under each condition consecutively Target oxygen saturation range: 87-93% Intervention: FiO_2 was adjusted by an automated system, which measured arterial oxygen saturation once per second Control: FiO_2 was adjusted manually by clinical staff members	• Time spent within optimal target saturation range • Number of manual adjustments of titration	
Hallenberger 2009 Germany	n= 34 Infants with gestational age at birth of <37 weeks, requiring mechanical ventilation or nasal CPAP.	Automated versus manual titration. Babies underwent 24hrs under each condition consecutively Target oxygen saturation range: 80-95% (depending on treatment centre) Intervention: FiO_2 was adjusted by an automated system, which measured arterial oxygen saturation once per second Control: FiO_2 was adjusted manually by clinical staff members	• Time spent within optimal target saturation range • Number of manual adjustments of titration	
Kaam 2015	n= 80	Automated versus manual titration. Babies underwent	• Time spent within optimal	

Study and setting	Population	Intervention/ comparison	Outcomes	Comments
Canada and pan-Europe	Infants with gestational age <33 weeks, requiring invasive or non-invasive supplementary oxygen.	24hrs under each condition consecutively Lower target oxygen saturation range: 89-93% Higher target saturation range: 91-95% Intervention: FiO_2 was adjusted by an automated system, which measured arterial oxygen saturation once per second Control: FiO_2 was adjusted manually by clinical staff members	target saturation range • Number of manual adjustments of titration	
Travers 2018	n= 25 Preterm babies with gestational age <37 weeks, receiving oxygen through either nasal cannula or oxygen environment	Nasal cannula versus incubator. 'ABAB' sequence with 24hrs in each condition Intervention: Nasal cannula Control: Incubator that maintained oxygen around the baby at a set level using a servo-controlled system	• Time spent within optimal target saturation range • Number of manual adjustments of titration	
Retrospective cohort studies				
Van Zanten 2017 The Netherlands	n= 42 Babies <30 weeks of gestation requiring either invasive or non-invasive supplementary oxygen	Automated versus manual titration Target oxygen saturation range: 90-95% Intervention: FiO_2 was adjusted by an automated system, which measured arterial oxygen saturation once per second Control: FiO_2 was adjusted manually by clinical staff members	• Days on respiratory support • Time spent within optimal target saturation • Number of manual adjustments of titration	

CPAP: continuous positive airway pressure; FiO_2: fraction of inspired oxygen; n: number of participants in study

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 oxygen administration for 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. Humidified versus non-humidified oxygen

- There was no evidence for this comparison.

Comparison 2. Nasal cannula versus incubator

Critical outcomes

Bronchopulmonary dysplasia at 36 weeks postmenstrual age or 28 days of age

- There was no evidence for this critical outcome.

Days of oxygen

- There was no evidence for this critical outcome.

Time spent within optimal target saturation limits

- Low quality evidence from 1 RCT (n=25) showed no clinically significant difference in the time spent within optimal target saturation limits between preterm babies with a gestational age of < 37 weeks who received oxygen via nasal cannula compared to via an incubator.

Important outcomes

Retinopathy of prematurity

- There was no evidence for this important outcome.

Nasal trauma

- There was no evidence for this important outcome.

Comfort score/pain score

- There was no evidence for this important outcome.

Number of manual adjustments of titration

- Very low quality evidence from 1 RCT (n=25) showed no clinically significant difference in the number of manual adjustments to titration between preterm babies with a gestational age of < 37 weeks who received oxygen via nasal cannula compared to incubator.

Comparison 3. Automated versus manual oxygen titration

Critical outcomes

Bronchopulmonary dysplasia at 36 weeks postmenstrual age or 28 days of age

- There was no evidence for this critical outcome.

Days of oxygen

- Very low quality evidence from 1 retrospective cohort study (n=42) showed no clinically significant difference in days on oxygen between preterm babies with a gestational age of < 30 weeks who received automated compared to manual oxygen titration.

Time spent within optimal target saturation limits

Gestational age not specified

- Very low quality evidence from 1 RCT (n=16) showed a clinically significant increase in the time spent within optimal target saturation limits between preterm babies who received automated compared to manual oxygen titration.

Babies 24-27 weeks

- Low quality evidence from 1 RCT (n=32) showed a clinically significant increase in the time spent within optimal target saturation limits between preterm babies with a gestational age of 24-27 weeks who received automated compared to manual oxygen titration.

Babies < 37 weeks

- Low quality evidence from 1 RCT (n=34) showed a clinically significant increase in the time spent within optimal target saturation limits between preterm babies with a gestational age of < 37 weeks who received automated compared to manual oxygen titration.

Target saturation range 91-95% - babies < 33 weeks

- Very low quality evidence from 1 RCT (n=80) showed a statistically significant, but not clinically significant, increase in the time spent within optimal target saturation limits between preterm babies with a gestational age of < 30 weeks who received automated compared to manual oxygen titration.

Target saturation range 89-93% - babies < 33 weeks

- Very low quality evidence from 1 RCT (n=80) showed a statistically significant, but not clinically significant, increase in the time spent within optimal target saturation limits between preterm babies with a gestational age of < 30 weeks who received automated compared to manual oxygen titration.

Babies < 30 weeks

- Very low quality evidence from 1 retrospective cohort study (n=42) showed a clinically significant increase in time spent within optimal target saturation limits between preterm babies with a gestational age of < 30 weeks who received automated compared to manual oxygen titration.

Important outcomes

Retinopathy of prematurity

- There was no evidence for this important outcome.

Nasal trauma

- There was no evidence for this important outcome.

Comfort score/pain score

- There was no evidence for this important outcome.

Number of manual adjustments of titration

Babies 24-27 weeks

- Moderate quality evidence from 1 RCT (n=32) showed a clinically significant decrease in the number of manual adjustments to titration between preterm babies with a gestational age of 24-27 weeks who received automated compared to manual oxygen titration.

Babies < 37 weeks

- Very low quality evidence from 1 RCT (n=34) showed a clinically significant decrease in the number of manual adjustments to titration between preterm babies with a gestational age of < 37 weeks who received automated compared to manual oxygen titration.

Lower target range (89-93%), babies < 33 weeks

- Very low quality evidence from 1 RCT (n=80) showed a clinically significant decrease in the number of manual adjustments to titration between preterm babies with a gestational age of < 33 weeks who received automated compared to manual oxygen titration.

Higher target range (91-95%), babies < 33 weeks

- Very low quality evidence from 1 RCT (n=80) showed a clinically significant decrease in the number of manual adjustments to titration between preterm babies with a gestational age of < 33 weeks who received automated compared to manual oxygen titration.

See appendix E for Forest plots.

Economic evidence statements

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

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The aim of this review was to determine the optimal method of supplemental oxygen administration (via prongs or an incubator; humidified or non-humidified) and the best method (automated or manual) of oxygen titration in preterm babies requiring respiratory support. Bronchopulmonary dysplasia, days on oxygen and time spent in the optimal target saturation range were chosen as they would indicate the clinical effectiveness of the administration method. The number of manual adjustments of titration was chosen as an important outcome as it indicates if automated adjustment is effective at reducing nursing workload, as well reducing parental anxiety and stress to babies related to the sound of alarms. Retinopathy of prematurity, nasal trauma, and comfort score/pain score were also chosen as important outcomes to help balance the potential benefits and harms of the different methods of administration.

Mortality was not included because it was thought unlikely that the method of administration of oxygen would effect mortality. There was no evidence for the critical outcome of bronchopulmonary dysplasia or the important outcomes of retinopathy of prematurity, nasal trauma and pain and comfort scales.

The quality of the evidence

The quality of the evidence in this review ranged from low to very low. Additionally imprecision could not be assessed for some of the outcomes due to the data being reported as medians.

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

Methodological limitations affecting the risk of bias were primarily due to the cross-over nature of studies preventing the blinding of staff, personnel and parents, as well as preventing the blinding of outcome assessment. Additionally, several studies had high levels of attrition due to loss of data and protocol violations.

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.

Evidence for nasal cannula versus incubator was only available from 1 study with an unclear risk of bias and imprecision around the risk estimate, which meant that a strong recommendation could not be made for this comparison. The quality of the evidence was low for automated versus manual titration, and although the committee thought there was a sufficient body of evidence to make a recommendation, they chose not to, due to other concerns about the implementation of automated titration. .

Benefits and harms

There was no difference in outcomes between oxygen administered via nasal cannula or via the incubator, although there was only data available for the time spent in the optimal oxygen saturation rage or the number of manual adjustments required. The committee agreed that it was useful to have a choice of techniques and the use of nasal cannula or incubator oxygen may depend on the age of the baby. For example, a baby born at 35 weeks and admitted to a neonatal unit might be placed in an incubator to assess their condition and then could be changed to nasal cannula if stable, or a younger, more unwell or unstable baby may be placed in an incubator. However nasal cannula may be preferred where they can be used as they allow babies to be held by their parents, and allow for skin to skin contact.

Although there was no evidence for the use of humidified versus non-humidified oxygen the committee discussed that it was normal clinical practice to humidify oxygen, especially at higher flow rates, such as more than 2 litres per minute, as non-humidifed oxygen can dry out mucous membranes and therefore made a recommendation to this effect. The committee acknowledged concerns regarding bacterial growth in stagnant water, but highlighted that current best practice of frequently changing circuits should eliminate this risk.

For the comparison of automated versus manual oxygen titration, it was found that automated oxygen titration increased the proportion of time spent in the target saturation range, thus reducing the likelihood of hypoxia or hyperoxia. As hypoxia is known to increase the risk of necrotising enterocolitis and mortality, while hyperoxia increases the risk of retinopathy of prematurity (which is treatable), the committee agreed that this was a clinical benefit of automated control. The committee noted that when manual adjustments were made by nursing staff and clinicians, the oxygen was usually adjusted to keep babies at the higher end of the pre-specified target saturation range, but if the pre-specified range was appropriate (91-95%, see evidence report D) then automated oxygen titration should be able to keep babies in the middle of this range.

However, the committee noted from their clinical experience and evidence in the included studies (Van Zanten 2017) that because nurses typically aim to maintain babies in the higher end of the target saturation range, frequency-saturation curves of manual oxygen titration are right skewed. This means that babies on manual oxygen titration are more likely to experience hyperoxia (which is associated with improvement in mortality and necrotizing enterocolitis but may be more associated with treatable retinopathy) than hypoxia. Automated titration creates a normal distribution of the frequency-saturation curve, targeting the mid-point of the target range and this reduces the mean saturation level achieved by babies. Therefore, the committee chose not to make a recommendation for the use of automated oxygen titration if an oxygen saturation target of 91-95% is used without adjusting for this affect.The committee discussed that when using automated oxygen titration it might be more appropriate to use a higher oxygen saturation target range but as there was no evidence to determine what this range should be, the committee made a research recommendation.

Automated oxygen titration decreased the number of manual adjustments needed to titrate oxygen levels: this would potentially reduce nurse workload, and would also reduce the noise from alarms which could disturb babies and cause anxiety to parents/carers. However, the committee noted that alarms from manual oxygen titration systems allow nursing staff to be aware of fluctuations in the baby's oxygen levels, which can indicate the potential deterioration in the baby's condition. Therefore, a potential harm of automated oxygen titration is that nurses and clinicians will be unaware of changes in the baby's stability.

Cost effectiveness and resource use

There was no evidence on the cost-effectiveness of different ways of administering oxygen during respiratory support. The committee explained that the recommendations are not expected to have a high resource impact on the NHS. There is little difference in the incremental costs between providing supplemental oxygen via nasal cannula or incubator oxygen. Having a choice was deemed essential in the care of these babies since the use of nasal cannula or incubator depends on the age, weight, gestation and clinical condition of the baby. For example, it is more practical to care for older and bigger babies in an incubator, with incubator oxygen, whilst nasal cannulae are more appropriate for babies who are smaller, sicker or less clinically stable. Furthermore, it is not possible to achieve very high oxygen concentration with incubator oxygen due to leakage.

As most units do not currently use automated oxygen titration, the committee agreed that not making a recommendation would not impact on current practice.

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Review question 3.2 What is the effectiveness and safety of the different assisted ventilation techniques in preterm babies?

Introduction

The lungs of preterm babies are structurally immature, deficient of surfactant and not supported by a rigid chest wall. They are therefore highly susceptible to injury from the different types of respiratory support available for use in this population.

Whereas pressure support ventilation (PSV) and continuous positive airway pressure (CPAP) have been used in neonatology for many years, newer modes of ventilation such as volume targeted ventilation (VTV) and, more recently, heated humidified high-flow nasal cannula (HHHFNC) have become popular. This review will look at the evidence available to assess the effectiveness of the different types of assisted ventilation techniques in preterm babies.

Summary of the protocol

See Table 7 for a summary of the population, intervention, comparison and outcome (PICO) characteristics of this review.

Table 7: 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, NEC, neurological disorders. • Preterm babies on respiratory support for post-extubation weaning • Studies with indirect populations
Intervention	**Non-invasive ventilation techniques:** **1.** Hi Flow (HF)/ Hi Flow Nasal Cannula (HFNC)/ Humidified, Hi Flow Nasal Cannula (HHFNC)/ Heated, Humidified, Hi Flow Nasal Cannula (HHHFNC) – delivered at equal to or more than 5L/min **2.** Continuous positive airway pressure therapy (CPAP) **3.** Bilevel Positive Airway pressure (BiPAP)/ Synchronised Positive Airway Pressure (SiPAP) **4.** Nasal intermittent positive pressure ventilation (NIPPV) **Invasive ventilation techniques:** **1. Volume targeted ventilation** • Volume guarantee ventilation (VGV) • Target tidal volume (TTV) • Pressure regulated volume control (PRVC) ventilation (PRVCV) • Volume limited ventilation (VLV)

	• Volume-assured pressure support (VAPS) • Any synchronised pressure limited ventilation + volume targeted ventilation • Synchronised intermittent-mandatory ventilation (SIMV) + volume targeted ventilation **2. Synchronised pressure limited ventilation** • Assist control ventilation (AC) • Synchronised intermittent positive pressure ventilation (SIPPV) • Patient triggered ventilation (PTV) • Pressure support ventilation (PSV) • Synchronised time cycled pressure limited ventilation (STCPL) **3. Synchronised Intermittent Mandatory Ventilation (SIMV)** **4. Non-synchronised pressure limited ventilation** • Conventional mandatory ventilation (CMV) • non-triggered / unsynchronised time cycled pressure limited ventilation (TCPL) • Intermittent mandatory ventilation (IMV) **5. High frequency ventilation (HFV)** • High frequency oscillatory ventilation (HFOV) • High frequency flow interruption (HFFI)
Comparison	**Non-invasive ventilation technique comparisons:** 1. Hi Flow vs CPAP 2. CPAP vs BiPAP/SiPAP 3. BiPAP/SiPAP vs Hi Flow 4. NIPPV vs BiPAP/SiPAP 5. NIPPV vs CPAP 6. NIPPV vs Hi Flow **Invasive ventilation technique comparisons:** 1. Volume targeted vs synchronised pressure limited 2. Volume targeted vs non-synchronised pressure limited 3. Volume targeted vs SIMV 4. Volume targeted vs HFOV 5. Synchronised pressure limited vs non-synchronised pressure limited 6. Synchronised pressure limited vs SIMV 7. Synchronised pressure limited vs HFOV 8. SIMV vs non-synchronised pressure limited 9. SIMV vs HFOV 10. Non-synchronised pressure limited vs HFOV
Outcome	**Critical outcomes:** • Mortality prior to discharge **(NMA outcome)** • Bronchopulmonary dysplasia (BPD) (oxygen dependency at 36 weeks postmenstrual age (PMA) or 28 days of age) **(NMA outcome)** • 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) 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:** • Number of days on invasive ventilation (reported as requiring intubation) • Failed non-invasive ventilation • Pneumothorax • Parental satisfaction

AC: assist control; BiPAP: Biphasic positive airways pressure; BPD: bronchopulmonary dysplasia; CMV: conventional mandatory ventilation; CP: cerebral palsy; CPAP: continuous positive airways pressure; HF: high flow; HFFI: high frequency flow interruption; HFNC: hi flow nasal cannula; HHFNC: humidified high flow nasal cannula; HHHFNC: heated humidified high flow nasal cannula; HFOV: high frequency oscillatory ventilation; HFV: high flow ventilation; IMV: intermittent mandatory ventilation; MDI: mental development index; NEC: necrotising enterocolitis; NIPPV: nasal intermittent positive pressure ventilation; NMA: Network meta-analysis; PDI: psychomotor developmental index; PRVC: pressure regulated volume control: PRVCV: pressure regulated volume controlled ventilation; PSV: pressure support ventilation; PTV: pressure triggered ventilation; RCT: randomised controlled trial; SD: standard deviation; SIMV: synchronised intermittent mandatory ventilation; SiPAP; synchronised positive airways pressure; SIPPV; synchronised intermittent positive pressure ventilation; STCPL: synchronised time-cycled pressure ventilation; TCPL: time-cycled pressure ventilation; TTV: target tidal volume; VAPS: volume-assured pressure support; VGV: volume guarantee ventilation; VLV: volume limited ventilation

Clinical evidence

Included studies

1. Non-invasive ventilation

In preterm babies receiving non-invasive ventilation, 2 Cochrane systematic reviews (Lemyre 2016; Wilkinson 2016) and 15 randomised controlled trials (RCTs) were included in this review (Bisceglia 2007; Kirpalani 2013; Klingenberg 2015; Kugelman 2007; Kugelman 2015; Lavizzari 2016; Lista 2010; Nair 2005; Oncel 2016; Ramanathan 2012; Roberts 2016; Salvo 2015; Shin 2017; Wood 2013; Yoder 2013). Of these 15 RCTs, 8 were identified from Cochrane systematic review and 7 were identified separately. Of these:

Five RCTs compared Hi Flow to continuous positive airway pressure therapy (CPAP) (Klingenberg 2015; Nair 2005; Roberts 2016; Shin 2017; Yoder 2013).

Two RCTs compared CPAP to bilevel positive airway pressure or synchronised positive airway pressure (BiPAP/SiPAP) (Lista 2010; Wood 2013).

One RCT compared BiPAP/SiPAP to Hi Flow (Lavizzari 2016)

One RCT compared nasal intermittent positive pressure ventilation (NIPPV) to BiPAP/SiPAP (Salvo 2015).

Five RCTs compared NIPPV to CPAP (Bisceglia 2007; Kirpalani 2013; Kugelman 2007; Oncel 2016; Ramanathan 2012)

One RCT compared NIPPV to Hi Flow (Kugelman 2015).

2. Invasive ventilation

In preterm babies receiving invasive ventilation, 3 Cochrane systematic reviews (Cools 2015; Greenough 2016; Klingenberg 2017) were included in this review. 27 RCTs from these systematic reviews were identified as being relevant to this review (Baumer 2000; Beresford 2000; Bernstein 1996; Chowdhury 2013; Courtney 2002; Craft 2003; D'Angio 2005; Donn 1994; Dunman 2012; Durand 2001; Gerstmann 1996; Guven 2013; Johnson 2002; Lista 2004; Lista 2008; Moriette 2001; Nafday 2005; Ogawa 2013; Piotrowski 1997; Piotrowski 2007; Rettwitz-Volk 1998; Salvo 2012; Singh 2006; Sinha 1997; Thome 1999; Van Reempts 2003; Vento 2005). An additional 4 publications reporting long term neurodevelopmental outcomes from 3 of these RCTs were identified (Greenough 2014 [Johnson 2002]; Marlow 2006 [Johnson 2002]; Singh 2009 [Singh 2006]; Truffert 2007 [Moriette 2001]). Of these:

Five publications compared volume targeted ventilation (VTV) to synchronised pressure limited ventilation (SPLV) (Dunman 2012; Lista 2004; Singh 2006; Singh 2009 [Singh 2006]; Sinha 1997)

One RCT compared VTV to non-synchronised pressure limited ventilation (NSPLV) (Piotrowski 1997).

Five RCTs compared VTV to synchronised intermittent mandatory ventilation (SIMV) (Chowdhury 2013; D'Angio 2005; Guven 2013; Nafday 2005; Piotrowski 2007)

One RCT compared VTV to high frequency ventilation (HFV) (Lista 2008).

Three RCTs compared SPLV to NSPLV (Baumer 2000; Beresford 2000; Donn 1994).

One RCT compared SIMV to NSPLV (Bernstein 1996).

Seven publications compared SIMV to HFV (Courtney 2002; Craft 2003; Durand 2001; Moriette 2001; Truffert 2006 [Moriette 2001]; Vento 2005; Salvo 2012).

Eight publications compared NSPLV to HFV (Gerstmann 1996; Johnson 2002; Greenough 2014 [Johnson 2002]; Marlow 2006 [Johnson 2002]; Ogawa 1993; Rettwitz-Volk 1998; Thome 1998; Van Reempts 2003)

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

Excluded clinical 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 8 provides a brief summary of the included studies for non-invasive ventilation.

Table 8: Summary of included studies: non-invasive ventilation

Study and setting	Population	Intervention/ comparison	Outcomes	Comments
Cochrane systematic reviews				
Lemyre 2016	• Studies that enrolled newly born preterm infants	Early NIPPV versus NCPAP	Mortality prior to discharge	

Study and setting	Population	Intervention/ comparison	Outcomes	Comments
	• < 37 weeks GA • Infants who received surfactant if the duration of endotracheal intubation was short and if application of NIPPV or NCPAP occurred before 6 hours of life		Bronchopulmonary dysplasia at 36 weeks PMA Failed non-invasive ventilation Pneumothorax	
Wilkinson 2016	• < 37 weeks GA • Receiving respiratory support after birth	Hi flow versus other non-invasive respiratory support methods	Mortality prior to discharge Bronchopulmonary dysplasia at 36 weeks PMA Failed non-invasive ventilation	
RCTs				
CPAP versus NIPPV				
Bisceglia 2007 Italy (Lemyre 2016)	n= 88 • 24-37 weeks GA • Mild to moderate RDS (defined as need for FiO2 < 0.4 and chest x-ray positive for early hyaline membrane disease)	NCPAP versus NIPPV	Mortality prior to discharge Bronchopulmonary dysplasia at 36 weeks PMA Failed non-invasive ventilation Pneumothorax	
Kirpalani 2013 US (Lemyre 2013)	n= 1009 • < 1000g BW • < 30 weeks GA • Candidates for non-invasive respiratory support	NIPPV versus CPAP	Mortality prior to discharge Bronchopulmonary dysplasia at 36 weeks PMA Failed non-invasive ventilation	"Twenty infants (7 in the nasal-IPPV group and 13 in the nasal-CPAP group) did not undergo a required oxygen-reduction test (typically owing to early transfer) and were thus not included in the primary analysis."

Study and setting	Population	Intervention/ comparison	Outcomes	Comments
Kugelman 2007 Israel (Lemyre 2016)	n= 84 • 24-34+6 weeks GA • RDS and needed nasal respiratory support	NCPAP versus NIMV	Bronchopulmonary dysplasia at 36 weeks PMA Failed non-invasive ventilation Pneumothorax	"Two infants in the NCPAP group were switched by the medical team to NIMV in violation of the study protocol but were included in the intention-to-treat analysis according to their primary assignment"
Ramanathan 2012 US (Lemyre 2016)	n= 110 • 26+0-29+6 weeks GA • Intubated for RDS	NCPAP versus NIPPV	Mortality prior to discharge Bronchopulmonary dysplasia at 36 weeks PMA Failed non-invasive ventilation Pneumothorax	Ramanathan 2012 US (Lemyre 2016)
Oncel 2016 Turkey	n= 100 • 26-32 weeks GA • Showed signs of RDS • Did not require intubation in the delivery room	NCPAP versus NIPPV	Mortality prior to discharge Bronchopulmonary dysplasia at 36 weeks PMA Number of days on invasive ventilation Failed non-invasive ventilation Pneumothorax	
CPAP versus HF				
Nair 2005 (Wilkinson 2016)	n=67 • RDS requiring CPAP • In the first 6 hours • 27-24 weeks GA	HFNC (flow rate 5-6 L/min) versus CPAP	Mortality prior to discharge Bronchopulmonary dysplasia at 36 weeks PMA Failed non-invasive ventilation	
Yoder 2013 US	n=125 • ≥ 1000g BW	HFNC (starting at 3-5 L/min, increasing as required to 3L	Mortality prior to discharge	

Study and setting	Population	Intervention/ comparison	Outcomes	Comments
(Wilkinson 2016)	• ≥ 28 weeks GA	above starting point) versus NCPAP	Bronchopulmonary dysplasia at 36 weeks PMA Failed non-invasive ventilation	
Klingenberg 2015 Norway	n=20 • < 34 weeks GA • Mild respiratory illness (treatment with CPAP for < 72 hours if post menstrual age (PMA) < 29 weeks and < 24hr if 29-33 weeks) • FiO2 < 0.3 • Last PCO2 < 8 kPa	HHHFNC (flow rate of 6L/min for >1500g; 5L/min for <1500g) versus NCPAP/SiPAP	Parental satisfaction	2 x 24 hours randomised cross-over study. Parental satisfaction assessed after each 24 hours epochs
Lavizzari 2016 Italy	n= 316 • 29+0-36+6 weeks GA • Mild to moderate RDS requiring non-invasive respiratory support • FiO2 > 0.3	HHHFNC versus NCPAP	Mortality prior to discharge Bronchopulmonary dysplasia at 36 weeks PMA Number of days on invasive ventilation Failed non-invasive ventilation Pneumothorax	
Shin 2017 South Korea	n= 87 • 30-34+6 weeks GA • Did not meet the invasive respiratory support criteria after birth, but required non-invasive respiratory support for RDS within	HHFNC versus NCPAP	Bronchopulmonary dysplasia at 36 weeks PMA Number of days on invasive ventilation Failed non-invasive ventilation Pneumothorax	

Study and setting	Population	Intervention/ comparison	Outcomes	Comments
	24 hr after birth • Clinical signs of RDS • Need for prolonged positive pressure ventilation during neonatal resuscitation • > 1250g BW			
CPAP versus SiPAP				
Wood 2013 UK (Lemyre 2016)	n= 120 • 28+0-31+6 GA • Inborn • < 6 hours old • No prior intubation • No major congenital disorders	SiPAP versus CPAP	Mortality prior to discharge Bronchopulmonary dysplasia at 36 weeks PMA Failed non-invasive ventilation Pneumothorax	
Lista 2010 Italy	n= 40 • 28-34 weeks GA • Inborn • Affected by moderate RDS	NCPAP versus Bi-level NCPAP	Mortality prior to discharge Bronchopulmonary dysplasia at 36 weeks PMA Pneumothorax	"All infants enrolled in the study were sequentially numbered after birth and were randomised at 1 h of life to the NCPAP group (group A) or bi-level NCPAP group (group B) using a table of random numbers and using a stratified randomisation for gestational age (GA 28–31 weeks; GA 32–34 weeks).
HF versus NIPPV				
Kugelman 2015 Israel (Wilkinson 2016)	n= 76 • < 35 weeks GA • > 1000g BW • Babies with RDS who needed NRS	HHFNC (flow rate 1-5 L/min) versus NIPPV	Mortality prior to discharge Bronchopulmonary dysplasia at 36 weeks PMA	Babies were able to cross between interventions according to the attending physician after optimizing each

Study and setting	Population	Intervention/ comparison	Outcomes	Comments
	as initial therapy		Number of days on invasive ventilation Failed non-invasive ventilation Pneumothorax	mode's ventilatory settings.
Roberts 2016 Australia	n= 583 • 28+0-36+6 weeks GA • < 24 hours old • Had not previously received endotracheal ventilation or surfactant treatment and if the attending clinician had decided to commence or continue non-invasive respiratory support	High-flow versus CPAP	Mortality prior to discharge Bronchopulmonary dysplasia at 36 weeks PMA Failed non-invasive ventilation Pneumothorax	"Infants assigned to highflow therapy who met the criteria for treatment failure could receive CPAP as rescue therapy, initiated at 7 to 8 cm of water."
NSIPPV versus BiPAP				
Salvo 2015 Italy	n= 124 • < 32 weeks GA • < 1500 g BW	NSIPPV versus BiPAP	Mortality prior to discharge Bronchopulmonary dysplasia at 36 weeks PMA Failed non-invasive ventilation Pneumothorax	

BiPAP: bilevel positive airway pressure; BW: birth weight; CPAP: continuous positive airway pressure therapy; FiO2: delivered oxygen; GA: gestational age; HF: hi flow; HFNC: hi flow nasal cannula; HHFNC: humidified high-flow nasal cannula; HHHFNC: heated, humidified, hi flow nasal cannula; NCPAP: nasal continuous positive airway pressure therapy; NIMV: nasal intermittent mandatory ventilation; NIPPV: nasal intermittent positive pressure ventilation; NRS: non-invasive respiratory support; NSIPPV: non-invasive synchronised nasal intermittent positive pressure ventilation; PCO2: partial pressure of carbon dioxide; PMA: post menstrual age; RCT: randomised controlled trial; RDS: respiratory disease syndrome; SiPAP: synchronised positive airway pressure

Table 9 provides a brief summary of the included studies for invasive ventilation.

Table 9: Summary of included studies: invasive ventilation

Study and setting	Population	Intervention/ Comparison	Outcomes	Comments
Cochrane systematic reviews				
Cools 2015	• Preterm or low birth weight infants • Pulmonary dysfunction mainly due to RDS • Considered to require IPPV	HFOV versus conventional ventilation	Clinical outcomes Complications of prematurity Neurodevelopmental follow-up	Classification of conventional ventilation not aligned with definition in the review protocol
Greenough 2016	• Neonates (less than 4 weeks of age) requiring assisted ventilation	Synchronised invasive ventilation versus conventional ventilation or HFOV Comparisons between different types of triggered ventilation techniques (A/C, SIMV, PRVCV, SIMV + PS, PSV)	Clinical outcomes Complications of prematurity	Classification of conventional ventilation and synchronised invasive ventilation not aligned with the definition in the review protocol
Klingenberg 2017	• Intubated newborn infants being invasively ventilated with PPV at the time of study entry • All gestational ages up to 44 weeks	VTV versus PLV	Clinical outcomes Complications of prematurity Neurodevelopmental follow-up	Classification of PLV not aligned with definition in the review protocol Only studies up to 37 weeks gestational age were included in the review
RCTs				
HFV versus SIMV				
Moriette 2001 France (Cools 2015)	n=273 • Preterm babies with a gestational age of 24-29 weeks • Age at start of ventilation <6 hours	HFOV versus SIMV	Mortality prior to discharge Bronchopulmonary dysplasia at 36 weeks PMA Pneumothorax	Cross-over: 15% in HFOV; 29% in SIMV
Truffert 2007 France	See Moriette 2001	See Moriette 2001	Neurodevelopmental outcomes	Truffert 2007 France

Study and setting	Population	Intervention/ Comparison	Outcomes	Comments
(Cools 2015)				(Cools 2015)
HFV versus NSPLV				
Gerstmann 1996 US (Cools 2015)	n=125 • Preterm babies of a gestational age <35 weeks Age at start of ventilation <12 hours	HFOV versus IMV	Mortality prior to discharge Bronchopulmonary dysplasia at 36 weeks PMA Days on invasive ventilation	Cross over: 2% in IMV; 15% in HFOV
Greenough 2014 Multinational (Cools 2015)	See Johnson 2002	See Johnson 2002	Neurodevelopmental outcomes	Greenough 2014 Multinational (Cools 2015)
Johnson 2002 Multinational (Cools 2015)	n=797 • Preterm babies <u>23-25 weeks</u> n=284 <u>26-28 weeks</u> n=513 Age at start of ventilation <1 hour	HFOV versus TCPL	Mortality prior to discharge Bronchopulmonary dysplasia at 36 weeks PMA Days on invasive ventilation	Cross-over: 10% in both groups HFOV: mix of OSC and HFFI using different ventilators
Marlow 2006 Multinational (Cools 2015)	See Johnson 2002	See Johnson 2002	Neurodevelopmental outcomes	Marlow 2006 Multinational (Cools 2015)
Ogawa 2013 Japan (Cools 2015)	n=52 • Preterm babies • Ventilation started soon after birth	HFOV versus TCPL	Mortality prior to discharge	Cross-over: 9% in HFOV; 2% in TCPL
Rettwitz-Volk 1998 Germany (Cools 2015)	n=96 • Preterm babies with a gestational age of <32 weeks • FiO2 >0.6	HFOV versus IMV	Mortality prior to discharge Bronchopulmonary dysplasia at 36 weeks PMA	Cross-over: 17% in HFOV; 18% in IMV
Thome 1999 Germany (Cools 2015)	n=188 • Preterm babies with a gestational age 24-29 weeks	HFOV versus IPPV	Mortality prior to discharge Bronchopulmonary dysplasia at 36 weeks PMA	

Study and setting	Population	Intervention/ Comparison	Outcomes	Comments
	• Age at start of ventilation <6 hours			
Van Reempts 2003 Belgium (Cools 2015)	n=300 • Preterm babies with a gestational age <32 weeks • Age at start of ventilation <6 hours • FiO2 >0.4	HFOV versus IMV	Mortality prior to discharge Pneumothorax	Cross-over: 12% in HFOV, 7% in IMV HFOV: mix of OSC and HFFI using different ventilators
HFV versus SIMV				
Durand 2001 US (Cools 2015)	n=48 • Preterm babies Age at start of ventilation <4 hours	SIMV versus HFOV	Mortality prior to discharge Bronchopulmonary dysplasia at 36 weeks PMA	Cross over: 29% in SIMV; 8% in HFOV
Vento 2005 Italy (Cools 2015)	n=40 • Preterm babies with a gestational age 24-29 weeks • Age at start of ventilation <0.5	HFOV versus SIMV	Mortality prior to discharge Bronchopulmonary dysplasia at 36 weeks PMA Days on invasive ventilation Pneumothorax	
HFV versus VTV				
Lista 2008 Italy (Cools 2015)	n=40 • Preterm babies with a gestational age of 25-32 weeks • Age at start of ventilation <1 hour	HFOV versus A/C + VG	Mortality prior to discharge Bronchopulmonary dysplasia at 36 weeks PMA	
HFV versus SPLV				
Salvo 2012 Europe (Cools 2015)	n=88 • Preterm babies with a gestational age of <30 weeks Age at start of ventilation <2 hours	HFOV versus SIMV	Mortality prior to discharge Bronchopulmonary dysplasia at 36 weeks PMA Days on invasive ventilation	

Study and setting	Population	Intervention/ Comparison	Outcomes	Comments
SIMV versus HFV				
Courtney 2002 US (Greenough 2016)	n=498 • Preterm babies • Age at start of ventilation <4 hours • Apgar score of >3 at 5 minutes	SIMV versus HFOV	Mortality prior to discharge Bronchopulmonary dysplasia at 36 weeks PMA Pneumothorax	Cross over: 19% in SIMV; 10% in HFOV
Craft 2003 US (Greenough 2016)	n=46 • Preterm babies with a gestational age of 23-34 weeks	SIMV versus HFFI	Mortality prior to discharge Bronchopulmonary dysplasia at 36 weeks PMA	
SIMV versus NSPLV				
Bernstein 1996 US (Greenough 2016)	n=350 • Preterm babies • Age at start of ventilation <36 hours • FiO2 >0.4	SIMV versus IMV	Mortality prior to discharge Days on invasive ventilation	
SIMV versus VTV				
D'Angio 2005 US (Greenough 2016)	n=212 Preterm babies with a gestational age >24 weeks	SIMV versus PRVCV	Mortality prior to discharge Bronchopulmonary dysplasia at 36 weeks PMA Days on invasive ventilation Pneumothorax	Different trigger modes used in both ventilation techniques
Piotrowski 2007 Poland (Klingenberg 2017)	n=56 Preterm babies with a gestational age 24-32 weeks	PRVCV versus SIMV	Mortality prior to discharge Pneumothorax	
SPLV versus NSPLV				
Baumer 2000 UK (Greenough 2016)	n=924 • Preterm babies with a gestational age of <32 weeks • Age at start of ventilation <72 hours	PTV versus IMV	Mortality prior to discharge Bronchopulmonary dysplasia at 36 weeks PMA Days on invasive ventilation	

Study and setting	Population	Intervention/ Comparison	Outcomes	Comments
			Pneumothorax	
Beresford 2000 UK (Greenough 2016)	n=386 • Preterm babies • Age at start of ventilation <24 hours	PTV versus CMV	Mortality prior to discharge Bronchopulmonary dysplasia at 36 weeks PMA Days on invasive ventilation Pneumothorax	
Donn 1994 US (Greenough 2016)	n=30 Preterm babies	PTV versus TCPL	Mortality prior to discharge Bronchopulmonary dysplasia at 36 weeks PMA Days on invasive ventilation Pneumothorax	
VTV versus NSPLV				
Piotrowski 1997 Poland (Klingenberg 2017)	n=57 • Preterm babies Age at start of ventilation <72 hours	PRVC versus IMV	Mortality prior to discharge Days on invasive ventilation Pneumothorax	
VTV versus SIMV				
Chowdhury 2013 UK (Klingenberg 2017)	n=40 • Preterm babies with a gestational age <34 weeks • Age at start of ventilation <24 hours	VTV versus SIMV	Mortality prior to discharge Days on invasive ventilation Pneumothorax	Imbalance in baseline gestational age SIMV: 26 weeks; VTV: 28 weeks
Guven 2013 Turkey (Klingenberg 2017)	n=72 • Preterm babies with a gestational age <32 weeks • Age at start of ventilation <2 hours	SIMV + VG versus SIMV	Mortality prior to discharge Bronchopulmonary dysplasia at 36 weeks PMA Days on invasive ventilation	Randomisation occurred before parent consent

Study and setting	Population	Intervention/ Comparison	Outcomes	Comments
Nafday 2005 US (Klingenberg 2017)	n=34 • Preterm babies Age at start of ventilation <12 hours	PSV + VG versus SIMV	Mortality prior to discharge Bronchopulmonary dysplasia at 36 weeks PMA Pneumothorax	
VTV versus SPLV				
Dunman 2012 Turkey (Klingenberg 2017)	n=45 • Preterm babies with a gestational age 23-31 weeks • Age at start of ventilation >24 hours	A/C + VG versus A/C	Mortality prior to discharge Bronchopulmonary dysplasia at 36 weeks PMA Days on invasive ventilation Pneumothorax	
Lista 2004 Italy (Klingenberg 2017)	N=53 • Preterm babies with a gestational age 25-32 weeks • Age at start of ventilation <24 hours	PSV + VG versus PSV	Mortality prior to discharge Bronchopulmonary dysplasia at 36 weeks PMA Days on invasive ventilation Pneumothorax	
Singh 2006 US (Klingenberg 2017)	n=109 • Preterm babies with a gestational age of 24-31 weeks	VCV vs A/C	Mortality prior to discharge Bronchopulmonary dysplasia at 36 weeks PMA Days on invasive ventilation Pneumothorax	
Singh 2009 US (Klingenberg 2017)	See Singh 2006	See Singh 2006	Neurodevelopmental outcomes	Singh 2009 US (Klingenberg 2017)
Sinha 1997 UK	n=50 Preterm babies	A/C + VG versus A/C	Mortality prior to discharge	Sinha 1997 UK

Study and setting	Population	Intervention/ Comparison	Outcomes	Comments
(Klingenberg 2017)			Bronchopulmonary dysplasia at 36 weeks PMA Days on invasive ventilation Pneumothorax	(Klingenberg 2017)

AC: assist control; A/C + VG: assist and control with volume guarantee; HFFI: high frequency flow interruption HFOV: high frequency oscillatory ventilation; IMV: intermittent mandatory ventilation; IPPV: intermittent positive pressure ventilation; PRVCV: pressure regulated volume control ventilation; PSV: pressure support ventilation; PSV + VG: pressure support ventilation with volume guarantee; PTV: patient triggered ventilation; SIMV: synchronised intermittent mandatory ventilation; SIMV + VG: synchronised intermittent mandatory ventilation with volume guarantee; TCPL: time cycled pressure limited ventilation; VCV: volume controlled ventilation; VTV: volume targeted ventilation

See appendix D for clinical evidence tables.

Quality assessment of clinical studies included in the evidence review

See appendix F for full GRADE tables.

Clinical evidence profile for network meta-analysis (NMA) outcomes

For both non-invasive ventilation and invasive ventilation mortality prior to discharge and BPD at 36 weeks post menstrual age (PMA) outcomes were synthesised using network meta-analytic techniques.

For the NMA protocol see appendix N, for a description of NMA methods see appendix O, for summary of studies included in the NMAs see appendix P and studies excluded from the NMAs see appendix Q.

Non-invasive ventilation techniques

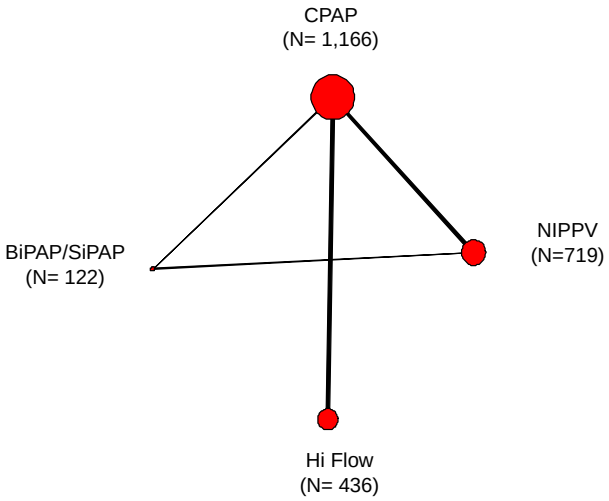
Mortality prior to discharge

Seven RCTs of 4 treatments were included in the network for mortality prior to discharge with a total sample size of 2,443 preterm babies (Figure 1). Of the included studies in the NMA:

- Five studies were at low risk and 2 studies were at unclear risk of selection bias;
- Six studies were at low risk and 1 study was at unclear risk of performance bias;
- Seven studies were at low risk of detection bias;
- One study was at high risk and 6 studies were at low risk of attrition bias;
- Five studies were at low risk and 2 studies were at unclear risk of reporting bias;
- One study was at high risk and 6 studies were at low risk of other biases.

The risk of bias graph and summary are presented in Figure 2 and Figure 3, respectively.

Figure 1: Network for mortality prior to discharge



BiPAP: bilevel positive airway pressure; CPAP: continuous positive airway pressure therapy; NIPPV: nasal intermittent positive pressure ventilation; SiPAP: synchronised positive airway pressure

Note: The size of nodes is proportional to the number of babies in the network who were randomised to a particular ventilation technique. The thickness of connecting lines is proportional to the number of studies directly comparing 2 ventilation techniques.

Figure 2: Risk of bias graph: review authors' judgement about each risk of bias item presented as percentages across all included studies

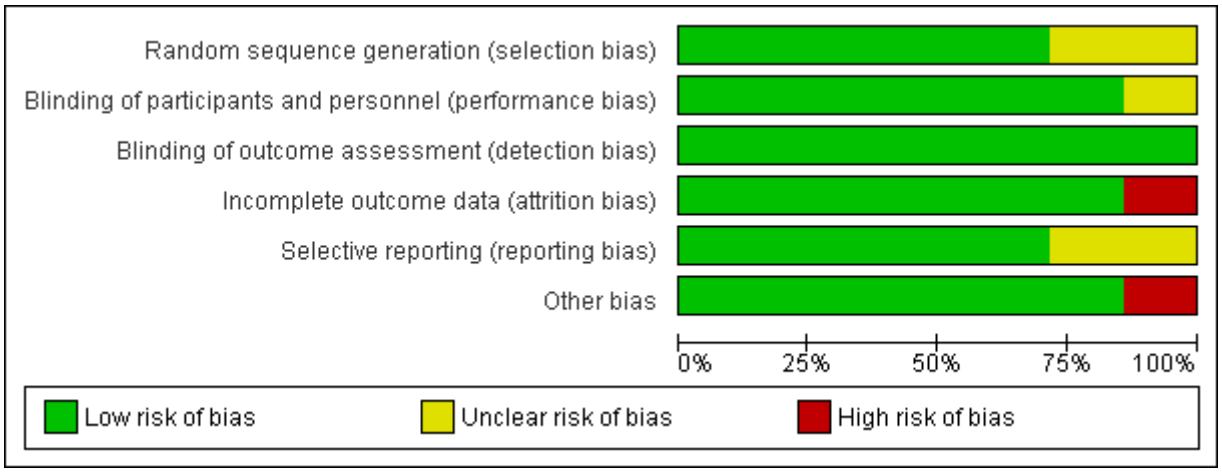


Figure 3: Risk of bias summary: review authors' judgements about each risk of bias item for each included study

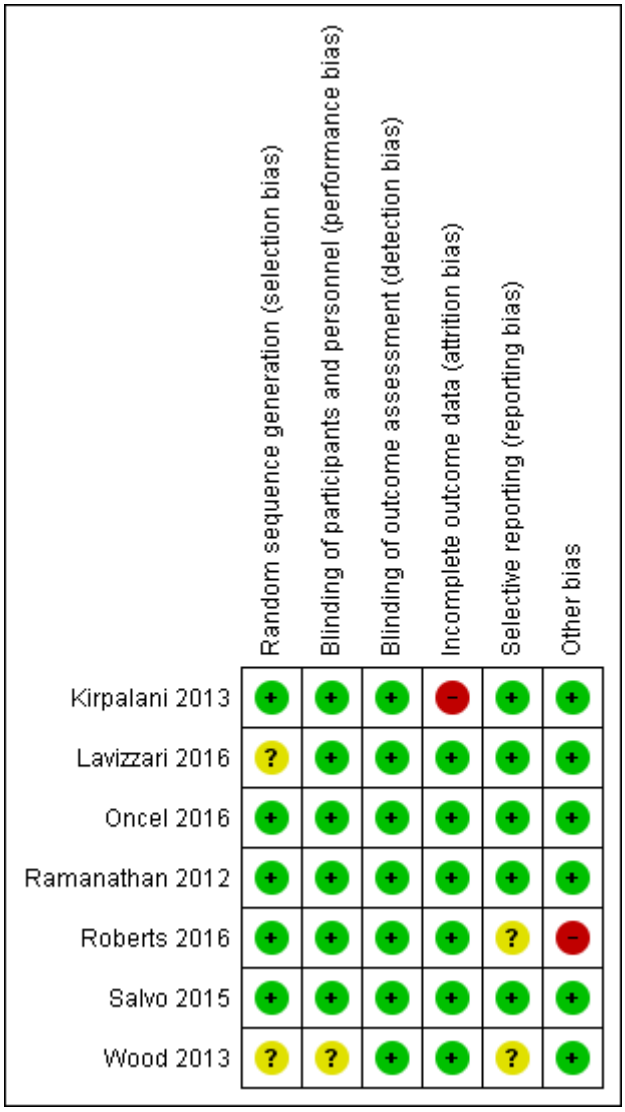


Table 10 presents the results of conventional pair-wise meta-analyses (direct comparisons; upper right section of table) together with the results from the NMA for every possible treatment comparison (lower left section of table), presented as posterior median odds ratios (ORs) and 95% credible intervals (CrI). These results were derived from a fixed effect model. For model fit characteristics see appendix R.

There was no evidence of difference between non-invasive ventilation techniques for mortality prior to discharge. Although, Hi Flow had the highest probability of being the best treatment for mortality prior to discharge (52%) (Table 11).

Table 10: Matrix of results for the NMA of mortality prior to discharge (ORs and 95% CrI)

BiPAP/SiPAP	-	9.70 (0.50, 5208.25)	0.10 (0.00, 1.98)
1.61 (0.10, 35.38)	**Hi Flow**	-	0.56 (0.04, 4.77)
1.14 (0.19, 6.80)	0.72 (0.05, 6.41)	**NIPPV**	0.79 (0.52, 1.21)
0.86 (0.14, 5.13)	0.55 (0.04, 4.67)	0.76 (0.49, 1.16)	**CPAP**

BiPAP: Bilevel positive airway pressure; CPAP: Continuous positive airway pressure therapy; CrI: Credible interval; NIPPV: Nasal intermittent positive pressure ventilation; NMA: Network meta-analysis; ORs: Odd Ratios; SiPAP: Synchronised positive airway pressure

Note: Lower diagonal: Posterior median ORs and 95% CrIs from NMA. ORs lower than 1 favour the column defining treatment, ORs higher than 1 favour the row defining treatment. Upper diagonal: OR and 95% CIs from direct pairwise meta-analysis. ORs lower than 1 favour the row defining treatment, ORs higher than 1 favour the column defining treatment.

Table 11: Probabilities of being the best ventilation technique and the treatment rank and 95% CrI

Ventilation technique	Number of babies	Number of studies	Probability of being best (%)	Median (95% CrI) treatment rank
CPAP	1166	6	1%	3 (2, 4)
NIPPV	719	4	21%	2 (1, 4)
Hi Flow	436	2	52%	1 (1, 4)
BiPAP/SiPAP	122	2	26%	3 (1, 4)

BiPAP: Bilevel positive airway pressure; CPAP: Continuous positive airway pressure therapy; CrI: Credible interval; NIPPV: Nasal intermittent positive pressure ventilation; NMA: Network meta-analysis; SiPAP: Synchronised positive airway pressure

Bronchopulmonary dysplasia (BPD) at 36 weeks PMA

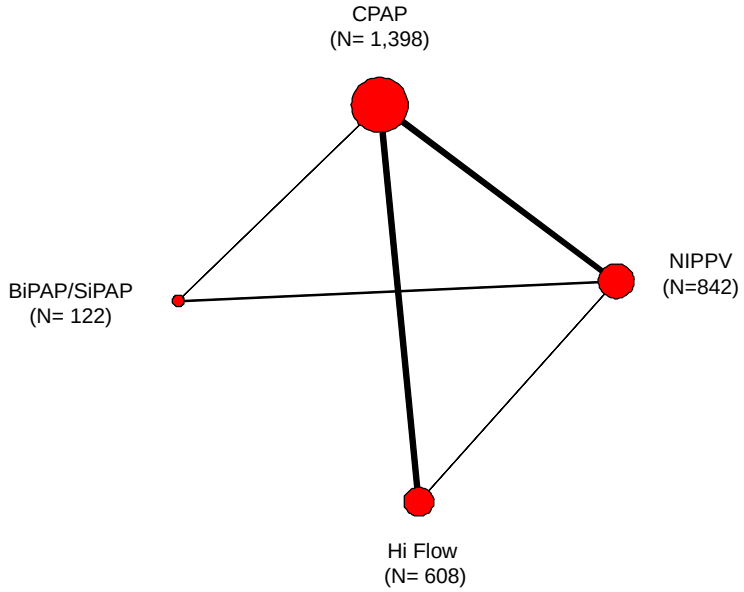
Thirteen RCTs of 4 treatments were included in the network for BPD at 36 weeks PMA with a total sample size of 2,970 preterm babies (Figure 4).

Of the included studies in the NMA:

- Seven studies were at low risk and 6 studies were at unclear risk of selection bias;
- Ten studies were at low risk and 3 studies were at unclear risk of performance bias;
- Thirteen studies were at low risk of detection bias;
- One study was at high risk, 11 studies were at low risk and 1 study was at unclear risk of attrition bias;
- Eight studies were at low risk and 5 studies were at unclear risk of reporting bias;
- Three studies were at high risk and 10 studies were at low risk of other biases.

The risk of bias graph and summary are presented in Figure 5 and Figure 6, respectively.

Figure 4: Network for BPD at 36 weeks PMA



BiPAP: Bilevel positive airway pressure; BPD: Bronchopulmonary dysplasia; CPAP: Continuous positive airway pressure therapy; NIPPV: Nasal intermittent positive pressure ventilation; SiPAP: Synchronised positive airway pressure

Note: The size of nodes is proportional to the number of babies in the network who were randomised to a particular ventilation technique. The thickness of connecting lines is proportional to the number of studies directly comparing 2 ventilation techniques.

Figure 5: Risk of bias graph: review authors' judgement about each risk of bias item presented as percentages across all included studies

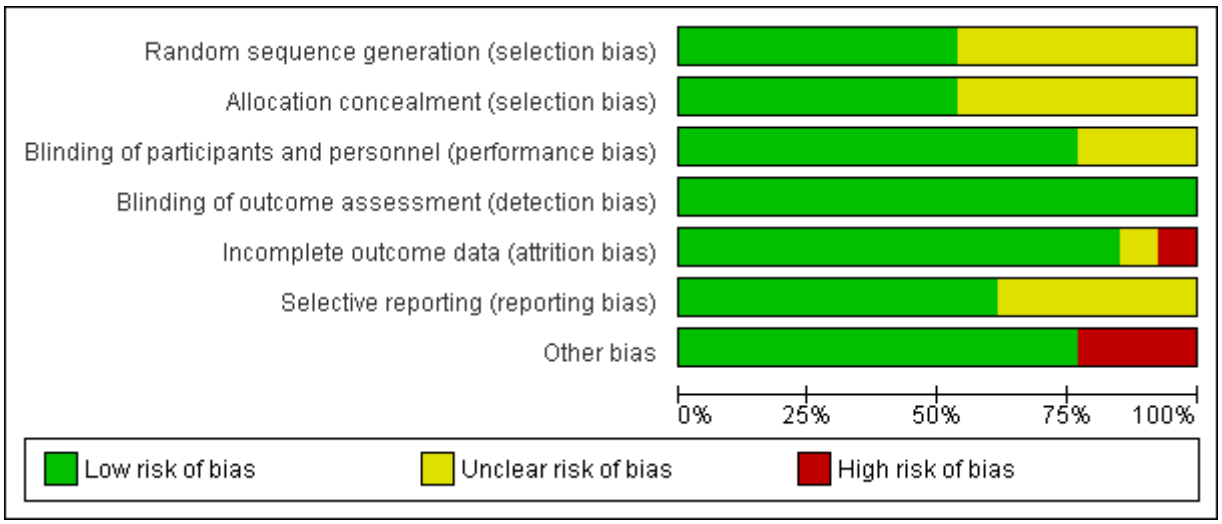


Figure 6: Risk of bias summary: review authors' judgements about each risk of bias item for each included study

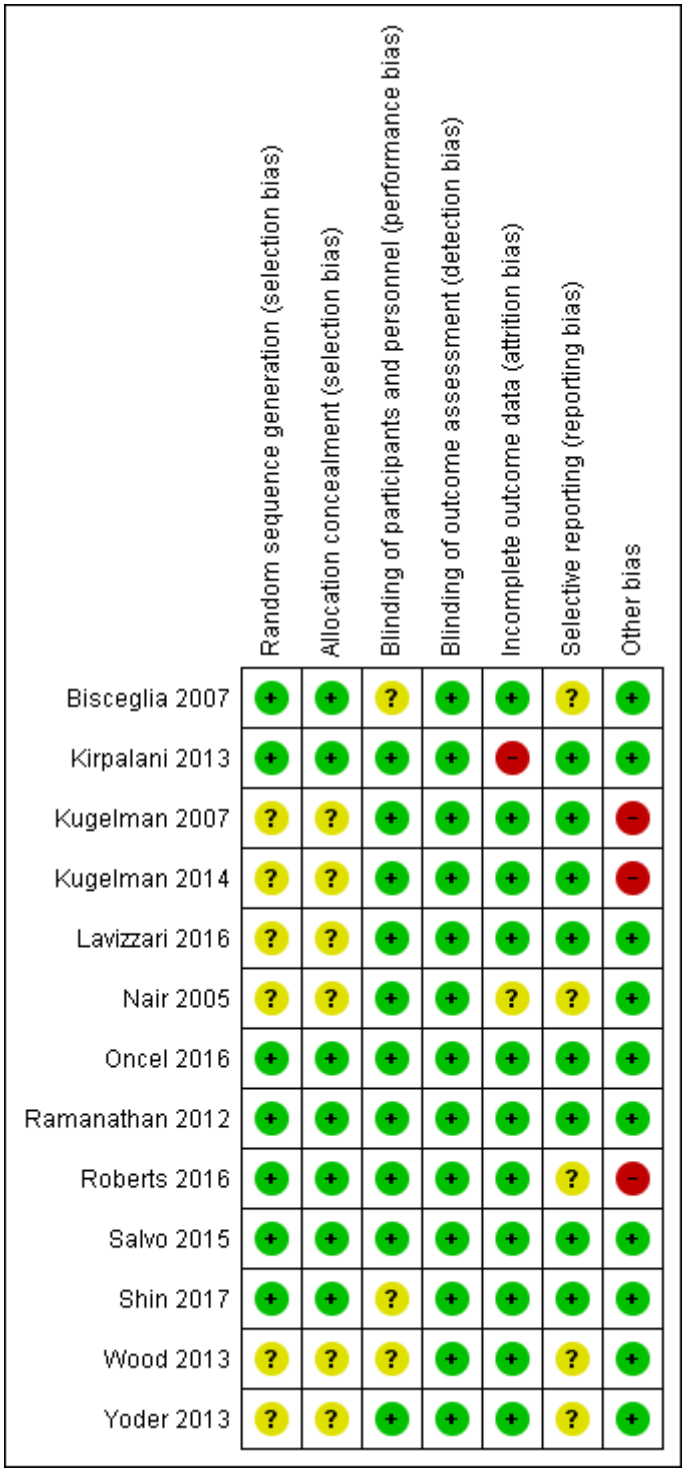


Table 12 presents the results of conventional pair-wise meta-analyses (direct comparisons; upper right section of table) together with the results from the NMA for every possible comparison (lower left section of table), presented as posterior median odds ratios (ORs and 95% CrI). These results were derived from a random effects model. For model fit characteristics see appendix R.

There was no evidence of differences between non-invasive ventilation techniques for BPD. Although, both BiPAP/SiPAP and NIPPV had highest probabilities of being the best treatments for BPD (47% and 43% for BiPAP/SiPAP and NIPPV, respectively) (Table 13)

Table 12: Matrix of results for the NMA of BPD at 36 weeks PMA (ORs and 95% CrI)

BiPAP/SiPAP	-	1.00 (0.08, 10.31)	0.68 (0.06, 7.16)
0.58 (0.10, 3.03)	**Hi Flow**	0.39 (0.01, 10.34)	1.33 (0.42, 5.17)
1.01 (0.25, 4.35)	1.73 (0.59, 6.36)	**NIPPV**	0.56 (0.16, 1.36)
0.66 (0.15, 2.60)	1.14 (0.43, 3.03)	0.66 (0.27, 1.31)	**CPAP**

BiPAP: Bilevel positive airway pressure; BPD: Bronchopulmonary dysplasia; CPAP: Continuous positive airway pressure therapy; CrI: Credible interval; NIPPV: Nasal intermittent positive pressure ventilation; NMA: Network meta-analysis; ORs: Odd Ratios; SiPAP: Synchronised positive airway pressure

Note: Lower diagonal: Posterior median ORs and 95% CrIs from NMA. ORs lower than 1 favour the column defining treatment, ORs higher than 1 favour the row defining treatment. Upper diagonal: OR and 95% CIs from direct pairwise meta-analysis. ORs lower than 1 favour the row defining treatment, ORs higher than 1 favour the column defining treatment.

Table 13: Probabilities of being the best ventilation technique and the treatment rank and 95% CrI

Ventilation technique	Number of babies	Number of studies	Probability of being best (%)	Median (95% CrI) treatment rank
CPAP	1398	11	3%	3 (1, 4)
NIPPV	842	7	43%	2 (1, 4)
Hi Flow	608	6	8%	4 (1, 4)
BiPAP/SiPAP	122	2	47%	2 (1, 4)

BiPAP: bilevel positive airway pressure; CPAP: continuous positive airway pressure therapy; CrI: Credible interval; NIPPV: nasal intermittent positive pressure ventilation; SiPAP: synchronised positive airway pressure

Inconsistency checks

The inconsistency checks did not identify any evidence of inconsistency between direct and indirect evidence included in the NMA for BPD at 36 weeks PMA outcome. However, there was some evidence of potential inconsistency in the mortality prior to discharge as the inconsistency model better predicted data points in two of the included studies. The full results of inconsistency checks are presented in appendix S.

Invasive ventilation techniques

Mortality prior to discharge

Twenty six RCTs of 5 treatments were included in the network for mortality prior to discharge with a total sample size of 5,093 preterm babies (Figure 7).

A further 3 studies (n = 183) comparing the same ventilation technique in both arms were included as they contributed to the estimation of between-study heterogeneity.

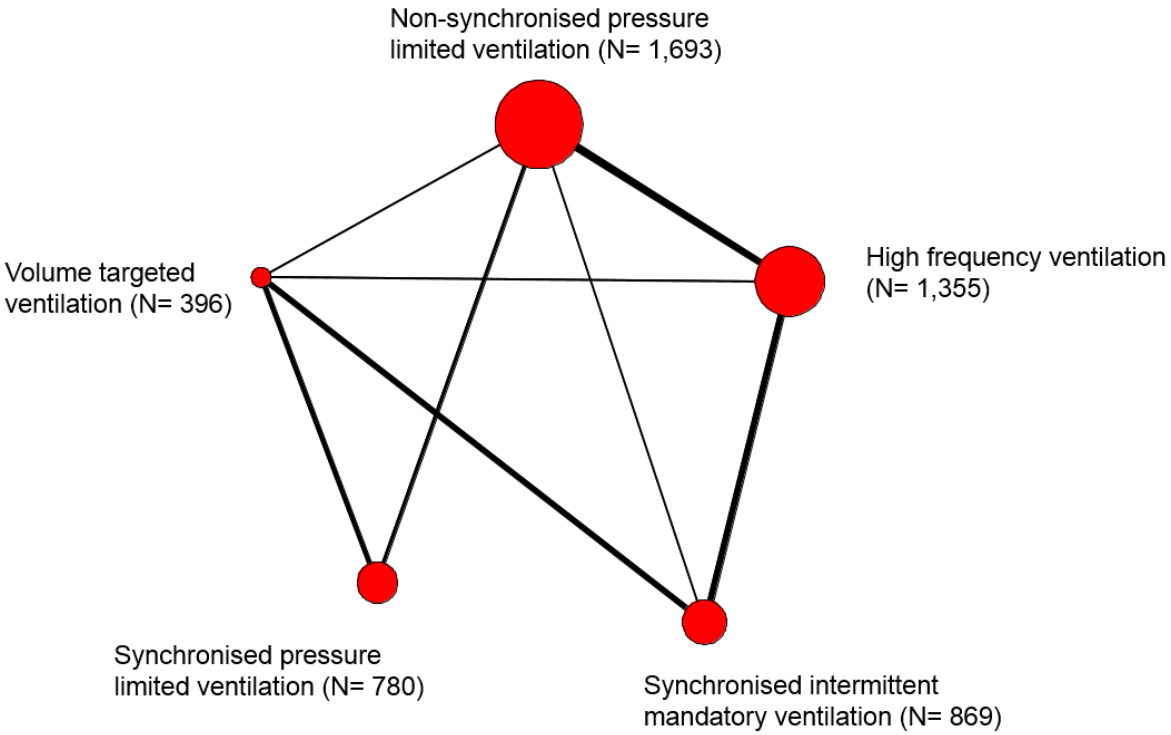
Of the included studies in the NMA of mortality prior to discharge:

- Six studies were at low risk and 23 studies were at unclear risk of selection bias;
- Twenty-nine studies were at high risk of performance bias;

- Twenty-nine studies were at low risk of detection bias;
- Twenty-seven studies were at low risk and 2 studies were at unclear risk of attrition bias;
- Two studies were at low risk and 27 studies were at unclear risk of reporting bias;
- Seventeen studies were at high risk and 12 studies were at low risk of other biases.

The risk of bias graph and summary are presented in Figure 8 and Figure 9, respectively.

Figure 7: Network for mortality prior to discharge



Note: The size of nodes is proportional to the number of babies in the network who were randomised to a particular ventilation technique. The thickness of connecting lines is proportional to the number of studies directly comparing 2 ventilation techniques. The numbers don't include the babies in studies that compared the same ventilation technique in both arms.

Figure 8: Risk of bias graph: review authors' judgement about each risk of bias item presented as percentages across all included studies

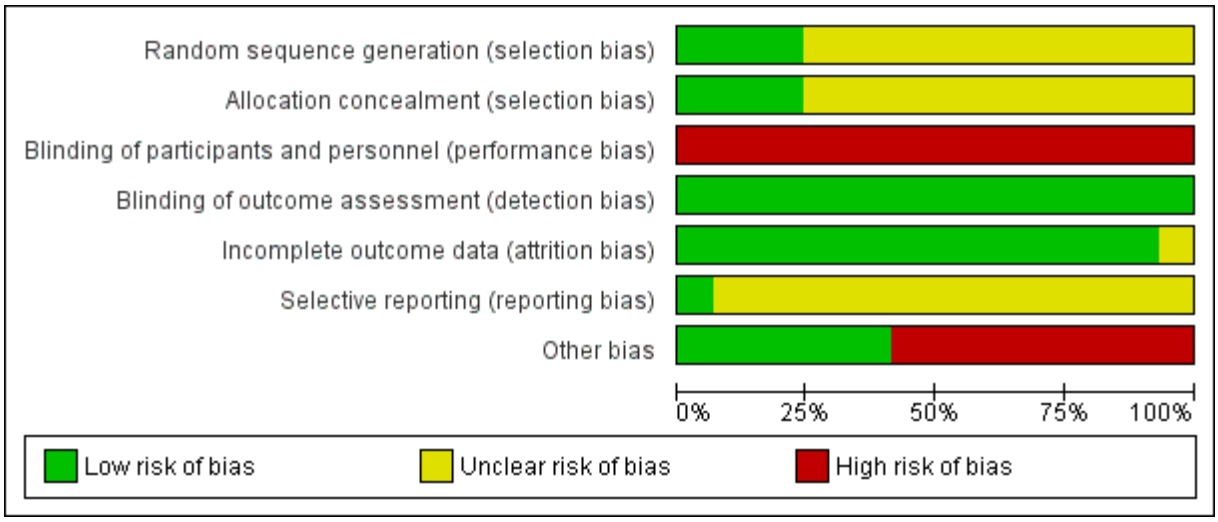


Figure 9: Risk of bias summary: review authors' judgements about each risk of bias item for each included study

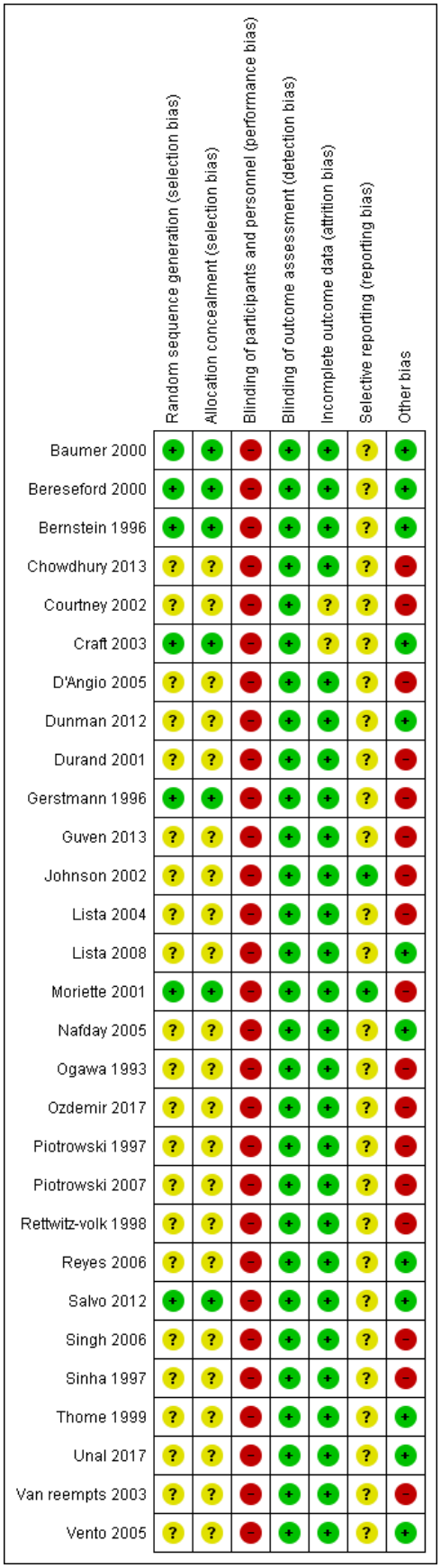


Table 14 presents the results of conventional pair-wise meta-analyses (direct comparisons; upper right section of table) together with the results from the NMA for every possible comparison (lower left section of table), presented as posterior median odds ratios (ORs and 95% CrI). These results were derived from a fixed effect model. For model fit characteristics see appendix R.

There was no evidence to suggest a difference between high frequency ventilation, synchronised intermittent mandatory ventilation and volume targeted ventilation when compared with non-synchronised pressure limited ventilation for mortality prior to discharge.

There was evidence that synchronised pressure limited ventilation was worse when compared with non-synchronised pressure limited ventilation and high frequency ventilation for mortality prior to discharge. There was evidence that volume targeted ventiliation was better when compared with synchronised pressure limited ventilation for mortality prior to discharge. Volume targeted ventilation had the highest probability of being the best treatment for mortality prior to discharge (73%) (Table 15). However, it should be noted that there was a lack of good fit for the model.

Table 14: Matrix of results for the NMA of mortality prior to discharge (ORs and 95% CrI)

Volume targeted	**0.44 (0.20, 0.90)**	1.02 (0.57, 1.84)	0.88 (0.02, 35.52)	0.45 (0.10, 1.72)
0.54 (0.33, 0.88)	**Synchronised pressure limited**	-	-	**1.35 (1.00, 1.82)**
0.81 (0.51, 1.30)	1.51 (0.98, 2.32)	**Synchronised intermittent mandatory**	1.04 (0.74, 1.46)	1.06 (0.43, 2.66)
0.80 (0.49, 1.30)	**1.47 (1.02, 2.13)**	0.98 (0.72, 1.33)	**High frequency**	0.98 (0.75, 1.27)
0.75 (0.46, 1.22)	**1.40 (1.05, 1.87)**	0.93 (0.66, 1.33)	0.95 (0.74, 1.21)	**Non-synchronised pressure limited**

Note: Lower diagonal: Posterior median ORs and 95% CrIs from NMA. ORs lower than 1 favour the column defining treatment, ORs higher than 1 favour the row defining treatment. Upper diagonal: OR and 95% CIs from direct pairwise meta-analysis. ORs lower than 1 favour the row defining treatment, ORs higher than 1 favour the column defining treatment

Table 15: Probabilities of being the best ventilation technique and the treatment rank and 95% CrI

Ventilation technique	Number of babies	Number of studies	Probability of being best	Median (95% CrI) treatment rank
Non-synchronised pressure limited	1693	10	5%	3 (1, 4)
High frequency	1355	13	10%	3 (1, 4)
Synchronised intermittent mandatory	869	12	12%	2 (1, 5)
Synchronised pressure limited	780	6	0%	5 (4, 5)
Volume targeted	396	11	73%	1 (1, 4)

CrI: Credible interval

Note: The numbers don't include the babies in studies that compared the same ventilation technique in both arms

Bronchopulmonary dysplasia (BPD) at 36 weeks PMA

Twenty RCTs of 5 treatments were included in the network for BPD a total sample size of 4,425 preterm babies (Figure 10).

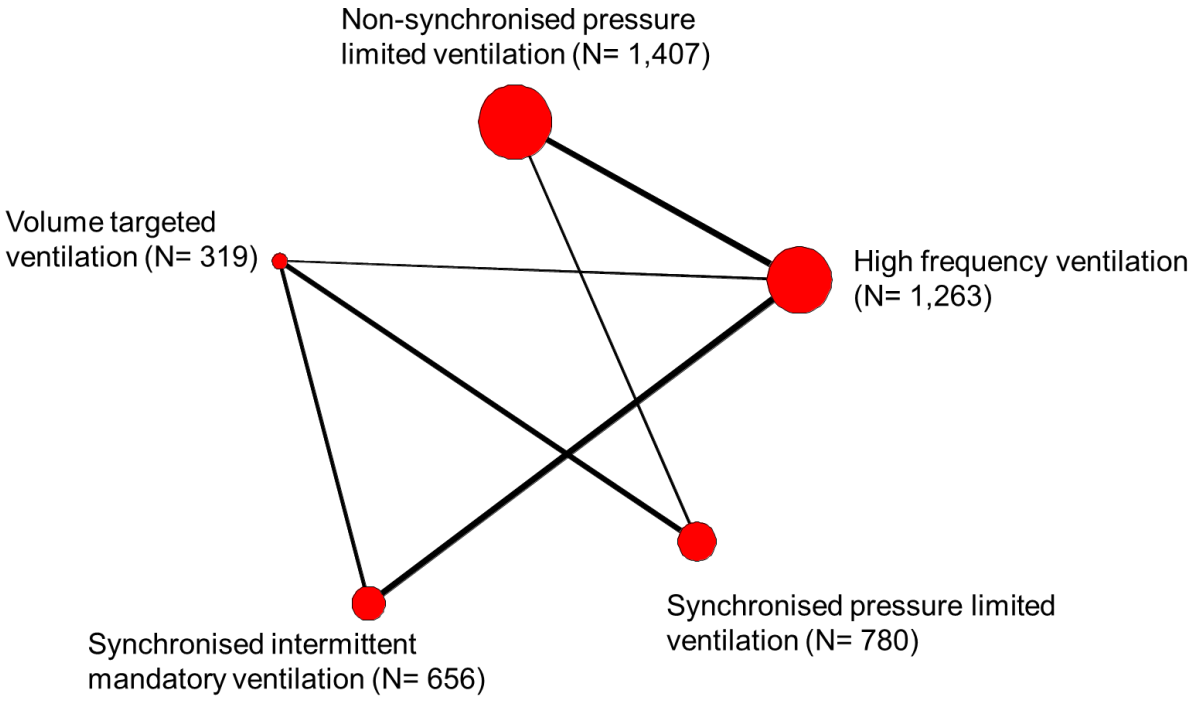
A further 3 studies (n = 183) comparing the same ventilation technique in both arms were included as they contributed to the estimation of between-study heterogeneity.

Of the included studies in the NMA of BPD:

- Six studies were at low risk and 17 studies were at unclear risk of selection bias;
- Twenty-three studies were at high risk of performance bias;
- Twenty-three studies were at low risk of detection bias;
- Twenty-one studies were at low risk and 2 studies were at unclear risk of attrition bias;
- Two studies were at low risk and 21 studies were at unclear risk of reporting bias;
- Twelve studies were at high risk and 11 studies were at low risk of other biases.

The risk of bias graph and summary are presented in Figure 11 and Figure 12, respectively.

Figure 10: Network for BPD at 36 weeks PMA



Note: The size of nodes is proportional to the number of babies in the network who were randomised to a particular ventilation technique. The thickness of connecting lines is proportional to the number of studies directly comparing 2 ventilation techniques. The numbers don't include the babies in studies that compared the same ventilation technique in both arms.

Figure 11: Risk of bias graph: review authors' judgement about each risk of bias item presented as percentages across all included studies

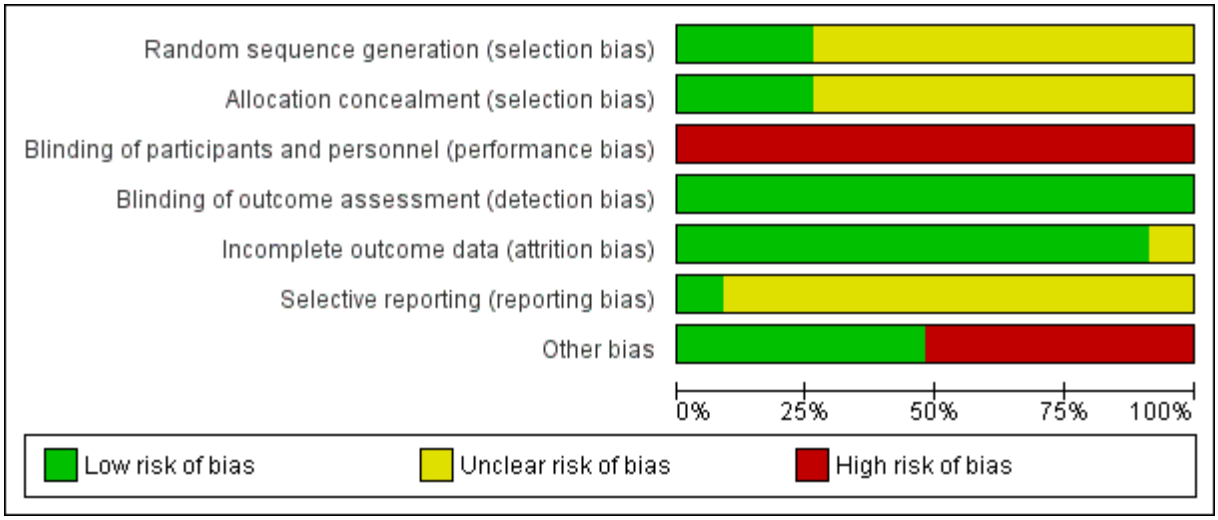


Figure 12: Risk of bias summary: review authors' judgements about each risk of bias item for each included study

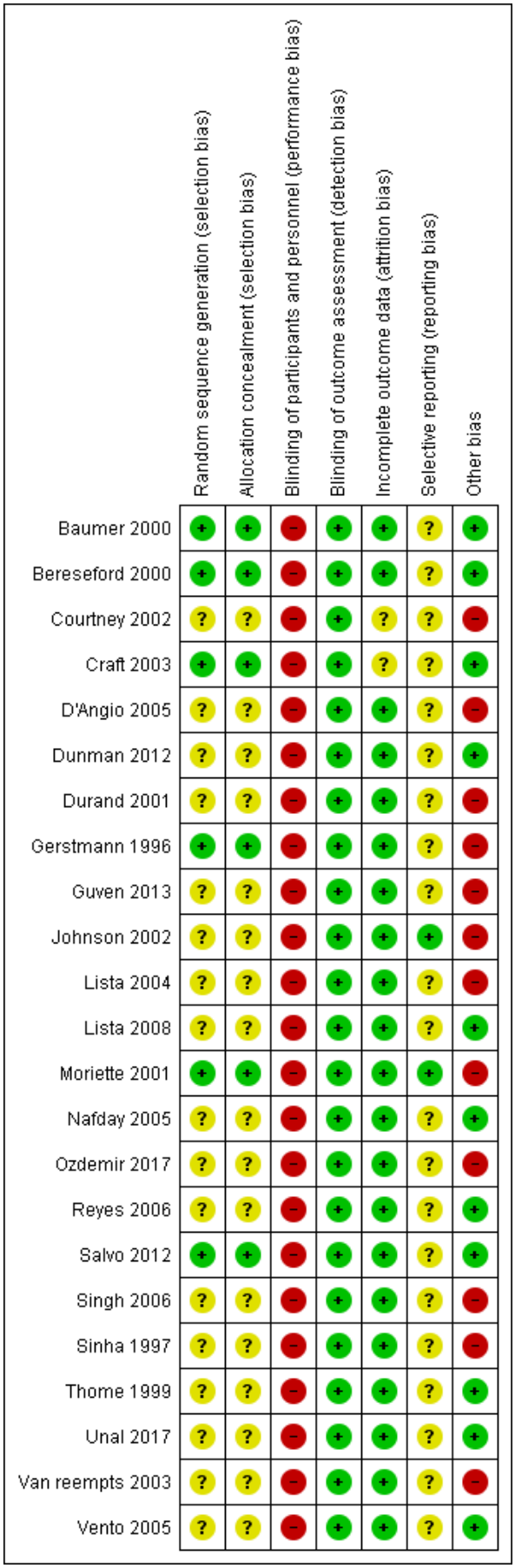


Table 16 presents the results of conventional pair-wise meta-analyses (direct comparisons; upper right section of table) together with the results from the NMA for every possible comparison (lower left section of table), presented as posterior median odds ratios (ORs and 95% CrI). These results were derived from a random effects model. For model fit characteristics see appendix R.

There was no evidence of differences between any ventilation techniques when compared with non-synchronised pressure limited ventilation for BPD at 36 weeks PMA.

There was evidence that synchronised intermittent mandatory ventilation was worse when compared with high frequency ventilation for BPD at 36 weeks PMA. There was evidence that volume targeted ventilation was better when compared with synchronised intermittent mandatory ventilation for BPD at 36 weeks PMA. Volume targeted ventilation had the highest probability of being the best treatment for BPD at 36 weeks PMA (88%) (Table 17). However, it should be noted that there was a lack of good fit for the model.

Table 16: Matrix of results for the NMA of BPD at 36 weeks PMA (ORs and 95% CrI)

Volume targeted	0.55 (0.27, 1.01)	**0.50** **(0.25, 0.97)**	0.90 (0.08, 10.00)	-
0.44 **(0.25, 0.73)**	**Synchronised intermittent mandatory**	-	**1.67** **(1.16, 2.63)**	-
0.65 (0.36, 1.10)	1.48 (0.84, 2.49)	**Synchronised pressure limited**	**-**	0.89 (0.59, 1.40)
0.69 (0.40, 1.20)	**1.55** **(1.11, 2.37)**	1.04 (0.68, 1.87)	**High frequency**	0.98 (0.67, 1.37)
0.63 (0.35, 1.09)	1.42 (0.91, 2.32)	0.96 (0.67, 1.52)	0.92 (0.64, 1.26)	**Non-synchronised pressure limited**

Note: Lower diagonal: Posterior median ORs and 95% CrIs from NMA. ORs lower than 1 favour the column defining treatment, ORs higher than 1 favour the row defining treatment. Upper diagonal: OR and 95% CIs from direct pairwise meta-analysis. ORs lower than 1 favour the row defining treatment, ORs higher than 1 favour the column defining treatment.

Table 17: Probabilities of being the best ventilation technique and the treatment rank and 95% CrI

Ventilation technique	Number of babies	Number of studies	Probability of being best	Median (95% CrI) treatment rank
Non-synchronised pressure limited	1407	6	2%	3 (2, 5)
High frequency	1263	11	7%	2 (1, 4)
Synchronised intermittent mandatory	763	9	0%	5 (3, 5)
Synchronised pressure limited	673	6	4%	3 (1, 5)
Volume targeted	319	8	88%	1 (1, 3)

CrI: Credible interval

Note: The numbers don't include the babies in studies that compared the same ventilation technique in both arms

Inconsistency checks

The inconsistency checks did not identify any evidence of inconsistency between direct and indirect evidence included in the network meta-analyses for mortality prior to discharge or for BPD at 36 weeks PMA. The full results of inconsistency checks are presented in appendix S.

Threshold analysis

If studies included in a NMA are assessed to have flaws in their conduct or reporting, the reliability of results from the NMA can be in doubt. Therefore, analysts and decision makers need to assess the robustness of any conclusions based on the NMA to potential biases in the included evidence. Suppose that we ask, “how much would the evidence have to change before the recommendation changes?” This is the motivation behind threshold analysis. The results of a threshold analysis describe how much each data point could change (or be adjusted for bias) before the recommendation changes and what the revised recommendation would be. Threshold analysis may be carried out at two levels: (i) at a study level, assessing the influence of individual study estimates on the recommendation and (ii) at a contrast level, where the influence of the combined evidence on each treatment contrast is considered.

The contrast level threshold analysis indicated that for BPD at 36 weeks PMA the conclusions from the NMA were robust for the best treatment (that is, VTV) and that large changes in odds ratios of BPD at 36 weeks PMA would be required for the conclusions from the base-case analysis to change (Figure 71, appendix T). The study level analysis reinforced the findings but indicated that the results were most sensitive to a single study (D'Angio 2005). However, the identified smallest threshold required for the conclusions to change was still very large and would require more than doubling the odds ratios of BPD at 36 weeks PMA (Figure 72, appendix T). Similarly, the conclusions were robust for the worst ranked treatment (that is, SIMV) for BPD at 36 weeks PMA (Figure 73 and Figure 74, appendix T).

Contrast level threshold analysis indicated that for mortality prior to discharge for the best-ranked treatment (that is, VTV) the upper credible interval value exceeded the upper invariant interval value and as a result, there was statistical uncertainty as to whether VTV or SIMV was the best-ranked invasive ventilation mode (Figure 75, appendix T). Study level threshold analysis for mortality prior to discharge outcome indicated that the findings were driven by the same large RCT (D'Angio 2005) that provides the most weight in this comparison (Figure 76, appendix T). Also, this RCT was rated as at high risk of bias due to a different duration of invasive ventilation when compared with other studies. The threshold analysis for the worst ranked treatment for mortality prior to discharge (that is, synchronised pressure limited) was fairly robust and only a large change in the odds ratios would be required for the base-case analysis conclusions to change (Figure 77 and Figure 78, appendix T).

For methods and full results of the threshold analysis see appendix T.

Economic evidence

Included studies

The systematic search of the economic literature undertaken for this review identified:

- one Australian study on the cost effectiveness of continuous positive airway pressure therapy verus high-flow ventilation in preterm babies (Huang 2018, Roberts 2016);
- one US study on the cost effectiveness of continuous positive airway pressure therapy versus nasal intermittent positive pressure ventilation in preterm babies (Mowitz 2017).

No economic evidence on the cost effectiveness of invasive ventilation techniques was identified by the systematic search of the economic literature undertaken for this review.

The evidence tables and full references for the economic evaluations included in the systematic literature review are provided in appendix H. Completed methodology checklists of all included studies are provided in appendix M. Economic evidence profiles of the studies are presented in appendix I.

Excluded economic studies

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

Summary of studies included in the economic evidence review

Roberts (2016) evaluated the cost effectiveness of nasal continuous positive airway pressure (CPAP) compared with nasal High Flow therapy as primary support for infants born preterm (≥28 weeks gestational age) alongside an RCT (Roberts 2016) conducted in Australia and Norway. However, the economic analysis was conducted on babies that were randomised to Australian sites (n=435) only. Huang (2018) is a more recent economic evaluation that is based on the same RCT and the results below are based on this more recent economic evaluation.

In the analysis, the comparator (that is, High Flow) was stratified according to whether rescue CPAP was allowed. So in effect, CPAP was compared with Hi Flow (with CPAP rescue) and with Hi Flow (without rescue CPAP). CPAP therapy was delivered via either an invasive ventilator or a 'bubble' CPAP system via standard circuits and nasal prongs or masks. To deliver High Flow, either Optiflow Junior or the Precision Flow (Vapotherm) system was used. The majority of the babies were on Optiflow Junior.

The analysis was conducted from a health care payer perspective. The study considered health care costs associated with the inpatient admission prior to discharge and included imaging, pathology, nursing, medical, pharmacy, theater, allied services and neonatal intensive care unit stay. The analysis also included the costs of the treatment-specific consumable equipment, including circuits and the interfaces; and consumable equipment used for invasive ventilation. The resource use estimates were based on the RCT. The source of unit costs data was obtained from local sources (that is, cost data provided by the participating tertiary centres). The measure of outcome for the economic analysis was treatment failure defined as the need of endotracheal intubation and invasive ventilation during inpatient stay. The time horizon of the analysis was until death or first discharge from hospital.

The CPAP group resulted in the lower rate of failure when compared with Hi Flow with rescue CPAP group (0.17 versus 0.19 respectively; difference of 0.02 in favour of CPAP, p=0.57). The mean total costs per baby were $43,453 (95% CI: $38,071; $48,834) for the CPAP group and $40,311 (95% CI: $35,643; $44,978) for the High Flow with rescue CPAP, a difference of $3,142 in favour of Hi Flow (p =0.39) in likely 2015 Australian dollars. Based on the above costs and outcomes CPAP (versus Hi Flow with rescue CPAP) resulted in the ICER of $179,000 per additional case of invasive ventilation avoided. However, it has to be noted that the difference in costs and outcomes was not significant. The probabilistic analysis indicated that at a willingness-to-pay (WTP) of $179,000 per additional case of invasive ventilation avoided the probability that CPAP was cost effective was <50%.

Similarly, the rate failure was lower for the CPAP group when compared with Hi Flow without rescue CPAP (0.17 versus 0.29 respectively; difference of 0.12 in favour of CPAP, p=0.006). The mean total costs per baby were $43,453 for CPAP and $42,620 for Hi Flow (without rescue CPAP), a difference of $833 in favour of Hi Flow (p =0.82). Based on the above costs and outcomes the ICER of CPAP (versus Hi Flow without rescue CPAP) was $7,000 per additional invasive ventilation case avoided. However, it has to be noted that the difference in costs was not significant. The probabilistic analysis indicated that at a WTP of >$23,000 per additional case of invasive ventilation avoided the probability that CPAP was cost effective was >70%.

Deterministic sensitivity analyses indicated that as a primary support CPAP remained more cost effective under alternative scenarios. When compared with Hi Flow with CPAP rescue the cost effectiveness of CPAP remained uncertain under alternative scenarios explored.

Sensitivity analyses indicated that the cost effectiveness of CPAP was not affected by the use of data from non-lead centres (as opposed to lead centres), the use of treatment specific consumable equipment, the use of dataset with imputed cost data, using imputed non-tertiary costs, changes Hi Flow consumable costs, and the use of CPAP ventilator costs (as opposed to bubble CPAP costs).

Overall the results suggest that CPAP was more effective as a sole primary support and is cost-effective intervention when compared with Hi Flow without rescue CPAP. However, the results for CPAP when compared with Hi Flow with rescue CPAP were uncertain and it may be cheaper to use Hi Flow with CPAP as a rescue as opposed to CPAP only.

The analysis was judged by the committee to be partially applicable to the NICE decision-making context since this was non-UK study. Also, the authors did not attempt to estimate quality adjusted life years (QALYs) which made it difficult to interpret the cost-effectiveness results and to compare the findings with other studies. However, overall, this was a well conducted study and was judged by the committee to have only minor methodological limitations.

Mowitz (2017) evaluated the cost effectiveness of non-invasive ventilation techniques (that is, CPAP compared with NIPPV), in babies <30 weeks gestation and 1000g at birth who required non-invasive ventilation. This was an economic evaluation conducted alongside a RCT (Kirpalani 2013) (n=987) conducted in the US. The analysis was conducted from a healthcare payer perspective. The authors also reported the findings from a societal perspective. However, in this review only the costs from the healthcare payer perspective are reported. The study considered a range of direct health care costs including hospital costs (that is, hospital stay, ventilation and cannula), physician costs, medication costs (that is, antibiotics, antifungals, surfactant, indomethacin, ibuprofen, caffeine, furosemide, thiazide, corticosteroids, vitamin A, parenteral nutrition and nitric oxide) and procedures costs (that is, packed red blood cell transfusions, chest x-ray, abdominal x-ray, echocardiogram, surgery for necrotising enterocolitis, PDA ligation and eye laser surgery). From a societal perspective parent out of pocket costs were included too. The resource use estimates were based on the RCT. The source of unit costs was unclear. The measures of outcome for the economic analysis included the percent of infants alive and without BPD. The time horizon of the analysis was up to 44 weeks PMA. Bootstrapping was undertaken to obtain uncertainty around cost and outcome estimates.

CPAP resulted in a greater proportion of babies alive and without BPD compared with NIPPV (0.633 versus 0.616, respectively; difference of 0.017 in favour of CPAP, p = 0.56). The mean total costs per baby were $140,404 (95% CI: $133,906 to $146,902) for CPAP and $143,745 (95% CI: $137,323 to $150,167) for NIPPV, a difference of $3,341 in favour of CPAP (95% CI: −$5,783 to $12,466) in 2013 US dollars. Based on the above costs and outcomes CPAP was dominant when compared with NIPPV (that is, it resulted in lower costs and better outcomes). However, it has to be noted that the difference in outcome was not significant.

Bootstrapping indicated that even at a WTP threshold of $300,000 per surviving baby without BPD the probability of NIPPV being cost effective was low (23.5%) or alternatively the probability of CPAP being cost effective was 76.5%. Deterministic sensitivity analyses found the conclusions robust to changes in cost estimates. Parent costs were comparable between the two arms of the study and the results did not change from the societal perspective.

The analysis was judged by the committee to be partially applicable to the NICE decision-making context. The authors did not attempt to estimate QALYs. However, this was not a problem since CPAP was found to be dominant. Overall, this was a well conducted study and was judged to have only minor methodological limitations.

Economic model

Non-invasive ventilation techniques

In the NMA for the outcome of mortality prior to discharge and BPD at 36 weeks PMA, there was no evidence to suggest a difference between CPAP, NIPPV, BiPAP/SiPAP or Hi Flow. Similarly, pairwise analyses did not identify any meaningful differences between non-invasive ventilation techniques. The committee acknowledged 2 existing non-UK economic evaluations comparing CPAP with NIPPV and Hi Flow, respectively. However these analyses do not include all ventilation techniques of interest. Given the lack of significant differences in clinical benefits between the alternative non-invasive ventilation techniques, the committee noted that there may be potentially important differences in intervention costs. For these reasons, a cost description of each technique was undertaken for the committee to aid considerations of cost effectiveness.

The costings were undertaken and considered the costs associated with equipment acquisition, consumables and maintenance. This was needed because the neonatal activity payments are based on the level of activity (that is, intensive care, high dependency and special care) rather than procedures.

For each non-invasive ventilation technique, the equivalent annual cost of equipment was calculated. In addition, the consumable costs were estimated and included circuits, prongs, bonnets, etc. Also, maintenance costs were estimated for each machine. The above were used to derive the cost of non-invasive ventilation per preterm infant requiring primary non-invasive respiratory support. The non-invasive techniques considered were CPAP (Flow drive), Hi Flow (Vapotherm), Hi Flow (Optiflow), Hi Flow (SLE), NIPPV (SLE), BiPAP (SLE) and SiPAP (Infant Flow).

Hi Flow (Optiflow) and CPAP using a dedicated device resulted in lower intervention costs when compared with any other non-invasive ventilation technique. The cost of Hi Flow (Vapotherm) was very sensitive to the frequency of circuit changes. Assuming that the circuit is changed only every 30 days Hi Flow (Vapotherm) results in similar costs to Hi Flow (Optiflow) and CPAP. However, when assuming the circuit changes every 7 days, as for other techniques, Hi Flow (Vapotherm) results in the highest cost when compared with all other techniques due to high consumable costs. There seems to be little difference between NIPPV and BiPAP (SLE6000) modes although SiPAP (Infant Flow) also has relatively low intervention costs when compared with other modes.

Full methods and results are presented in appendix J

Invasive ventilation techniques

The committee explained that the same ventilator can switch between different ventilation modes. As a result, there are no differences in intervention costs between various invasive ventilation techniques and following the review of clinical evidence the committee concluded that economic analysis was not required.

Clinical evidence statements

Non-invasive ventilation

Comparison 1. Hi flow versus CPAP

Critical outcomes

Mortality prior to discharge

- NMA outcome, see Clinical evidence profile for network meta-analysis (NMA) outcomes.

BPD at 36 weeks PMA

- NMA outcome, see clinical evidence profile for NMA outcomes.

Neurodevelopmental outcomes at ≥18 months

- There was no evidence for this critical outcome.

Important outcomes

Number of days on invasive ventilation

- There was no evidence for this important outcome.

Failed non-invasive ventilation

All infants

- Very low quality evidence from 3 RCTs (n=774) showed no clinically significant difference in failed non-invasive ventilation (defined as requiring intubation) among preterm babies who received Hi Flow compared to CPAP

28-32 weeks gestational age

- Very low quality evidence from 1 RCT (n=289) showed no clinically significant difference in failed non-invasive ventilation (defined as requiring intubation) among preterm babies with a gestational age 28-32 weeks who received Hi Flow compared to CPAP

≥32 weeks gestational age

- Very low quality evidence from 1 RCT (n=275) showed no clinically significant difference in failed non-invasive ventilation (defined as requiring intubation) among preterm babies with a gestational age 28-32 weeks who received Hi Flow compared to CPAP

Pneumothorax

- Very low quality evidence from 3 RCTs (n=277) showed no clinically significant difference in those who developed pneumothorax among preterm babies with a gestational age of 30^{+0} – 34^{+6} weeks who received Hi Flow compared to CPAP.

Parental satisfaction

Parent satisfaction, Visual Analgoue Scale 1-10

Baby satisfied

- Low quality evidence from 1 RCT (n=20) showed a clinically significant increase in parent satisfaction regarding their perception of their baby's satisfaction among parents of preterm babies with a gestational age of < 34 weeks who received Hi Flow compared to CPAP.

Contact and interaction

- Low quality evidence from 1 RCT (n=20) showed a clinically significant increase in parent satisfaction regarding contact and interaction with their baby among parents of preterm babies with a gestational age of < 34 weeks who received Hi Flow compared to CPAP.

Possibility to take part in care

- Very low quality evidence from 1 RCT (n=20) showed a clinically significant increase in parent satisfaction regarding the possibility to take part in care among parents of preterm babies with a gestational age of < 34 weeks who received Hi Flow compared to CPAP.

Comparison 2. CPAP versus BiPAP/SiPAP

Critical outcomes

Mortality prior to discharge

- NMA outcome, see clinical evidence profile for NMA outcomes.

BPD at 36 weeks PMA

- NMA outcome, see clinical evidence profile for NMA outcomes.

Neurodevelopmental outcomes at ≥ 18 months

- There was no evidence for this critical outcome.

Important outcomes

Number of days on invasive ventilation

- There was no evidence for this important outcome.

Failed non-invasive ventilation

- Very low quality evidence from 2 RCTs (n=160) showed no clinically significant difference in failed non-invasive ventilation (defined as requiring intubation) among preterm babies with a gestational age of 28^{+0} – 31^{+6} weeks who received CPAP compared to BiPAP.

Pneumothorax

- Very low quality evidence from 2 RCTs (n=160) showed no clinically significant difference in those who developed pneumothorax among preterm babies with a gestational age of 28^{+0} – 34^{+0} weeks who received CPAP compared to BiPAP.

Parental satisfaction

- There was no evidence for this important outcome.

Comparison 3. BiPAP/SiPAP versus Hi Flow

Critical outcomes

Mortality prior to discharge

- NMA outcome, see Clinical evidence profile for NMA outcomes.

BPD at 36 weeks PMA

- NMA outcome, see Clinical evidence profile for NMA outcomes.

Neurodevelopmental outcomes at ≥ 18 months

- There was no evidence for this critical outcome.

Important outcomes

Number of days on invasive ventilation

- Low quality evidence from 1 RCT (n=316) showed no clinically significant difference in the median days on invasive ventilation among preterm babies with a gestational age of 29-37 weeks who received BiPAP compared to Hi Flow.

Failed non-invasive ventilation

All infants

- Very low quality evidence from 1 RCT (n=316) showed no clinically significant difference in failed non-invasive ventilation (defined as requiring intubation) among preterm babies with a gestational age of 29^{+0} – 36^{+6} weeks who received BiPAP compared to Hi Flow.

29^{+0} to 32^{+6} weeks gestational age

- Very low quality evidence from 1 RCT (n=144) showed no clinically significant difference in failed non-invasive ventilation (defined as requiring intubation) among preterm babies with a gestational age of 29^{+0} – 32^{+6} weeks who received BiPAP compared to Hi Flow.

33^{+0} to 36^{+6} weeks gestational age

- Very low quality evidence from 1 RCT (n=172) showed no clinically significant difference in failed non-invasive ventilation (defined as requiring intubation) among preterm babies with a gestational age of 33^{+0} – 36^{+6} weeks who received BiPAP compared to Hi Flow.

Pneumothorax

- There was no evidence for this important outcome.

Parental satisfaction

- There was no evidence for this important outcome.

Comparison 4. NIPPV versus BiPAP/SiPAP

Critical outcomes

Mortality prior to discharge

- NMA outcome, see clinical evidence profile for NMA outcomes.

BPD at 36 weeks PMA

- NMA outcome, see clinical evidence profile for NMA outcomes.

Neurodevelopmental outcomes at ≥ 18 months

- There was no evidence for this critical outcome.

Important outcomes

Number of days on invasive ventilation

- There was no evidence for this important outcome.

Failed non-invasive ventilation

- Low quality evidence from 1 RCT (n= 124) showed no clinically significant difference in failed non-invasive ventilation (defined as requiring intubation) among preterm babies with a gestational age of < 32 weeks who received NIPPV compared to BiPAP.

Pneumothorax

- Low quality evidence from 1 RCT (n= 124) showed no clinically significant difference in those who developed pneumothorax among preterm babies with a gestational age of < 32 weeks who received NIPPV compared to BiPAP.

Parental satisfaction

- There was no evidence for this important outcome.

Comparison 5. NIPPV versus CPAP

Critical outcomes

Mortality prior to discharge

- NMA outcome, see clinical evidence profile for NMA outcomes.

BPD at 36 weeks PMA

- NMA outcome, see clinical evidence profile for NMA outcomes.

Neurodevelopmental outcomes at ≥18 months

- There was no evidence for this critical outcome.

Important outcomes

Number of days on invasive ventilation

All infants

- Moderate quality evidence from 1 RCT (n=110) showed a clinically significant decrease in the number of days on invasive ventilation via endotracheal tube among preterm babies with a gestational age of 26^{+0} – 29^{+6} weeks who received NIPPV compared to CPAP.

- Moderate quality evidence from 1 RCT (n=200) showed no clinically significant difference in the median days on invasive ventilation among preterm babies with a gestational age of 26-32 weeks who received NIPPV compared to CPAP.

< 30 weeks gestational age

- Moderate quality evidence from 1 RCT (n=200) showed no clinically significant difference in the median days on invasive ventilation among preterm babies with a gestational age of < 30 weeks who received NIPPV compared to CPAP.

Failed non-invasive ventilation

All infants

- Low quality evidence from 4 RCTs (n=1,379) showed no clinically significant difference in failed non-invasive ventilation (defined as requiring intubation) among preterm babies who received NIPPV compared to CPAP

< 30 weeks gestational age

- Moderate quality evidence from 1 RCT (n=115) showed no clinically significant difference in failed non-invasive ventilation (defined as requiring intubation) among preterm babies with a gestational age of < 30 weeks who received NIPPV compared to CPAP.

Pneumothorax

- Low quality evidence from 3 RCTs (n=282) showed no difference in those who experienced pneumothorax among preterm babies with a gestational age of 24-37 weeks who received NIPPV compared to CPAP.

Parental satisfaction

- There was no evidence for this important outcome.

Comparison 6. NIPPV versus Hi Flow

Critical outcomes

Mortality prior to discharge

- NMA outcome, see clinical evidence profile for NMA outcomes.

BPD at 36 weeks PMA

- NMA outcome, see clinical evidence profile for NMA outcomes.

Neurodevelopmental outcomes at ≥ 18 months

- There was no evidence for this critical outcome.

Important outcomes

Days on invasive ventilation

- Moderate quality evidence from 1 RCT (n=76) showed no clinically significant difference in the median days on invasive ventilation among preterm babies with a gestational age of < 35 weeks who received NIPPV compared to Hi Flow.

Failed non-invasive ventilation

- Low quality evidence from 1 RCT (n=76) showed no clinically significant difference in the failed non-invasive ventilation among preterm babies with a gestational age of < 35 weeks who received NIPPV compared to Hi Flow.

Pneumothorax

- Low quality evidence from 1 RCT (n=76) showed no clinically significant difference in the number of babies who experienced pneumothorax among preterm babies with a gestational age of < 35 weeks who received NIPPV compared to Hi Flow.

Parental satisfaction

- There was no evidence for this important outcome.

Invasive ventilation

Comparison 1. Volume targeted ventilation versus synchronised pressure limited ventilation

Critical outcomes

Mortality prior to discharge

- NMA outcome, see clinical evidence profile for NMA outcomes.

BPD at 36 weeks PMA

- NMA outcome, see clinical evidence profile for NMA outcomes.

Neurodevelopmental outcomes at ≥ 18 months: cerebral palsy

- Very low quality evidence from 1 RCT (n=85) showed no clinically significant difference in cerebral palsy among preterm babies with a gestational age of 24-31 weeks who received volume targeted ventilation compared to synchronised pressure limited ventilation.

Important outcomes

Days on invasive ventilation

- Low quality evidence from 4 RCTs (n=232) showed no clinically significant difference in days on invasive ventilation among surviving preterm babies who received volume targeted ventilation compared to synchronised pressure limited ventilation.

Failed non-invasive ventilation

- Outcome not applicable for invasive ventilation techniques

Pneumothorax

- Low quality evidence from 4 RCTs (n=257) showed a clinically significant reduction in pneumothorax among preterm babies who received volume targeted ventilation compared to synchronised pressure limited ventilation.

Parental satisfaction

- No studies reported on this important outcome.

Comparison 2. Volume targeted ventilation versus non-synchronised pressure limited ventilation

Critical outcomes

Mortality prior to discharge

- NMA outcome, see clinical evidence profile for NMA outcomes.

BPD at 36 weeks PMA

- NMA outcome, see clinical evidence profile for NMA outcomes.

Neurodevelopmental outcomes at ≥ 18 months

- No studies reported on this critical outcome.

Important outcomes

Days on invasive ventilation

- Low quality evidence from 1 RCT (n=45) showed no clinically significant difference in days on invasive ventilation among surviving preterm babies who received volume targeted ventilation compared to non-synchronised pressure limited ventilation.

Failed non-invasive ventilation

- Outcome not applicable for invasive ventilation techniques

Pneumothorax

- Very low quality evidence from 1 RCT (n=57) showed no clinically significant difference in pneumothorax among preterm babies who received volume targeted ventilation compared to non-synchronised pressure limited ventilation.

Parental satisfaction

- No studies reported on this important outcome

Comparison 3. Volume targeted ventilation versus synchronised intermittent mandatory ventilation

Critical outcomes

Mortality prior to discharge

- NMA outcome, see clinical evidence profile for NMA outcomes.

BPD at 36 weeks PMA

- NMA outcome, see clinical evidence profile for NMA outcomes.

Neurodevelopmental outcomes at ≥ 18 months

- No studies reported on this critical outcome.

Important outcomes

Days on invasive ventilation

- Low quality evidence from 3 RCTs (n=293) showed no clinically significant difference in days on invasive ventilation among surviving preterm babies who received volume targeted ventilation compared to synchronised intermittent mandatory ventilation.

Failed non-invasive ventilation

- Outcome not applicable for invasive ventilation techniques

Pneumothorax

- Very low quality evidence from 3 RCTs (n=308) showed no clinically significant difference in pneumothorax among preterm babies who received volume targeted ventilation compared to synchronised intermittent mandatory ventilation.

Parental satisfaction

- No studies reported on this important outcome.

Comparison 4. Volume targeted ventilation versus high frequency ventilation

Critical outcomes

Mortality prior to discharge

- NMA outcome, see clinical evidence profile for NMA outcomes.

BPD at 36 weeks PMA

- NMA outcome, see clinical evidence profile for NMA outcomes.

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.

Failed non-invasive ventilation

- Outcome not applicable for invasive ventilation techniques

Pneumothorax

- No studies reported on this important outcome.

Parental satisfaction

- No studies reported on this important outcome.

Comparison 5. Synchronised pressure limited ventilation versus non-synchronised pressure limited ventilation

Critical outcomes

Mortality prior to discharge

- NMA outcome, see clinical evidence profile for NMA outcomes.

BPD at 36 weeks PMA

- NMA outcome, see clinical evidence profile for NMA outcomes.

Neurodevelopmental outcomes at ≥ 18 months

- No studies reported on this critical outcome.

Important outcomes

Days on invasive ventilation

- Low quality evidence from 1 RCT (n=924) showed no clinically significant difference in median days on invasive ventilation among preterm babies with a gestational age of <32 weeks who received synchronised pressure limited ventilation compared to non-synchronised pressure limited ventilation.
- Low quality evidence from 1 RCT (n=386) showed a clinically significant reduction in median days on invasive ventilation among preterm babies who received synchronised pressure limited ventilation compared to non-synchronised pressure limited ventilation, however there is uncertainty around this estimate.
- Very low quality evidence from 1 RCT (n=30) showed no clinically significant difference in days on invasive ventilation among preterm babies who received synchronised pressure limited ventilation compared to non-synchronised pressure limited ventilation.

Failed non-invasive ventilation

- Outcome not applicable for invasive ventilation techniques

Pneumothorax

- Low quality evidence from 3 RCTs (n=1,340) showed no clinically significant difference in pneumothorax among preterm babies who received synchronised pressure limited ventilation compared to non-synchronised pressure limited ventilation.

Parental satisfaction

- No studies reported on this important outcome.

Comparison 6. Synchronised pressure limited ventilation versus synchronised intermittent mandatory ventilation

- No studies reported on this comparison

Comparison 7. Synchronised pressure limited ventilation versus high frequency ventilation

- No studies reported on this comparison

Comparison 8. Synchronised intermittent mandatory ventilation versus non-synchronised pressure limited

Critical outcomes

Mortality prior to discharge

- NMA outcome, see clinical evidence profile for NMA outcomes.

BPD at 36 weeks PMA

- NMA outcome, see clinical evidence profile for NMA outcomes.

Neurodevelopmental outcomes at ≥ 18 months

- No studies reported on this critical outcome.

Important outcomes

Days on invasive ventilation

- Low quality evidence from 1 RCT (n=350) showed a clinically significant reduction in median days on invasive ventilation among preterm babies who received synchronised intermittent mandatory ventilation compared to non-synchronised pressure limited ventilation, however there is uncertainty around this estimate.

Failed non-invasive ventilation

- Outcome not applicable for invasive ventilation techniques

Pneumothorax

- No studies reported on this important outcome.

Parental satisfaction

- No studies reported on this important outcome.

Comparison 9. Synchronised intermittent mandatory ventilation versus high frequency ventilation

Critical outcomes

Mortality prior to discharge

- NMA outcome, see clinical evidence profile for NMA outcomes.

BPD at 36 weeks PMA

- NMA outcome, see clinical evidence profile for NMA outcomes.

Neurodevelopmental outcomes at ≥ 18 months: cerebral palsy

- Moderate quality evidence from 1 RCT (n=192) showed a clinically significant increase in cerebral palsy among preterm babies with a gestational age of 24-29 weeks who received synchronised intermittent mandatory ventilation compared to high frequency ventilation

Important outcomes

Days on invasive ventilation

- Moderate quality evidence from 2 RCTs (n=125) showed a clinically significant increase in days on invasive ventilation among preterm babies with a gestational age of 24-29 weeks who received synchronised intermittent mandatory ventilation compared to high frequency ventilation.

Failed non-invasive ventilation

- Outcome not applicable for invasive ventilation techniques

Pneumothorax

- Very low quality evidence from 3 RCTs (n=811) showed no clinically significant difference in pneumothorax among preterm babies who received synchronised intermittent mandatory ventilation compared to high frequency ventilation.

Parental satisfaction

No studies reported on this important outcome.

Comparison 10. Non-synchronised pressure limited ventilation versus high frequency ventilation

Critical outcomes

Mortality prior to discharge

- NMA outcome, see clinical evidence profile for NMA outcomes.

BPD at 36 weeks PMA

- NMA outcome, see clinical evidence profile for NMA outcomes.

Neurodevelopmental outcomes at ≥ 18 months: moderate cognitive impairment

- Very low quality evidence from 1 RCT (n=224) showed no clinically significant difference in moderate cognitive impairment at 18 months or older of age (defined as moderate learning difficulty at 11-14 years of age [undefined assessment tool]) in preterm babies who received non-synchronised pressure limited ventilation compared to high frequency ventilation.

Neurodevelopmental outcomes at ≥ 18 months: severe cognitive impairment

- Very low quality evidence from 1 RCT (n=224) showed no clinically significant difference in severe cognitive impairment at 18 months or older of age (defined as severe learning difficulty at 11-14 years of age [undefined assessment tool]) in preterm babies who received non-synchronised pressure limited ventilation compared to high frequency ventilation.
- Very low quality evidence from 1 RCT (n=288) showed no clinically significant difference in severe cognitive impairment at 18 months or older of age (defined as a parent composite score of <49 at 2 years of age [undefined assessment tool]) in preterm babies who received non-synchronised pressure limited ventilation compared to high frequency ventilation.

Neurodevelopmental outcomes at ≥ 18 months: neurosensory impairment

- Very low quality evidence from 1 RCT (n=359) showed no clinically significant difference in neurosensory impairment at 18 months or older of age (defined as profound hearing loss despite aids and parental report of visual problems at 2 years of age) in preterm babies who received non-synchronised pressure limited ventilation compared to high frequency ventilation.

Important outcomes

Days on invasive ventilation

- Low quality evidence from 1 RCT (n=125) showed a clinically significant increase in median days on invasive ventilation among preterm babies with a gestational age of <35 weeks who received non-synchronised pressure limited ventilation compared to high frequency ventilation, however there is uncertainty around this estimate.
- Low quality evidence from 1 RCT (n=797) showed no clinically significant difference in median hours on invasive ventilation among preterm babies who received non-synchronised pressure limited ventilation compared to high frequency ventilation.

Failed non-invasive ventilation

- Outcome not applicable for invasive ventilation techniques

Pneumothorax

- Low quality evidence from 1 RCTs (n=40) showed no clinically significant difference in pneumothorax among preterm babies with a gestational age of <32 weeks who received non-synchronised pressure limited ventilation compared to high frequency ventilation.

Parental satisfaction

No studies reported on this important outcome

See appendix E for Forest plots.

Economic evidence statements

Non-invasive ventilation

- There was evidence from one Australian study conducted alongside a randomised controlled trial (n=435) showing that CPAP when compared with High Flow without CPAP rescue was potentially cost-effective treatment in preterm babies requiring respiratory support. At a willingness-to-pay of >$23,000 per additional case of invasive ventilation avoided the probability that CPAP was cost effective was >70%. The cost effectiveness of CPAP was uncertain when compared with Hi Flow with rescue CPAP. At a willingness-to-pay of $179,000 per additional case of invasive ventilation avoided the probability that CPAP was cost effective was <50%.This evidence came from a partially applicable study that was characterised by minor methodological limitations.
- There was evidence from one US study conducted alongside a randomised controlled trial (n=987) showing that CPAP when compared with NIPPV was dominant in preterm babies requiring respiratory support. The probability of CPAP being cost effective at any willingness-to-pay value below $300,000 per surviving baby without BPD was >76%.This evidence came from a partially applicable study that was characterised by minor methodological limitations.
- Costings undertaken for this guideline found that Hi Flow and CPAP using dedicated devices resulted in lower intervention costs when compared with all other non-invasive ventilation techniques. There was little difference between NIPPV and BiPAP modes. Although, SiPAP had also relatively low intervention costs when compared with other modes.

Invasive ventilation

- No economic evidence on invasive ventilation techniques in preterm babies requiring respiratory support was available.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee agreed that the use of invasive and non-invasive ventilation in preterm babies on respiratory support aims to reduce the incidence of BPD and mortality, thus BPD and mortality prior to discharge were both considered critical outcomes for decision making. However, the committee also agreed that neurodevelopmental outcomes were important as these could have a life-long impact on the baby and their parents or carers and there was concern regarding the paucity of evidence on neurodevelopmental outcomes for this evidence review.

For non-invasive ventilation, the committee agreed that the use of non-invasive ventilation as primary respiratory support in preterm babies aims to avoid the need for invasive ventilation, therefore failure of non-invasive ventilation and subsequently, days on invasive ventilation were both considered important outcomes for decision making. Parental satisfaction was also considered an important outcome for decision making, because some methods of non-invasive ventilation make it more difficult for parents to see their baby's face or remove them from their cot.

For invasive ventilation, total days on invasive ventilation (which may itself increase the risk of BPD) was considered an important outcome. Pneumothorax, a possible adverse event associated with invasive ventilation, was also considered as an important outcome in decision-making and in considering the balance of benefit and harm.

The quality of the evidence

Included studies were assessed using the Cochrane Collaboration's tool for assessing risk of bias. The evidence in the pairwise comparisons was also assessed using GRADE methodology.

The quality of evidence in these reviews ranged from very low to high with most evidence being of low quality. Although inevitable, the quality of evidence was most often downgraded because of the lack of blinding. For non-invasive ventilation this was pertinent to subjective outcomes such as failed non-invasive ventilation (where there may have been poorly defined criteria for intubation) and neurodevelopmental outcomes. Therefore, the committee did not make strong recommendations for non-invasive ventilation. For invasive ventilation, bias was applied to all outcomes as the ability to violate the protocol and switch from one mode of invasive ventilation to another with the same equipment would have been possible. However, due to the strength of the evidence, as demonstrated by the network meta analyses (NMAs), the committee still made strong recommendations for invasive ventilation.

For both the non-invasive and invasive ventilation comparisons, the RCTs allowed pre-defined cross-over from one technique to another in cases of treatment failure. The committee agreed that this could introduce bias because the ventilation technique that the preterm baby was initially randomised to, may not be the ventilation technique that was received. This was managed by assessing heterogeneity for studies that allowed cross-over. Studies that had high levels of heterogeneity were discussed with the committee to determine whether they should be excluded due to the potential bias.

The committee agreed that because of the timeframe associated with the assessment of neurodevelopmental outcomes, there was inevitable attrition which led to the quality of evidence being downgraded.

The committee discussed the heterogenous population of preterm babies included in the studies, with gestational ages crossing pre-specifed stratifications set in the protocol. In

addition, the age at which ventilation was started also crossed pre-specified stratifications or was not stipulated in the inclusion critera. The committee agreed that although it would be very useful to draft recommendations by gestational age and age at start of ventilation, the available data from the included studies prevented these stratifications from being analysed.

In the non-invasive and invasive ventilation comparisons, there was a high level of imprecision for pneumothorax and neurodevelopmental outcomes, which was attributed to the low event rate in the study populations.

No evidence was found on neurodevelopmental outcomes for the invasive ventilation comparison of VTV versus HFV. The committee prioritised research recommendations on the neurodevelopmental follow-up of VTV versus HFV because of the criticality of this outcome and that there was no clinically significant differences between these two invasive ventilation methods for other critical outcomes.

In terms of the NMA, for both non-invasive and invasive ventilation, considerable heterogeneity and uncertainty indicated by wide credible intervals and high model standard deviation was observed in the studies investigating BPD at 36 weeks PMA. There was also the lack of good fit for the models of mortality prior to discharge and BPD of invasive techniques. The committee acknowledged the lack of good fit for the models and heterogenity in the NMAs and attributed it to the varying populations across studies including gestational age and age at start of ventilation across studies.

For non-invasive ventilation the inconsistency checks did not identify any evidence of inconsistency between direct and indirect evidence included in the NMA for BPD at 36 weeks PMA. However, the inconsistency checks found some evidence of potential inconsistency between direct and indirect evidence included in the NMA for mortality prior to discharge but it did not reach statistical significance. However, overall there was not much difference between non-invasive ventilation techniques on any of the outcomes including the ones explored in the pairwise meta-analyses and as a result the committee did not explore this finding any further.

For invasive ventilation the inconsistency checks did not identify any evidence of inconsistency between direct and indirect evidence included in the NMA for mortality prior to discharge or BPD at 36 weeks PMA, thus strengthening the findings for the invasive ventilation modes.

For the invasive ventilation NMA, the threshold analysis that was undertaken to test the robustness of the results of the NMA to bias indicated that for the BPD at 36 weeks PMA outcome the conclusions were robust for the best and worst ranked treatment, thus strengthening the findings. However, for mortality prior to discharge, there was a potential for SIMV to be better than VTV. The study level analysis indicated that the most influential study comparing these treatments was D'Angio 2005 and this was characterised as being at high risk of bias due to babies being on ventilation for a long time. The committee acknowledged that statistically there was uncertainty as to whether VTV or SIMV was better for mortality prior to discharge. However, the committee rationalised this finding by acknowledging that mortality prior to discharge is well controlled and low in the population of interest and that the finding for BPD at 36 weeks PMA was more important and was reassuring that recommendations from the base-case analysis were robust to this outcome.

Benefits and harms

For recommendations on the primary respiratory support of preterm babies, the modes of ventilation were divided into 2 groups:

- Non-invasive ventilation (BiPAP, CPAP, Hi Flow, NIPPV and SiPAP)
- Invasive ventilation (HFV, NSPLV, SIMV, SPLV and VTV)

The committee discussed that the division of primary respiratory support into these 2 groups, was aligned to the severity of the preterm baby's condition and the combination of all ventilation techniques would result in a heterogenous population. The committee highlighted that a

preterm baby initiated on invasive ventilation as primary respiratory support was in need of more intensive respiratory support, in contrast to preterm babies initiated on a less intensive non-invasive respiratory support, thus combining these two populations would be inappropriate to draft recommendations. The rationale behind this division was reinforced by the paucity of evidence comparing non-invasive to invasive ventilation techniques in the literature.

Non-invasive ventilation

The committee noted that the evidence made it difficult to distinguish between the different modes of non-invasive ventilation, with the NMA indicating that Hi Flow had the highest probability of being the best treatment for reducing mortality prior to discharge (although there was some evidence of potential inconsistency) and BiPAP/SiPAP and NIPPV had the highest probabilities of reducing BPD at 36 weeks PMA, as primary respiratory support, compared with other non-invasive ventilation techniques.

The committee noted that a benefit of Hi Flow is its ease of use. Hi Flow also negates the need to use invasive instruments to maintain the CPAP apparatus in the baby's nose, which can limit the baby's movements and increase nasal trauma. CPAP may also inhibit parental involvement in their baby's care as it makes it more difficult to remove the baby from the cot, and their face is covered. However, although CPAP was associated with lower levels of parental satisfaction in regard to parents' perceived satisfaction of the baby, contact and interaction and the possibility to take part in care, the committee also recognised that CPAP is a well researched and established technique that has been used in practice for over 30 years.

The committee noted that compared to CPAP, NIPPV had statistically lower rates of failed non-invasive ventilation requiring intubation and a fewer number of days on invasive ventilation. However, the committee highlighted that the delivery of NIPPV in the studies were significantly different to routine clinical practice in the UK, with ventilator pressures being used to deliver NIPPV. In view of this and significant heterogeneity in the meta-analysis, the committee agreed that further research was required comparing NIPPV and CPAP using delivery methods in line with clinical practice in the UK before recommending NIPPV.

The committee discussed that the trials assessing CPAP used different modes of delivery, mainly being ventilator and flow driver driven. The committee highlighted that the ventilator driven CPAP maybe less efficient in clinical practice than flow driver CPAP as it can cause dips in peak pressure of the inspiratory drive. However, it was noted that generally they do not expect there to be important differences between the two and they are not aware of any studies comparing the two techniques. It was further explained that generally the preference is for CPAP using flow-drivers since this type is cheaper and flow-drivers can be utilised on other patients too.

The committee also discussed the classification of NIPPV in the studies, with concern around the inconsistent and sometimes inaccurate distinction between NIPPV and BiPAP. For example, some studies defined techniques as NIPPV but babies actually had BiPAP. The opposite could also be true. The committee discussed that having homogenous NIPPV group could potentially result in more favourable findings. It was also noted that there is direct evidence suggesting that there is no difference between the two techniques i.e. NIPPV and BiPAP. This is also supported by the NMA findings which found that NIPPV and BiPAP/SiPAP had very similar probabilities of being best and simillar rankings for mortality prior to discharge and BPD at 36 weeks PMA outcomes.

Invasive ventilation

The committee decided that VTV should be used as a primary mode of ventilation in preterm babies requiring invasive ventilation. The evidence in this population showed that VTV had the

highest probability of being the best treatment for reducing mortality prior to discharge and BPD at 36 weeks PMA as primary respiratory support, compared with other invasive ventilation techniques. Furthermore, the evidence showed that there was a reduction in the incidence of pneumothorax and days on invasive ventilation with VTV, compared to SPLV and SPLV, NSPLV and SIMV, respectively. The committee highlighted that VTV is widely used in clinical practice, can be used in combination with other modes of synchronised ventilation, and that there is clinical plausibility behind better respiratory outcomes given that volutrauma and atelectrauma induced by excessive volume and inadequate volume, respectively, of other invasive ventilation techniques can lead to chronic lung disease.

The committee discussed that although VTV had the highest probability of being the best treatment for reducing mortality prior to discharge and BPD at 36 weeks PMA that there was no evidence to suggest a difference between VTV and HFV for any of the outcomes reported. In addition to VTV having the highest probability of being the best treatment, the committee further supported the use of VTV as first line-treatment by highlighting that not all neonatal units are trained to use HFV appropriately, which could lead to hypocapnia. In view of this, neonatal units should be trained in safe practice techniques of HFV before HFV is used. Even though VTV is the invasive ventilation mode of choice for primary respiratory support, the committee highlighted that it may not be appropriate for all preterm babies, for example where there is an airleak. In this situation, HFV should be considered as an alternative method of invasive ventilation in appropriately trained units.

The committee agreed that SPLV should be avoided as the evidence showed an increase in the incidence of mortality prior to discharge, compared with NSPLV, HFV and VTV. The evidence also showed an increase in days on invasive ventilation and pneumothorax, compared to VTV. The committee highlighted that this in line with their general clinical experience i.e. that preterm babies do not perform as well with SPLV as other invasive ventilation techniques for primary respiratory support. Additionally, the committee explained that, in their experience, the synchronisation of every single breath in SPLV can result less favourable outcomes for the preterm baby in comparison to other invasive ventilation techniques as a primary mode of respiratory support.

The evidence showed an increase in the incidence of BPD at 36 weeks PMA with SIMV compared to VTV and HFV, however, the committee agreed that as there was no evidence to suggest a difference between SIMV compared with NSPLV and SPLV for the outcomes assessed that it should remain a treatment option in preterm babies where VTV and HFV are not clinically suitable, and so the committee made a recommendation to this effect. Furthermore, the committee highlighted that SIMV was a useful weaning strategy in clinical practice, even though it was acknowledged that secondary respiratory support was outside the scope of this review question.

The committee discussed the clinically significant increase in the neurodevelopmental outcome of cerebral palsy with SIMV compared to HFV. Credibility surrounding this result was criticised as more infants were switched from SIMV to HFV secondary to treatment failure, therefore this may be a particular severe subset of babies possibly increasing the risk of cerebral palsy.

The committee discussed the categorisation of the different invasive ventilation techniques in the studies, this was of particular importance to NSPLV, SIMV and SPLV, where techniques were often labelled as NSPLV in the title of studies, however the methods described synchronisation of breaths. The committee agreed to categorise the different invasive ventilation techniques according to the methods described as it was the most accurate depiction of the ventilation technique. Furthermore, the committee highlighted that some papers failed to describe in their methods that the pressure limited ventilation strategy was synchronised, however the Cochrane systematic reviews (Cools 2015; Greenough 2016; Klingenberg 2017) labelled the techniques as SPLV. In this situation, the committee agreed to label the invasive ventilation techinques in line with the methods in the original papers and

acknowledged that for some techniques labelled NSPLV that in fact synchronisation may have been used.

In the pre-defined protocol, the committee decided to use the GRADE default minimally important differences (MIDs) for days on invasive ventilation. When presented with the evidence the committee realised that because of the large standard deviations in the control arm, a number of the comparisons assessing days on ventilation that were statistically significant were not clinically significant and this did not seem sensible clinically. In view of this, the committee decided that an additional 2 days on invasive ventilation was a clinically significant result as longer periods could result in an increased risk of infection, lung damage and extubation failure.

Cost effectiveness and resource use

Non-invasive ventilation

Existing economic evidence on non-invasive ventilation was limited to two non-UK studies. A US study found CPAP dominant when compared with NIPPV using survivors without BPD as an outcome measure. Similarly, one Australian study found CPAP potentially cost effective when compared with Hi Flow without rescue CPAP. However, the cost effectiveness of CPAP was uncertain when compared with Hi Flow with rescue CPAP.

The costings undertaken for this guideline found CPAP using a dedicated device and Hi Flow to be the least costly non-invasive ventilation modes. There was little difference between NIPPV and BiPAP modes with the costs dependent on the equipment used. Also, SiPAP had relatively low intervention costs when compared with other non-invasive ventilation modes. The committee explained that the costings reinforced the standard clinical practice which is to use CPAP or Hi Flow using dedicated devices. The committee noted the potential cost difference between Hi Flow (Vapotherm) and Hi Flow (Optiflow). However, the costs of equipment and consumables are insignificant compared to standard preterm care costs. Nevertheless, the committee recognised that most of the costs associated with ventilation are due to consumables. The committee also were of a view that even though Hi Flow (Optiflow) is potentially cheaper, nurses may prefer Vapotherm system and perceive it to be more effective. The clinical practice varies significantly across centres with some some units using only Hi Flow (Vapotherm) and others use the Vapotherm system only if they run out of Optiflow machines. The committee explained that given a difference in intervention costs between the two systems there is a need for further research comparing Optiflow and Vapotherm systems in preterm babies requiring primary non-invasive ventilation.

The committee explained that there were other types of CPAP including bubble CPAP and ventilator-based CPAP. However, the latter is not used much in the NHS and generally the preference is for CPAP using flow-drivers since it is cheaper when compared with ventilator-based CPAP. Also, flow-drivers can be utilised on other patients. This view was supported by the costings that found CPAP using flow-drivers to be the least costly option.

The committee discussed potential savings associated with the new hybrid systems. For example, in babies on hybrid system who are being switched from standard invasive ventilation a user can discard the expiratory limb, retaining the inspiratory limb plus the humidifying chamber and convert to non-invasive circuit simply by adding in a generator. It allows converting to non-invasive ventilation without the need and cost of use of two completely separate circuits. This could also eliminate or reduce the need for multiple platforms. Nevertheless, the committee noted that even though such new devices can provide various respiratory support methods using one system, the preference is to use dedicated machines for CPAP and Hi Flow as units generally want to save their ventilators for invasive ventilation. The committee noted that in practice this argument is more relevant for weaning (that is, not in babies requiring primary non-invasive ventilation) and that for most units the capital outlay on the hybrid machine is too high. The committee were of a view

that it doesn't make much financial sense to place a baby on expensive devices for CPAP or Hi Flow that could be better utilised for providing invasive support.

Invasive ventilation

There was no economic evidence assessing the cost effectiveness of invasive ventilation techniques in preterm babies requiring invasive ventilation.

The committee explained that the same ventilator can switch between different ventilation modes and as a result there are no differences in intervention costs between different invasive ventilation techniques.

The committee noted that the intervention costs might vary only if the ventilator had to be changed for different modes of ventilation. However, the circuits commonly in use can be used on different makes of ventilator so cost is not different with different manufacturers of ventilators. The only ventilation model which may be potentially costlier is high-frequency ventilation if units are still using a Senor Medics machine. The circuit for this is likely to be expensive. However, the committee noted that this is an exception and they would expect ventilators that can switch between different modes to be used in most centres.

The committee also acknowledged that flow sensors required for VTV are expensive but are required for VTV. Although, it was explained that most centres caring for such preterm babies would have access to the required equipment to facilitate VTV and the impact of this would be negligible, if any, on the practice and the NHS costs (i.e. most units have flow sensors already for triggered ventilation and the same sensor could be used for VTV).

According to the committee, in terms of clinical staff, all ventilation techniques would take approximately the same time. It was noted that the infant on high-frequency ventilation may take more clinical time but this is due to the infants being sicker on the whole, not the ventilator technique as such. Small preterm babies requiring respiratory invasive support would be in intensive care requiring a nursing ratio of at least 1 nurse to 1 baby. The committee noted that small preterm babies stepping off invasive invasive ventilation will not go straight to high dependency care and as such there are no immediate costs savings associated with the reduction in the nursing costs. The committee also noted that the costs associated with invasive ventilation (that is, equipment and consumable costs) are likely to be insignificant when compared with nursing and other standard preterm care costs.

Also, it was hypothesised that there may be differences in the duration of invasive ventilation between different ventilation modes. However, based on the clinical review findings the committee concluded that it is unlikely that there are important and meaningful differences between different invasive modes in terms of days on invasive ventilation.

Given no difference in intervention costs the committee made recommendations based on the clinical benefits.

Other factors the committee took into account

Non-invasive ventilation

The committee discussed that studies on HFOV are a mix of old and new studies. In older studies, HFOV was delivered using SensorMedics circuit which is generally not used anymore in clinical practice. The committee acknowledged the HUNTER trial (Manley et al. 2017), which is a multi-centre RCT comparing nasal High Flow with nasal CPAP as primary support for newborn babies with early RDS. Though the trial was completed at the time of guideline development and preliminary results presented at a conference showed that nasal High Flow was less effective than nasal CPAP, the results have not been published as of yet and thus could not be included in this review.

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Review question 3.7 What is the effectiveness of nitric oxide in preterm babies requiring invasive ventilation?

Introduction

Inhaled nitric oxide is a potent, selective pulmonary vasodilator. It has a clearly defined role in the management of pulmonary hypertension in term babies, where it has been shown to improve oxygenation and reduce the need for extracorporeal membrane oxygenation. However, its role in preterm babies requiring invasive respiratory support is less well defined.

Recently, a number of studies have been published looking at the effect of inhaled nitric oxide on the incidence of bronchopulmonary dysplasia (BPD) in preterm babies and its potential role in hypoxic respiratory failure. This review aims to determine the effectiveness of inhaled nitric oxide in preterm babies requiring invasive ventilation, both in hypoxic respiratory failure and in the prevention of bronchopulmonary dysplasia

Summary of the protocol

See Table 18 for a summary of the population, intervention, comparison and outcome (PICO) characteristics of this review.

Table 18: 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	Inhaled nitric oxide
Comparison	**Control:** • Placebo **Comparisons:** • Nitric oxide versus control • Low dose versus high dose nitric oxide • Early administration versus late administration nitric oxide

Outcome	**Critical outcomes:**
	• Mortality prior to discharge
	• Bronchopulmonary dysplasia (oxygen dependency at 36 weeks postmenstrual age [PMA] 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 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:** • Days on ventilation • Severe intraventricular haemorrhage (grade 3 or 4) • Pulmonary haemorrhage • Methaemoglobinaemia

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

One Cochrane systematic review (Barrington 2017) that included 14 trials (Ballard 2006; Dani 2006; EUNO 2009; Hascoet 2005; INNOVO 2005; Kinsella 1999; Kinsella 2006; Kinsella 2014; Mercier 1999; Schreiber 2003; Srisuparp 2003; Subhedar 1997; Van Meurs 2005; Van Meurs 2007), 2 additional trials (Hamon 2005; Hasan 2017) and 5 follow-up studies (Bennett 2001 [Subhedar 1997a]; Durrmeyer 2013 [EUNO 2009]; Hintz 2007 [Van Meurs 2005]; Mestan 2004 [Schreiber 2003]; Walsh 2010 [Ballard 2006]) examined the use of nitric oxide in preterm babies requiring invasive ventilation were included in this review.

All of the included studies compared inhaled nitric oxide to placebo.

No studies were identified that compared low dose to high dose nitric oxide or early to late administration of nitric oxide.

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 19 provides a brief summary of the included studies.

Table 19: Summary of included studies

Study and setting	Population	Intervention/ comparison	Outcomes	Comments
Cochrane systematic review				
Barrington 2017	Preterm babies < 35 weeks GA with respiratory failure after adequate treatment with surfactant	Inhaled nitric oxide versus placebo	• Mortality before discharge • Bronchopulmonary dysplasia at 36 weeks PMA • Severe IVH • Neurodevelopmental outcomes	

Study and setting	Population	Intervention/ comparison	Outcomes	Comments
RCTs included in the Cochrane Systematic Review				
Ballard 2006 US	n= 582 Preterm babies < 1250g on assisted ventilation at 7-21 days or, if < 800g, on CPAP	Inhaled nitric oxide versus placebo	• Mortality prior to discharge • Bronchopulmonary dysplasia at 36 weeks PMA • Severe IVH	
Bennett 2001	See Subhedar 1997a for study details		• Neurodevelopmental outcomes	
Dani 2006 Italy	n= 40 Preterm infants ventilated with severe RDS with FiO2 > 0.5 and arterial-alveolar oxygen ratio < 0.15, despite surfactant treatment	Inhaled nitric oxide versus placebo	• Mortality prior to discharge	
Durrmeyer 2009	See Mercier 2010 for study details		• Neurodevelopmental outcomes	
EUNO (2009) 9 countries in the European Union	n=207 Babies between 24 weeks' and 28 weeks' gestation and 6 days enrolled at less than 24 hours of age. If intubated, they had to have received surfactant and could be enrolled if on CPAP requiring > 30% oxygen	Inhaled nitric oxide versus placebo	• Mortality prior to discharge • Bronchopulmonary dysplasia at 36 weeks PMA • Severe IVH • Pulmonary haemorrhage	
Hascoet 2005 France	n=145 RDS requiring CPAP, within the first 6 hours after birth, 27-24 weeks GA	Inhaled nitric oxide versus placebo	• Mortality prior to discharge • Bronchopulmonary dysplasia at 36 weeks postmenstrual age • Severe IVH	
Hintz 2007	See Van Meurs 2005 for study details		• Neurodevelopmental outcomes	
INNOVO 2005 UK	n= 108 Preterm babies < 34 weeks gestational age less than 28 days of age, with	Inhaled nitric oxide versus placebo	• Mortality prior to discharge • Bronchopulmonary dysplasia at 36 weeks PMA • Days on ventilation	

Study and setting	Population	Intervention/ comparison	Outcomes	Comments
	"severe respiratory failure"		• Pulmonary haemorrhage	
Kinsella 1999 US	n= 80 Preterm babies ≤ 34 weeks, < 7 days of age, with a/AO_2 < 0.1 on 2 blood gases after surfactant treatment	Inhaled nitric oxide versus placebo	• Mortality prior to discharge • Bronchopulmonary dysplasia at 36 weeks PMA • Days on ventilation • Severe IVH	
Kinsella 2006 US	n=793 Preterm babies < 34 weeks, respiratory failure needing assisted ventilation in first 48 hours	Inhaled nitric oxide versus placebo	• Mortality prior to discharge • Bronchopulmonary dysplasia at 36 weeks PMA • Severe IVH • Pulmonary haemorrhage	
Kinsella 2014 US	n=124 Preterm babies with birth weight of 500g to 1250g, receiving oxygen by non-invasive means at < 72 hours of age	Inhaled nitric oxide versus placebo	• Mortality prior to discharge • Bronchopulmonary dysplasia at 36 weeks PMA • Days on ventilation • Severe IVH	
Mercier 1999 France, Belgium	n=85 Preterm babies (< 33 weeks) with OI of 12.5 to 30 at < 7 days	Inhaled nitric oxide versus placebo	• Mortality prior to discharge • Bronchopulmonary dysplasia at 36 weeks PMA • Severe IVH	
Mestan 2005	See Schreiber 2003 for study details		• Neurodevelopmental outcomes	
Schreiber 2003 US	n=207 Babies < 34 weeks, < 72 hours of age, intubated and ventilated for RDS, birth weight < 2000g	Inhaled nitric oxide versus placebo	• Mortality prior to discharge • Bronchopulmonary dysplasia at 36 weeks PMA • Pulmonary haemorrhage	
Srisuparp 2002 US	n=34 Preterm infants < 2000g ventilated after surfactant with an arterial catheter at < 72 hours of age. Also required to satisfy a severity of illness criterion.	Inhaled nitric oxide versus placebo	• Mortality prior to discharge • Pulmonary haemorrhage	

Study and setting	Population	Intervention/ comparison	Outcomes	Comments
	OI > 4 for birth weight < 1000g, > 6 for birth weight 1001-1250g, > 8 for 1251-1500g, > 10 for 1501-1750g and > 12 for 1751-2000g			
Subhedar 1997 UK	n=42 Preterm babies < 32 weeks' gestation with "high risk" of developing BPD	Inhaled nitric oxide versus placebo	• Mortality prior to discharge • Bronchopulmonary dysplasia at 36 weeks PMA • Days on ventilation • Pulmonary haemorrhage	
Van Meurs 2005 US	n=420 Preterm babies < 34 weeks, OI ≥ 10 on 2 blood gases 30 minutes to 12 hours apart. ≥ 4 hours after surfactant	Inhaled nitric oxide versus placebo	• Mortality prior to discharge • Days on ventilation • Severe IVH • Methaemoglobinaemia	
Van Meurs 2007 US	n=29 Preterm babies < 34 weeks' gestation with birth weight > 1500g; ventilated with OI > 15 on 2 consecutive blood gases between 30 minutes and 12 hours apart	Inhaled nitric oxide versus placebo	• Mortality prior to discharge • Bronchopulmonary dysplasia at 36 weeks PMA • Neurodevelopmental outcomes • Days on ventilation	Less than 15 patients in the intervention arm
Walsh 2010	See Ballard 2006 for study details		• Neurodevelopmental outcomes	
RCTs				
Hamon 2005 France	n=20 GA < 32 weeks, < 48 hours of life	Inhaled nitric oxide versus placebo	• Bronchopulmonary dysplasia at 28 days of life	
Hasan 2017 Canada and US	n= 316 GA < 30 weeks, birth weight < 1250g, postnatal age 5-14 days at study entry, requirement of invasive ventilation, or, for those < 800g, positive pressure	Inhaled nitric oxide versus placebo	• Bronchopulmonary dysplasia at 36 weeks PMA • Neurodevelopmental outcomes • Days on ventilation	

Study and setting	Population	Intervention/ comparison	Outcomes	Comments
	respiratory support			

CPAP: continuous positive airway pressure GA: gestational age; IVH: intraventricular haemorrhage; 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

Included studies

The systematic search of the economic literature undertaken for the guideline identified 1 UK study on the cost-effectiveness (Field 2005; Huddy 2008 long term follow-up), 1 US study on the cost utility (Watson 2009) and 1 US study on the cost effectiveness (Zupancic 2009) of inhaled nitric oxide (iNO) versus no iNO in preterm infants requiring respiratory support.

References to the included studies and evidence tables for the economic evaluations included in the systematic literature review are provided in appendix H. Completed methodology checklists of the included studies are provided in appendix M. Economic evidence profiles of the studies considered during guideline development are presented in appendix I.

Excluded economic studies

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

Summary of studies included in the economic evidence review

Field (2005) evaluated the cost effectiveness of iNO compared with no iNO in preterm infants of ≤34 weeks of gestational age (GA), <28 days old and with severe respiratory failure requiring respiratory support. The suggested starting dose of iNO was 5 parts per million (ppm), doubling to 10 ppm in no response achieved; if necessary, the dose was doubled again to 20 ppm and then again if required to 40 ppm.

This was economic evaluation conducted alongside a randomised controlled trial (RCT) (Field 2005, INNOVO, n=108). A study by Huddy (2008) was a follow-up study (n=38) and reported long term outcomes and costs in year 4. The analysis was conducted from NHS and personal social services (PSS) perspective.

The study considered a range of direct health care costs including iNO acquisition costs, initial hospitalisation, subsequent hospitalisation, outpatient, GP and community and personal costs. It was unclear of what personal costs were comprised. The resource use estimates were based on the RCT (n=108 at 1 year and n=38 in year 4). The unit costs were from national sources.

In Field (2005) the measures of outcome for the economic analysis were death or severe disability; death; death or supplemental oxygen at 36 weeks post-menstrual age (PMA). Huddy (2008) included a range of outcomes including proportion of children with general disability; cognitive functioning impairment; disability in the neuromotor, visual and hearing or communication domains; and abnormal behaviour.

The time horizon of the analysis was 1 year and Hubby (2008) reported clinical outcomes over 4 years and costs in year 4. Bootstrapping was undertaken to obtain uncertainty around cost and outcome estimates.

At year 1 iNO resulted in a reduction in infants dead or with severe disability compared with no iNO (0.673 versus 0.679, respectively; difference -0.006, p = ns). Similarly, iNO resulted in a reduction in infants dead at 1 year (0.545 versus 0.642, respectively; difference -0.096, p = ns). Also, at year 1 iNO resulted in a reduction in infants dead or on supplemental oxygen at 36 weeks PMA (0.890 versus 0.906; difference -0.016, p = ns). The mean total costs per infant were £35,306 (SD £35,941) for iNO and £20,391 (SD £26,680) for no iNO, a difference of £14,915 (95% CI: £2,803; £27,026) (reported in 2002/2003 prices).

Based on the above costs and outcomes the incremental cost-effectiveness ration (ICER) of iNO (versus no iNO) was £2.4 million per additional death or severe disability avoided; £155,365 per additional death avoided; and £932,187 per additional death or case of BPD avoided. However, these findings are based on non-significant differences in the primary outcomes.

Similarly, at 4 years there were no significant differences between the groups in any of the clinical outcomes (that is, proportion of children with disability, cognitive functioning, neuromotor, sensory and communication and abnormal behaviour). The mean total cost at year 4 (over preceding 12 months) per infant were £2,638 (SD: £9,454) for iNO and £2,416 (SD £5,604) for no iNO, a difference of £223 (95% CI: -£5,159 to £5,605).

Sensitivity analysis (on results at 1 year) found the results robust to variations in the unit cost of iNO and hospitalisation costs. No sensitivity analysis was undertaken to test of the robustness of the findings at the long-term follow-up.

The analysis was judged by the committee to be directly applicable to the NICE decision-making context, since this was a UK study. The authors did not attempt to estimate quality-adjusted life years (QALYs) which made it difficult to interpret the findings. Overall, this was a well conducted study and was judged by the committee to have only minor methodological limitations.

Watson (2009) evaluated the cost utility of iNO compared with no iNO in preterm infants of ≤34 weeks GA, weighing 500-1250g, <48 hours old and who required respiratory support. The suggested dose of iNO was 5 ppm, doubling to 10 ppm as required.

This was economic evaluation conducted alongside an RCT (Watson 2005, n=793) conducted in the US. The analysis was conducted from a healthcare payer perspective (plus indirect costs). The study considered a range of direct health care costs including iNO acquisition costs, hospital stay, physician fees, readmissions, emergency department visits and outpatient visits. It also included indirect costs (that is, parent/carer lost work). The resource use estimates were based on the RCT (n=631 prior to discharge and n=512 post-discharge). Unit costs were from local and national sources (billing information, cost reports, Medicare fee schedule).

The measures of outcome for the economic analysis were QALYs. The utility weights were obtained from various published sources and included utilities of older children or adults living with similar conditions.

The time horizon of the analysis was 1 year. Bootstrapping was undertaken to obtain uncertainty around cost and outcome estimates.

INO resulted in a greater number of QALYs compared with no iNO (0.604 versus 0.593, respectively; difference 0.011 [SD 0.026]). The mean total costs per infant were $285,200 for iNO and $260,700 for no iNO, a difference of $24,400 in 2005 US dollars. Based on the above costs and outcomes the ICER of iNO (versus no iNO) was $2.25 million per additional quality-adjusted life year (QALY) gained. The probability of iNO being cost effective at a

willingness–to-pay (WTP) of $500,000 per additional QALY gained was 12.9%. According to the deterministic sensitivity analyses the findings were robust to the cost of iNO and utilities. However, the results were sensitive to physician reimbursement and post-discharge costs. The inclusion of indirect costs did not impact the conclusions.

Sub-group analysis among babies in the 750-999g stratum was undertaken. The ICER of iNO (versus no iNO) was $102,500 per QALY gained in this sub-group. The probability of iNO being cost effective at a WTP of $500,000 per additional QALY gained increased to 81.2%.

The analysis was judged by the committee to be partially applicable to the NICE decision-making context, since it was a non-UK study. Overall, this was a well conducted study and was judged by the guideline committee to have only minor methodological limitations.

Zupancic (2009) evaluated the cost effectiveness of iNO compared with no iNO in preterm infants of ≤34 weeks of GA, weighing 500-1250g and who required respiratory support. iNO was administered at weekly decreasing doses, beginning at 20 ppm, for a minimum of 24 days.

This was economic evaluation conducted alongside an RCT (Hibbs 2008) (n=582) conducted in the US. The analysis was conducted from a healthcare payer perspective. The study considered a range of direct health care costs including iNO acquisition costs, hospital stay, physician fees, invasive ventilation, continuous positive airways pressure (CPAP) and oxygen.

The resource use estimates were based on the RCT (n=582). Resource use information on hospital stay were supplemented with information from a database on a cohort of similar infants from 1 neonatal intensive care unit (NICU). Unit costs were from national sources (Medicare fee schedule). The measures of outcome for the economic analysis included the percent of infants alive and without BPD. The time horizon of the analysis was under 1 year (that is, up to discharge). Bootstrapping was undertaken to obtain uncertainty around cost and outcome estimates. The results were reported for infants initiated on iNO between 7 and 21 days and also those initiated between 7 and 14 days.

In infants initiated on iNO between 7 and 21 days iNO resulted in a greater proportion of babies alive and without BPD compared with no iNO (0.439 versus 0.365, respectively; difference 0.074, p = 0.04). The mean total costs per infant were $194,702 for iNO and $193,125 for no iNO, a difference of $1,576 in 2006 US dollars.

In infants initiated on iNO between 7 and 14 days iNO resulted in a greater proportion of babies alive and without BPD compared with no iNO (0.491 versus 0.270, respectively; difference 0.221, p = 0.0004). The mean total costs per infant were $181,525 for iNO and $187,407 for no iNO, a difference of -$5,882 in 2006 US dollars.

Based on the above costs and outcomes in infants initiated between 7 and 21 days the ICER of iNO (versus no iNO) was $21,297 per additional survivor without BPD. The probability that iNO reduces costs and improves outcomes was 43%. In infants initiated on iNO between 7 and 14 days iNO was dominant (versus no iNO). That is, iNO resulted in lower costs and higher proportion of babies surviving without BPD. The probability that iNO reduces costs and improves outcomes was 71% and the probability of iNO being cost effective was never below 70%.

According to one way sensitivity analyses for infants initiated on iNO between 7 and 21 days iNO was cost saving through a cost of approximately $10,000 per course of iNO and $17,000 per course of iNO for infants initiated on iNO between 7 and 14 days (base case cost of iNO was $12,000 per course). When varying hospital costs 50-150% around their base case values the ICER of iNO (versus no iNO) was $80,889 and -$36,479, respectively. Higher hospital costs resulted in a more favourable ICER since iNO shortened admission and time on more expensive respiratory support. When varying physician costs 50-150% around their

base case values the ICER of iNO ranged from $7,485 to $36,925, respectively. When varying all non-iNO costs 50-150% around their base case values the ICER of iNO was $95,610 and -$51,199, respectively.

The analysis was judged by the committee to be partially applicable to the NICE decision-making context. The authors did not attempt to estimate QALYs. However, this was not a problem since iNO was found to be dominant in babies who are initiated on iNO between 7 and 14 days. Overall, this was a well conducted study and was judged by the guideline committee to have only minor methodological limitations.

Economic model

This question was prioritised as a high priority for de novo economic modelling. However, there was convincing existing UK evidence showing that iNO was cost ineffective when compared with no iNO. This was in line with the clinical review that failed to identify clinical benefits associated with iNO when compared with placebo. The only significant finding favouring iNO was reduction in the mean duration of ventilation (that is, iNO resulted in the mean reduction of 8 days on invasive ventilation).

In the UK-based RCT (Field 2005) the mean hours on iNO were 84.4 (SD: 115.7) and 7.1 (SD: 29.6) for iNO and no iNO groups; the mean difference was 77.3 hours (95% CI: 44.8 to 109.8). The associated mean costs of iNO were £2,601 (SD: £1,757) and £244 (SD: £957); the mean difference of £2,357 (95% CI: £1,814 to £2,899) in 2016/17 prices. Based on these costings the daily cost of invasive ventilation would need to be approximately £300 to outweigh iNO acquisition costs. However, based on the exploratory costings done for this guideline (Question 3.2, appendix J) the apportioned daily cost of equipment and consumables is likely to be well below £300. Moreover, all babies stepping off invasive invasive ventilation will not go straight to high dependency care and as such there are no immediate costs savings associated with the reduction in the nursing costs. As a result, iNO is unlikely to represent cost effective use of limited NHS resources.

Clinical evidence statements

Comparison 1. Inhaled nitric oxide versus placebo

Critical outcomes

Mortality prior to discharge

Studies with entry before 3 days of age based on oxygenation

- Low quality evidence from 8 RCTs (n=941) showed no clinical difference in mortality prior to discharge between preterm babies with a gestational age of ≤ 34 weeks who received inhaled nitric oxide compared to placebo.

Studies with entry after 3 days of age based on BPD risk

- Very low quality evidence from 2 RCTs (n=624) showed no clinically significant difference in mortality prior to discharge between preterm babies with a gestational age of < 32 weeks who received inhaled nitric oxide compared to those who received placebo.

Studies of routine use in preterm infants on respiratory support

- Very low quality evidence from 4 RCTs (n=1924) showed no clinically significant difference in mortality prior to discharge between preterm babies with a gestational age of < 34 weeks who received inhaled nitric oxide compared to those who received placebo.

BPD at 36 weeks postmenstrual age (PMA)

Studies with entry before 3 days of age based on oxygenation

- Very low quality evidence from 6 RCTs (n=487) showed no clinically significant difference in bronchopulmonary dysplasia at 36 weeks PMA between preterm babies with a gestational age of ≤ 34 weeks who received inhaled nitric oxide compared to those who received placebo.

Studies with entry after 3 days of age based on BPD risk

- High quality evidence from 3 RCTs (n=1075) showed there may be a clinically significant decrease in bronchopulmonary dysplasia at 36 weeks PMA between preterm babies with a gestational age of < 32 weeks who received inhaled nitric oxide compared to those who received placebo, but there is uncertainty around the estimate.

Studies of routine use in preterm infants on respiratory support

- High quality evidence from 4 RCTs (n=1924) showed no clinically significant difference in bronchopulmonary dysplasia at 36 weeks PMA between preterm babies with a gestational age of < 34 weeks who received inhaled nitric oxide compared to those who received placebo.

BPD at 28 days of age

Studies with entry before 3 days of age based on oxygenation

- Moderate quality evidence from 1 RCT (n=76) showed no clinically significant difference in bronchopulmonary dysplasia at 28 days of age between preterm babies with a gestational age of < 32 weeks who received inhaled nitric oxide compared to those who received placebo.

Neurodevelopmental outcomes at ≥ 18 months: cerebral palsy

Studies with entry before 3 days of age based on oxygenation

- Very low quality evidence from 2 RCTs (n=209) showed no clinically significant difference in cerebral palsy at ≥ 18 months post-menstrual age between preterm babies with a gestational age of < 34 weeks who received inhaled nitric oxide compared to those who received placebo.

Studies with entry after 3 days of age based on BPD risk

- Very low quality evidence from 2 RCTs (n=498) showed no clinically significant difference in cerebral palsy at ≥ 18 months post-menstrual age between preterm babies with a gestational age of < 32 weeks who received inhaled nitric oxide compared to those who received placebo.

Studies of routine use in preterm infants on respiratory support

- Very low quality evidence from 2 RCTs (n=768) showed no clinically significant difference in cerebral palsy at ≥ 18 months post-menstrual age between preterm babies with a gestational age of < 34 weeks who received inhaled nitric oxide compared to those who received placebo.

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

Studies with entry after 3 days of age based on BPD risk

- Low quality evidence from 1 RCT (n=360) showed no clinically significant difference in cerebral palsy at ≥ 18 months post-menstrual age between preterm babies with a

gestational age of < 32 weeks who received inhaled nitric oxide compared to those who received placebo.

Neurodevelopmental outcomes at ≥ 18 months: severe cognitive impairment (BSID-III cognitive score <70)

Studies with entry after 3 days of age based on BPD risk

- Very low quality evidence from 2 RCTs (n=369) showed no clinically significant difference in severe neurodevelopmental delay at ≥ 18 months post-menstrual age between preterm babies with a gestational age of < 34 weeks who received inhaled nitric oxide compared to those who received placebo.

Studies of routine use in preterm infants on respiratory support

- Very low quality evidence from 1 RCT (n=630) showed no clinically significant difference in severe neurodevelopmental delay at ≥ 18 months post-menstrual age between preterm babies with a gestational age of 24-28 weeks who received inhaled nitric oxide compared to those who received placebo.

Neurodevelopmental outcomes at ≥ 18 months: moderate cognitive impairment (BSID-III cognitive score 70-84)

Studies with entry after 3 days of age based on BPD risk

- Very low quality evidence from 2 RCTs (n=403) showed no clinically significant difference in moderate neurodevelopmental delay at ≥ 18 months post-menstrual age between preterm babies with a gestational age of < 34 weeks who received inhaled nitric oxide compared to those who received placebo.

Studies of routine use in preterm infants on respiratory support

- Low quality evidence from 1 RCT (n=685) showed a clinically significant increase in moderate neurodevelopmental delay at ≥ 18 months post-menstrual age between preterm babies with a gestational age of 24-28 weeks who received inhaled nitric oxide compared to those who received placebo.

Neurodevelopmental outcomes at ≥ 18 months: severe cognitive impairment (Mental Developmental Index <70)

Studies with entry before 3 days of age based on oxygenation

- Very low quality evidence from 2 RCTs (n=201) showed no clinically significant difference in severe cognitive impairment at ≥ 18 months post-menstrual age between preterm babies with a gestational age of < 34 weeks who received inhaled nitric oxide compared to those who received placebo.

Studies of routine use in preterm infants on respiratory support

- Low quality evidence from 1 RCT (n=138) showed no clinically significant difference in severe cognitive impairment at ≥ 18 months post-menstrual age between preterm babies who received inhaled nitric oxide compared to those who received placebo.

Neurodevelopmental outcomes at ≥ 18 months: severe psychomotor impairment (Psychomotor Developmental Index <70)

Studies with entry before 3 days of age based on oxygenation

- Very low quality evidence from 2 RCTs (n=201) showed no clinically significant difference in severe psychomotor impairment at ≥ 18 months post-menstrual age between preterm

babies with a gestational age of < 34 weeks who received inhaled nitric oxide compared to those who received placebo.

Studies of routine use in preterm infants on respiratory support

- Very low quality evidence from 1 RCT (n=138) showed no clinically significant difference in severe psychomotor impairment at ≥ 18 months post-menstrual age between preterm babies who received inhaled nitric oxide compared to those who received placebo.

Neurodevelopmental outcomes at ≥ 18 months: severe hearing impairment

Studies with entry before 3 days of age based on oxygenation

- Very low quality evidence from 3 RCTs (n=250) showed no clinically significant difference in severe hearing impairment at ≥ 18 months post-menstrual age between preterm babies with a gestational age of < 34 weeks who received inhaled nitric oxide compared to those who received placebo.

Studies with entry after 3 days of age based on BPD risk

- Very low quality evidence from 1 RCT (n=477) showed no clinically significant difference in severe hearing impairment at ≥ 18 months post-menstrual age between preterm babies who received inhaled nitric oxide compared to those who received placebo.

Studies of routine use in preterm infants on respiratory support

- Very low quality evidence from 2 RCTs (n=768) showed no clinically significant difference in severe hearing impairment at ≥ 18 months post-menstrual age between preterm babies with a gestational age of < 34 weeks who received inhaled nitric oxide compared to those who received placebo.

Neurodevelopmental outcomes at ≥ 18 months: severe visual impairment

Studies with entry before 3 days of age based on oxygenation

- Very low quality evidence from 3 RCTs (n=250) showed no clinically significant difference in severe visual impairment at ≥ 18 months post-menstrual age between preterm babies with a gestational age of < 34 weeks who received inhaled nitric oxide compared to those who received placebo.

Studies with entry after 3 days of age based on BPD risk

- Very low quality evidence from 1 RCT (n=477) showed no clinically significant difference in severe visual impairment at ≥ 18 months post-menstrual age between preterm babies who received inhaled nitric oxide compared to those who received placebo.

Studies of routine use in preterm infants on respiratory support

- Very low quality evidence from 2 RCTs (n=768) showed no clinically significant difference in severe visual impairment at ≥ 18 months post-menstrual age between preterm babies with a gestational age of < 34 weeks who received inhaled nitric oxide compared to those who received placebo.

Important outcomes

Days on ventilation

Mean days on ventilation

Studies with entry before 3 days of age based on oxygenation

- Moderate quality evidence from 2 RCTs (n=449) showed no clinically significant difference in mean days on ventilation between preterm babies with a gestational age of < 34 weeks who received inhaled nitric oxide compared to those who received placebo.

Studies with entry after 3 days of age based on BPD risk

- High quality evidence from 1 RCT (n=451) showed no clinically significant difference in mean days on ventilation between preterm babies with a gestational age of < 32 weeks who received inhaled nitric oxide compared to those who received placebo.

Studies of routine use in preterm infants on respiratory support

- Low quality evidence from 1 RCT (n=124) showed no clinically significant difference in mean days on ventilation between preterm babies who received inhaled nitric oxide compared to those who received placebo.

Median days on ventilation for survivors

Studies with entry before 3 days of age based on oxygenation

- Low quality evidence from 1 RCT (n= 40) showed a clinically significant decrease in median days on ventilation between preterm babies with a gestational age of < 34 weeks who received inhaled nitric oxide compared to those who received placebo.

Median days on ventilation

Studies with entry before 3 days of age based on oxygenation

- Low quality evidence from 1 RCT (n= 108) showed no clinically significant difference in median days on ventilation between preterm babies with a gestational age of < 34 weeks who received inhaled nitric oxide compared to those who received placebo.

Studies with entry after 3 days of age based on BPD risk

- Low quality evidence from 1 RCT (n= 42) showed no clinically significant diffence between median days on ventilation of 11 (5-44) for preterm babies with a gestational age of < 32 weeks who received inhaled nitric oxide and 19 (5-39) for those who received placebo.

Severe intraventricular haemorrhage (grade 3 or 4)

Studies with entry before 3 days of age based on oxygenation

- Very low quality evidence from 5 RCTs (n=708) showed there may be a clinically significant increase in severe intraventricular haemorrhage between preterm babies with a gestational age of ≤ 34 weeks who received inhaled nitric oxide compared to those who received placebo, but there is uncertainty around the estimate.

Studies of routine use in preterm infants on respiratory support

- Moderate quality evidence from 4 RCTs (n=1913) showed no clinically significant difference in severe intraventricular haemorrhage between preterm babies with a gestational age of < 34 weeks who received inhaled nitric oxide compared to those who received placebo.

Pulmonary haemorrhage

Studies with entry before 3 days of age based on oxygenation

- Very low quality evidence from 2 RCTs (n=150) showed no clinically significant difference in pulmonary haemorrhage between preterm babies with a gestational age of < 34 weeks who received inhaled nitric oxide compared to those who received placebo.

Studies of routine use in preterm infants on respiratory support

- Low quality evidence from 3 RCTs (n=1792) showed no clinically significant difference in pulmonary haemorrhage between preterm babies with a gestational age of < 34 weeks who received inhaled nitric oxide compared to those who received placebo.

Methaemoglobineamia

Methaemoglobin level ≥ 4%

Studies with entry before 3 days of age based on oxygenation

- Very low quality evidence from 1 RCT (n=420) showed no clinically significant difference in methaemoglobin levels greater than 4% between preterm babies with a gestational age of < 34 weeks who received inhaled nitric oxide compared to those who received placebo.

Methaemoglobin level ≥ 8%

Studies with entry before 3 days of age based on oxygenation

- Very low quality evidence from 1 RCT (n=420) showed no clinically significant difference in methaemoglobin levels greater than 8% between preterm babies with a gestational age of < 34 weeks who received inhaled nitric oxide compared to those who received placebo.

Comparison 2. Low dose versus high dose nitric oxide

There was no evidence for this comparison.

Comparison 3. Early administration versus late administration nitric oxide

There was no evidence for this comparison.

See appendix E for Forest plots.

Economic evidence statements

- There was evidence from simple costings indicating that the reduction in days on ventilation between preterm babies who received inhaled nitric oxide compared to those who received placebo is insufficient to outweigh inhaled nitric oxide acquisition costs and as such inhaled nitric oxide is unlikely to represent cost effective use of limited NHS resources.
- There was evidence from one UK study conducted alongside a randomised controlled trial (n=108) showing that inhaled nitric oxide when compared with no inhaled nitric oxide was not cost effective in preterm infants requiring respiratory support. There was also evidence from a follow-up study (n=38) showing no difference in costs in year 4 or outcomes at 4 year follow-up between inhaled nitric oxide and no inhaled nitric oxide groups. This evidence came from directly applicable study that was characterised by minor methodological limitations.
- There was evidence from one US study conducted alongside a randomised controlled trial (n=793) showing that inhaled nitric oxide when compared with no inhaled nitric oxide was not cost effective in preterm infants requiring respiratory support. The probability of inhaled nitric oxide being cost effective at a willingness–to-pay of $500,000 per additional

QALY gained was only 12.9%. This evidence came from a partially applicable study that was characterised by minor methodological limitations.

- There was evidence from one US study conducted alongside a randomised controlled trial (n=582) showing that inhaled nitric oxide when compared with no inhaled nitric oxide was cost effective in preterm infants requiring respiratory support and who were initiated on inhaled nitric oxide between 7 and 21 days. However, the probability that iNO reduces costs and improves outcomes was only 43%. There was also evidence that inhaled nitric oxide was dominant when initiated between 7 and 14 days. The probability that iNO reduces costs and improves outcomes was 71% and the probability of iNO being cost effective was never below 70%. This evidence came from a partially applicable study that was characterised by minor methodological limitations.

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 nitric oxide in preterm babies requiring invasive ventilation. Mortality prior to discharge and bronchopulmonary dysplasia were considered as critical outcomes as the aim of treatment with nitric oxide is to improve blood flow to the lungs and so increase oxygenation of the blood, preventing hypoxia and death and also reducing lung damage due to ventilation. Neurodevelopmental outcomes at ≥ 18 months were also considered critical outcomes as impaired oxygenation can lead to cerebral palsy, delayed cognitive and psychomotor development and sensory impairments such as blindness and deafness, which can have a profound and long-lasting effects on a baby's life, with an impact on the parents/carers too.

As nitric oxide may be used as a 'rescue therapy' in babies who may be difficult to ventilate successfully, or wean from a ventilator, days on invasive ventilation was considered an important outcome. Potential adverse outcomes of severe (grade 3 or 4) intraventricular haemorrhage (IVH), pulmonary haemorrhage and methaemoglobinaemia were considered important outcomes to allow the benefits versus risks of treatment with nitric oxide to be evaluated.

There was evidence for all the outcomes for the comparison of nitric oxide versus placebo.

The quality of the evidence

Evidence was available from 1 Cochrane systematic review with 14 RCTs, 2 additional RCTs and 5 follow-up studies that compared inhaled nitric oxide with placebo. No studies were found that compared low dose to high dose nitric oxide or early administration to late administration nitric oxide. No research recommendations were made for these comparisons due to the availability of studies comparing inhaled nitric oxide to placebo and because the committee did not think this area was a priority for research.

The committee noted that the Cochrane systematic review (Barrington 2017) reported neurodevelopmental delay as a composite outcome, which included death along with neurodevelopmental delay as measured by validated scales. Composite outcomes can produce results that are more favourable than if each outcome was reported separately and outcomes are often combined inconsistently (Cordoba 2010). Therefore the neurodevelopmental outcomes were extracted and reported individually.

The quality of the evidence ranged from very low to high: the majority of the evidence was of low and very low quality, but there was some medium quality and high quality evidence for the outcomes of BPD and days on ventilation. 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. However, the committee agreed that there was a big enough body of evidence and of sufficient quality to allow tham to make a strong recommendation.

Methodological limitations affecting the risk of bias were generally attributed to many studies terminating early and others not reporting the method for randomisation, treatment allocation, or blinding. Additionally, neurodevelopmental outcomes were at risk of bias as a result of sample attrition due to death or loss to follow-up.The imprecision of the evidence for some of the outcomes could not be assessed due to the data being presented as medians.

Potential inconsistency in results was seen for the outcome of mortality prior to discharge in the subgroup of trials of routine use of nitric oxide in preterm infants on respiratory support. The EUNO 2009 trial reported increased risk for with nitric oxide whereas the other trials observed decreased risk, this could be attributed to heterogeneity in gestational age between the trial populations.

Uncertainty around the risk estimate was generally attributable to low event rates and small sample sizes.

Benefits and harms

The use of inhaled nitric oxide in preterm babies had no effect on mortality prior to discharge or BPD at 36 weeks or 28 days of age, although for one sub-group (entry after 3 days of age based on BPD risk) there may have been some benefit at reducing BPD at 36 weeks but there was uncertainty around the estimate. There was also no evidence of effect on neurodevelopmental delay at ≥ 18 months, apart from an increase in moderately severe cognitive impairment in the 'routine use' sub-group. There was evidence for a decrease in days of ventilation – this was statistically significant and not clinically significant, but was an absolute difference of 8 days which the committee thought was important to consider. There was evidence for an increased rate of severe IVH with nitric oxide.

The committee were aware there was some heterogeneity in the populations of the included studies and discussed that some of the studies included older babies (up to 34 weeks) and babies with oxygenation index of ≥10 or ≥15.

Based on the evidence that inhaled nitric oxide had no beneficial effect on mortality or BPD, and with possible harms including cognitive impairment and IVH, the committee agreed that nitric oxide could not be recommended for use in preterm babies with respiratory distress. The committee agreed, however, based on their clinical experience that nitric oxide may be beneficial for other indications such as pulmonary hypertension or pulmonary hypoplasia and so included these exceptions as part of the recommendation.

Cost effectiveness and resource use

There was UK-based economic evidence indicating that nitric oxide was not cost effective when compared with no nitric oxide. The committee discussed the problem of using composite outcomes in economic evaluations and the fact that there were no significant differences in any of the primary outcomes used in the analysis. The committee acknowledged the non-UK evidence. In particular, the economic evaluation by Zupancic 2009 based on a randomised controlled trial which appeared to have a statistically significant result for survival without BPD in favour of iNO, which was not consistent with what the clinical evidence review for this guideline concluded. The committee explained that this evidence came from a single randomised controlled trial. Also, it was noted that these non-UK studies were funded by the manufacturer and as such the findings should be interpreted with caution.

The committee acknowledged the potential decrease in days on ventilation between preterm babies who received nitric oxide compared to those who received placebo. The committee

discussed potential cost savings associated with clinical staff arising from a reduction in days on ventilation. However, they came to a conclusion that all preterm babies would be in an intensive care and babies stepping off invasive ventilation will not go straight to high dependency care and as such there are no immediate costs savings associated with the reduction in the nursing costs. Moreover, simple costings undertaken indicated that the cost savings due to a reduction in days on ventilation are insufficient to outweigh high nitric oxide acquisition costs given that the daily apportioned equipment and consumable costs for invasive ventilation are relatively low.

Other considerations

The committee were aware of a study (Chock 2009) that performed a retrospective subset analysis of data reported in Van Meurs 2005 and Van Meurs 2007, which were both included in the evidence review. Chock 2009 identified a small subset (n=12) of babies who had pulmonary hypoplasia as a result of premature rupture of membranes (PPROM) in whom inhaled nitric oxide improved oxygenation and potentially decreased the rate of BPD and death, without increasing severe IVH or periventricular haemorrhage (PVL). This subset analysis was not included in the review because it was not one of the pre-specified subgroups and the cases that had been included in the subset analyses were already counted in the original trials (Van Meurs 2005; Van Meurs 2007). However, based on the evidence from Chock 2009, the committee were concerned that a recommendation to not use nitric oxide in all babies might lead to babies with pulmonary hypoplasia (who could benefit from inhaled nitric oxide) not receiving appropriate treatment. The committee were also aware that nitric oxide could be used to treat pulmonary hypertension (a condition that was specifically excluded from the scope of this guideline).

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Appendices

Appendix A – Review protocols

Review protocol for question 1.1 What respiratory support (excluding resuscitation) is the most effective for preterm babies before admission to the neonatal unit?

Field (based on PRISMA-P	Content
Review question in SCOPE	What respiratory support is most effective for babies who need it at birth and before transfer to the neonatal unit?
Review question in guideline	What respiratory support (excluding resuscitation) is the most effective for preterm babies before admission to the neonatal unit?
Type of review question	Intervention
Objective of the review	To determine the optimal method of early respiratory support in preterm babies
Eligibility criteria – population/disease/condition/issue/domain	Preterm babies before admission to the neonatal unit Exclusions: • Preterm babies with congenital abnormalities except patent ductus arteriosus • 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.
Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	Assisted ventilation techniques: • Non-invasive ventilation techniques: ○ Hi Flow (HF)/ Hi flow nasal cannula (HFNC)/ Humidified hi flow nasal cannula (HHFNC)/ Heated,

Field (based on PRISMA-P	Content
	humidified, hi flow nasal cannula (HHHFNC) – delivered at equal to or more than 5L/min ○ Continuous positive airway pressure therapy (CPAP) • Invasive ventilation techniques: ○ Invasive ventilation (all types) delivered following intubation Surfactant administration: • Minimally Invasive Techniques: ○ Minimally invasive surfactant therapy (MIST) ○ Less invasive surfactant administration (LISA) ○ Avoidance of mechanical ventilation (AMV) • Surfactant administered via endotracheal tube: ○ Early extubation administration: ▪ Intubate surfactant extubate (INSURE) ▪ Intubate surfactant extubate (ISX) ▪ Take care method ○ Conventional endotracheal administration
Eligibility criteria – comparator(s)/control or reference (gold) standard	<u>Assisted ventilation technique comparisons</u> Non-invasive ventilation versus no ventilation comparisons: • CPAP versus no assisted ventilation • Hi Flow versus no assisted ventilation Non-invasive ventilation technique comparisons: • CPAP versus Hi Flow

Field (based on PRISMA-P	Content
	Invasive versus non-invasive ventilation technique comparisons: • CPAP versus invasive ventilation (both ventilation techniques received surfactant) • Hi Flow versus invasive ventilation (both ventilation techniques received surfactant) <u>Ventilation versus surfactant comparisons</u> Non-invasive ventilation technique with or without surfactant comparisons: • CPAP with surfactant versus CPAP alone • Hi Flow with surfactant administrations versus Hi Flow alone Invasive ventilation with surfactant versus non-invasive ventilation without surfactant comparison: • CPAP alone versus invasive ventilation with surfactant • Hi Flow alone versus invasive ventilation with surfactant

Outcomes and prioritisation	Critical outcomes:
	• Mortality prior to discharge
	• Bronchopulmonary dysplasia (BPD) (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)
	  ○ 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

Field (based on PRISMA-P	Content
	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 outcomes: • Failed non-invasive ventilation requiring intubation • Pneumothorax • Severe intraventricular haemorrhage (grade 3 or 4)
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

Field (based on PRISMA-P	Content
Proposed sensitivity/sub-group analysis, or meta-regression	Stratified analyses based on the following sub-groups of pre-term babies: Gestational age: • <26 + 6 weeks • 27-31 + 6 weeks • 32-36 + 6 weeks Failed non-invasive ventilation: • FiO2 <30 • FiO2 31-49 • FiO2 >50
Selection process – duplicate screening/selection/analysis	Dual sifting will be undertaken for this question using NGA STAR software. 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 sifting 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.

Field (based on PRISMA-P	Content
	NGA STAR software will be used for study sifting, data extraction, recording quality assessment using checklists and generating bibliographies/citations, Data management for the corresponding Network meta-analysis are recorded in a separate protocol.
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 antenatal and postnatal 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).

Field (based on PRISMA-P	Content
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 for all outcomes. When meta-analysing continuous data, change scores will be pooled in preference to final scores. For details regarding inconsistency, please see the methods chapter of the full guideline 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 Committee or in the literature.

Field (based on PRISMA-P	Content
	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
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

Review protocol for question 3.3 What is the most effective way of using surfactant in managing respiratory distress syndrome?

Field (based on PRISMA-P	Content
Review question in SCOPE	What is the effectiveness and safety of surfactant in managing respiratory distress syndrome and preventing bronchopulmonary dysplasia?
Review question in guideline	What is the most effective way of using surfactant in managing respiratory distress syndrome?
Type of review question	Intervention
Objective of the review	To determine the optimal dosing schedule and mode of administration, in preventing or alleviating the effects of RDS and longer-term sequelae including BPD
Eligibility criteria – population/disease/condition/issue/domain	Preterm babies receiving surfactant Exclusions: Preterm babies with any congenital abnormalities except patent ductus arteriosus 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 50% or less of the mothers of preterm babies have not received antenatal steroids 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)	Surfactant regimens available in the U.K: Porcactant (Curosurf®) Beractant (Survanta®)

Field (based on PRISMA-P	Content
	Administration techniques of surfactant: *Minimally Invasive Techniques:* -Minimally invasive surfactant therapy (MIST) -Less invasive surfactant administration (LISA) -Avoidance of mechanical ventilation (AMV) -Take care method *Laryngeal Mask Airway (LMA)* *Intubated Administered Surfactant:* -Early extubation administration: -Intubate, surfactant, extubate (InSuRE) -Intubate surfactant extubate (ISX) -Conventional endotracheal administration
Eligibility criteria – comparator(s)/control or reference (gold) standard	Comparisons **Surfactant administration techniques:** Early extubation following administration of surfactant (INSURE/ISX) versus conventional endotracheal administration of surfactant with mechanical ventilation Minimally invasive techniques (MIST/LISA/AMV) versus endotracheal tube administration of surfactant Laryngeal mask airway (LMA) versus endotracheal tube administration of surfactant Minimally invasive techniques (MIST/LISA/AMV) versus laryngeal mask airway (LMA)

Field (based on PRISMA-P	Content
	Surfactant dosing schedules: Single dose 100mg/kg surfactant A administration versus single dose 200mg/kg surfactant A administration Multiple dose surfactant A administration versus single dose surfactant A administration

Outcomes and prioritisation	**Critical outcomes:**
	Mortality prior to discharge
	
	Bronchopulmonary Dysplasia (Oxygen requirements 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)
	  o 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)
	  o 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)
	  o Severe hearing impairment (e.g deaf)
	  o Severe visual impairment (e.g blind)

Field (based on PRISMA-P	Content
	Important outcomes: Days on invasive ventilation Severe intraventricular haemorrhage (grade 3 or 4) Pneumothorax Pulmonary haemorrhage
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: FiO2 at randomisation <0.29 0.30-0.39 0.4-0.59 ≥0.6 Time to randomisation from birth: <2 hours 2-6 hours

Field (based on PRISMA-P	Content
	>6 hours Gestational age: <26+6 weeks 27-31+6 weeks >32-36+6 weeks Ventilation: Invasive ventilation Non-invasive ventilation
Selection process – duplicate screening/selection/analysis	Dual sifting will be undertaken for this question using NGA STAR software. 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 will not be performed 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, Data management for the corresponding Network meta-analysis are recorded in a separate protocol.
Information sources – databases and dates	Sources to be searched: Medline, Medline In-Process, CCTR, CDSR, DARE, HTA, Embase

Field (based on PRISMA-P	Content
	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	A standardised evidence table format will be used, and published as 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: For details regarding inconsistency, please see the methods chapter of the full guideline 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 – 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
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

Field (based on PRISMA-P	Content
	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

Review protocol for question 3.1 What is the most effective way to administer oxygen during respiratory support?

Field (based on PRISMA-P	Content
Review question in SCOPE	How should oxygen be administered to ensure effectiveness and safety?
Review question in guideline	What is the most effective way to administer oxygen during respiratory support?
Type of review question	Intervention
Objective of the review	To determine the optimal method of oxygen administration in preterm babies requiring respiratory support.
Eligibility criteria – population/disease/condition/issue/domain	Preterm babies born who require oxygen during respiratory support: Exclusions: - Preterm babies with congenital abnormalities - Preterm babies who are ventilated solely due to a specific non-respiratory comorbidity, such as sepsis, NEC, neurological disorders, congenital heart disease - Delivery room resuscitation

Field (based on PRISMA-P	Content
	- RCTs with <15 participants in each arm will not be included - Studies with indirect populations will not be considered

Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	**Type of low-flow oxygen delivered at <1L/min**
	- Humidified
	- Non-humidified
	
	Method of oxygen administration:
	- Low-flow systems
	  ○ Nasal cannula
	  ○ Incubator
	
	Method of oxygen titration:
	- Automated
	- Manual

Eligibility criteria – comparator(s)/control or reference (gold) standard	1. Type of low-flow oxygen delivered at <1L/min: - Humidified oxygen vs non-humidified oxygen 2. Method of oxygen administration: - Nasal cannula vs incubator 3. Method of oxygen titration: - Automated vs. manual
Outcomes and prioritisation	**Critical outcomes:** - Bronchopulmonary dysplasia at 36 weeks postmenstrual age or 28 days of age - Days of oxygen - Time spent within optimal target saturation limits **Important outcomes:**

Field (based on PRISMA-P	Content
	- Retinopathy of prematurity - Nasal trauma - Comfort score/ pain score - Number of manual adjustments of titration
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: Gestational age: - <26+6 weeks - 27-31+6 weeks - 32-36+6 weeks Type of low flow oxygen delivered: - Incubator - Nasal cannula
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.

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	A standardised evidence table format will be used, and published as appendix D (clinical evidence tables) or H (economic evidence tables).
Methods for assessing bias at outcome/study level	Appraisal of methodological quality: The methodological quality of each study will be assessed using an appropriate checklist: - AMSTAR for systematic reviews

Field (based on PRISMA-P	Content
	- 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. 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	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: The following default values will be used: 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 – any change (statistically significant) Double sifting, data extraction and methodological quality assessment: Sifting, data extraction, appraisal of methodological quality and GRADE assessment will be performed by the systematic reviewer. Quality control will be performed by the senior systematic reviewer. Dual quality assessment and data extraction will be performed when capacity allows.
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual.

Field (based on PRISMA-P	Content
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 to PROSPERO

Review protocol for question 3.2 What is the effectiveness and safety of the different assisted ventilation techniques in preterm babies?

Field (based on PRISMA-P	Content
Review question in SCOPE	What is the effectiveness and safety of the different assisted ventilation techniques?
Review question in guideline	What is the effectiveness and safety of the different ventilation techniques in preterm babies needing respiratory support?
Type of review question	Intervention

Field (based on PRISMA-P	Content
Objective of the review	To determine the optimal method of ventilation in preterm babies requiring respiratory support.
Eligibility criteria – population/disease/condition/issue/domain	Preterm babies born 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, NEC, neurological disorders. • Preterm babies on respiratory support for post-extubation weaning 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 with indirect populations will not be considered
Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	**Non-invasive ventilation techniques:** • Hi Flow (HF)/ Hi Flow Nasal Cannula (HFNC)/ Humidified, Hi Flow Nasal Cannula (HHFNC)/ Heated, Humidified, Hi Flow Nasal Cannula (HHHFNC) – delivered at equal to or more than 5L/min • Continuous positive airway pressure therapy (CPAP) • Bilevel Positive Airway pressure (BiPAP)/ Synchronised Positive Airway Pressure (SiPAP) • Nasal intermittent positive pressure ventilation (NIPPV) **Invasive ventilation techniques:** <u>Volume targeted ventilation</u> • Volume guarantee ventilation (VGV) • Target tidal volume (TTV) • Pressure regulated volume control (PRVC) ventilation (PRVCV)

Field (based on PRISMA-P	Content
	• Volume limited ventilation (VLV) • Volume-assured pressure support (VAPS) • Any synchronised pressure limited ventilation + volume targeted ventilation • SIMV + volume targeted ventilation <u>Synchronised pressure limited ventilation</u> • Assist control ventilation (AC) • Synchronised intermittent positive pressure ventilation (SIPPV) • Patient triggered ventilation (PTV) • Pressure support ventilation (PSV) • Synchronised time cycled pressure limited ventilation (STCPL) • Synchronised Intermittent Mandatory Ventilation (SIMV) <u>Non-synchronised pressure limited ventilation</u> • Conventional mandatory ventilation (CMV) • non-triggered / unsynchronised time cycled pressure limited ventilation (TCPL) • Intermittent mandatory ventilation (IMV) <u>High frequency ventilation (HFV)</u> • High frequency oscillatory ventilation (HFOV) • High frequency flow interruption (HFFI)
Eligibility criteria – comparator(s)/control or reference (gold) standard	Non-invasive ventilation technique comparisons: 1. Hi Flow vs CPAP 2. CPAP vs BiPAP/SiPAP 3. BiPAP/SiPAP vs Hi Flow

Field (based on PRISMA-P	Content
	4. NIPPV vs BiPAP/SiPAP 5. NIPPV vs CPAP 6. NIPPV vs Hi Flow Invasive ventilation technique comparisons: 1. Volume targeted vs synchronised pressure limited 2. Volume targeted vs non-synchronised pressure limited 3. Volume targeted vs SIMV 4. Volume targeted vs HFOV 5. Synchronised pressure limited vs non-synchronised pressure limited 6. Synchronised pressure limited vs SIMV 7. Synchronised pressure limited vs HFOV 8. SIMV vs non-synchronised pressure limited 9. SIMV vs HFOV 10. Non-synchronised pressure limited vs HFOV
Outcomes and prioritisation	**Critical outcomes:** • Mortality prior to discharge • Bronchopulmonary dysplasia (BPD) (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

Field (based on PRISMA-P	Content
	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:** • Number of days on invasive ventilation (reported as requiring intubation) • Failed non-invasive ventilation • Pneumothorax • Parental satisfaction
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: Age at randomisation:

Field (based on PRISMA-P	Content
	• <2 hours after birth • 2-6 hours • >6 hours Gestational age: • <26+6 weeks • 27-31+6 weeks • 32-36+6 weeks
Selection process – duplicate screening/selection/analysis	Dual sifting will be undertaken for this question using NGA STAR software. 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 will not be performed 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, Data management for the corresponding Network meta-analysis are recorded in a separate protocol.
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

Field (based on PRISMA-P	Content
	• 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 antenatal and postnatal 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: The methodological quality of each study will be assessed using an appropriate checklist: • AMSTAR for systematic reviews

Field (based on PRISMA-P	Content
	• 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 for all other outcomes. Network meta-analysis (see separate protocol) When meta-analysing continuous data, change scores will be pooled in preference to final scores. For details regarding inconsistency, please see the methods chapter of the full guideline 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 – 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
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.

Field (based on PRISMA-P	Content
	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

Review protocol for question 3.7 What is the effectiveness of nitric oxide in preterm babies requiring invasive ventilation?

Field (based on PRISMA-P	Content
Review question in SCOPE	New question
Review question in guideline	What is the effectiveness of nitric oxide in preterm babies requiring invasive respiratory support?
Type of review question	Intervention
Objective of the review	To determine the effectiveness of inhaled nitric oxide in babies born preterm babies that require invasive respiratory support.
Eligibility criteria – population/disease/condition/issue/domain	Preterm babies born who require invasive respiratory support: • Babies born preterm requiring invasive respiratory support **Exclusions:**

Field (based on PRISMA-P	Content
	• 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.
Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	Inhaled nitric oxide
Eligibility criteria – comparator(s)/control or reference (gold) standard	Control: • Placebo/control Comparisons: • Nitric oxide vs control • Low dose vs high dose nitric oxide • Early administration vs late administration nitric oxide

Outcomes and prioritisation	**Critical outcomes:**
	• Mortality before discharge
	• Bronchopulmonary dysplasia (Oxygen dependency at 36 weeks postmenstrual age or 28 days of age)
	• Neurodevelopmental outcome 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)

Field (based on PRISMA-P	Content
	▪ 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) o Severe hearing impairment (e.g deaf) o Severe visual impairment (e.g blind) **Important outcomes:** • Days on invasive ventilation • Severe intraventricular haemorrhage (grade 3 or 4) • Pulmonary haemorrhage • Methaemoglobinaemia
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

Field (based on PRISMA-P	Content
Proposed sensitivity/sub-group analysis, or meta-regression	Stratified analyses based on the following sub-groups of preterm babies Severity of disease as defined by oxygenation index: ▪ <10 ▪ 10-19.9 ▪ >20 Post-natal age at initiation of therapy ▪ <3 days ▪ >3 days Gestational age at birth: ▪ < 26+6 weeks ▪ 27-31+6 weeks ▪ 32-36+6 weeks
Selection process – duplicate screening/selection/analysis	Dual sifting will be undertaken for this question using NGA STAR software. 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 will not be performed 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.

Field (based on PRISMA-P	Content
	NGA STAR software will be used for study sifting, data extraction, recording quality assessment using checklists and generating bibliographies/citations, Data management for the corresponding Network meta-analysis are recorded in a separate protocol.
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 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 andpublished 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

Field (based on PRISMA-P	Content
	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. Trial registries will be examined to identify missing evidence: Clinical trials.gov, NIHR Clinical Trials GatewayD

Field (based on PRISMA-P	Content
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 anddrafted 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 andsocial care in England
PROSPERO registration number	Not registered

Appendix B – Literature search strategies

Literature search strategies for question 1.1 What respiratory support (excluding resuscitation) is the most effective for preterm babies before admission to the neonatal unit?

Systematic reviews and RCTs

Date of initial search: 22/11/2017

Database(s): Embase 1980 to 2017 Week 47, 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: 03/07/2018

Database(s): Embase 1980 to 2018 Week 27, 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	(special and care and baby and unit*).tw.
16	((newborn or neonatal or neo-natal) adj ICU*1).tw.
17	((newborn or neonat* or neo-nat* or prematur* or preterm or pre-term or pre?mie* or premie*1) adj2 (unit or care or department* or facilit* or hospital*)).tw.
18	(SCBU or NICU).tw.
19	or/1-18
20	Time Factors/
21	Time-to- Treatment/
22	exp Perinatal Care/
23	Infant Mortality/
24	or/20-23 use ppez
25	Premature Birth/
26	Delivery Rooms/
27	25 or 26 use ppez
28	24 and 27
29	time factor/
30	time to treatment/
31	perinatal period/
32	newborn period/
33	newborn morbidity/ or newborn mortality/ or infant mortality/
34	or/29-33 use emez
35	exp "immature and premature labor"/
36	delivery room/ or delivery/
37	35 or 36 use emez
38	34 and 37
39	(birth or born or labo?r or gold* hour or first hour or first day or twenty four hours or (gold* adj2 minute*) or ((delivery or labo?r or obstetric) adj2 (room* or suite*))).ti.
40	((initial or first or early) adj2 (manag* or stabili* or support*)).ti.
41	((before or prior or time) adj2 admission).ti.
42	or/39-41
43	28 or 38 or 42
44	19 and 43

#	Searches
45	exp Respiration, Artificial/
46	exp Ventilators, Mechanical/
47	exp Intubation, Intratracheal/
48	exp Pulmonary Surfactants/
49	Airway Extubation/
50	Oxygen Inhalation Therapy/
51	or/45-50 use ppez
52	exp artificial ventilation/
53	exp assisted ventilation/
54	exp respiratory tract intubation/
55	respiratory care/
56	oxygen therapy/
57	extubation/
58	*surfactant/
59	lung surfactant/
60	or/52-59 use emez
61	((respirat* or breath* or airway* or oxygen*) adj3 (support* or assist* or artificial or control* or oscillat* or pressure)).tw.
62	ventilat*.tw.
63	nasal cannula.tw.
64	(hi flow or HF or HFNC or HHFNC or HHHFNC or CPAP or MIST or LISA or AMV or INSURE or ISX).tw.
65	surfactant*.tw.
66	(intubat* or extubat* or endotracheal).tw.
67	or/61-66
68	51 or 60 or 67
69	44 and 68
70	Letter/ use ppez
71	letter.pt. or letter/ use emez
72	note.pt.
73	editorial.pt.
74	Editorial/ use ppez
75	News/ use ppez
76	exp Historical Article/ use ppez
77	Anecdotes as Topic/ use ppez
78	Comment/ use ppez
79	Case Report/ use ppez
80	case report/ or case study/ use emez
81	(letter or comment*).ti.
82	or/70-81
83	randomized controlled trial/ use ppez
84	randomized controlled trial/ use emez
85	random*.ti,ab.
86	or/83-85
87	82 not 86
88	animals/ not humans/ use ppez
89	animal/ not human/ use emez
90	nonhuman/ use emez
91	exp Animals, Laboratory/ use ppez
92	exp Animal Experimentation/ use ppez
93	exp Animal Experiment/ use emez
94	exp Experimental Animal/ use emez
95	exp Models, Animal/ use ppez
96	animal model/ use emez
97	exp Rodentia/ use ppez
98	exp Rodent/ use emez
99	(rat or rats or mouse or mice).ti.
100	or/87-99
101	69 not 100
102	Meta-Analysis/
103	Meta-Analysis as Topic/
104	systematic review/
105	meta-analysis/
106	(meta analy* or metanaly* or metaanaly*).ti,ab.
107	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
108	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
109	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
110	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
111	(search* adj4 literature).ab.
112	(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.

#	Searches
113	cochrane.jw.
114	((pool* or combined) adj2 (data or trials or studies or results)).ab.
115	or/102-103,106,108-113 use ppez
116	or/104-107,109-114 use emez
117	or/115-116
118	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.
119	118 use ppez
120	(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.
121	120 use ppez
122	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.
123	122 use emez
124	119 or 121
125	123 or 124
126	117 or 125
127	101 and 126
128	limit 127 to english language
129	limit 128 to yr="1990 -Current"
130	remove duplicates from 129

Observational studies

Date of initial search: 22/11/2017

Database(s): Embase 1980 to 2017 Week 47, 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: 03/07/2018

Database(s): Embase 1980 to 2018 Week 27, 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	(special and care and baby and unit*).tw.
16	((newborn or neonatal or neo-natal) adj ICU*1).tw.
17	((newborn or neonat* or neo-nat* or prematur* or preterm or pre-term or pre?mie* or premie*1) adj2 (unit or care or department* or facilit* or hospital*)).tw.
18	(SCBU or NICU).tw.
19	or/1-18
20	Time Factors/
21	Time-to- Treatment/
22	exp Perinatal Care/
23	Infant Mortality/
24	or/20-23 use ppez
25	Premature Birth/
26	Delivery Rooms/
27	25 or 26 use ppez
28	24 and 27
29	time factor/
30	time to treatment/

#	Searches
31	perinatal period/
32	newborn period/
33	newborn morbidity/ or newborn mortality/ or infant mortality/
34	or/29-33 use emez
35	exp "immature and premature labor"/
36	delivery room/ or delivery/
37	35 or 36 use emez
38	34 and 37
39	(birth or born or labo?r or gold* hour or first hour or first day or twenty four hours or (gold* adj2 minute*) or ((delivery or labour or labor or obstetric) adj2 (room* or suite*))).ti.
40	((initial or first or early) adj2 (manag* or stabili* or support*)).ti.
41	((before or prior or time) adj2 admission).ti.
42	or/39-41
43	28 or 38 or 42
44	19 and 43
45	exp Respiration, Artificial/
46	exp Ventilators, Mechanical/
47	exp Intubation, Intratracheal/
48	exp Pulmonary Surfactants/
49	Airway Extubation/
50	Oxygen Inhalation Therapy/
51	or/45-50 use ppez
52	exp artificial ventilation/
53	exp assisted ventilation/
54	exp respiratory tract intubation/
55	respiratory care/
56	oxygen therapy/
57	extubation/
58	*surfactant/
59	lung surfactant/
60	or/52-59 use emez
61	((respirat* or breath* or airway* or oxygen*) adj3 (support* or assist* or artificial or control* or oscillat* or pressure)).tw.
62	ventilat*.tw.
63	nasal cannula.tw.
64	(hi flow or HF or HFNC or HHFNC or HHHFNC or CPAP or MIST or LISA or AMV or INSURE or ISX).tw.
65	surfactant*.tw.
66	(intubat* or extubat* or endotracheal).tw.
67	or/61-66
68	51 or 60 or 67
69	44 and 68
70	Letter/ use ppez
71	letter.pt. or letter/ use emez
72	note.pt.
73	editorial.pt.
74	Editorial/ use ppez
75	News/ use ppez
76	exp Historical Article/ use ppez
77	Anecdotes as Topic/ use ppez
78	Comment/ use ppez
79	Case Report/ use ppez
80	case report/ or case study/ use emez
81	(letter or comment*).ti.
82	or/70-81
83	randomized controlled trial/ use ppez
84	randomized controlled trial/ use emez
85	random*.ti,ab.
86	or/83-85
87	82 not 86
88	animals/ not humans/ use ppez
89	animal/ not human/ use emez
90	nonhuman/ use emez
91	exp Animals, Laboratory/ use ppez
92	exp Animal Experimentation/ use ppez
93	exp Animal Experiment/ use emez
94	exp Experimental Animal/ use emez
95	exp Models, Animal/ use ppez
96	animal model/ use emez
97	exp Rodentia/ use ppez
98	exp Rodent/ use emez

#	Searches
99	(rat or rats or mouse or mice).ti.
100	or/87-99
101	69 not 100
102	Epidemiologic Studies/
103	Case Control Studies/
104	Retrospective Studies/
105	Cohort Studies/
106	Longitudinal Studies/
107	Follow-Up Studies/
108	Prospective Studies/
109	Cross-Sectional Studies/
110	or/102-109 use ppez
111	clinical study/
112	case control study/
113	family study/
114	longitudinal study/
115	retrospective study/
116	prospective study/
117	cohort analysis/
118	or/111-117 use emez
119	((retrospective$ or cohort$ or longitudinal or follow?up or prospective or cross section$) adj3 (stud$ or research or analys$)).ti.
120	110 or 118 or 119
121	101 and 120
122	limit 121 to english language
123	limit 122 to yr="1990 -Current"
124	remove duplicates from 123

Health economics

Date of initial search: 22/11/2017

Database(s): Embase 1980 to 2017 Week 47, 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: 03/07/2018

Database(s): Embase 1980 to 2018 Week 27, 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	(special and care and baby and unit*).tw.
16	((newborn or neonatal or neo-natal) adj ICU*1).tw.
17	((newborn or neonat* or neo-nat* or prematur* or preterm or pre-term or pre?mie* or premie*1) adj2 (unit or care or department* or facilit* or hospital*)).tw.
18	(SCBU or NICU).tw.
19	or/1-18
20	Time Factors/
21	Time-to- Treatment/
22	exp Perinatal Care/
23	Infant Mortality/
24	or/20-23 use ppez
25	Premature Birth/

#	Searches
26	Delivery Rooms/
27	25 or 26 use ppez
28	24 and 27
29	time factor/
30	time to treatment/
31	perinatal period/
32	newborn period/
33	newborn morbidity/ or newborn mortality/ or infant mortality/
34	or/29-33 use emez
35	exp "immature and premature labor"/
36	delivery room/ or delivery/
37	35 or 36 use emez
38	34 and 37
39	(birth or born or labo?r or gold* hour or first hour or first day or twenty four hours or (gold* adj2 minute*) or ((delivery or labour or labor or obstetric) adj2 (room* or suite*))).ti.
40	((initial or first or early) adj2 (manag* or stabili* or support*)).ti.
41	((before or prior or time) adj2 admission).ti.
42	or/39-41
43	28 or 38 or 42
44	19 and 43
45	exp Respiration, Artificial/
46	exp Ventilators, Mechanical/
47	exp Intubation, Intratracheal/
48	exp Pulmonary Surfactants/
49	Airway Extubation/
50	Oxygen Inhalation Therapy/
51	or/45-50 use ppez
52	exp artificial ventilation/
53	exp assisted ventilation/
54	exp respiratory tract intubation/
55	respiratory care/
56	oxygen therapy/
57	extubation/
58	*surfactant/
59	lung surfactant/
60	or/52-59 use emez
61	((respirat* or breath* or airway* or oxygen*) adj3 (support* or assist* or artificial or control* or oscillat* or pressure)).tw.
62	ventilat*.tw.
63	nasal cannula.tw.
64	(hi flow or HF or HFNC or HHFNC or HHHFNC or CPAP or MIST or LISA or AMV or INSURE or ISX).tw.
65	surfactant*.tw.
66	(intubat* or extubat* or endotracheal).tw.
67	or/61-66
68	51 or 60 or 67
69	44 and 68
70	Letter/ use ppez
71	letter.pt. or letter/ use emez
72	note.pt.
73	editorial.pt.
74	Editorial/ use ppez
75	News/ use ppez
76	exp Historical Article/ use ppez
77	Anecdotes as Topic/ use ppez
78	Comment/ use ppez
79	Case Report/ use ppez
80	case report/ or case study/ use emez
81	(letter or comment*).ti.
82	or/70-81
83	randomized controlled trial/ use ppez
84	randomized controlled trial/ use emez
85	random*.ti,ab.
86	or/83-85
87	82 not 86
88	animals/ not humans/ use ppez
89	animal/ not human/ use emez
90	nonhuman/ use emez
91	exp Animals, Laboratory/ use ppez
92	exp Animal Experimentation/ use ppez
93	exp Animal Experiment/ use emez

#	Searches
94	exp Experimental Animal/ use emez
95	exp Models, Animal/ use ppez
96	animal model/ use emez
97	exp Rodentia/ use ppez
98	exp Rodent/ use emez
99	(rat or rats or mouse or mice).ti.
100	or/87-99
101	69 not 100
102	Economics/
103	Value of life/
104	exp "Costs and Cost Analysis"/
105	exp Economics, Hospital/
106	exp Economics, Medical/
107	Economics, Nursing/
108	Economics, Pharmaceutical/
109	exp "Fees and Charges"/
110	exp Budgets/
111	or/102-110 use ppez
112	health economics/
113	exp economic evaluation/
114	exp health care cost/
115	exp fee/
116	budget/
117	funding/
118	or/112-117 use emez
119	budget*.ti,ab.
120	cost*.ti.
121	(economic* or pharmaco?economic*).ti.
122	(price* or pricing*).ti,ab.
123	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
124	(financ* or fee or fees).ti,ab.
125	(value adj2 (money or monetary)).ti,ab.
126	or/119-124
127	111 or 118 or 126
128	101 and 127
129	limit 128 to english language
130	limit 129 to yr="1990 -Current"
131	remove duplicates from 130

Systematic reviews, RCTs and Health economics

Date of initial search: 23/11/2017

Database(s): The Cochrane Library, issue 11 of 12, November 2017

Date of updated search: 02/07/2018

Database(s): The Cochrane Library, issue 7 of 12, July 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: [Time Factors] this term only
#12	MeSH descriptor: [Time-to-Treatment] this term only
#13	MeSH descriptor: [Perinatal Care] this term only
#14	MeSH descriptor: [Infant Mortality] explode all trees
#15	{or #11-#14}
#16	MeSH descriptor: [Obstetric Labor, Premature] explode all trees
#17	MeSH descriptor: [Delivery Rooms] this term only
#18	#16 or #17
#19	#15 and #18

ID	Search
#20	(birth or born or labo?r or gold* hour or first hour or first day or twenty four hours or (gold* near/2 minute*) or ((delivery or labour or labor or obstetric) near/2 (room* or suite*))):ti
#21	((initial or first or early) near/2 (manag* or stabili* or support*)):ti
#22	((before or prior or time) near/2 admission):ti
#23	{or #20-#22}
#24	#19 or #23
#25	#10 and #24
#26	MeSH descriptor: [Respiration, Artificial] explode all trees
#27	MeSH descriptor: [Ventilators, Mechanical] explode all trees
#28	MeSH descriptor: [Intubation, Intratracheal] explode all trees
#29	MeSH descriptor: [Pulmonary Surfactants] explode all trees
#30	MeSH descriptor: [Airway Extubation] explode all trees
#31	MeSH descriptor: [Oxygen Inhalation Therapy] this term only
#32	((respirat* or breath* or airway* or oxygen*) near/3 (support* or assist* or artificial or control* or oscillat* or pressure))
#33	ventilat*
#34	nasal cannula
#35	(hi flow or HF or HFNC or HHFNC or HHHFNC or CPAP or MIST or LISA or AMV or INSURE or ISX)
#36	surfactant*
#37	(intubat* or extubat* or endotracheal)
#38	{or #26-#37}
#39	#25 and #38 Publication Year from 1990 to 2017

Literature search strategies for question 3.3 What is the most effective way of using surfactant in managing respiratory distress syndrome?

Systematic reviews and RCTs

Date of initial search: 01/11/2017

Database(s): Embase 1980 to 2017 Week 41, 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: 03/07/2018

Database(s): Embase 1980 to 2018 Week 27, 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 or ELBW).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	newborn care/ use emez
14	(special and care and baby and unit*).tw.
15	((newborn or neonatal or neo-natal) adj3 (ICU*1 or unit*)).tw.
16	(SCBU or NICU).tw.
17	or/1-16
18	exp Pulmonary Surfactants/ use ppez
19	surfactant/ use emez
20	lung surfactant/ use emez
21	poractant/ use emez
22	beractant/ use emez
23	surfactant*.tw.
24	(poractant* or curosurf).tw.
25	(beractant* or survanta or alveofact).tw.
26	or/18-25
27	17 and 26

#	Searches
28	Letter/ use ppez
29	letter.pt. or letter/ use emez
30	note.pt.
31	editorial.pt.
32	Editorial/ use ppez
33	News/ use ppez
34	exp Historical Article/ use ppez
35	Anecdotes as Topic/ use ppez
36	Comment/ use ppez
37	Case Report/ use ppez
38	case report/ or case study/ use emez
39	(letter or comment*).ti.
40	or/28-39
41	randomized controlled trial/ use ppez
42	randomized controlled trial/ use emez
43	random*.ti,ab.
44	or/41-43
45	40 not 44
46	animals/ not humans/ use ppez
47	animal/ not human/ use emez
48	nonhuman/ use emez
49	exp Animals, Laboratory/ use ppez
50	exp Animal Experimentation/ use ppez
51	exp Animal Experiment/ use emez
52	exp Experimental Animal/ use emez
53	exp Models, Animal/ use ppez
54	animal model/ use emez
55	exp Rodentia/ use ppez
56	exp Rodent/ use emez
57	(rat or rats or mouse or mice).ti.
58	or/45-57
59	27 not 58
60	limit 59 to english language
61	limit 60 to yr="1990 -Current"
62	Meta-Analysis/
63	Meta-Analysis as Topic/
64	systematic review/
65	meta-analysis/
66	(meta analy* or metanaly* or metaanaly*).ti,ab.
67	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
68	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
69	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
70	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
71	(search* adj4 literature).ab.
72	(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.
73	cochrane.jw.
74	((pool* or combined) adj2 (data or trials or studies or results)).ab.
75	or/62-63,66,68-73 use ppez
76	or/64-67,69-74 use emez
77	or/75-76
78	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.
79	78 use ppez
80	(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.
81	80 use ppez
82	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.
83	82 use emez
84	79 or 81
85	83 or 84
86	77 or 85
87	61 and 86
88	remove duplicates from 87

Observational studies

Date of initial search: 01/11/2017

Database(s): Embase 1980 to 2017 Week 44, 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: 03/07/2018

Database(s): Embase 1980 to 2018 Week 27, 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 or ELBW).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	newborn care/ use emez
14	(special and care and baby and unit*).tw.
15	((newborn or neonatal or neo-natal) adj3 (ICU*1 or unit*)).tw.
16	(SCBU or NICU).tw.
17	or/1-16
18	exp Pulmonary Surfactants/ use ppez
19	surfactant/ use emez
20	lung surfactant/ use emez
21	poractant/ use emez
22	beractant/ use emez
23	surfactant*.tw.
24	(poractant* or curosurf).tw.
25	(beractant* or survanta or alveofact).tw.
26	or/18-25
27	17 and 26
28	Letter/ use ppez
29	letter.pt. or letter/ use emez
30	note.pt.
31	editorial.pt.
32	Editorial/ use ppez
33	News/ use ppez
34	exp Historical Article/ use ppez
35	Anecdotes as Topic/ use ppez
36	Comment/ use ppez
37	Case Report/ use ppez
38	case report/ or case study/ use emez
39	(letter or comment*).ti.
40	or/28-39
41	randomized controlled trial/ use ppez
42	randomized controlled trial/ use emez
43	random*.ti,ab.
44	or/41-43
45	40 not 44
46	animals/ not humans/ use ppez
47	animal/ not human/ use emez
48	nonhuman/ use emez
49	exp Animals, Laboratory/ use ppez
50	exp Animal Experimentation/ use ppez
51	exp Animal Experiment/ use emez
52	exp Experimental Animal/ use emez
53	exp Models, Animal/ use ppez
54	animal model/ use emez
55	exp Rodentia/ use ppez
56	exp Rodent/ use emez
57	(rat or rats or mouse or mice).ti.
58	or/45-57
59	27 not 58
60	limit 59 to english language

#	Searches
61	limit 60 to yr="1990 -Current"
62	Epidemiologic Studies/
63	Case Control Studies/
64	Retrospective Studies/
65	Cohort Studies/
66	Longitudinal Studies/
67	Follow-Up Studies/
68	Prospective Studies/
69	Cross-Sectional Studies/
70	or/62-69 use ppez
71	clinical study/
72	case control study/
73	family study/
74	longitudinal study/
75	retrospective study/
76	prospective study/
77	cohort analysis/
78	or/71-77 use emez
79	((retrospective$ or cohort$ or longitudinal or follow?up or prospective or cross section$) adj3 (stud$ or research or analys$)).ti.
80	70 or 78 or 79
81	61 and 80
82	remove duplicates from 81

Health economics

Date of initial search: 01/11/2017

Database(s): Embase 1980 to 2017 Week 44, 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: 03/07/2018

Database(s): Embase 1980 to 2018 Week 27, 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 or ELBW).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	newborn care/ use emez
14	(special and care and baby and unit*).tw.
15	((newborn or neonatal or neo-natal) adj3 (ICU*1 or unit*)).tw.
16	(SCBU or NICU).tw.
17	or/1-16
18	exp Pulmonary Surfactants/ use ppez
19	surfactant/ use emez
20	lung surfactant/ use emez
21	poractant/ use emez
22	beractant/ use emez
23	surfactant*.tw.
24	(poractant* or curosurf).tw.
25	(beractant* or survanta or alveofact).tw.
26	or/18-25
27	17 and 26
28	Letter/ use ppez
29	letter.pt. or letter/ use emez
30	note.pt.

#	Searches
31	editorial.pt.
33	News/ use ppez
34	exp Historical Article/ use ppez
35	Anecdotes as Topic/ use ppez
36	Comment/ use ppez
37	Case Report/ use ppez
38	case report/ or case study/ use emez
39	(letter or comment*).ti.
40	or/28-39
41	randomized controlled trial/ use ppez
42	randomized controlled trial/ use emez
43	random*.ti,ab.
44	or/41-43
45	40 not 44
46	animals/ not humans/ use ppez
47	animal/ not human/ use emez
48	nonhuman/ use emez
49	exp Animals, Laboratory/ use ppez
50	exp Animal Experimentation/ use ppez
51	exp Animal Experiment/ use emez
52	exp Experimental Animal/ use emez
53	exp Models, Animal/ use ppez
54	animal model/ use emez
55	exp Rodentia/ use ppez
56	exp Rodent/ use emez
57	(rat or rats or mouse or mice).ti.
58	or/45-57
59	27 not 58
60	limit 59 to english language
61	limit 60 to yr="1990 -Current"
62	Economics/
63	Value of life/
64	exp "Costs and Cost Analysis"/
65	exp Economics, Hospital/
66	exp Economics, Medical/
67	Economics, Nursing/
68	Economics, Pharmaceutical/
69	exp "Fees and Charges"/
70	exp Budgets/
71	or/62-70 use ppez
72	health economics/
73	exp economic evaluation/
74	exp health care cost/
75	exp fee/
76	budget/
77	funding/
78	or/72-77 use emez
79	budget*.ti,ab.
80	cost*.ti.
81	(economic* or pharmaco?economic*).ti.
82	(price* or pricing*).ti,ab.
83	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
84	(financ* or fee or fees).ti,ab.
85	(value adj2 (money or monetary)).ti,ab.
86	or/79-84
87	71 or 78 or 86
88	61 and 87
89	remove duplicates from 88

The Cochrane Library

Date of initial search: 01/11/2017

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

Date of updated search: 02/07/2018

Database(s): The Cochrane Library, issue 7 of 12, July 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: [Pulmonary Surfactants] explode all trees
#12	surfactant*
#13	(poractant* or curosurf)
#14	(beractant* or survanta or alveofact)
#15	{or #11-#14}
#16	#10 and #15 Publication Year from 1990 to 2017

Literature search strategies for question 3.1 What is the most effective way to administer oxygen during respiratory support?

Date of initial search: 27/03/18

Database(s): Embase 1980 to 2018 Week 13, 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: 03/07/2018

Database(s): Embase 1980 to 2018 Week 27, 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.
16	exp Respiratory Distress Syndrome, Newborn/ use ppez
17	neonatal respiratory distress syndrome/ use emez
18	or/1-17
19	exp *oxygen therapy/ use emez
20	oxygen/ad, ih, na use emez
21	exp Oxygen/ad, th use ppez
22	exp *Oxygen Inhalation Therapy/ use ppez
23	((oxygen* or o2) adj3 (admin* or automat* or deliver* or humidif* or non humidif* or nonhumidif* or unhumidif* or incubat* or inhal* or low flow* or manual or method* or nasal cannula* or intranasal* or titrat*)).tw.
24	or/19-23
25	18 and 24
26	limit 25 to english language
27	limit 26 to yr="1990 -Current"
28	Letter/ use ppez
29	letter.pt. or letter/ use emez
30	note.pt.
31	editorial.pt.
32	Editorial/ use ppez
33	News/ use ppez
34	exp Historical Article/ use ppez

#	Searches
35	Anecdotes as Topic/ use ppez
36	Comment/ use ppez
37	Case Report/ use ppez
38	case report/ or case study/ use emez
39	(letter or comment*).ti.
40	or/28-39
41	randomized controlled trial/ use ppez
42	randomized controlled trial/ use emez
43	random*.ti,ab.
44	or/41-43
45	40 not 44
46	animals/ not humans/ use ppez
47	animal/ not human/ use emez
48	nonhuman/ use emez
49	exp Animals, Laboratory/ use ppez
50	exp Animal Experimentation/ use ppez
51	exp Animal Experiment/ use emez
52	exp Experimental Animal/ use emez
53	exp Models, Animal/ use ppez
54	animal model/ use emez
55	exp Rodentia/ use ppez
56	exp Rodent/ use emez
57	(rat or rats or mouse or mice).ti.
58	or/45-57
59	27 not 58
60	remove duplicates from 59

Health economics

Date of initial search: 27/03/18

Database(s): Embase 1980 to 2018 Week 13, 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: 03/07/2018

Database(s): Embase 1980 to 2018 Week 27, 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.
16	exp Respiratory Distress Syndrome, Newborn/ use ppez
17	neonatal respiratory distress syndrome/ use emez
18	or/1-17
19	exp *oxygen therapy/ use emez
20	oxygen/ad, ih, na use emez
21	oxygen breathing/ use emez
22	oxygen administration kit/ use emez
23	oxygen delivery device/ use emez
24	neonatal incubator/ use emez
25	nasal oxygen catheter/ use emez or exp nasal cannula/ use emez
26	exp respiratory gas humidifier/ use emez
27	exp Oxygen/ad, th use ppez

#	Searches
28	exp *Oxygen Inhalation Therapy/ use ppez
29	Incubators, Infant/ use ppez
30	Cannula/ use ppez
31	Humidifiers/ use ppez
32	((oxygen* or o2) adj3 (admin* or automat* or deliver* or humidif* or non humidif* or nonhumidif* or unhumidif* or incubat* or inhal* or low flow* or manual* or method* or nasal cannula* or intranasal* or titrat*)).tw.
33	or/19-32
34	18 and 33
35	limit 34 to english language
36	limit 35 to yr="1990 -Current"
37	Letter/ use ppez
38	letter.pt. or letter/ use emez
39	note.pt.
40	editorial.pt.
41	Editorial/ use ppez
42	News/ use ppez
43	exp Historical Article/ use ppez
44	Anecdotes as Topic/ use ppez
45	Comment/ use ppez
46	Case Report/ use ppez
47	case report/ or case study/ use emez
48	(letter or comment*).ti.
49	or/37-48
50	randomized controlled trial/ use ppez
51	randomized controlled trial/ use emez
52	random*.ti,ab.
53	or/50-52
54	49 not 53
55	animals/ not humans/ use ppez
56	animal/ not human/ use emez
57	nonhuman/ use emez
58	exp Animals, Laboratory/ use ppez
59	exp Animal Experimentation/ use ppez
60	exp Animal Experiment/ use emez
61	exp Experimental Animal/ use emez
62	exp Models, Animal/ use ppez
63	animal model/ use emez
64	exp Rodentia/ use ppez
65	exp Rodent/ use emez
66	(rat or rats or mouse or mice).ti.
67	or/54-66
68	36 not 67
69	remove duplicates from 68
70	Economics/
71	Value of life/
72	exp "Costs and Cost Analysis"/
73	exp Economics, Hospital/
74	exp Economics, Medical/
75	Economics, Nursing/
76	Economics, Pharmaceutical/
77	exp "Fees and Charges"/
78	exp Budgets/
79	(or/70-78) use ppez
80	health economics/
81	exp economic evaluation/
82	exp health care cost/
83	exp fee/
84	budget/
85	funding/
86	(or/80-85) use emez
87	budget*.ti,ab.
88	cost*.ti.
89	(economic* or pharmaco?economic*).ti.
90	(price* or pricing*).ti,ab.
91	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
92	(financ* or fee or fees).ti,ab.
93	(value adj2 (money or monetary)).ti,ab.
94	or/87-92
95	79 or 86 or 94
96	69 and 95

Date of initial search: 27/03/2018

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

Date of updated search: 02/07/2018

Database: The Cochrane Library, issue 7 of 12, July 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: [Oxygen] explode all trees and with qualifier(s): [Administration & dosage - AD]
#12	MeSH descriptor: [Oxygen Inhalation Therapy] explode all trees
#13	MeSH descriptor: [Incubators, Infant] this term only
#14	MeSH descriptor: [Cannula] this term only
#15	MeSH descriptor: [Humidifiers] this term only
#16	((oxygen* or o2) near/3 (admin* or automat* or deliver* or humidif* or non humidif* or nonhumidif* or unhumidif* or incubat* or inhal* or low flow* or manual* or method* or nasal cannula* or intranasal* or titrat*))
#17	{or #11-#16}
#18	#10 and #17 Publication Year from 1990 to 2018

Literature search strategies for question 3.2 What is the effectiveness and safety of the different assisted ventilation techniques in preterm babies?

Date of initial search: 09/08/2017

Database(s): Embase 1980 to 2017 Week 32, 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: 01/05/2018

Database(s): Embase 1980 to 2018 Week 18, 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 neo-nat* or newborn* 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

#	Searches
24	((artificial* or assist* or bilevel or bi-level or continu* or control* or conventional or high flow or high-flow or high frequency or high-frequency or intermittent or invasive or mandatory or mechanic* or nasal cannula or non-invasive or noninvasive or non-synchroni* or nonsynchroni* or non-trigger* or oscillat* or positive or pressure* or support* or sychroni* or target* or trigger* or volume or unsynchroni*) adj2 ventilat*).tw.
25	(AC or BIPAP or CIMV or CMV or CPAP or HFNC or HHFNC or HHHFNC or HFOV or IMV or NIPPV or PRVC or PRVCV or PSV or PTV or SIMV or SIPPV or TCPL or TTV or VAPS or VGV).tw.
26	or/19-25
27	18 and 26
28	limit 27 to english language
29	limit 28 to yr="1990 -Current"
30	Letter/ use ppez
31	letter.pt. or letter/ use emez
32	note.pt.
33	editorial.pt.
34	Editorial/ use ppez
35	News/ use ppez
36	exp Historical Article/ use ppez
37	Anecdotes as Topic/ use ppez
38	Comment/ use ppez
39	Case Report/ use ppez
40	case report/ or case study/ use emez
41	(letter or comment*).ti.
42	or/30-41
43	randomised controlled trial/ use ppez
44	randomised controlled trial/ use emez
45	random*.ti,ab.
46	or/43-45
47	42 not 46
48	animals/ not humans/ use ppez
49	animal/ not human/ use emez
50	nonhuman/ use emez
51	exp Animals, Laboratory/ use ppez
52	exp Animal Experimentation/ use ppez
53	exp Animal Experiment/ use emez
54	exp Experimental Animal/ use emez
55	exp Models, Animal/ use ppez
56	animal model/ use emez
57	exp Rodentia/ use ppez
58	exp Rodent/ use emez
59	(rat or rats or mouse or mice).ti.
60	or/47-59
61	29 not 60
62	Meta-Analysis/
63	Meta-Analysis as Topic/
64	systematic review/
65	meta-analysis/
66	(meta analy* or metanaly* or metaanaly*).ti,ab.
67	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
68	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
69	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
70	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
71	(search* adj4 literature).ab.
72	(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.
73	cochrane.jw.
74	((pool* or combined) adj2 (data or trials or studies or results)).ab.
75	or/62-63,66,68-73 use ppez
76	or/64-67,69-74 use emez
77	or/75-76
78	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.
79	78 use ppez
80	(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.
81	80 use ppez
82	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.
83	82 use emez
84	79 or 81
85	83 or 84

#	Searches
86	77 or 85
87	61 and 86

Date of initial search: 09/08/2017

Database: The Cochrane Library, issue 8 of 12, August 2017

Date of updated search: 01/05/2018

Database: The Cochrane Library, issue 4 of 4, April 2018

ID	Search
#1	MeSH descriptor: [Infant, Newborn] explode all trees
#2	(infan* or neonat* orneo-nat* 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) 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	((artificial* or assist* or bilevel or bi-level or continu* or control* or conventional or high flow or high-flow or high frequency or high-frequency or intermittent or invasive or mandatory or mechanic* or nasal cannula or non-invasive or noninvasive or non-synchroni* or nonsynchroni* or non-trigger* or oscillat* or positive or pressure* or support* or sychroni* or target* or trigger* or volume or unsynchroni*) near/2 ventilat*)
#12	(AC or BIPAP or CIMV or CMV or CPAP or HFNC or HHFNC or HHHFNC or HFOV or IMV or NIPPV or PRVC or PRVCV or PSV or PTV or SIMV or SIPPV or TCPL or TTV or VAPS or VGV)
#13	{or #9-#12}
#14	#8 and #13 Publication Year from 1990 to 2017

Health economics

Date of initial search: 09/08/2017

Database(s): Embase 1980 to 2017 Week 32, 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: 02/05/2018

Database(s): Embase 1980 to 2018 Week 18, 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 neo-nat* or newborn* 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

#	Searches
23	exp ventilator/ use emez
24	((artificial* or assist* or bilevel or bi-level or continu* or control* or conventional or high flow or high-flow or high frequency or high-frequency or intermittent or invasive or mandatory or mechanic* or nasal cannula or non-invasive or noninvasive or non-synchroni* or nonsynchroni* or non-trigger* or oscillat* or positive or pressure* or support* or sychroni* or target* or trigger* or volume or unsynchroni*) adj2 ventilat*).tw.
25	(AC or BIPAP or CIMV or CMV or CPAP or HFNC or HHFNC or HHHFNC or HFOV or IMV or NIPPV or PRVC or PRVCV or PSV or PTV or SIMV or SIPPV or TCPL or TTV or VAPS or VGV).tw.
26	or/19-25
27	18 and 26
28	limit 27 to english language
29	limit 28 to yr="1990 -Current"
30	Letter/ use ppez
31	letter.pt. or letter/ use emez
32	note.pt.
33	editorial.pt.
34	Editorial/ use ppez
35	News/ use ppez
36	exp Historical Article/ use ppez
37	Anecdotes as Topic/ use ppez
38	Comment/ use ppez
39	Case Report/ use ppez
40	case report/ or case study/ use emez
41	(letter or comment*).ti.
42	or/30-41
43	randomised controlled trial/ use ppez
44	randomised controlled trial/ use emez
45	random*.ti,ab.
46	or/43-45
47	42 not 46
48	animals/ not humans/ use ppez
49	animal/ not human/ use emez
50	nonhuman/ use emez
51	exp Animals, Laboratory/ use ppez
52	exp Animal Experimentation/ use ppez
53	exp Animal Experiment/ use emez
54	exp Experimental Animal/ use emez
55	exp Models, Animal/ use ppez
56	animal model/ use emez
57	exp Rodentia/ use ppez
58	exp Rodent/ use emez
59	(rat or rats or mouse or mice).ti.
60	or/47-59
61	29 not 60
62	Economics/
63	Value of life/
64	exp "Costs and Cost Analysis"/
65	exp Economics, Hospital/
66	exp Economics, Medical/
67	Economics, Nursing/
68	Economics, Pharmaceutical/
69	exp "Fees and Charges"/
70	exp Budgets/
71	or/62-70 use ppez
72	health economics/
73	exp economic evaluation/
74	exp health care cost/
75	exp fee/
76	budget/
77	funding/
78	or/72-77 use emez
79	budget*.ti,ab.
80	cost*.ti.
81	(economic* or pharmaco?economic*).ti.
82	(price* or pricing*).ti,ab.
83	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
84	(financ* or fee or fees).ti,ab.
85	(value adj2 (money or monetary)).ti,ab.
86	or/79-84
87	71 or 78 or 86
88	61 and 87
89	remove duplicates from 88

Literature search strategies for question 3.7 What is the effectiveness of nitric oxide in preterm babies requiring invasive ventilation?

Systematic reviews and RCTs

Date of initial search: 09/01/18

Database(s): Embase 1980 to 2018 Week 02, 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	Nitric Oxide/ use ppez
25	Endothelium-Dependent Relaxing Factors/ use ppez
26	nitric oxide/ use emez
27	((nitric or nitrogen) adj3 (oxide or monoxide or oxygen)).tw.
28	endothelial?derived relax*.tw.
29	endothelial?dependent relax*.tw.
30	or/24-29
31	23 and 30
32	limit 31 to english language
33	limit 32 to yr="1990 -Current"
34	Letter/ use ppez
35	letter.pt. or letter/ use emez
36	note.pt.
37	editorial.pt.
38	Editorial/ use ppez
39	News/ use ppez
40	exp Historical Article/ use ppez
41	Anecdotes as Topic/ use ppez
42	Comment/ use ppez
43	Case Report/ use ppez
44	case report/ or case study/ use emez
45	(letter or comment*).ti.
46	or/34-45
47	randomised controlled trial/ use ppez
48	randomised controlled trial/ use emez
49	random*.ti,ab.
50	or/47-49

#	Searches
51	46 not 50
52	animals/ not humans/ use ppez
53	animal/ not human/ use emez
54	nonhuman/ use emez
55	exp Animals, Laboratory/ use ppez
56	exp Animal Experimentation/ use ppez
57	exp Animal Experiment/ use emez
58	exp Experimental Animal/ use emez
59	exp Models, Animal/ use ppez
60	animal model/ use emez
61	exp Rodentia/ use ppez
62	exp Rodent/ use emez
63	(rat or rats or mouse or mice).ti.
64	or/51-63
65	33 not 64
66	Meta-Analysis/
67	Meta-Analysis as Topic/
68	systematic review/
69	meta-analysis/
70	(meta analy* or metanaly* or metaanaly*).ti,ab.
71	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
72	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
73	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
74	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
75	(search* adj4 literature).ab.
76	(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.
77	cochrane.jw.
78	((pool* or combined) adj2 (data or trials or studies or results)).ab.
79	or/66-67,70,72-77 use ppez
80	or/68-71,73-78 use emez
81	or/79-80
82	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.
83	82 use ppez
84	(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.
85	84 use ppez
86	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.
87	86 use emez
88	83 or 85
89	87 or 88
90	81 or 89
91	65 and 90
92	remove duplicates from 91

Observational studies

Date of initial search: 09/01/2018

Database(s): Embase 1980 to 2018 Week 02, 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

#	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	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	Nitric Oxide/ use ppez
25	Endothelium-Dependent Relaxing Factors/ use ppez
26	nitric oxide/ use emez
27	((nitric or nitrogen) adj3 (oxide or monoxide or oxygen)).tw.
28	endothelial?derived relax*.tw.
29	endothelial?dependent relax*.tw.
30	or/24-29
31	23 and 30
32	limit 31 to english language
33	limit 32 to yr="1990 -Current"
34	Letter/ use ppez
35	letter.pt. or letter/ use emez
36	note.pt.
37	editorial.pt.
38	Editorial/ use ppez
39	News/ use ppez
40	exp Historical Article/ use ppez
41	Anecdotes as Topic/ use ppez
42	Comment/ use ppez
43	Case Report/ use ppez
44	case report/ or case study/ use emez
45	(letter or comment*).ti.
46	or/34-45
47	randomised controlled trial/ use ppez
48	randomised controlled trial/ use emez
49	random*.ti,ab.
50	or/47-49
51	46 not 50
52	animals/ not humans/ use ppez
53	animal/ not human/ use emez
54	nonhuman/ use emez
55	exp Animals, Laboratory/ use ppez
56	exp Animal Experimentation/ use ppez
57	exp Animal Experiment/ use emez
58	exp Experimental Animal/ use emez
59	exp Models, Animal/ use ppez
60	animal model/ use emez
61	exp Rodentia/ use ppez
62	exp Rodent/ use emez
63	(rat or rats or mouse or mice).ti.
64	or/51-63
65	33 not 64
66	Epidemiologic Studies/
67	Case Control Studies/
68	Retrospective Studies/
69	Cohort Studies/
70	Longitudinal Studies/
71	Follow-Up Studies/
72	Prospective Studies/
73	Cross-Sectional Studies/
74	or/66-73 use ppez
75	clinical study/

#	Searches
76	case control study/
77	family study/
78	longitudinal study/
79	retrospective study/
80	prospective study/
81	cohort analysis/
82	or/75-81 use emez
83	((retrospective$ or cohort$ or longitudinal or follow?up or prospective or cross section$) adj3 (stud$ or research or analys$)).ti.
84	74 or 82 or 83
85	65 and 84
86	remove duplicates from 85

Health economics

Date of initial search: 09/01/2018

Database(s): Embase 1980 to 2018 Week 02, 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	Nitric Oxide/ use ppez
25	Endothelium-Dependent Relaxing Factors/ use ppez
26	nitric oxide/ use emez
27	((nitric or nitrogen) adj3 (oxide or monoxide or oxygen)).tw.
28	endothelial?derived relax*.tw.
29	endothelial?dependent relax*.tw.
30	or/24-29
31	23 and 30
32	limit 31 to english language
33	limit 32 to yr="1990 -Current"
34	Letter/ use ppez
35	letter.pt. or letter/ use emez
36	note.pt.
37	editorial.pt.
38	Editorial/ use ppez
39	News/ use ppez
40	exp Historical Article/ use ppez

#	Searches
41	Anecdotes as Topic/ use ppez
42	Comment/ use ppez
43	Case Report/ use ppez
44	case report/ or case study/ use emez
45	(letter or comment*).ti.
46	or/34-45
47	randomised controlled trial/ use ppez
48	randomised controlled trial/ use emez
49	random*.ti,ab.
50	or/47-49
51	46 not 50
52	animals/ not humans/ use ppez
53	animal/ not human/ use emez
54	nonhuman/ use emez
55	exp Animals, Laboratory/ use ppez
56	exp Animal Experimentation/ use ppez
57	exp Animal Experiment/ use emez
58	exp Experimental Animal/ use emez
59	exp Models, Animal/ use ppez
60	animal model/ use emez
61	exp Rodentia/ use ppez
62	exp Rodent/ use emez
63	(rat or rats or mouse or mice).ti.
64	or/51-63
65	33 not 64
66	Economics/
67	Value of life/
68	exp "Costs and Cost Analysis"/
69	exp Economics, Hospital/
70	exp Economics, Medical/
71	Economics, Nursing/
72	Economics, Pharmaceutical/
73	exp "Fees and Charges"/
74	exp Budgets/
75	or/66-74 use ppez
76	health economics/
77	exp economic evaluation/
78	exp health care cost/
79	exp fee/
80	budget/
81	funding/
82	or/76-81 use emez
83	budget*.ti,ab.
84	cost*.ti.
85	(economic* or pharmaco?economic*).ti.
86	(price* or pricing*).ti,ab.
87	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
88	(financ* or fee or fees).ti,ab.
89	(value adj2 (money or monetary)).ti,ab.
90	or/83-88
91	75 or 82 or 90
92	65 and 91
93	remove duplicates from 92

Cochrane Library

Date of initial search: 09/01/2018

Database: The Cochrane Library: issue 1 of 12, January 2018

Date of updated search: 05/06/2018

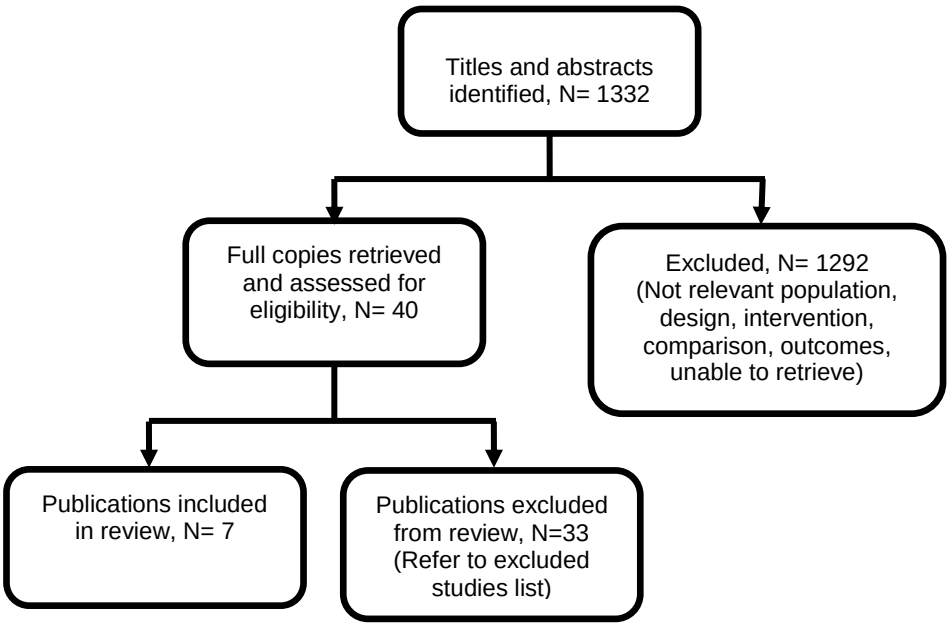
Database: The Cochrane Library: issue 6 of 12, June 2018

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

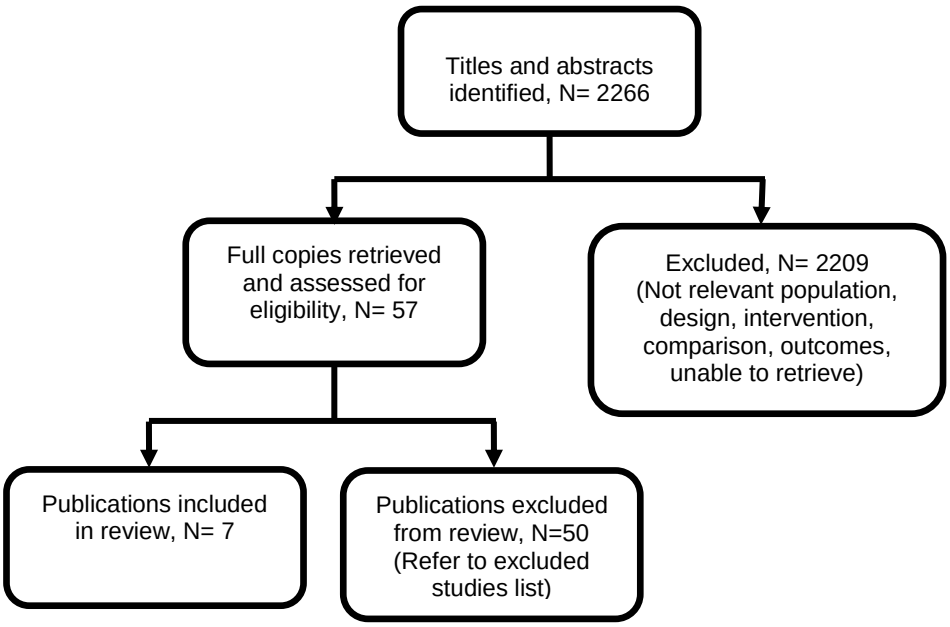
ID	Search
#6	MeSH descriptor: [Intensive Care Units, Neonatal] this term only
#7	(special and care and baby and unit*)
#8	((newborn or neonatal or neo-natal) near (ICU*1 or unit*))
#9	(SCBU or NICU)
#10	{or #1-#9}
#11	MeSH descriptor: [Nitric Oxide] this term only
#12	MeSH descriptor: [Endothelium-Dependent Relaxing Factors] this term only
#13	((nitric or nitrogen) near (oxide or monoxide or oxygen))
#14	"endothelial* derived relax*"
#15	"endothelial* dependent relax*"
#16	{or #11-#15}
#17	#10 and #16 Publication Year from 1990 to 2018

Appendix C – Clinical evidence study selection

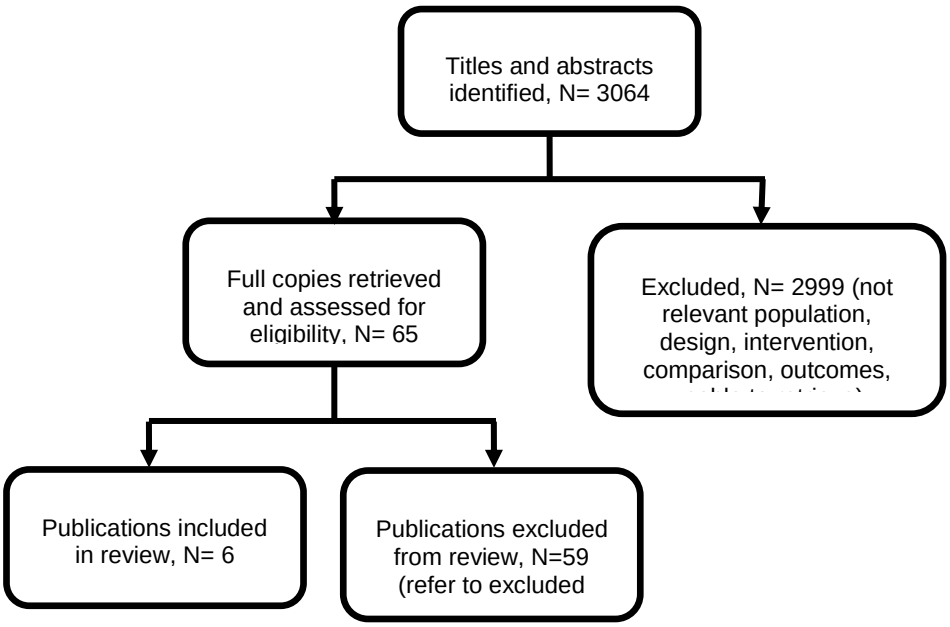
Clinical evidence study selection for question 1.1 What respiratory support (excluding resuscitation) is the most effective for preterm babies before admission to the neonatal unit?



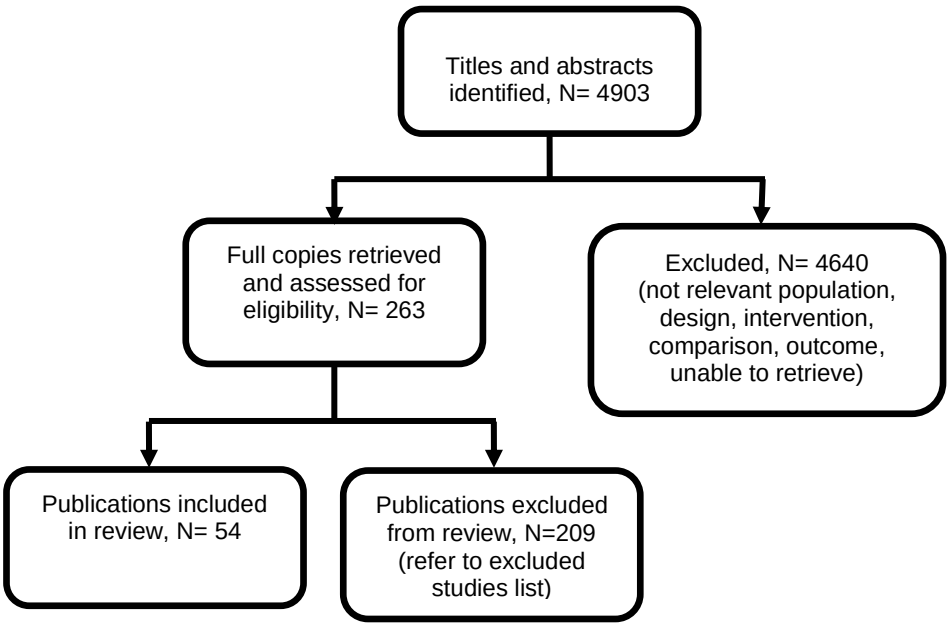
Clinical evidence study selection for question 3.3 What is the most effective way of using surfactant in managing respiratory distress syndrome?



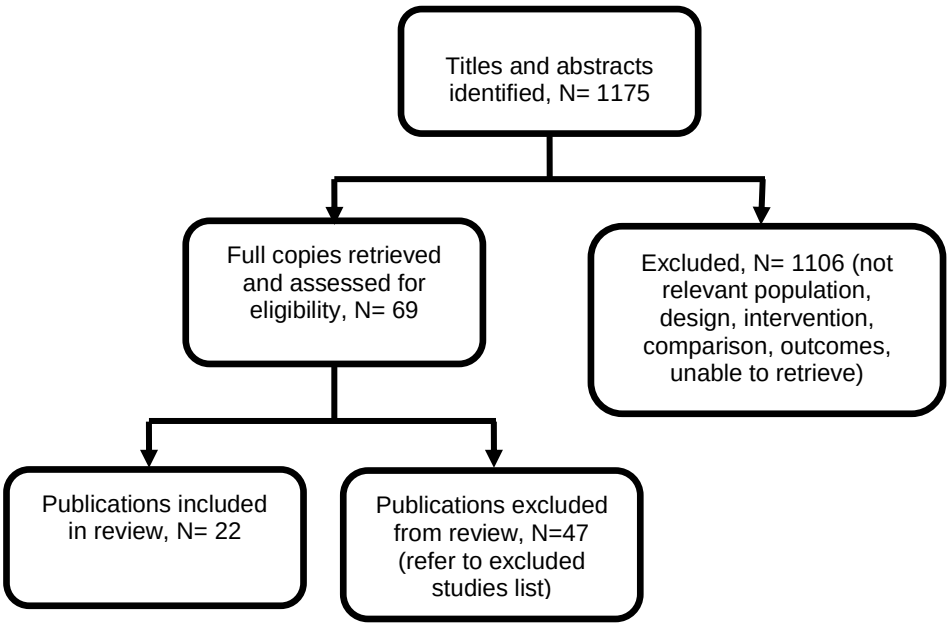
Clinical evidence study selection for question 3.1 What is the most effective way to administer oxygen during respiratory support?



Clinical evidence study selection for question 3.2 What is the effectiveness and safety of the different assisted ventilation techniques in preterm babies?



Clinical evidence study selection for question 3.7 What is the effectiveness of nitric oxide in preterm babies requiring invasive ventilation?



Appendix D – Clinical evidence tables

Clinical evidence tables for question 1.1 What respiratory support (excluding resuscitation) is the most effective for preterm babies before admission to the neonatal unit

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Dunn, M. S., Kaempf, J., De Klerk, A., De Klerk, R., Reilly, M., Howard, D., Ferrelli, K., O'Conor, J., Soll, R. F., Randomized trial comparing 3 approaches to the initial respiratory management of preterm neonates, Pediatrics, 128, e1069-e1076, 2011 **Ref Id** 653648 **Country/ies where the study was carried out** **Study type** **Aim of the study**	**Sample size** Please see Subramaniam 2016 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 Finer, N. N., Carlo, W. A., Walsh, M. C., Rich, W., Gantz, M. G., Laptook, A. R., Yoder, B. A., Faix, R. G., Das, A., Poole, W. K., Donovan, E. F., Newman, N. S., Ambalavanan, N., Frantz, Iii I. D., Buchter, S., Sanchez, P. J., Kennedy, K. A., Laroia, N., Poindexter, B. B., Cotten, C. M., Van Meurs, K. P., Duara, S., Narendran, V., Sood, B. G., O'Shea, T. M., Bell, E. F., Bhandari, V., Watterberg, K. L., Higgins, R. D., Early CPAP versus surfactant in extremely preterm infants, New England Journal of	**Sample size** Please see Subramaniam 2016 Cochrane systematic review **Characteristics** **Inclusion criteria** **Exclusion criteria**	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Medicine, 362, 1970-1979, 2010 **Ref Id** 619572 **Country/ies where the study was carried out** **Study type** **Aim of the study** **Study dates** **Source of funding**					
Full citation Morley, C. J., Davis, P. G., Doyle, L. W., Brion, L. P., Hascoet, J. M., Carlin, J. B., Coin Trial Investigators, Nasal CPAP or intubation at birth for very preterm infants.[Erratum appears in N Engl J Med. 2008 Apr	**Sample size** Please see Subramaniam 2016 Cochrane systematic review **Characteristics**	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
3;358(14):1529], New England journal of medicine, 358, 700-8, 2008 **Ref Id** 667416 **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 Sandri, Fabrizio, Plavka, Richard, Ancora, Gina, Simeoni, Umberto, Stranak, Zbyněk, Martinelli, Stefano, Mosca, Fabio, Nona, José, Thomson, Merran, Verder, Henrik,	**Sample size** n= 208 NCPAP= 103 Prophylactic surfactant= 105 **Characteristics**	**Interventions** Prophylactic surfactant= During surfactant administration, infants were manually ventilated to facilitate surfactant	**Details** **Randomisation** Central interactive voice response system **Blinding**	**Results** **Critical outcomes** **Mortality prior to discharge** Mortality by 36 wks postmenstrual age **25-26 weeks** NCPAP, n/total= 3/31	**Limitations** **Selection bias** Unclear risk: Unclear whether randomisation was computer-generated

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Fabbri, Laura, Halliday, Henry, Prophylactic or Early Selective Surfactant Combined With nCPAP in Very Preterm Infants, Pediatrics, 125, e1402-e1409, 2010 **Ref Id** 742270 **Country/ies where the study was carried out** Italy **Study type** Multi-centre RCT **Aim of the study** The aim of the study was to assess whether prophylactic surfactant followed by NCPAP compared with early NCPAP with early selective surfactant would reduce the need for mechanical ventilation in the first 5 days of life.	**NCPAP Group:** Gestational age, mean (SD), wk: 27.0 (1.0) Birth weight, mean (SD), g: 913 (200) Antenatal steroid use, completed course, n (%): 81 (78.6%) CRIB score, median (IQR): 2 (0–15) Apgar score at 5min, median (IQR): 8 (4-10) **Surfactant group:** Gestational age, mean (SD), wk: 27.0 (1.0) Birth weight, mean (SD), g: 967 (221) Antenatal steroid use, completed course, n (%): 82 (87.1%) CRIB score, median (IQR): 1 (0–9) Apgar score at 5min, median (IQR): 8 (5-10) **Inclusion criteria** • GA 25+0 to 28+6 weeks **Exclusion criteria**	distribution and then extubated to nCPAP as soon as possible within 1 hour if respiratory drive was present NCPAP= In case NCPAP failed as verified by chest radiograph, early selective surfactant was administered in a dose of 200mg/kg	Unblinded **Attrition** Intention to treat analysis; power calculations were made to account for mortality and loss to follow up after discharge **Statistical analysis** Confidence intervals were calculated at the 95% level. Normal distributions were assessed and were transformed if data were skewed; median difference between treatments and associated p-values were used if data could not be transformed.	Intubation, n/total= 4/32 **27-28 weeks** NCPAP, n/total= 8/72 Intubation, n/total= 5/73 **BPD (oxygen dependency at 36 weeks PMA or 28 days of age** Moderate and Severe BPD at 36 weeks GA amongst survivors **25-26 weeks** NCPAP, n/total= 7/30 Intubation, n/total= 7/28 **27-28 weeks** NCPAP, n/total= 4/66 Intubation, n/total= 7/68 **Important outcomes** **Failed non-invasive ventilation** On respiratory support (mechanical ventilation or NCPAP) at 36 weeks PMA NCPAP, n/total= 6/103 Intubation, n/total= 9/105 **Pneumothorax/pneumomediastinum** NCPAP, n/total= 1/103 PS, n/total= 7/105	**Performance bias** High risk: Not blinded **Detection bias** Low risk: Study had specific criteria for NCPAP failure **Attrition bias** Low risk: ITT analysis used, all patients accounted for in results **Reporting bias** Low risk: all outcomes stated in methods reported in results **Other sources of bias** Unclear risk: "During stabilization and transport to the

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates March 2007 to May 2008 **Source of funding** Chiesi Farmaceutici SpA	• Severe birth asphyxia • 5 minute Apgar score < 3 • Endotracheal intubation for resuscitation or insufficient respiratory drive • Known genetic disorders • potentially life-threatening conditions unrelated to prematurity • Premature rupture of membranes for > 3 weeks			**Severe IVH (grade 3 or 4)** **25-26 weeks** NCPAP, n/total= 4/31 PS, n/total= 3/32 **27-28 weeks** NCPAP, n/total= 4/72 PS, n/total= 3/73	NICU, any CPAP device was allowed according to the practice of each investigative site" **Other information**
Full citation Subramaniam, P., Ho, J. J., Davis, P. G., Prophylactic nasal continuous positive airway pressure for preventing morbidity and mortality in very preterm infants,	**Sample size** **Of selected studies:** **Dunn 2011** n= 648 n prophylactic surfactant (PS)=209 n intubate-surfactant-extubate (ISX)= 216 n nCPAP= 223 **Finer 2010**	**Interventions** **Of selected studies:** **Dunn 2011** Intervention 1: Prophylactic surfactant (PS). Intubated 5-15 minutes after birth, given	**Details** **Randomisation** **Of selected studies:** **Dunn 2011** "Investigators randomly allocated infants to 1 of the 3 treatment arms by	**Results** **Critical outcomes** **Mortality prior to discharge** **Of selected studies:** **Dunn 2011**	**Limitations** **Quality of Cochrane SR:** Systematic review assessed using AMSTAR checklist. Total score: 16/16 All checklist items addressed

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Cochrane Database of Systematic Reviews, 2016 (6) (no pagination), 2016 **Ref Id** 675298 **Country/ies where the study was carried out** **Study type** Cochrane systematic review **Aim of the study** To assess if prophylactic NCPAP started shortly after birth regardless of respiratory status in preterm babies 28-31^{+6} weeks reduces the use of IPPV and the incidence of BPD without adverse effects. **Study dates** January 2016	n= 1316 CPAP= 663 Surfactant= 653 **Morley 2008** n= 610 CPAP= 307 Intubation= 303 **Characteristics** Of selected studies: **Dunn 2011** **PS group:** Gestational age, mean (SD), wk: 28.0 (1.1) Birth weight, mean (SD), g: 1040 (244) Apgar score at 1min, median: 6 Apgar score at 5min, median: 8 **ISX group**: Gestational age, mean (SD), wk: 28.1 (1.3) Birth weight, mean (SD), g: 1066 (270) Apgar score at 1min, median: 6 Apgar score at 5min, median: 8 **PS group:**	surfactant, then stabilised on mechanical ventilation for a minimum of 6 hours. Infants could be extubated to nCPAP Intervention 2: Intubate-surfactant-extubate (ISX). Intubated 5-15 minutes after birth, given surfactant. Infants who needed a fraction of inspired Ox (Fi)2) < 0.6 without severe respiratory distress or apea were extubated to nCPAP 15-30 minutes after surfactant was given Intervention 3: Nasal continuous positive airway pressure (nCPAP). Infants were supported with nCPAP	drawing a card contained within a sealed envelope. Stratification and block randomization was according to center and according to gestational age." **Finer 2010** "Randomization was stratified according to center and gestational-age group, with the use of specially prepared double-sealed envelopes, and was performed before the actual delivery." **Morley 2008** Randomised envelopes **Sandri 2004** Computer generate number list **Blinding** **Of selected studies:** **Dunn 2011** Unblinded **Finer 2010** Unblinded **Morley 2008** Unblinded **Sandri 2004**	CPAP, n/total= 9/124 Assisted ventilation, n/total= 14/209 **Finer 2010** CPAP, n/total= 94/663 Assisted ventilation, n/total= 114/653 **Morley 2008** CPAP, n/total= 20/307 Assisted ventilation, n/total= 18/303 **Sandri 2004** CPAP = 4/115 No assisted ventilation = 5/115 **BPD (oxygen dependency at 36 weeks PMA or 28 days of age** **Of selected studies:** **BPD at 36 weeks** **Dunn 2011** CPAP, n/total= 59/223 Assisted ventilation, n/total= 61/209 **Finer 2010*** CPAP, n/total= 229/663 Assisted ventilation, n/total= 239/656 **Morley 2008** CPAP, n/total= 84/307 Assisted ventilation, n/total= 100/303 **Sandri 2004** CPAP = 2/115 No assisted ventilation = 1/115 *Data extracted for all babies, as opposed to survivors	**Selection bias** **Of selected studies:** **Dunn 2011** High risk: randomisation not computer-generated; allocation was not concealed **Finer 2010** Unclear risk: unclear whether computer generated randomisation was used; unclear method of allocation **Morley 2008** Unclear risk: Unclear whether randomisation was computer-generated **Sandri 2004** Low risk: computer generated number list **Performance bias** **Of selected studies:** **Dunn 2011** High risk: Not blinded **Finer 2010** High risk: Not blinded

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding Eunice Kennedy Shriver National Institute of Child Health and Human Development National Institutes of Health	Gestational age, mean (SD), wk: 28.1 (1.1) Birth weight, mean (SD), g: 1053 (252) Apgar score at 1min, median: 7 Apgar score at 5min, median: 8 **Finer 2010** **CPAP group:** Gestational age, mean (SD), wk: 26.2 (1.1) Birth weight, mean (SD), g: 834.6 (188.2) Surfactant use in the delivery room, n (total): 93 (660) Surfactant use in the delivery room or NICU, n (total): 443 (660) Antenatal steroid use, any, %: 96.8 Apgar score < 3 at 1min, n (total): 154 (661) Apgar score < 3 at 5min, n (total): 26 (663) **Surfactant group:** Gestational age, mean (SD), wk: 26.2 (1.1) Birth weight, mean (SD), g: 825.5 (198.1)	within 15 minutes after birth and intubated only if a) > 12 episodes of apnea that required stimulation or > 1 episode that required bagging in a 6-hour period; or b) PCO2 > 65mmHg on arterial or capillary blood gas; or c) requireent for FIO2 of > 0.4 to maintain O2 saturation of 86-94% **Finer 2010** CPAP group: CPAP or ventilation with positive end-expiratory pressure (PEEP) (at a recommended pressure of 5 cm of water) was used if the infant received positive-pressure ventilation during	Unblinded **Attrition** **Of selected studies:** **Dunn 2011** "Planned sample size was based on a 30% reduction in the number of infants with BPD per death from 36% to 25% (at 0.05 significance level). Baseline incidence of BPD/death for infants born at 26 0⁄7 to29 6⁄7 weeks' gestation was determined from the Vermont Oxford Network database." **Finer 2010** Intention to treat analysis; power calculations were made to account for mortality, loss to follow up after discharge, and to minimise Type I errors **Morley 2008** Intention to treat analysis; power calculations were made to account for mortality	**Important outcomes** **Failed non-invasive ventilation** **Of selected studies:** **Dunn 2011** **CPAP started a 5cm H2O** CPAP, n/total= 116/223 **Morley 2008** **CPAP started at 8 cm H2O** CPAP, n/total= 141/307 **Sandri 2004** CPAP = 14/115 **Pneumothorax/pneumomediastinum** **Of selected studies:** **Dunn 2011** CPAP, n/total= 12/222 Assisted ventilation, n/total= 10/209 **Finer 2010** CPAP, n/total= 45/663 Assisted ventilation, n/total= 48/653 **Morley 2008** CPAP, n/total= 28/307 Assisted ventilation, n/total= 9/303 **Sandri 2004** CPAP = 3/115 No assisted ventilation = 3/115 **Severe IVH (grade 3 or 4)** **Of selected studies:** **Dunn 2011** CPAP, n/total= 6/218 Assisted ventilation, n/total= 12/203	**Morley 2008** High risk: Not blinded **Sandri 2004** High risk: not blinded **Detection bias** **Of selected studies:** **Dunn 2011** High risk: "Decisions regarding subsequent management with ongoing mechanical ventilation or extubation to nCPAP were at the discretion of the clinical team." **Finer 2010** Low risk: Lack of blinding unlikely to affect outcome assessment; study had prespecified intubation, reintubation, and extubation criteria **Morley 2008** High risk: "surfactant treatment, ventilation settings, and

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Surfactant use in the delivery room, n (total): 335 (652) Surfactant use in the delivery room or NICU, n (total): 646 (653) Antenatal steroid use, any, %: 96.5 Apgar score < 3 at 1min, n (total): 167 (653) Apgar score < 3 at 5min, n (total): 32 (653) **Morley 2008** **CPAP group:** Gestational age, mean (SD), wk: 26.91 (1.0) Birth weight, mean (SD), g: 964 (212) Antenatal steroid use, n (total): 289 (307) Apgar score at 5min, median (IQR): 9 (8-9) **Intubation group:** Gestational age, mean (SD), wk: 26.87 (1.0) Birth weight, mean (SD), g: 952 (217) Antenatal steroid use, n (total): 285 (303) Apgar score at 5min, median (IQR): 8 (8-9) **Sandri 2004**	resuscitation. CPAP was continued until the infant's admission to the NICU. Intubation was not performed for the sole purpose of surfactant administration in infants who were randomly assigned to the CPAP group. Extubation of an infant in the CPAP group was to be attempted within 24 hours after the infant met prespecified intubation criteria. Surfactant group: All the infants in the surfactant group were to be intubated in the delivery room and were to receive surfactant within 1 hr after birth with continued ventilation	and loss to follow up after discharge **Sandri 2004** Complete follow up **Statistical analysis Of selected studies: Dunn 2011** Intention to treat analysis. "X2 test for categorical variables and analysis of variance for continuous variables were used. Relative risks and 95% confidence intervals (CIs) were calculated to compare outcomes of ISX and nCPAP groups to the PS group. Logistic regression was used to assess the effect of study group on the primary outcome, adjusting for gender, birth weight, antenatal steroid administration, mode of delivery, multiple birth, and chorioamnionitis." **Finer 2010** The results were adjusted, as pre-specified, for	**Finer 2010** CPAP, n/total= 92/462 Assisted ventilation, n/total= 72/628 **Morley 2008** CPAP, n/total= 27/307 Assisted ventilation, n/total= 28/303 **Sandri 2004** CPAP = 3/115 No assisted ventilation = 1/115	extubation and reintubation criteria were not mandated and followed local protocols." **Sandri 2004** Low risk: "criteria for MV were the following: persistence of a FiO2 >0.4 on nCPAP to maintain a SpO2 of 93-96% after surfactant administration; at any point of the study severe apnoea (defined as more than 4 episodes of apnoea/hour or more than 2 episodes of apnoea/hour if ventilation with a bag and mask were required), PaCO2 > 70mmHg and pH <7.2; FiO2 rapidly increasing above 0.8 even before 30 min" **Attrition bias Of selected studies: Dunn 2011** Unclear risk: stated that ITT analysis was

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Prophylaxis group Gestational age in weeks (SD in parentheses): 30.0 (1) Birth weight in grams (SD in parentheses): 1370 (356) Age at start of nCPAP in minutes (SD in parentheses): 18.7 (7.8) Prenatal steroids: 83.3% Male/female: 58/57 CRIB score (SD in parentheses): 1.45 (2.09) **Rescue group** Gestational age in weeks (SD in parentheses): 29.9 (1.0) Birth weight in grams (SD in parentheses): 1339 (335) Age at start of nCPAP in minutes (SD in parentheses): 445.4 (810.6) Prenatal steroids: 82.4% Male/female: 60/55 CRIB score (SD in parentheses): 1.46 (1.80)	thereafter. The infants were to be extubated within 24 hrs after meeting all of the prespecified extubation criteria. **Morley 2008** NCPAP= started at a pressure of 8cm of H2O with short single or binasal prongs. After admittance to the nursery, short binasal prongs were used. Intubated or underwent ventilation only if pre-specified intubation requirements were met. Criteria for extubation were not specified Intubation and ventilation= method not specified **Sandri 2004** Prophylactic nasal CPAP of 4	gestational-age strata, cenrte, and familial clustering. Two-sided P values of less than 0.05 were considered to indicate statistical significance, and no adjustments have been made for multiple comparisons. Categorical outcomes were analysed using Poisson regressions and continuous outcomes were analysed using mixed-effects linear models. **Morley 2008** 95% confidence intervals and 2-sided p-values were used. Categorical outcomes were assessed using odds ratios, chi-squared tests, and multi-variate regressions. Wilcox rank-sum tests were used to compare continuous outcomes.		used, but not all patients accounted for in results **Finer 2010** Moderate risk: some results only reported for survivors **Morley 2008** Low risk: ITT analysis used, all patients accounted for in results **Sandri 2004** Low risk: all babies followed-up **Reporting bias Of selected studies:** **Dunn 2011** Low risk: all outcomes stated in methods were reported as results **Finer 2010** Low risk: all outcomes stated in methods reported in results **Morley 2008** Low risk: all outcomes stated in methods reported in results **Sandri 2004:**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Inclusion criteria Of selected studies: Dunn 2011 • If parent was considered at high risk of having a preterm delivery at 26+0 - 29+6 week's gestation **Finer 2010** • GA 24 + 0 to 27 + 6 weeks • No congenital malformations • Decision had been made to provide full resuscitation **Morley 2008** • GA 25+0 to 28+6 weeks • No congenital malformations	to 6 cm H20 applied within 30 min of birth. Rescue nasal CPAP when the FiO2 >0.4 for more than 30 minutes, to maintain SpO2 93-96%. Nweborns receiving nasal CPAP at a pressure of 6 cm water pressure requiring a FiO2 > 4 for more than 30 minutes to maintain SpO2 in the range of 93-96% and showed radiological signs of RDS were endotracheally intubated, treated with surfactant and manaually ventilated for 5 minutes			Low risk: all outcomes stated in methods were reported as results **Other sources of bias Of selected studies: Finer 2010** Unclear risk: cross over was allowed for infants in the CPAP group **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	• Birth in a hospital participating in the trial • Ability to breathe at 5 mins after birth, but needing respiratory support Sandri 2004 • GA 28-31 weeks • No congenital malformations **Exclusion criteria Of selected studies Dunn 2011** • Women who were carrying a fetus with a potentially life-threatening				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	anomaly or condition **Finer 2010** Not reported **Morley 2008** • Intubated before randomisation • Required no respiratory support or oxygen **Sandri 2004** Intubated before randomisation				
Full citation Vaucher, Y. E., Peralta-Carcelen, M., Finer, N. N., Carlo, W. A., Gantz, M. G., Walsh, M. C., Laptook, A. R., Yoder, B. A., Faix, R. G., Das, A., Schibler, K., Rich, W., Newman, N. S., Vohr, B. R., Yolton, K., Heyne, R. J., Wilson-Costello, D. E., Evans,	**Sample size** n= 990 CPAP= 511 Surfactant= 479 **Characteristics** **CPAP group:** Gestational age, mean (SD), wk: 26.3 (1.1) Birth weight, mean (SD), g: 849 (186)	**Interventions** Please see Finer 2010	**Details** **Randomisation** Please see Finer 2010 **Blinding** For neurodevelopmental outcomes: At 18 to 22 months of corrected age, surviving infants	**Results** **Critical outcomes** **Neurodevelopmental outcomes at ≥18 months** **Neurodevelopmental impairment, n/total*** CPAP= 55/511 Surfactant= 43/479 **BSID-III cognitive score < 70, n/total* (Bayleys Scales of Infant and Toddler**	**Limitations** **Selection bias** Unclear risk: unclear whether computer generated randomisation was used; unclear method of allocation

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
P. W., Goldstein, R. F., Acarregui, M. J., Adams-Chapman, I., Pappas, A., Hintz, S. R., Poindexter, B., Dusick, A. M., McGowan, E. C., Ehrenkranz, R. A., Bodnar, A., Bauer, C. R., Fuller, J., O'Shea, T. M., Myers, G. J., Higgins, R. D., Neurodevelopmental outcomes in the early CPAP and pulse oximetry trial, New England Journal of Medicine, 367, 2495-2504, 2012 **Ref Id** 340863 **Country/ies where the study was carried out** US **Study type** Secondary analysis of multi-centre RCT **Aim of the study**	Corrected age at followup, months (SD): 19.9 (2.4) **Surfactant group:** Gestational age, mean (SD), wk: 26.3 (1.1) Birth weight, mean (SD), g: 852 (193) Corrected age at followup, months (SD): 20.1 (2.7) **Inclusion criteria** • 18-22 months corrected age • Surviving from Finer 2010 SUPPORT study **Exclusion criteria** Please see Finer 2010		underwent a comprehensive neurodevelopmental assessment performed by neurologic examiners and neurodevelopmental testers who were unaware of the treatment assignments and were evaluated annually for testing reliability **Attrition** Please see Finer 2010 **Statistical analysis** Please see Finer 2010	**Development, third edition, assessed relative to standardised mean, higher scores indicate better performance)** CPAP= 36/511 Surfactant= 36/479 **GMFCS score ≥ 2, n/total (gross motor function assessed by modified Gross Motor Function Classification System (GMFCS) with higher scores indicating greater impairment)** CPAP= 26/511 Surfactant= 23/479 **Moderate or severe cerebral palsy, n/total** CPAP= 21/511 Surfactant= 19/479 **Bilateral blindness** CPAP= 4/511 Surfactant= 7/479 **Hearing impairment** CPAP= 17/511 Surfactant= 7/479 *Data analysed for total patients, as opposed to survivors	**Performance bias** High risk: study not blinded **Detection bias** Low risk for Cerebral palsy and cognitive impairment as outcome assessors blinded to intervention received High risk for hearing impairment and visual impairment as parents who were unblinded to intervention took part in the assessment **Attrition bias** Moderate risk: some results only reported for survivors **Reporting bias** Low risk: all outcomes stated in

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
The aim of the study was to report the long-term follow-up results from a previous study that assessed whether early, non-invasive CPAP with a limited ventilation strategy, as compared with early surfactant administration. **Study dates** Please see Finer 2010 **Source of funding** Please see Finer 2010					methods reported in results **Other sources of bias** Moderate risk: cross over was allowed for infants in the CPAP group for ethical concerns **Other information**
Full citation Sandri,F., Ancora,G., Lanzoni,A., Tagliabue,P., Colnaghi,M., Ventura,M.L., Rinaldi,M., Mondello,I., Gancia,P., Salvioli,G.P., Orzalesi,M., Mosca,F., Prophylactic nasal continuous positive	**Sample size** Please see Subramaniam 2016 Cochrane systematic review **Characteristics** **Inclusion criteria**	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
airways pressure in newborns of 28-31 weeks gestation: multicentre randomised controlled clinical trial, Archives of Disease in Childhood Fetal and Neonatal Edition, 89, F394-F398, 2004 **Ref Id** 225836 **Country/ies where the study was carried out** Italy **Study type** RCT **Aim of the study** To evaluate the benefits and risks of prophylactic nCPAP in infants 28-31 weeks gestation **Study dates** November 1999 to December 2000	**Exclusion criteria**				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding					

Clinical evidence tables for question 3.3 What is the most effective way of using surfactant in managing respiratory distress syndrome?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Dani, C, Bertini, G, Pezzati, M, Cecchi, A, Caviglioli, C, Rubaltelli, Ff, Early extubation and nasal continuous positive airway pressure after surfactant treatment for respiratory distress syndrome among preterm infants <30 weeks' gestation, Pediatrics, 113, e560-3, 2004 **Ref Id** 666246 **Country/ies where the study was carried out** Italy **Study type**	**Sample size** n= 27 randomised (surf-nCPAP n= 13; surf-MV n= 14) **Characteristics** Gestational age (weeks in mean, SD in parentheses): surf-nCPAP= 29 (2.2); surf-MV= 28.3 (1.32) Apgar score at 5 min (mean, SD in parentheses): surf-nCPAP= 8.2 (0.70); surf-MV= 7.4 (0.9) Pre-natal steroid treatment: surf-nCPAP= 62%; surf-MV=93%	**Interventions** All enrolled patients were intubated for surfactant treatment (curosurf 200mg/kg), which was administered in 2 bolus fractions of 100mg/kg each, instilled through a tracheal tube, with an interval of a few minutes. The patients then randomly received the reinstitution of nCPAP (surf-nCPAP group) or MV (surf-MV group). Operators were allowed to administer an additional dose of surfactant (100mg/kg) 12 hours later if the infant still required an Fi02 of >0.5.	**Details** **Methods** Randomisation: No details Allocation concealment: The randomisation was performed at the same time of enrolment by opening sealed envelopes. Blinding: Because of the impossiblity of masking the different post-extubation strategies to the operators, a non blinded study was performed Attrition: complete follow-up Selective reporting: none **Outcomes** Primary: need for MV at 7 days of life Secondary: a/APO2 6 hours after surfactant administration, need for MV, death before discharge,	**Results** **Outcome: Death before discharge** Surf-nCPAP: 0/13; surf-MV: 1/14 **Outcome: BPD at 36 weeks PMA** Surf-nCPAP: 0/13; surf-MV: 3/14 **Outcome: Pneumothorax** Surf-nCPAP: 0/13; surf-MV: 1/14 **Outcome: Days on MV** Surf-nCPAP: 2 (1.4)*; surf-MV: 5.6 (3.1) *only 2 patients in this group received MV	**Limitations** **Quality of study:** Risk of bias assessed using Cochrane risk of bias tool Random sequence generation: Unclear risk, no details provided on sequence Allocation concealment: Unclear risk, sealed envelopes used, however no details as they were opaque or non-opaque Blinding of participants and personnel: High risk for subjective outcomes as unblinded due to the nature of the study, low risk for objective outcomes

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Randomised controlled trial **Aim of the study** To test the hypothesis that preterm infants (<30 weeks gestation) with iRDS who were treated with nCPAP and surfacant administration followed by immediate reinstitution of nCPAP could fare better than those who received MV after surfactant adminstration and who were weaned progressively from MV. **Study dates** June 2001-May 2003 **Source of funding** Not reported	FiO2 at study entry (mean, SD in parentheses): surf-nCPAP= 0.33 (0.13); surf-MV=0.35 (0.09) **Inclusion criteria** Inborn infants of 0-6 hours of age and <30 weeks gestation with iRDS were enrolled consecutively in the study if they required nCPAP (4-7cm H2O) and a fraction of inspired oxygen of ≥30% to maintain arterial hemaglobin oxygen saturation of >88% and PO2 of >50 mmHg. **Exclusion criteria** major congenital malformations, IVH of more than grade 2, or the requirement for MV within the first 6 hours of life	Infants in the surf-nCPAP group were extubated as soon as the respiratory rate, heart rate, and arterial haemoglobin oxygen saturation were satisfactory (usually withing 5 min), where as infants in the surf-MV group were extubated after a loading dose of caffeine (20mg/kg) , FiO2 ≤0.4, mean arterial pressure was ≤6 cm H2O, and PO2 and PCO2 were ≥50 and <65 mmHg, respectively.	duration of oxygen treatment, nCPAP, and MV, the need for a second dose of surfactant, pneumothorax, PDA, BPD (36 weeks PMA), IVH (grade I), PVL, ROP, and necrotising enterocolitis.		Blinding of outcome assessment: High risk for subjective outcomes as unblinded due to the nature of the study, low risk for objective outcomes Incomplete outcome data: Low risk, all participants followed-up Selective reporting: Low risk, those notes in the methods to be assessed were assessed Other bias: None reported **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Dunn, M. S., Kaempf, J., de Klerk, A., de Klerk, R., Reilly, M., Howard, D., Ferrelli, K., O'Conor, J., Soll, R. F., Vermont Oxford Network, D. R. M. Study Group, Randomized trial comparing 3 approaches to the initial respiratory management of preterm neonates, Pediatrics, 128, e1069-76, 2011 **Ref Id** 653649 **Country/ies where the study was carried out** US **Study type** Multicentre randomised controlled trial **Aim of the study** To compare 3 approches to the initial repsiratory management of preterm neonates: prophylactic surfactant followed by a	**Sample size** n=656 randomised (PS group n=213; ISX group n=219; nCPAP group n=224 [not of interest for this review question]) PS group= 209 analysed (2 excluded due to lack of consent; 2 excluded as stillborn) ISX group= 216 analysed (1 excluded due to birth defect; 2 excluded as stillborn) **Characteristics** Gestational age (weeks in mean, SD in parentheses): PS= 28 (1.1); ISX= 28.1 (1.3) Apgar score at 5 min (median): PS= 8; ISX=8 Antenatal steroids: PS= 206 (98.6%); ISX= 213 (98.6%) **Inclusion criteria** Preterm babies 26-30 weeks gestation	**Interventions** PS: Infants were to be intubated 5-15 minutes after birth for the purposes of surfactant admministration, then stabilised on MV for a minimum of 6 hours after which time they could be extubated to nCPAP. ISX: Infants were to be intubated 5 -15 minutes after birth for the purposes of surfactant administration. Infants who required a fraction of inspired oxygen <0.6 without severe respiratory distress or apnoea were to be extubated to nCPAP 15-30 minutes after surfactant instillation	**Details** **Methods** Randomisation: Stratification and block randomisation was according to center and according to gestational age Allocation concealment: Drawing a card contained within a sealed envelope Blinding: unblinded Attrition: complete follow-up Selective reporting: none **Outcomes** Primary: death or moderate to severe BPD at 36 weeks PMA. Secondary: number of infants who received surfactant, number of surfactant doses; use of postnatal steroids, growth, days on assisted ventilation, days on nCPAP, and days on supplemental oxygen. Other outcomes: incidence of common complications of prematurity and mortality Long term outcomes including health and neurodevelopmental status determined by a questionnaire at 2 years corrected age will form the basis of a future report	**Results** **Outcome: Death before discharge at 36 weeks PMA** PS: 7.2% (15/209); ISX: 7% (15/216) [RR 0.97 (0.49-1.94)] GA 26-27 PS: 11.2% (11/98); ISX: 10.1% (10/101) [RR 0.90 (0.4-2.02)] GA 28-29 PS: 3.6% (4/111); ISX: 4.4% (5/115) [RR 1.20 (0.33-4.34)] **Outcome: BPD at 36 weeks PMA** PS: 61/209; ISX: 47/216 GA 26-27 PS: 41/98; ISX: 34/101 GA 28-29 PS: 20/111; ISX: 13/115 **Outcome: Duration on any mode of ventilation, days** PS: 7.7 (12.4); ISX: 7.1 (13.8) **Outcome: Pneumothorax** PS: 10/209; ISX: 7/216	**Limitations** **Quality of study:** Risk of bias assessed using Cochrane risk of bias tool Random sequence generation: Low risk, block randomisation Allocation concealment: Unclear risk, sealed envelopes used, however no details as they were opaque or non-opaque Blinding of participants and personnel: High risk for subjective outcomes as unblinded due to the nature of the study, low risk for objective outcomes Blinding of outcome assessment: High risk for subjective outcomes as unblinded due to the nature of the study, low risk for objective outcomes Incomplete outcome data: Low risk, all participants followed-up

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
period or mechanical ventilation (prophylactic surfactant [PS]), prophylactic surfactant with rapid extubation to bubble nCPAP (intubate-surfactant-extubate [ISX]) or initial management with bubble nCPAP and selective surfactant treatment (nCPAP) **Study dates** September 2003-January 2009 **Source of funding** Not reported	**Exclusion criteria** Preterm babies stillborn or with a potentially life-threatening anomaly or condition			**Outcome: Pulmonary haemorrhage** PS: 6/209; ISX: 7/216	Selective reporting: Low risk, those notes in the methods to be assessed were assessed Other bias: None reported **Other information**
Full citation G?pel, W, Kribs, A, Ziegler, A, Laux, R, Hoehn, T, Wieg, C, Avoidance of mechanical ventilation by surfactant treatment of spontaneously breathing preterm infants (AMV): an open-label, randomised, controlled trial,	**Sample size** n=220 randomised (standard treatment group n=112; surfactant without ventilation n=108) standard treatment group n=112 (39 never received surfactant; 73 recevied surfactant [72 whilst on mechanical	**Interventions** After birth, infants were preferentially stabilised with CPAP. No infants was intubated solely to give surfactant. Infants were intubated and mechanically ventilated if they had any of the following symptoms: RDS or asphyxia	**Details** **Methods** Randomisation: Randomly assigned with RITA (version 1.2) Allocation concealment: Independent statistician who prepared sequentially numbered, sealed, opaque envelopes stratified by	**Results** **Outcome: Death before discharge** Standard treatment: 5/112; intervention group: 7/108 **Outcome: BPD at 36 weeks of PMA (in survivors)**	**Limitations** **Quality of study:** Risk of bias assessed using Cochrane risk of bias tool Random sequence generation: Low risk, computer generated block randomisation Allocation concealment: Low risk,

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Lancet, 378, 1627 // 34, 2011 **Ref Id** 666540 **Country/ies where the study was carried out** Germany **Study type** Multicentre randomised controlled trial **Aim of the study** To asses if non-invasive application of surfactant to spontaneously breathing preterm infatns would reduce the percentage of infants who subsequently need mechanical ventilation **Study dates** October 2007-January 2010 **Source of funding** German ministry of research and technology, university of	ventilation; 1 while breathing spontaneously]) Surfactant without ventilation group n=108 (28 never received surfactant; 80 received surfactant [15 while on mechanical ventilation; 65 while spontaneously breathing]) **Characteristics** Gestational age (weeks in mean, SD in parentheses): standard treatment group=27.5 (0.8); intervention group= 27.6 (0.8) Use of antenatal steroids: standard treatment group= 107 (96%)' intervention group= 104 (96%) First recorded FiO2: standard treatment group (SD in parentheses) = standard treatment group=0.33 (0.18); intervention group=0.32 (0.14)	requiring intubation and mechanical ventilation by judgement of the attending physician, high FiO2 (0.3-0.6), low pH (7.15-7.20), or high partial pressure of carbon dioxide (pCO2) (8-9.3 kPa). **Intervention group** For spontaneously breathing infants receiving nCPAP with a Fi02 of >0.3, a thin catheter (diameter 2.5-5 french) was placed in the trachea with the use of magill forceps with direct visualisation of the vocal cords with a laryngoscope. After catheter placement, the laryngoscope was removed and surfactant (100mg/kg bodyweight) was instilled intratracheally for 1-3 min. After instillation, a catheter was immedietaly removed. Asecond person observed the procedure. Sedation and analgesia were used at the discretion of each	centre and multiple birth status. Blinding: unblinded. Attrition: complete follow-up Selective reporting: none Other bias: criteria for providing surfactant were not similar accross the two groups. **Outcomes** Primary: need for any mechanical ventilation, or being not ventilated but having pCO2 more than 65 mmHg or a FiO2 more than 0.6, or both, for morethan 2h between 25h and 72h of age. Secondary: incidence and duration of any mechanical ventilation during the infants time in hospital, duration of oxygen supplmentation or CPAP, or both; the number of surfactant doses given per infant; BPD at 36 weeks PMA, death or treatment with supplemental oxygen at discharge, FiO2 and oxygen saturation in the first 3 days after birth; drug treatments given; and serious adverse events	Standard treatment: 14/112; intervention group: 8/108 **Outcome: Duration of mechanical ventilation in days, range** Standard treatment : 2 (0-5); intervention group: 0 (0-3) **Outcome: Pneumothorax** Standard treatment: 8/112; intervention group: 4/108 **Outcome: Pulmonary haemorrhage** Standard treatment: 3/112; intervention group: 1/108 **Outcome: IVH (grade 3 or 4)** Standard treatment: 6/112; intervention group: 8/108	opaque sealed envelopes used Blinding of participants and personnel: High risk for subjective outcomes as unblinded due to the nature of the study, low risk for objective outcomes Blinding of outcome assessment: High risk for subjective outcomes as unblinded due to the nature of the study, low risk for objective outcomes Incomplete outcome data: Low risk, all participants followed-up Selective reporting: Low risk, those noted in the methods to be assessed were assessed Other bias: criteria for providing surfactant were not similar accross the two groups, not all preterm babies received surfactant. Funding by pharmaceutical

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Lubeck, and Chiesi Pharmaceuticals	**Inclusion criteria** Preterm infants with a gestational age from 26 weeks to 28 weeks plus 6 days, and with a birthweight of less than 1.5kg were enrolled within 12 hours of birth. **Exclusion criteria** Lethal malformations or those who had already been given surfactant without intubation	neonatologist. The use of atropine was optional. Surfactant without ventilation was allowed to be repeated if a FiO2 od more than 0.4 was reached. **Standard group** No specific details regarding surfactant administration, other than physicians were encouraged to extubate infants as soon as possible after successful stabilisation to minimise the time of respiratory support. Unclear whether InSuRe protocol or not.			company, however the paper stated that the sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. **Other information**
Full citation Kanmaz, H. G., Erdeve, O., Canpolat, F. E., Mutlu, B., Dilmen, U., Surfactant administration via thin catheter during spontaneous breathing: Randomized controlled trial, Pediatrics, 131, e502-e509, 2013	**Sample size** n=200 randomised (n=100 take care group; n=100 InSuRe group) **Characteristics** Gestational age (weeks in mean, SD in	**Interventions** Take care: Exogenous surfactant administration via the new technique called the Take Care procedure was performed once the infant was in a stable condition. A 5F, flexible, sterile nasogastric tube was used for the	**Details** **Methods** Randomisation: No details provided other than randomised and stratified by GA Allocation concealment: Sequentially numbered sealed opaque envelopes Blinding: unblinded Attrition: complete follow-up	**Results** **Outcome: Death before discharge** Take care: 16/100; InSuRe: 13/100 **Outcome: BPD at 36 weeks PMA** Take care: 9/100; InSuRe: 17/100 **Outcome: Pneumothorax**	**Limitations** **Quality of study:** Risk of bias assessed using Cochrane risk of bias tool Random sequence generation: Unclear risk, no details provided on randomisation process

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ref Id 653877 **Country/ies where the study was carried out** Turkey **Study type** Randomised controlled trial **Aim of the study** To describe the feasibility of early administration of surfactant via a thin catheter during spontaneous breathing (take care) and compare early mechanical ventilation (MV) requirement with the InSuRe (Intubate, Surfactant, Extubate) procedure **Study dates** December 2010-December 2011 **Source of funding** None reported	parentheses): take care: 28 (2); InSuRe: 28.3 (2) Birth weight (grams in mean, SD in parentheses): take care: 1093 (270); InSuRe: 1121 (270) Antenatal steroids (%): take care: 73; InSuRe: 81 5-min Apgar (median, range in parentheses): take care: 7 (5-9); InSuRe: 7 (6-9) **Inclusion criteria** Inborn preterm infants with a GA <32 weeks and who suffered from RDS were enrolled in the study **Exclusion criteria** Congenital abnormalities, no parental consent, and who required PPV or intubation in the delivery room and who were not resuscitated	procedure. The catheter was prepared by shortening at 33-cm depth from the catheter hub. Desired depths of insertion beyong the vocal cords for preterm infatns with 25-26, 27-28, and 29-32 weeks GA were 1.0, 1.5, and 2.0cm, respectively. After catheter placement, the laryngoscope was removed. Porcine surfactant (Curosurf) at a dose of 100mg/kg (1.25ml/kg) Wwas drawn up in a 5-ml syringe, and an additional 1ml of air was drawn up into the syringe taking account of the dead volume of the instillation catherter. Exogenous surfactant was administered in 1 bolus in 30 to 60 seconds and the tracheal catheter was immedietaly withdrawn. During the Take care procedure, direct laryngoscopy was performed by using a standard laryngoscope and Miller 00 blade, and	Selective reporting: none **Outcomes** Primary: need for intubation and MV in the first 72 hours and thereafter of life. Secondary: repeated surfactant therapy, duration of respiratory support, rates of pneumothorax, PDA requiring medical or surgical treatment, IVH (grade > 2), ROP (> stage 2), length of hospitalisation, NEC (> stage 2), BPD at 36 weeks PMA or death.	Take care: 7/100; InSuRe: 10/100 **Outcome: Pulmonary Haemorrhage** Take care: 5/100; InSuRe: 7/100 **Outcome: Days on MV (median in hours, range in parentheses)** Take care: 35.6 (0-756); InSuRe: 64.1 (0-489), p-value=0.006	Allocation concealment: Low risk, opaque sealed envelopes used Blinding of participants and personnel: High risk for subjective outcomes as unblinded due to the nature of the study, low risk for objective outcomes Blinding of outcome assessment: High risk for subjective outcomes as unblinded due to the nature of the study, low risk for objective outcomes Incomplete outcome data: Low risk, all participants followed-up Selective reporting: Low risk, those noted in the methods to be assessed were assessed **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	by trial investigators in the DR were excluded.	CPAP support was not disrupted. If visualisation of vocal cords and replacement of catheter was not possible within 20-30 seconds a further catheterisation attempt was postponed for at least 1 min. InSuRe: Patients who received surfactant via the InSuRe technique, were first orally intubated with a double-lumen endotracheal tube, and porcine surfactant at a dose of 100mg/kg (1.25 ml/kg) was instilled to the trachea in 30 seconds. Manual lung inflation by a T-piece device at 20/5-com H2O pressure was performed during the surfactant instillation and then the patient was promptly extubated. Right after extubation, nCPAP support was recommenced as described in the Take Care technique. No premedication, such s sedation or atropine,			

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
		was used during both procedures			
Full citation Kribs, A., Roll, C., Gopel, W., Wieg, C., Groneck, P., Laux, R., Teig, N., Hoehn, T., Bohm, W., Welzing, L., Vochem, M., Hoppenz, M., Buhrer, C., Mehler, K., Stutzer, H., Franklin, J., Stohr, A., Herting, E., Roth, B., Ninsapp Trial Investigators, Nonintubated Surfactant Application vs Conventional Therapy in Extremely Preterm Infants: A Randomized Clinical Trial, JAMA Pediatrics, 169, 723-30, 2015 **Ref Id** 653926 **Country/ies where the study was carried out** Germany **Study type** Multicentre, randomised controlled trial	**Sample size** n= 211 randomised (n=107 LISA; n=104 control) **Characteristics** Gestational age (weeks in mean, SD in parentheses): LISA: 25.3 (1.1); Control: 25.2 (0.91) Birth weight (grams in mean, SD in parentheses: LISA: 711 (195); Control: 674 (165) Apgar score at 5 min (median, IQR in parentheses): LISA: 8 (7-9); Control: 8 (7-8) Antenatal contricosteroids (%): LISA: 98; Control: 98 **Inclusion criteria**	**Interventions** LISA: Surfactant was administered to infants in the intervention group according to the following protocol. A 4F endhole catheter was marked with a wax pencil approximately 1.5cm above one end. A syringe was connected, and this syringe and the catheter were prefilled with at least 1.25ml/kg of body weight (100mg/kg) of the surfactant preparation. While the infant was breathing via nasal CPAP, a laryngoscope was introduced to provide a glottal view. The tube was grasped with a Magill forceps at an angle of approximately 120 degrees and the infant was intubated up to the mark; the tube was fixed in this position and the laryngoscope	**Details** **Methods** Randomisation: Random allocation was designed in a 1:1 ratio with variable block sizes by an independent statistician Allocation concealment: Serially numbered opaque, sealed envelopes. Blinding: unblinded Attrition: complete follow-up Selective reporting: none **Outcomes** Primary: Survival without BPD at 36 weeks GA Secondary: survival without major complications. These complications included BPD, severe IVH, PVL, and surgery for NEC, pneumothorax, laser therapy for ROP, persistent PDA requiring surgery, treatment failure (need for intubation and MV within first 72 hours of life), duration of MV; CPAP; oxygen	**Results** **Outcome: Death before discharge** LISA: 10/107; Control: 13/104 **Outcome: BPD at 36 weeks in survivors** LISA: 25/107; Control: 31/104 **Outcome: Duration of MV (days in median, IQR in parentheses)** LISA: 5 (0-17); Control: 7 (2.5-19.5) **Outcome: Pulmonary Haemorrhage** LISA: 4/107; Control: 6/104 **Outcome: Pneumothorax** LISA: 5/107; Control: 13/104 **Outcome: IVH (grade 3 or 4)** LISA: 11/107; Control: 23/104	**Limitations** **Quality of study:** Risk of bias assessed using Cochrane risk of bias tool Random sequence generation: Low risk, 1:1 ratio with variable block sizes by an independent statistician Allocation concealment: Low risk, opaque sealed envelopes used Blinding of participants and personnel: High risk for subjective outcomes as unblinded due to the nature of the study, low risk for objective outcomes Blinding of outcome assessment: High risk for subjective outcomes as unblinded due to the nature of the study,

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study To test the hypothesis that LISA increases survival without BPD at 36 weeks gestational age in extremely preterm infants **Study dates** April 2009-June 2012 **Source of funding** Sponsored by the university of Cologne and supported by grants from the German Ministry of Research and Technology and Koln Fortune.	Infants with a GA between 23 weeks and 26 weeks + 6 were eligible. Inclusion criterion were spontaneous breathing, age 10-120 min, signs of respiratory distress (FiO2 >0.3), written informed consent. **Exclusion criteria** Prenatally diagnosed severe underlying disease, had cardiopulmonary failure, or were enrolled in any other interventional trial.	was removed. The infant's mouth was closed, and the surfactant was instilled by hand during 30 to 120 seconds by mini-boluses. Control: Infants were intubated, mechanical ventilation was initiated, and surfactant was administered via the endotracheal tube. Sedation and analgesia for intubation were not used routinely.	supplementation, length of stay, and daily weight gain.		low risk for objective outcomes Incomplete outcome data: Low risk, all participants followed-up Selective reporting: Low risk, those noted in the methods to be assessed were assessed **Other information**
Full citation Pinheiro, J. M., Santana-Rivas, Q., Pezzano, C., Randomized trial of laryngeal mask airway versus endotracheal intubation for surfactant delivery, Journal of	**Sample size** n= 61 randomised (n=30 LMA; n=31 InSuRe) n= 60 analyses (n=30 LMA; n=30 InSuRe [1 discontinued as had pre-existing	**Interventions** LMA: Neonates in the laryngeal mask airways group (LMA) were given atropine before the insertion of a size 1 classic LMA using standard techniques. Adequate PPV was	**Details** **Methods** Randomisation: Random allocation was designed in a 1:1 ratio within each of two gestational age blocks to the study groups, using a computerised algorithm	**Results** **Outcome: Death before discharge** LMA: 0/30; INsUrE: 0/30 **Outcome: BPD at 28 days of age or 36 weeks PMA**	**Limitations** **Quality of study:** Risk of bias assessed using Cochrane risk of bias tool Random sequence generation: Low risk, 1:1 ratio with variable block sizes by a

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
perinatology, 36, 196-201, 2016 **Ref Id** 667653 **Country/ies where the study was carried out** US **Study type** Randomised controlled trial **Aim of the study** To evaluate whether surfactant therapy delivered through an LMA in moderately preterm neonates with mild-to-moderate RDS can effectively replace an InSuRe approach while decreasing the need for subsequent mechanical ventilation **Study dates** January 2010-August 2012	undetected pneumothorax]) **Characteristics** Gestational age < 33: LMA: 11/30; InSuRe: 18/30 Gestational age ≥ 33: LMA: 19/30: InSuRe: 12/30 Birth weight (mean in grams, range in parentheses): LMA: 2118 (1150-3984); InSuRe: 1945 (1015-3700) Antenatal steroids (%): LMA: 15/30; InSuRe: 16/30 Age at randomisation (hours in mean, range in parentheses): LMA: 17.3 (3-43); InSuRe: 15.8 (3-42) **Inclusion criteria** 29 to 36 + 7 weeks gestation, diagnosis of RDS between 4 and 48 h of age, nCPAP ≥5 cm H2O (with or without NIPPV), plus	verified by noting adequate chest movements and SpO2 for at least 1 min; CO2 colorimetry was monitored throughout the procedure. Calfactant was instilled in two aliquots to spontaneously breathing infants, at the distal end of the LMA using a shortened five French-feeding catheter, with PPV for about 1 min between aliquaots. Post-surfactant PPV, resumption of nCPAP, and pre-specified criteria for intubation and mechanical ventilation were described as for InSuRe. InSuRe: Infants were intubated after premedication with atropine 0.01mg/kg plus morphine 0.1 mg/kg, per protocol; a CO2 detector was used to verify the endotracheal tube position and ventilation throughout the procedure. Calfactant 3ml/kg per dose was	Allocation concealment: Conealed by clerical staff in serially numbered opaque envelopes. Blinding: unblinded Attrition: complete follow-up Selective reporting: none **Outcomes** Primary: need for mechanical ventilation or a sustained FiO2 >0.6 beyond 1 hr after surfactant treatment, requirement of a second dose of surfactant within 8 hours of the first, needing more than 2 doses of surfactant. Secondary: Days on any respiratory support, pneumothorax, BPD at 36 weeks PMA, complications during LMA insertion, complications of surfactant delivery and mortality.	LMA: 3/30: InSuRe: 2/30 **Outcome: Pneumothorax** LMA: 6/30; InSuRe: 4/30	computerised algorithm Allocation concealment: Low risk, opaque sealed envelopes used Blinding of participants and personnel: High risk for subjective outcomes as unblinded due to the nature of the study, low risk for objective outcomes Blinding of outcome assessment: High risk for subjective outcomes as unblinded due to the nature of the study, low risk for objective outcomes Incomplete outcome data: Low risk, all participants followed-up and the 1 patient excluded from analysis was accounted for Selective reporting: Low risk, those noted in the methods to be assessed were assessed

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding None reported	FiO2 0.3-0.6 to maintain SpO2 88-95% and signed parental consent. **Exclusion criteria** Previous intubation or surfactant therapy, weight <1000g, major malformations (craniofacial, cardiac or thoracic), apgar score of ≤3 at 5 min, pneumothorax prior to enrolment or severe RDS indicated by an FiO2 >0.6.	delivered by an ETT in two aliquots followed by PPV for at least 5 minutes before reinstituting the prior nCPAP or NIPPV if possiblem, withing 15 minutes of surfactant administration. Assisted ventilation via ETT was continued in patients with persistent apnea., severe retractions and/ or inability to wean FiO2 below 0.6			**Other information**
Full citation Speer, C. P., Robertson, B., Curstedt, T., Halliday, H. L., Compagnone, D., Gefeller, O., Harms, K., Herting, E., McClure, G., Reid, M., Tubman, R., Herin, P., Noack, G., Kok, J., Koppe, J., Van Sonderen, L., Laufkotter, E., Kohler, W., Boenisch, H., Randomized European multicenter trial of	**Sample size** n=357 randomised (n=184 to single dose; n=173 to multiple doses) 14 patients violated entry criteria n= 343 included in study (n=176 single dose; n=167 to multiple doses)	**Interventions** Single dose Curosurf (100mg/kg) vs multiple dose curosurf (100mg/kg) x 3 doses. Multiple dose group received additional doses of curosurf at 12 and 24 hours after initial dose if on assisted ventilation	**Details** Methods: multicentre randomised controlled trial Outcomes: primary - BPD or death; secondary - ventilatory requirements; oxygenation; complications of prematurity	**Results** **Outcome: Mortality prior to discharge (during first 28 days of life)** Single dose: 37/176; multiple doses: 22/167 **Outcome: Bronchopulmonary Dysplasia at 28 days of age**	**Limitations** Risk of bias assessed using Cochrane risk of bias tool Random sequence generation: Unclear risk, no details specified Allocation concealment: Low risk, cochrane stated bliniding of randomisation,

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
surfactant replacement therapy for severe neonatal respiratory distress syndrome: Single versus multiple doses of Curosurf, PediatricsPediatrics, 89, 13-20, 1992 **Ref Id** 703825 **Country/ies where the study was carried out** Europe **Study type** Randomised controlled trial **Aim of the study** To determine the effect of multiple doses of exogenous surfactnat compared to single doses of exogenous surfactant on mortality and complications of prematurity in premature infants at risk of having respiratory distress syndrome **Study dates** Not reported	**Characteristics** Gestational age (weeks in mean, SD in parentheses): single dose= 29.2 (2.5); multiple doses= 28.9 (2.2) Age at randomisation (hours in median, range in parentheses): single dose: 6 (4.5-10.5); multiple doses= 6.7 (4.4-9.7) FiO2 at randomisation (median, range in parentheses): single dose: 0.83 (0.7-1.0); multiple doses= 0.9 (0.72-1) **Inclusion criteria** Premature infants, birthweight 700-2000g, respiratory distress syndrome, assisted ventilation. supplemental oxygen equal or greater to 60%, age 2-15 hours **Exclusion criteria**			Single dose: 21/176; multiple doses: 22/167 **Outcome: Severe IVH (grade 3 or 4)** Single dose: 34/176; multiple doses: 38/167 **Outcome: Pneumothorax** Single dose: 32/176; multiple doses: 15/167 **Outome: Pulmonary haemorrhage** Speer 1992 Single dose: 4/176; multiple doses: 3/167	however no details provided Blinding of participants and personnel: High risk for subjective outcomes, cochrane stated no blinding of intervention, however no details provided. Low risk for objective outcomes. Blinding of outcome assessment: High risk for subjective outcomes, cochrane stated no blinding of outcome measurement, however no details provided. Low risk for objective outcomes. Incomplete outcome data: Low risk, cochrane stated complete follow-up Other bias: none reported **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding Bundesministerium Frorschungund Technologie,' FRG (project 93 607 27) The development of the surfactant used in this trial was supported by the Swedish Medical Research Council (project 3351), Oscar II:s Jubileumsfond, and the General Maternity Hospital Foundation.	Not specified				

Clinical evidence tables for question 3.1 What is the most effective way to administer oxygen during respiratory support?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Claure, N., Bancalari, E., D'Ugard, C., Nelin, L., Stein, M., Ramanathan, R., Hernandez, R., Donn, S. M., Becker, M.,	**Sample size** Results collected from thirty-two infants, out of thirty-five initially enrolled. **Characteristics**	**Interventions** In the treatment condition the fraction of inspired oxygen (FiO_2) ventilated to infants was adjusted by an automated system. The system measured arterial oxygen saturation (SpO_2) once per second with a neonatal	**Details** Randomisation: Order of conditions was randomised to each infant in blocks according to centre. Unclear if a computer was used for randomisation.	**Results** SpO_2 of 87%-93% (target range), proportion of time, mean (SD) Manual (n=16)= 32 (13)	**Limitations** Although significant, the results may not be clinically important. In the control condition individual caregivers may have varied significantly in practice, e.g. due to

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Bachman, T., Multicenter crossover study of automated control of inspired oxygen in ventilated preterm infants, Pediatrics, 127, e76-e83, 2011 **Ref Id** 666163 **Country/ies where the study was carried out** US **Study type** Multicenter crossover study **Aim of the study** To asses the efficacy and safety of using automatically adjusted inspired oxygen in order to maintain the arterial oxygen saturation of ventilated infants within the intended	Babies, n= 32 Gestational age, weeks, median (IQR) = 25(24–27) Birth weight, grams, median (IQR) = 622(568–770) Ventilation types: Synchronized intermittent mandatory ventilation (n) = 16; Synchronized intermittent mandatory ventilation and pressure support (n) = 15; Assist/control ventilation (n) = 1 **Inclusion criteria** Preterm infants who needed mechanical ventilation of supplemental oxygen due to frequent episodes of decreased blood oxygen saturation. For inclusion they must have had 4 or more episodes of arterial oxygen saturation falling	pulse oximeter, and was programmed to deliver oxygen at a quantity to keep SpO_2 within the range 87%–93%. Nurses and respiratory staff were trained in advanced to use the system. Under the control condition FiO_2 was instead adjusted manually by clinical staff members as was currently routine in their centres, to keep the range between 87%–93%. Eligible infants went through a 24hr period under one condition, followed consecutively by a 24hr period under the other.	Allocation concealment: Allocation was concealed in opaque envelopes until the study start. Blinding: Once underway nurses and respiratory staff were aware of which condition the infant was currently under. Attrition: Of the 35 initially enrolled, one was enrolled erroneously against the inclusion criteria and was removed shortly after starting when they started to deteriorate. Their participation data was excluded, along with two further infants who's data was lost to a an electronic data-logging failure. The remaining 32 infants completed both conditions and all their data was analysed. Selective reporting: All stated outcomes were subsequently reported on in the results section Outcomes: Primary outcome was the number of times per hour that blood oxygen saturation fell out of the range 87%–93%, and how long these episodes lasted	Automated (n=16)= 40 (14) No of manual FiO_2 adjustments, mean (SD) Manual (n=16)= 112 (59) Automated (n=16)= 10 (9)	individual attentiveness, varying workloads and different standards of care between practices. Insufficient statistical power to test this. Automated processes ma y mask infant's deterioration and make caregivers less attentive to changes, preventing timely & needed interventions. The study population was restricted, limiting the generalisability to other preterm infants. **Other information** Random sequence generation - Unclear risk. "The sequence of the manual and automated periods was assigned at random to each infant, in blocks according to center." Allocation concealment - High risk. Some initial concealment, but ultimately compromised due to alternation.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
range, compared to manual adjustment. **Study dates** February - September 2008 **Source of funding** Not stated	below 80% in the 24hrs prior to study. **Exclusion criteria** Grounds for exclusion included major congenital anomalies, hemodynamic instability, seizures, ongoing sepsis and meningitis.		for. Recordings of oxygen saturation were taken every 5 seconds, along with infant's pulse, and the fraction of inspired oxygen (FiO_2) being ventilated.		Blinding of participants and personnel - High risk. Caregiving staff were aware of the study objectives and couldn't be blinded to the treatment they were administering. Blinding of outcome assessment - Unclear risk. "Off-line computerized analysis without operator intervention was used to evaluate the recorded data for each infant for both 24-hour periods." Incomplete outcome data - Low risk. All participants completed both conditions. Intention to treat analysis. Selective reporting - Low risk. All outcomes outlined in the protocol shown in results. Other sources of bias - Low risk. Cross-over trials often risk carry-over effects, but this is less likely with this outcomes and population.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Claure, N., D'Ugard, C., Bancalari, E., Automated adjustment of inspired oxygen in preterm infants with frequent fluctuations in oxygenation: a pilot clinical trial, Journal of pediatrics, 155, 640-5.e1-2, 2009 **Ref Id** 666165 **Country/ies where the study was carried out** US **Study type** Pilot crossover study **Aim of the study** To pilot a study to asses the efficacy and safety of using automatically adjusted inspired oxygen compared to	**Sample size** Sixteen infants, all completed both conditions. **Characteristics** Babies, n= 16 Gestational age, weeks, (median/mean not clear) = 24.9 ±1.4 Birth weight, grams, (median/mean not clear) = 678 ±144 At the time of inclusion they had been on a ventilator for 28 ±17 days **Inclusion criteria** Preterm infants receiving supplemental oxygen from mechanical ventilation, and who'd had eight or more episodes of hypoxemia in 4 hours. **Exclusion criteria**	**Interventions** In the treatment condition the fraction of inspired oxygen (FiO_2) ventilated to infants was adjusted by an automated system. The system measured arterial oxygen saturation once per second with a neonatal pulse oximeter, and was programmed to deliver oxygen supply in a quantity to keep oxygen saturation ($Sp0_2$) within the range established by the user (88%–95%). Nurses and respiratory staff were trained in advanced to use the system. Under the control condition the fraction of inspired oxygen (FiO_2) ventilated to infants was instead adjusted manually by clinical staff members, as was routine in their centres, to keep the ranges of $Sp0_2$ between 88%–95%. In both conditions alarms would sound if $Sp0_2$ remained outside of this range for more than 2 minutes. Infants completed a 4hr period under one condition, followed consecutively by a 4hr period under the other.	**Details** Randomisation: Sequence of conditions was reportedly randomised, although it is not stated how. Allocation concealment: Not stated. Blinding: Not stated. Attrition: Sixteen infants reportedly enrolled, and sixteen datasets subsequently analysed. Selective reporting: All stated outcomes were subsequently reported. Outcomes: The primary outcome was the amount of time spent with $Sp0_2$ spent within, above or bellow the intended range of 88%–95%. Other outcomes included amount of time spent in hypoexemia and hyperoxemia (with $Sp0_2$<75% or >87%) as a percentage of recorded time, and number of episodes of bradycardia (heartbeat <100 beats per minute for ten seconds or more).	**Results** SpO_2 88%-95%) (intended SpO_2 range), percent of time, mean (SD) Routine= 42 (9) Automated= 58 (10)	**Limitations** Although significant, the results may not be big enough to be clinically important. Awareness of the study and its aims, and the presence of a researcher observing, may have introduced a bias making the caregiving staff more attentive. Each condition was tested for only a very limited period of four hours. Automated processes ma y mask infant's deterioration and make caregivers less attentive to changes, preventing timely & needed interventions. **Other information** Random sequence generation- Unclear risk. No information stated. Allocation concealment- Unclear risk. No information stated.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
manual adjustment in order to maintain the arterial oxygen saturation of ventilated infants within an intended range. **Study dates** Decemeber 2006 - July 2007 **Source of funding** Author's department was supported by Viasys Healthcare, The University of Miami "Project: New Born", and The Bank of America Charitable Foundation	Major congenital anomalies, acute respiratory failure, or hemodynamic instability.				Blinding of participants and personnel- High risk. Caregiving staff were aware of the study objectives and couldn't be blinded to conditions. Blinding of outcome assessment- Unclear risk. No information stated. Incomplete outcome data- Low risk. All enrolled participants completed both conditions. Intention to treat analysis. Selective reporting- Low risk. All outcomes outlined in the protocol shown in results. Other sources of bias- Low risk. Cross-over trials often risk carry-over effects, but this is less likely with these outcomes and population.
Full citation Hallenberger, A., Poets, C. F., Horn,	**Sample size** Thirty-four infants' datasets collected and analysed, out of forty-	**Interventions** In the treatment condition the fraction of inspired oxygen (FiO_2) ventilated to infants was	**Details** Randomisation: Group allocation was randomised by computer list,	**Results** Overall, n=34	**Limitations** Didn't have the statistical power to look at practice

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
W., Seyfang, A., Urschitz, M. S., Miksch, S., Mueller-Hansen, I., Hummler, H., Schmid, M., Essers, J., Mendler, M., Hentschel, R., Freisinger, P., Schneider, H. C., Closed-loop automatic oxygen control (CLAC) in preterm infants: A randomized controlled trial, Pediatrics, 133, e379-e385, 2014 **Ref Id** 666671 **Country/ies where the study was carried out** Germany **Study type** Multicenter, randomized controlled, crossover clinical trial **Aim of the study**	four infants initially enrolled. Infants were from four centres - each recruting eighteen, seven, four and five infants respectively. **Characteristics** Babies, n= 34 Gestational age, weeks, median (range)= 26.4 (23.0 - 35.3) Birth weight, grams, median (range)= 840 (410-2460) **Inclusion criteria** Infants with gestational age at birth of <37 weeks, requiring mechanical ventilation or nasal CPAP. **Exclusion criteria** Congenital diaphragmatic hernia,	adjusted by an automated system. The ventilator was programmed to monitor arterial oxygen saturation ($Sp0_2$) from a neonatal pulse oximeter, and deliver oxygen supply in a quantity that would regulate oxygen saturation within the range established by the user. The target range was subdivided into 'upper' (94-95%), 'middle' (92-93%) and 'lower' (90-91%), and from these combined with temporal data one of five different FiO_2 adjustments were calculated and implemented. Nurses and respiratory staff were trained in advanced to use the system. In the control condition the fraction of inspired oxygen (FiO_2) ventilated to infants was adjusted manually by clinical staff members, according to their experience and routine in their centres. Standard target levels in centres ranged from 80% - 95%. Eligible infants went through a 24hr period under one condition, followed consecutively by a 24hr period under the other.	prepared into sequentially numbered, sealed opaque envelopes by an investigator with no clinical involvement. Allocation concealment: Participants opened an envelopes at the start allocating them to one of two groups of treatment order. Blinding: Randomisation and group allocation were blinded. However it was not feasible to blind carestaff to treatment conditions delivered. Attrition: Fourty-four infants were initially enrolled, of which thirty-four were included for final analysis. Six were excluded after completion due to protocol non-adherence, and four were excluded as more than 10% of their oximetry data was accidentally lost. Selective reporting: All stated outcomes were subsequently reported on, apart from a secondary analysis of the primary outcome stratified by centre due to insufficient statistical power. Outcomes: The primary outcome was the percentage of time spent within the target	Time within target range, %, mean (SD) Manual= 61.0 (15.2) Automated= 72.1 (13.6) Number of manual FiO_2 adjustments, median (IQR) Manual= 77 (0-224) Automated= 52 (10-317) p-value= 0.007	effects by stratifying the main results by centre. Nurses didn't receive any additional training on their manual practice, and so this may have varied widely between centre and practitioner. Lack of training with the control condition may have enlarged the effect size found. Although told to ignore it, the intervention's equipment was present during the control condition and nurses may have used its readings. **Other information** Random sequence generation- Low Risk. " For group allocation, a computer-generated list of random numbers was used" Allocation concealment- Low Risk. "After recruitment, infants were randomly assigned by a senior doctor to 1 of 2 study groups by opening corresponding

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
To test the effectiveness of using automatically adjusted fraction of inspired oxygen, compared to manual adjustment, in order to maintain arterial oxygen saturation of ventilated infants within the intended range. **Study dates** April 2009 - March 2012 **Source of funding** Four ventilators and a research grant were granted from Heinen & Loewenstein GmbH (Bad Ems, Germany)	cyanotic heart disease, or another medical condition necessitating a deviation from the usual SpO2 target range. Individuals were also excluded from the study following cases of resuscitation, termination of mechanical ventilation/CPAP, or withdrawal of parental consent.		SpO_2 range, with a 2% increase judged as clinically relevant. Time spent above the target range, as well as time spent below, were secondary outcomes. So too was the number of manual adjustments made by carestaff.		sequentially numbered and sealed opaque envelopes." Blinding of participants and personnel- High risk. Randomisation prepared by an investigator without clinical involvement in the trial, and concealed. But caregiving staff were aware of the study objectives and couldn't be blinded to the treatment they were administering. Blinding of outcome assessment- High risk. Caregiving staff were aware of the study objectives and couldn't be blinded to the treatment they were administering. Incomplete outcome data- High risk. Ten exclusions (23% of those initially enrolled) due to either lost data or protocol non-adherence, and this data may have been important to understanding the intervention's effectiveness. Selective reporting- Low risk. Outcomes were

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					clearly stated and subsequently reported on. Other sources of bias- Low risk. Study seems to be free of other important risks of bias.
Full citation Kaam, Ah, Hummler, Hd, Wilinska, M, Swietlinski, J, Lal, Mk, Pas, Ab, Lista, G, Gupta, S, Fajardo, Ca, Onland, W, Waitz, M, Warakomska, M, Cavigioli, F, Bancalari, E, Claure, N, Bachman, Te, Automated versus Manual Oxygen Control with Different Saturation Targets and Modes of Respiratory Support in Preterm Infants, Journal of pediatrics, 167, 545-550.e2, 2015 **Ref Id**	**Sample size** Eighty infants had their data included in the final analysis, out of ninety-one that were initially enrolled. **Characteristics** Babies, n= 80 Gestational age, weeks, median (IQR) = 26(25–28) Birth weight, grams, median (IQR) = 794(674–950) **Inclusion criteria** Infants with gestational age <33 weeks, requiring invasive or non-invasive supplementary	**Interventions** Infants were randomised to either the higher arterial oxygen saturation (SpO_2) group or the lower lower arterial oxygen saturation (SpO_2) group. Those in the higher group had a target SpO_2 range of 91%-95%, while those in the lower SpO_2 group had a target range of 89%-93%. Then in a randomised order for two consecutive twenty-four hour periods they received oxygen either from an automated system first followed by a manual system first, or vice-versa. The automated system monitored changes in SpO_2 with a neonatal pulse oximeter and automatically varied the fraction of inspired oxygen (FiO_2) accordingly to keep oxygen saturation within range. In the manual condition the fraction of inspired oxygen (FiO2) ventilated to infants was instead adjusted	**Details** Randomisation: The target SpO_2 range and the sequence of conditions was randomised, although it is not stated how. Allocation concealment: At the start allocation was concealed in sequentially numbered, sealed opaque envelopes. Blinding: No blinding was reported. Carestaff coul d not be blinded to the target SpO_2 range or condition once treatment was underway. Attrition: Ninety-one infants were initially enrolled, but eleven were excluded from the final analysis. Two of these cases this was due to data-logging errors, five were due to a change in respiratory support mode, and four were due to	**Results** % time in SpO_2 target range 89%-93%, mean (SD) n=40 Manual= 54 (16) Automated= 62 (17) % time in SpO_2 target range 91%-95%, mean (SD) n=40 Manual= 58 (15) Automated= 62 (17) No. manual adjustments per 24 hours, median (IQR) SpO_2 target range 89%-93% Manual= 102 (73-173) Automated=1 (0-3) $p < 0.01$	**Limitations** The inclusion of more stable infants as well as trained nurses may have reduced their effect size compared to previous studies. The study was only over 48 hours, while preterm infants often remain on oxygen for many weeks. The nurses were not blinded and had received training, and so this may be 'improved care' rather than standard care. The exclusion of infants for several reasons may have obscured an evaluation the treatment's effectiveness in real terms.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
666874 **Country/ies where the study was carried out** Pan-Europe & Canada **Study type** Multicenter, randomized controlled, crossover clinical trial **Aim of the study** To test the efficacy and safety of using automatically adjusted fraction of inspired oxygen in order to maintain arterial oxygen saturation of ventilated infants within the ranges of 91-95% and 89%-93%. **Study dates**	oxygen. Unlike most previous studies frequent hypoxemia was not required. Weight between 0.4kg and 4kg at the time of study. **Exclusion criteria** Major congenital anomalies, hemodynamic instability or sepsis within the past 72hrs were excluded.	manually by clinical staff members. Nurses were trained on titration of FiO2 at the start.	exclusionary health episodes. Selective reporting: All stated outcomes were subsequently reported. Outcomes: The primary outcome was the percentage of time spent within the target SpO_2 range. Secondary outcomes included the number of episodes and percentage of time spent either above or below the target range, as well as the average SpO_2 (%) and FiO_2.	SpO_2 target range 91%-95% Manual= 109 (79-156) Automated= 1 (0-3) $p < 0.01$	**Other information** Random sequence generation- Unclear Risk. Sequence generation method was not clearly stated. Allocation concealment- Low Risk. Allocations contained numbered and sealed opaque envelopes. Blinding of participants and personnel- High risk. No blinding reported. Blinding of outcome assessment- High risk. Caregiving staff were aware of the study objectives and couldn't be blinded to the treatment they were administering. Incomplete outcome data- High risk. Eleven exclusions due to either lost data or protocol non-adherence, and this data may have been important to understanding the intervention's effectiveness. Selective reporting- Low risk. Outcomes were

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
April 2013 - February 2014 **Source of funding** Carefusion loaned ventilators to three centres and provided funding for the study's data collection and management, but was not involved in the data analysis, interpretation, or drafting of the manuscript					clearly stated and subsequently reported on. Other sources of bias- Low risk. Study seems to be free of other important risks of bias.
Full citation Van Zanten, H. A., Kuypers, K. L. A. M., Stenson, B. J., Bachman, T. E., Pauws, S. C., te Pas, A. B., The effect of implementing an automated oxygen control on oxygen saturation in preterm infants, Archives of Disease in Childhood., 16, 2017	**Sample size** 42 infants' data analysed, 21 treated before implementation and 21 treated after. **Characteristics** Babies, n= 42 (21 pre-implementation and 21 post-implementation) Gestational age, weeks+days, median (IQR): pre =	**Interventions** Before the implementation of automated oxygen nurses would set the fraction of inspired oxygen (FiO_2) titrated to infants manually, adjusting in accordance to the arterial oxygen saturation (SpO_2) readings from a neonatal pulse exhibitor. Following the implementation an automated system was instead programmed to the adjust FiO_2 automatically in accordance with rises or falls in the	**Details** Randomisation: This was an implementation study in a naturalistic setting. Infants received treatment according to the date of their admittance. Allocation concealment: None. Blinding: None. Attrition: It was reported that all eligible infants from 4 months before implementation and 5	**Results** No. of days on respiratory support, median (IQR) Manual (n=21)= 16 (10-22) Automated (n=21)= 14 (3-28) p-value not statistically significant Proportion of time within target	**Limitations** This was not a controlled study, but rather focused on longer term effects in a naturalistic setting. Lack of randomisation so infants may have been different between groups in a way not measured. **Other information** Risk of bias assessed using the Newcastle-Ottawa Quality

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ref Id 802470 **Country/ies where the study was carried out** Netherlands **Study type** Prospective observational study **Aim of the study** Assess the effects of implementing automated oxygen into routine care on maintaining arterial oxygen saturation. **Study dates** May 2015 - January 2016 **Source of funding** None stated	27+6(26+3 – 28+4), post = 27+3(26 – 28+2) Birth weight, grams, median (IQR): pre = 966(843 – 1235), post = 940(825 - 1242) Apgar score 5 minutes, median (IQR): pre = 7(6 - 9), post = 8(6 - 9) **Inclusion criteria** Infants <30 weeks of gestation requiring either invasive or non-invasive supplementary oxygen. As part of standard are all infants had received caffeine. All eligible infants admitted to the NICU were enrolled in the study, further consent is not required in the Netherlands for analysing anonymised routine data and charts.	SpO_2 readings from the neonatal pulse exhibitor. Nurses, and subsequently the automated system, were tasked to keep SpO_2 levels within the range of 90-95%.	months after had their data included. Selective reporting: All stated outcomes were subsequently reported on in the results section. Outcomes: Primary outcome was the percentage of time spent with SpO_2 within the target range 90-95%. Percentages spent at intervals above and below the target range were also calculated.	range (90-95%), median (IQR) Manual (n=21)= 48.4 (41.5-56.4) Automated (n=21)= 62.0 (56.4-68.6) p < 0.01 Mortality prior to discharge, n/N Manual= 0/12 Automated= 3/13	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 record (hospital routine records)* Demonstration that outcome of interest was not present at start of study: a) yes* **Comparability** Study controls for: Gestational age, birth weight, sex, 5-minute APGAR score, singletons, invasive ventilated days, use of Dopram, Mortality* Study controls for any additional factor: a) yes* **Outcome** Assessment of outcome: b) record linkage* Was follow-up long enough for outcomes to

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Exclusion criteria Preterm infants with major congenital heart disease were excluded.				occur: a) yes (until discharge)* Adequacy of follow-up of cohorts: d) no statement
Full citation Travers, C. P., Carlo, W. A., Nakhmani, A., Bhatia, S., Gentle, S. J., Amperayani, V. A., Indic, P., Aban, I., Ambalavanan, N., Environmental or Nasal Cannula Supplemental Oxygen for Preterm Infants: A Randomized Cross-Over Trial, Journal of Pediatrics, 2018 **Ref Id** 861277 **Country/ies where the study was carried out** US	**Sample size** Results analysed from twenty-five infants, out of twenty-seven initially enrolled. **Characteristics** Babies, n= 25 Gestational age, weeks, mean (±SD) = 27(±2) Birth weight, grams, mean (±SD) = 933(±328) **Inclusion criteria** The study included preterm infants with gestational age <37 weeks, receiving oxygen through either	**Interventions** The environmental condition utilised incubators that maintain the oxygen level around the infant at a set level utilising a servo-controlled system. In the comparison condition oxygen was delivered by nasal cannular. For both conditions the effective fraction of inspired oxygen (FiO_2) was calculated for the infants using standardized charts based on infant weight, set FiO_2, and flow rate. Participants were randomly assigned to complete one intervention for 24hrs followed by the other in an 'ABAB' sequence.	**Details** Randomisation: The order that infants underwent the two conditions was randomised by partnering research office. Allocation concealment: Allocation was concealed using sequentially numbered sealed opaque envelopes Blinding: Not clear. Attrition: Of twenty-seven infants enrolled, two were excluded from the study. Of the twenty-five analysed, eighteen (72%) completed all four conditions. Selective reporting: All stated outcomes were subsequently reported on in the results section. Outcomes: Primary outcome was number of episodes of	**Results** Proportion of time SpO_2 in target range (91-95%), mean (SD) Incubator (n=12)= 50 (9) Nasal cannula (n=13)= 49 (10) No. FiO_2 adjustments per 24 hours, mean (SD) Incubator (n=12)= 5 (3) Nasal cannula (n=13)= 5 (3)	**Limitations** The staff's knowledge of treatment conditions may have resulted in some information bias. **Other information** Random sequence generation- Unclear Risk. Sequence generation method was not clearly stated. Allocation concealment- Low Risk. Allocations contained numbered and sealed opaque envelopes. Blinding of participants and personnel- High risk. No blinding reported.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study type Single centre, randomised, crossover trial **Aim of the study** Test whether episode s of intermittent hypoxemia are decreased by environmental compared with nasal cannula oxygen. **Study dates** April - September 2016 **Source of funding** Supported by the Agency for Healthcare Research and Quality; the National Institutes of Health; the Dixon Fellowship of the University of Alabama at Birmingham and Children's of	nasal cannula or or oxygen environment. To be eligible they had to have been off ventillator or continuous positive airway pressure for more than 48 hours, and in an incubator or thermoregulation. Parental consent was required. **Exclusion criteria** Major malformation, neuromuscular conditions affecting respiration, terminal illness, or some reason for withholding or limiting support.		hypoxemia, where SpO_2 fell below 85% for 10 seconds or more. Other outcomes included the percentage of time in hypoxemia, that percentage of time that SpO_2 was within the target range of 91-95% and proportion of time otherwise below or above this range. Number of Bradycardia episodes (heart ate greater than 100bpm for ten seconds or more), and overall oxygen supply stability were also assessed. All outcomes were per 24hr treatment period.		Blinding of outcome assessment- High risk. Caregiving staff were aware of the study objectives and couldn't be blinded to the treatment they were administering. Incomplete outcome data- Low risk. Only two excluded from those initially enrolled, and the rest included in an intention to treat analysis. Selective reporting- Low risk. Outcomes were clearly stated and subsequently reported on. Other sources of bias- Low risk. Study seems to be free of other important risks of bias.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Alabama; and the National Science Foundation					

Clinical evidence tables for question 3.2 What is the effectiveness and safety of the different assisted ventilation techniques in preterm babies?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Alkan Ozdemir, S., Arun Ozer, E., Ilhan, O., Sutcuoglu, S., Impact of targeted-volume ventilation on pulmonary dynamics in preterm infants with respiratory distress syndrome, Pediatric Pulmonology, 52, 213-216, 2017 **Ref Id** 619407 **Country/ies where the study was carried out** **Study type**	**Sample size** NMA only to assess heterogeneity **Characteristics**	**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 Baumer, J. H., International randomised controlled trial of patient triggered ventilation in neonatal respiratory distress syndrome, Archives of Disease in Childhood Fetal & Neonatal EditionArch Dis Child Fetal Neonatal Ed, 82, F5-F10, 2000 **Ref Id** 665906 **Country/ies where the study was carried out** **Study type** **Aim of the study**	**Sample size** Please see Greenough 2016 Cochrane systematic review **Characteristics**	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates **Source of funding**					
Full citation Beresford, M. W., Shaw, N. J., Manning, D., Randomised controlled trial of patient triggered and conventional fast rate ventilation in neonatal respiratory distress syndrome, Archives of Disease in Childhood Fetal & Neonatal EditionArch Dis Child Fetal Neonatal Ed, 82, F14-8, 2000 **Ref Id** 653459 **Country/ies where the study was carried out** **Study type** **Aim of the study** **Study dates**	**Sample size** Please see Greenough 2016 Cochrane systematic review **Characteristics**	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding					
Full citation Bernstein, G., Mannino, F. L., Heldt, G. P., Callahan, J. D., Bull, D. H., Sola, A., Ariagno, R. L., Hoffman, G. L., Frantz, Iii I. D., Troche, B. I., Roberts, J. L., Dela Cruz, T. V., Costa, E., Randomized multicenter trial comparing synchronized and conventional intermittent mandatory ventilation in neonates, Journal of pediatrics, 128, 453-463, 1996 **Ref Id** 665939 **Country/ies where the study was carried out** **Study type** **Aim of the study** **Study dates**	**Sample size** Please see Greenough 2016 Cochrane systematic review	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding					
Full citation Bisceglia, M., Belcastro, A., Poerio, V., Raimondi, F., Mesuraca, L., Crugliano, C., Pio Corapi, U., A comparison of nasal intermittent versus continuous positive pressure delivery for the treatment of moderate respiratory syndrome in preterm infants, Minerva Pediatrica, 59, 91-95, 2007 **Ref Id** 665969 **Country/ies where the study was carried out** **Study type** **Aim of the study** **Study dates** **Source of funding**	**Sample size** Please see Lemyre 2016 cochrane systematic review **Characteristics**	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Chowdhury, O., Patel, D. S., Hannam, S., Lee, S., Rafferty, G. F., Peacock, J. L., Greenough, A., Randomised trial of volume-targeted ventilation versus pressure-limited ventilation in acute respiratory failure in prematurely born infants, NeonatologyNeonatology, 104, 290-294, 2013 **Ref Id** 643116 **Country/ies where the study was carried out** **Study type** **Aim of the study** **Study dates** **Source of funding**	**Sample size** Please see Klingenberg 2017 Cochrane systematic review **Characteristics**	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Cools, F., Henderson-Smart, D. J., Offringa, M., Askie, L. M., Elective high frequency oscillatory ventilation versus conventional ventilation for acute pulmonary dysfunction in preterm infants, Cochrane Database of Systematic Reviews, (3) (no pagination), 2015 **Ref Id** 653565 **Country/ies where the study was carried out** **Study type** Cochrane systematic review **Aim of the study** Determine the effect of the elective use of high frequecy oscillatory ventilation (HFOV) when compared to conventional ventilation on the incidence of chronic lung disease, mortality and other complications. **Study dates** Up to Feburary 2013	**Sample size** **Of relevant studies:** **Durand 2001** n= 48 (SIMV: 24; HFOV: 24) **Gerstmann 1996** n=125 (IMV: 61; HFOV: 64) **Johnson 2002** n= 797 (TCPL: 397; HFOV: 400) <u>23-25 weeks</u> n=284 (TCPL: 136; HFOV: 148) <u>26-28 weeks</u> n=513 (TCPL: 261; HFOV: 252) **Lista 2008** n=40 (A/C + VG: 21; HFOV: 19) **Moriette 2001** n=273 (SIMV: 134; HFOV: 139) **Ogawa 1993** n=52 (TCPL: 46; HFOV: 46) **Salvo 2012** n=88 (SIMV: 44; HFOV: 44) **Thome 1999** n=188 (IPPV: 50; HFFI: 46) **Van Reempts 2003** n=300 (IMV: 153; HFOV: 147)	**Interventions** **Of relevant studies:** **Durand 2001** SIMV vs HFOV <u>Ventilator type:</u> HFOV: OSC using Sensormedics 3100A. Settings: initial MAP 2 cm H20 higher than with SIMV, 15 Hz, I/T 0.33 SIMV: Drager Babylog, Bearcub, VIP Bird. Settings: rate < 60/min, PEEP 4 to 6 cm H20, Ti 0.25 to 0.35 sec, target Vt 5-6 ml/kg Target PCO2: 40 to 55 mmHg (45-65 mmHg for infants with CLD) Cross-over: no **Gerstmann 1996** IMV vs HFOV <u>Ventilator type:</u> HFOV: OSC using sensormedics 3100 (A). Settings: initial MAP 1-2 cm H20	**Details** **Randomisation** **Of relevant studies:** **Durand 2001** Randomisation: “Randomly assigned” No information on randomisation procedure **Gerstmann 1996** Randomisation: “Randomisation was by blind card draw from separate sets of...” Insufficient information regarding concealment procedures **Johnson 2002** Randomisation: “infants were randomly assigned" No information on randomisation procedure **Lista 2008** Randomisation: “following a sequence of random numbers...”	**Results** **Critical outcomes** **Mortality before discharge** NMA outcome **BPD (oxygen dependency at 36 weeks corrected gestation or 28 days of age** NMA outcome **Neurodevelopmental outcomes at ≥18 months** Not all included in the Cochrane review, extracted from original papers **Important outcomes** **Number of days on invasive ventilation** **Of relevant studies:**	**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) **Other information** **Selection bias** **Durand 2001** Unclear risk: randomisation proceedure not reported

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding Eunice Kennedy Shriver National Institute of Child Health and Human Development National Institutes of Health, Department of Health and Human Services, US.	**Vento 2005** n=40 (SIMV: 20; HFOV: 20) **Characteristics Of relevant studies:** **Durand 2001** Gestational age in weeks, mean HFOV: 25.9; SIMV: 26.1 Age at start of ventilation in hours, mean HFOV: 2.8; SIMV: 2.4 Birthweight in grams, mean HFOV: 823; SIMV: 856 Antenatal steroid use HFOV: 42%; SIMV: 50% FiO2 at enrollment HFOV: 0.63; SIMV: 0.64 **Gerstmann 1996** Gestational age in weeks, mean HFOV: 30.8; IMV: 30.1 Age at start of ventilation in hours, mean HFOV: 2.9; IMV: 2 Birthweight in grams, mean HFOV: 1560; IMV: 1460 Antenatal steroid use 100% **Johnson 2002** Gestational age in weeks, mean <u>23-25 weeks</u> HFOV: 24.9; TCPL: 24.7	> with CV, I:E ratio 0.33, 10 to 15 Hz IMV: Sechrist. Settings: IT 0.35-0.55 sec, rate <60/min, PEEP 3-7 cm H20, PIP up to 30 cm H20 if < 1 kg and up to 35 cm H20 if > 1 kg. Target PCO2: 35-45 mmHg Cross-over: if infants meet failure crtieria (insufficient oxygenation or ventilation for >2hr; persistent haemodynamic problems, destabilising problem of airleak; requiring hand ventilation) **Johnson 2002** TCPL vs HFOV* <u>Ventilator type:</u> HFOV: mix of OSC using SLE2 2000 or sensormedics 3100A, and HFFI using Drager	No information on concealment of allocation sequence. **Moriette 2001** Randomisation: “computer-generated randomization” Allocation concealment: “using sealed envelopes” **Ogawa 1993** Randomisation: “eligible for randomisation” Allocation concealment: “randomisation with opaque envelopes” **Salvo 2012** Randomisation: “computer generated random numbers” No information on allocation concealment **Thome 1999** Randomisation: “randomly assigned” Allocation concealment: “consecutively numbered computer-printed opaque envelopes” **Van Reempts 2003** Randomisation: “were randomised”	**Gerstmann 1996*** Median (5, 95% confidence intervals in parentheses) ≤1kg: HFOV: 24.7 (3.7, 61.4); IMV: 53.7 (28.4, 103) >1 kg: HFOV: 4.1 (1.7, 6); IMV: 4.5 (3.0, 6.1) **Johnson 2002** Median in days (range in parentheses) HFOV: 7 (3-21); TCPL: 7 (2-20) p-value=0.58 **Salvo 2012*** Mean in hours (SD in parentheses) HFOV: 45 (17); SIMV: 177 (84) **Vento 2005*** Mean in hours (SD in parentheses) HFOV: 310 (313); SIMV: 656 (981) ***Data referred to survivors only. 7 infants in the the HFOV group and 12 infants in the SIMV group recevied late systemic corticosteroids***	**Gerstmann 1996** low risk: “Randomisation was by blind card draw from separate sets of...” **Johnson 2002** Unclear risk: did not report how random sequence was generated **Lista 2008** Unclear risk: did not report how random sequence was generated **Moriette 2001** low risk **Ogawa 1993** Unclear risk: Did not report whether randomisation was computer generated **Salvo 2012** low risk **Thome 1999** Unclear risk: did not report how random sequence was generated **Van Reempts 2003** Unclear risk: did not report how random sequence was generated **Vento 2005**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	26-28 weeks HFOV: 27.4; TCPL: 27.4 Birthweight in grams, mean 23-25 weeks HFOV: 704; TCPL: 710 26-28 weeks HFOV: 926; TCPL: 942 Surfactant use 23-25 weeks HFOV: 97%; TCPL: 99% 26-28 weeks HFOV: 95%; TCPL: 97% Antenatal steroid use HFOV: 91%; TCPL: 92% **Lista 2008** Gestational age in weeks, mean HFOV: 27.3; A/C + VG: 27.4 Age at start of ventilation in hours, mean HFOV: 1.5; A/C + VG: 1.5 Birthweight in grams, mean HFOV: 1015; A/C + VG: 1006 Surfactant use: 100% Antenatal steroid use: 100% FiO2 at enrollment HFOV: 0.52; A/C + VG: 0.54 **Moriette 2001** Gestational age in weeks, mean HFOV: 27.5; SIMV: 27.6 Age at start of ventilation in hours, median HFOV: 2.4; SIMV: 2.4	Babylog 8000. Settings: 10 Hz, MAP 6-8 cm H20; I:E 1:1 or 1:2, FiO2 weaned before MAP TCPL: SLE 2000, Drager Babylog 8000, other ventilators. Settings: IT 0.4 sec, initial rate 60/min Target PCO2: 34 to 53 mmHg Cross-over: if infants meet failure criteria (failure to achieve adequate oxygenation or ventilation during > 1 hr) **Lista 2008** A/C + VG vs HFOV Ventilator type: HFOV: Babylog 8000 plus. Settings: 10 Hz, initial MAP 8 to 10 cm H20, amplitutde 40% A/C + VG: Babylog 8000	Allocation concealment: "using sealed folded papers" **Vento 2005** Randomisation: "random number allocation" Allocation concealment: "opaque numbered sealed envelopes" **Blinding** **Of relevant studies:** **Durand 2001** Unblinded **Gerstmann 1996** unblinded **Johnson 2002** unblinded **Lista 2008** unblinded **Moriette 2001** unblinded **Ogawa 1993** unblinded **Salvo 2012** unblinded **Thome 1999** unblinded **Van Reempts 2003** unblinded **Vento 2005**	***Data extracted from original papers by NGA technical team*** **Failed non-invasive ventilation** Not included in review. Not reported in any of the primary papers of RCTs included **Pneumothorax** **Of relevant studies:** **Moriette 2001** HFOV: 7/139; SIMV: 4/134 **Van Reempts 2003** HFOV: 11/147; IMV: 7/153 **Vento 2005** HFOV: 2/20; SIMV: 1/20 **Parental satisfaction** Not included in review. Not reported in any of the primary papers of RCTs included.	Unclear risk: did not report how random sequence was generated **Performance bias** **Durand 2001** high risk: unblinded **Gerstmann 1996** high risk: unblinded **Johnson 2002** high risk: unblinded **Lista 2008** high risk: unblinded **Moriette 2001** high risk: unblinded **Ogawa 1993** high risk: unblinded **Salvo 2012** high risk: unblinded **Thome 1999** high risk: unblinded **Van Reempts 2003** high risk: unblinded **Vento 2005** high risk: unblinded **Detection bias** **Durand 2001** low risk: unblinded, however outcome measures of interest for

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Birthweight in grams, mean HFOV: 976; SIMV: 997 Surfactant use: 100% Antenatal steroid use HFOV: 52%; SIMV: 55% **Ogawa 1993** Gestational age in weeks, mean HFOV: 29; TCPL: 29 Age at start of ventilation in hours, mean HFOV: 2; TCPL: 1.7 Birthweight in grams, mean HFOV: 1243: TCPL: 1258 Surfactant use: 78% Apgar score at enrollment HFOV: 6.9 at 5 min; TCPL: 7.5 at 5 min **Salvo 2012** Gestational age in weeks, mean HFOV: 26.4; SIMV: 26.5 Birthweight in grams, mean HFOV: 869; SIMV: 913 Surfactant use: 100% Antenatal steroid use: 0% FiO2 at enrollment HFOV: 0.71; SIMV: 0.72 **Thome 1999** Gestational age in weeks, median HFOV: 27; IPPV: 27+2 Age at start of ventilation in hours, median HFOV: 0.2; IPPV: 0.2	plus. Settings: Vt 5ml/kg, PEEP 5cm H20, rate 60/min, inspiratory time 0.35 sec. Target PCO2: 40 to 65 mmHg Cross-over: no **Moriette 2001** SIMV vs HFOV <u>Ventilator type:</u> HFOV: OSC using OHF1 piston oscillator (Dufour, France). Settings: initial MAP 2 cm H20 > than on SIMV, I:E ratio 1:1, 15 Hz, high volume strategy (higher mean airway pressure) SIMV: Drager Babylog 8000. Settings: TI < 0.45 sec, PEEP 4-5 cm H20, minimal PIP to achieve target PCO2. Target PCO2: 40 to 500 mmHg Cross-over: allowed during first 10 days if infant meets	unblinded **Attrition** **Of relevant studies:** **Durand 2001** Complete follow-up - 2 infants withdrawn from HFOV arm at parental request **Gerstmann 1996** Complete follow-up for primary outcomes. Long-term follow-up of infants of 1 centre: 87% completeness of follow-up **Johnson 2002** Complete follow-up for primary outcomes **Lista 2008** Comment: 5/45 eligible infants were excluded before randomisation. All enrolled infants were analysed **Moriette 2001** Complete follow-up: yes (7% loss) **Ogawa 1993** Complete follow-up for primary outcome and for long-term follow-up **Salvo 2012**		review all objective outcomes **Gerstmann 1996** low risk: unblinded, however outcome measures of interest for review all objective outcomes **Johnson 2002** low risk: unblinded, however outcome measures of interest for review all objective outcomes **Lista 2008** low risk: unblinded, however outcome measures of interest for review all objective outcomes **Moriette 2001** low risk: unblinded, however outcome measures of interest for review all objective outcomes **Ogawa 1993** low risk: unblinded, however outcome measures of interest for review all objective outcomes **Salvo 2012** low risk: unblinded, however outcome

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Birthweight in grams, median HFOV: 888; IPPV: 870 Surfactant use HFOV: 71%; IPPV: 68% Antenatal steroid use HFOV: 81%; IPPV: 86% Apgar score at enrollment, median HFOV: 5 at 1 min; IPPV: 8 at 5 min **Van Reempts 2003** Gestational age in weeks, mean HFOV: 28.5; IMV: 28.8 Birthweight in grams, mean HFOV: 1173; IMV: 1217 Antenatal steroid use HFOV: 48%; IMV: 58% FiO2 at enrollment HFOV: 0.55; IMV: 0.56 **Vento 2005** Gestational age in weeks, mean HFOV: 27.1; SIMV: 27.4 Birthweight in grams, mean HFOV: 1107; SIMV: 1111 Surfactant use: 100% Antenatal steroid use HFOV: 100%; SIMV: 90% Apgar score at enrollment, median: 7 at 5 min	failure criteria (criteria for ventilatory failure, criteria for radiographic failure such as air leak) **Ogawa 1993** TCPL vs HFOV <u>Ventilator type</u> HFOV: OSC using Hummingbird. Settings - high initial MAP, 15 Hz TCPL: Bear cub or Sechrist Target PCO2: 35-50 mmHg Cross-over allowed if they meet failure criteria **Salvo 2012** SIMV vs HFOV <u>Ventilator type:</u> HFOV: OSC using Sensormedics 3100A. Settings: initial MAP 6 to 8 cm H20, 15 Hz, I:E ratio 1:2, amplitude producing visible chest vibrations	Complete follow-up of enrolled infants: although it is mentioned that infants who crossed over would be excluded from the analyses (’as treated’ instead of ’intention to treat’ analysis), all 78 survivors (39 in each group) are represented in the table results. One patient crossed over in each arm **Thome 1999** Complete follow-up (98.3%) **Van Reempts 2003** Complete follow-up for primary outcome. For long-term outcome: only 57% follow-up for HFOV, and 51% follow-up for CV **Vento 2005** Completeness of follow-up is 95%: two infants (one from each group) excluded after randomisation due to diagnosis of congenital pneumonia		measures of interest for review all objective outcomes **Thome 1999** low risk: unblinded, however outcome measures of interest for review all objective outcomes **Van Reempts 2003** low risk: unblinded, however outcome measures of interest for review all objective outcomes **Vento 2005** low risk: unblinded, however outcome measures of interest for review all objective outcomes **Attrition bias** **Durand 2001** low risk **Gerstmann 1996** low risk **Johnson 2002** low risk **Lista 2008** low risk **Moriette 2001** low risk **Ogawa 1993**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Inclusion criteria **Of relevant studies:** **Durand 2001** Preterm babies Age at start of ventilation: ≤4 hours FiO2 on enrollment: >0.25 Apgar score on enrollment: ≥3 at 5 min **Gerstmann 1996** Preterm babies <36 weeks gestation age Age at start of ventilation: ≤12 hours **Johnson 2002** Preterm babies 23-28 weeks gestation age Age at start of ventilation: ≤1 hour **Lista 2008** Preterm babies 25-32 weeks gestation age Age at start of ventilation: ≤1 hour **Moriette 2001** Preterm babies 24-29 weeks gestation age Age at start of ventilation: <6 hours **Ogawa 1993** Preterm babies birthweight 750g to 2000g Age at start of ventilation: soon after birth **Salvo 2012**	SIMV: Bear Cub 750 PSV. Settings: PIP 18-24 H20, PEEP 5 to 8cm H20, IT 0.30 to 0.40 sec, rate 40 to 60/min Target PCO2: <65 mmHg Cross-over: Swtich to alternative moder permitted but not mandatory if failure criteria are met (inadequate oxygenation or ventilation as described in trial protocol: signs of decreased cardiac output) **Thome 1999** IPPV vs HFOV <u>Ventilator type:</u> HFFI: Infant star ventilator (software version 83). Settings: initial MAP 1-2 cm H20 higher than with IPPV or 10-12 cm H20 if HFFI started immediately.	**Statistical analysis**		low risk **Salvo 2012** low risk **Thome 1999** low risk **Van Reempts 2003** low risk **Vento 2005** low risk **Reporting bias** **Durand 2001** unclear risk: trial not registered **Gerstmann 1996** unclear risk: trial not registered **Johnson 2002** low risk **Lista 2008** unclear risk: trial not registered **Moriette 2001** low risk **Ogawa 1993** unclear risk: trial not registered **Salvo 2012** unclear risk: trial not registered **Thome 1999** low risk **Van Reempts 2003**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Pretem babies <30 weeks gestation age Age at start of ventilation: <2 hours No antenatal corticosteroids **Thome 1999** Preterm babies 24-29 weeks gestation age Age at start of ventilation: <6 hours **Van Reempts 2003** Preterm babies <32 weeks gestation age Age at start of ventilation: <6 hours FiO2 at enrollment: >0.4 **Vento 2005** Preterm babies 24-29 weeks gestation age Age at start of ventilation: <0.5 hours **Exclusion criteria Of relevant studies:** **Durand 2001** Growth not appropriate for gestational age 5 min Apgar sore < 3 Base deficit > 14 Severe hypotension **Gerstmann 1996** > 12 hours old severe congenital defects	IPPV: Drager Babylog 8000, Stephn HF300, Infant star, Sechrist IV-100b. Settings: initial rates 60-80/min, aimed at lower PIP and PEEP ≥3 cm H20 Target PCO2: 40-60 mmHG, up to 70 mmHg from day 7 Cross-over: in first 10 days allowed if infants meets failure criteria (air leak, oxygenatuib index as defined in primary outcome), decision left to the attending physician. **Van Reempts 2003** IMV vs HFOV <u>Ventilator type:</u> HFOV: mix of OSC using snesormedics 3100A and HFFI using infant star. Settings: initial			unclear risk: trial not registered **Vento 2005** unclear risk: trial not registered **Other sources of bias** **Durand 2001** high risk: cross-over - 8% HFOV; 29% in CV **Gerstmann 1996** high risk: cross-over - 15% HFOV; 29% in CV **Johnson 2002** high risk: cross-over - 2% HFOV; 15% in CV. HFOV: mix of OSC and HFFI using different ventilators **Moriette 2001** high risk: cross-over - 15% HFOV; 29% in CV **Ogawa 1993** high risk: cross-over - 9% HFOV; 2% in CV **Van Reempts 2003** high risk: cross-over - 12% HFOV; 7% in CV. HFOV: mix of OSC and HFFI using different ventilators

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	pre-existing air leak **Johnson 2002** Treansfer to another hospital shortly after birth Congenital malformations **Lista 2008** Lethal congenital anomalies IVH > grade 2 Suspected infection **Moriette 2001** IVH grade 3 or 4 Pre-existing pneumothorax ROM before 24 weeks gestational age Severe congenital malformation or hydrops fetalis **Ogawa 1993** >12 hours old Presence of IVH within 1 hour after birth for inborns and within 6 hours for transferred babies **Salvo 2012** Major congenital malformation; hydrops fetalis; congenital diaphragmatic hernia; congenital pneumonia, multiple pregnancies; congenital heart disease **Thome 1998** Major congenital or chromosomal anomalies, hydrops fetalis.	MAP 8cm H20 if <29 weeks and 10cm H20 if 29-31 weeks, 10 Hz. IMV: Drager Babylog 8000 or Infant Star. Settings: PIP 20cm H20 (aim low), PEEP 4cm H20, it <0.35 sec, rate 80/min, I:E ratio 1: 1.1 Target PCO2: 35 to 45 mmHg Cross-over: infant was changed to alternative mode if failure crtieria were met (one of the following: 1) inadequate oxygenation or ventilation, as described in the trial, in the first 7 days of life, 2) uncontrollable air leak, 3) cardiovascular dysfunction, 4) need for hand ventilation to maintain			

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Van Reempts 2003 Active infection at birth Congenital abnormalities **Vento 2005** Congenital malformations Prenatal infections	adequate gas exchange) **Vento 2005** SIMV vs HFOV <u>Ventilator type:</u> HFOV: Drager Babylog 8000+. Settings: initial MAP 2cm H20 higher than with SIMV or at 10cm H20, 10Hz. SIMV: Drager Babylog 8000+. Setting: Vt 4-6 ml/kg, PEEP 4-5 cm H20, TI 0.30 to 0.40 sec, maximum rate 60/min, PIP weaned first. Target PCO2: 45 to 55 mmHg			
Full citation Courtney, Se, Durand, Dj, Asselin, Jm, Hudak, Ml, Aschner, Jl, Shoemaker, Ct, High-frequency oscillatory ventilation versus conventional mechanical ventilation for very-low-birth-weight infants, New England journal of medicine, 347, 643-652, 2002 **Ref Id**	**Sample size** Please see Greenough 2016 Cochrane systematic review **Characteristics**	**Interventions**	**Details**	**Results** **Parental satisfaction**	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
666209 **Country/ies where the study was carried out** **Study type** **Aim of the study** **Study dates** **Source of funding**					
Full citation Craft, A. P., Bhandari, V., Finer, N. N., The sy-fi study: a randomized prospective trial of synchronized intermittent mandatory ventilation versus a high-frequency flow interrupter in infants less than 1000 g, Journal of perinatology, 23, 14-9, 2003 **Ref Id** 666218	**Sample size** Please see Greenough 2016 Cochrane systematic review **Characteristics**	**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 D'Angio, Ct, Chess, Pr, Kovacs, Sj, Sinkin, Ra, Phelps, Dl, Kendig, Jw, Myers, Gj, Reubens, L, Ryan, Rm, Pressure-regulated volume control ventilation vs synchronized intermittent mandatory ventilation for very low-birth-weight infants: a randomized controlled trial, Archives of pediatrics & adolescent medicine, 159, 868-875, 2005 **Ref Id** 666240	**Sample size** Please see Greenough 2016 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 Donn, S. M., Nicks, J. J., Becker, M. A., Flow-synchronized ventilation of preterm infants with respiratory distress syndrome, Journal of perinatology, 14, 90-4, 1994 **Ref Id** 666388 **Country/ies where the study was carried out** **Study type**	**Sample size** Please see Greenough 2016 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 Duman, N., Tuzun, F., Sutcuoglu, S., Yesilirmak, C. D., Kumral, A., Ozkan, H., Impact of volume guarantee on synchronized ventilation in preterm infants: a randomized controlled trial, Intensive Care Medicine, 38, 1358-64, 2012 **Ref Id** 666403 **Country/ies where the study was carried out** **Study type** **Aim of the study**	**Sample size** Please see Klingenberg 2017 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 Durand,D.J., Asselin,J.M., Hudak,M.L., Aschner,J.L., McArtor,R.D., Cleary,J.P., VanMeurs,K.P., Stewart,D.L., Shoemaker,C.T., Wiswell,T.E., Courtney,S.E., Early high-frequency oscillatory ventilation versus synchronized intermittent mandatory ventilation in very low birth weight infants: a pilot study of two ventilation protocols, Journal of Perinatology, 21, 221-229, 2001 **Ref Id** 225540 **Country/ies where the study was carried out** **Study type** **Aim of the study**	**Sample size** Please see Cools 2015 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 Gerstmann, Dr, Minton, Sd, Stoddard, Ra, Meredith, Ks, Monaco, F, Bertrand, Jm, Battisti, O, Langhendries, Jp, Francois, A, Clark, Rh, The Provo multicenter early high-frequency oscillatory ventilation trial: improved pulmonary and clinical outcome in respiratory distress syndrome, Pediatrics, 98, 1044-1057, 1996 **Ref Id** 666555 **Country/ies where the study was carried out** **Study type** **Aim of the study** **Study dates**	**Sample size** Please see Cools 2015 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 Greenough, A., Murthy, V., Milner, A. D., Rossor, T. E., Sundaresan, A., Synchronized mechanical ventilation for respiratory support in newborn infants, Cochrane Database of Systematic Reviews, 2016 (8) (no pagination), 2016 **Ref Id** 653738 **Country/ies where the study was carried out** **Study type** Cochrane systematic review **Aim of the study** To determine whether high frequency positive pressure ventilation or triggered ventilation were associated with postive outcomes for prematurely born neonates.	**Sample size** **Of relevant studies:** **Baumer 2000** n=924 (PTV: 465; IMV: 459) **Beresford 2000** n= 386 (PTV: 193; CMV: 193) **Bernstein 1996** n= 350 (SIMV: 178; IMV: 172) **Courtney 2002** n=498 (SIMV: 254; HFOV: 244) **Craft 2003** n= 46 (SIMV: 24; HFFI: 22) **D'Angio 2005** n=212 (SIMV: 108; PRVCV: 105) **Donn 1994** n=30 (PTV: 15; TCPL: 15)	**Interventions** **Of relevant studies:** **Baumer 2000** PTV vs IMV Ventilator type: PTV - SLE 2000 (airway pressure trigger), Draeger baby log 8000 (airway flow trigger) IMV - SLE 2000, Draegaer Babylog, Sechrist **Beresford 2000** PTV vs CMV Ventilator types: SLE 2000 (airway pressure trigger) **Bernstein 1996** SIMV vs IMV Ventilator types: Infant star with star sync module (abdominal movement monitor) **Courtney 2002**	**Details** **Randomisation** **Of relevant studies:** **Baumer 2000** Randomisation: "randomly allocated by telephone" Allocation concealment: "Within each centre, randomisation was performed in blocks" **Beresford 2000** Randomisation: "Computer generated sequence" Allocation concealment: "Hidden in sequentially numbered, sealed, opaque envelopes". **Bernstein 1996** Randomisation: "Randomisation schedules were generated for each centre by computer"	**Results** **Critical outcomes** **Mortality before discharge** NMA outcome **BPD (oxygen dependency at 36 weeks corrected gestation or 28 days of age** NMA outcome **Neurodevelopmental outcomes at ≥18 months** Not included in review. Not reported in any of the primary paper of RCTs included	**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) **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates Search up to July 2015 **Source of funding** Eunice Kennedy Shriver National Institute of Child Health and Human Development National Institutes of Health, Department of Health and Human Services, US	**Characteristics Of relevant studies:** **Baumer 2000** Gestational age in weeks, mean PTV: 27.8; IMV: 27.8 Birthweight in grams, mean PTV: 1097; IMV: 1123 Surfactant use PTV: 92%; 94% Antenatal steroid use PTV: 73%; IMV: 74% CRIB score at enrollment, mean PTV: 6.2; IMV: 6 **Beresford 2000** Gestational age in weeks, median PTV: 27.8; CMV: 29 Birthweight in grams, median PTV: 1336 ; CMV: 1320 Surfactant use: PTV: 98%; CMV: 96% Antenatal steroid use PTV: 83%; CMV: 86% **Bernstein 1996** Gestational age in weeks, mean SIMV: 30.7; IMV: 30.6 Age at start of ventilation in hours, mean: 7.5 Birthweight in grams, mean	SIMV vs HFOV Ventilator types: SIMV - VIP BIRD, Babylog 8000, Bear Cub with neonatal monitoring or Bear Cub 750vs **Craft 2003** SIMV vs HFFI <u>Ventilator type:</u> Infant star ventilator. Graesby capsule used for synchronisation. Extubation when rate reduced to 8-12 bpm **D'Angio 2005** SIMV vs PRVCV <u>Ventilator type:</u> Servo 300, infants who required slow rates >40 bpm (maximum for the servo 300) were transfered to the BIRD VIP ventilator **Donn 1994** PTV vs TCPL <u>Ventilator type:</u> PTV - VIP BIRD (airflow trigger)	Allocation concealment: “Sequential, opaque, sealed envelopes” **Courtney 2002** Randomisation: Randomised by off-site clinical coordination centre. Allocation concealment: Off-site allocation **Craft 2003** Randomisation: “Infant swere randomly assigned by a sealed opaque envelope, with a previously generated random number sequence” Allocation concealment: Clinicians blinded to allocation **D'Angio 2005** Randomisation: "randomly assigned" Allocation concealment: no details **Donn 1994** Randomisation: "randomised" Allocation concealment: “lottery (sampling without replacement)”	**Important outcomes** **Number of days on invasive ventilation** **Baumer 2000*** Median in days (range in parentheses) PTV: 6 (3-15); IMV: 6 (3-15) **Beresford 2000*** Median in days (range in parentheses) PTV: 3 (1-42); CMV: 4 (1-150) p-value= 0.19 **Bernstein 1996*** Median in hours (range in parentheses) SIMV: 103 (94-118); IMV: 120 (101-142) **D'Angio 2005**** Mean in days in survivors (SD in parentheses) PRVCV: 27.6 (23.8); SIMV: 24 (22.4) **Donn 1994** Mean in hours (SD in parentheses) PTV: 119 (156); TCPL: 271 (218) *Extracted from the original paper by the NGA technical team	**Selection bias** **Baumer 2000** Unclear risk: "randomly allocated by telephone" **Beresford 2000** low risk **Bernstein 1996** Low risk **Courtney 2002** Unclear risk: "randomised by off-site clinical co-ordination centre" **Craft 2003** Low risk **D'Angio 2005** Unclear risk: "randomly assigned" **Donn 1994** Unclear risk: "randomised" **Performance bias** **Baumer 2000** high risk: unblinded **Beresford 2000** high risk: unblinded **Bernstein 1996** high risk: unblinded **Courtney 2002** high risk: unblinded **Craft 2003** high risk: unblinded

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	SIMV: 1654 ; IMV: 1654 Surfactant use: SIMV: 86%; IMV: 87% FiO2 at enrollement, mean SIMV: 0.63; IMV: 0.66 **Courtney 2002** Gestational age in weeks, mean HFOV: 26; SIMV: 26.1 Age at start of ventilation in hours, mean: 2.7 Birthweight in grams, mean HFOV: 859 ; SIMV: 848 Surfactant use: 100% Antenatal steroid use HFOV: 80%; SIMV: 81% FiO2 at enrollment, mean HFOV: 0.57; SIMV: 0.60 **Craft 2003** Gestational age in weeks, mean 500-750g HFFI: 24.3; SIMV: 24.7 751-1000g HFFI: 26.8; SIMV: 27.3 Birthweight in grams, mean 500-750g HFFI: 570; SIMV: 621 751-1000g HFFI: 872; SIMV: 865 Antenatal steroid use 500-750g 50% 751-1000g HFFI: 40%; SIMV: 58%	TCPL - Sechrist IV - 100B, VIP BIRD	**Blinding** **Of relevant studies:** **Baumer 2000** Unblinded **Beresford 2000** Unblinded **Bernstein 1996** Unblinded **Courtney 2002** Unblinded **Craft 2003** Unblinded **D'Angio 2005** Unblinded **Donn 1994** Unblinded **Attrition** **Of relevant studies:** **Baumer 2000** outcome for death (912/924); pneumothorax(922/924) **Beresford 2000** Complete data present **Bernstein 1996** Outcome for all participants reported **Courtney 2002** 10 infants from HFOV and 4 from SIMV withdrawn - data	**Extracted from Klingenberg 2017 **Failed non-invasive ventilation** Not included in review. Not reported in any of the primary paper of RCTs included **Pneumothorax** **Baumer 2000*** PTV: 62/465; IMV: 47/459 **Beresford 2000*** PTV: 20/193; CMV: 21/193 **Courtney 2003*** SIMV: 33/254 HFOV: 32/244 **D'Angio 2005*** PRVCV: 6/104 SIMV: 9/108 **Donn 1994** PTV: 0/15; TCPL: 0/15 *Extracted from original papers by NGA technical team	**D'Angio 2005** high risk: unblinded **Donn 1994** high risk: unblinded **Detection bias** **Baumer 2000** low risk: unblinded, however outcome measures of interest for review all objective outcomes **Beresford 2000** low risk: unblinded, however outcome measures of interest for review all objective outcomes **Bernstein 1996** low risk: unblinded, however outcome measures of interest for review all objective outcomes **Courtney 2002** low risk: unblinded, however outcome measures of interest for review all objective outcomes **Craft 2003** low risk: unblinded, however outcome measures of interest for

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	D'Angio 2005 Gestational age in weeks, mean PRVCV: 26.8; SIMV: 27 Birthweight in grams, mean PRVCV: 884 ; SIMV: 888 Surfactant use: PRVCV: 92%; SIMV: 96% Antenatal steroid use PRVCV: 83%; SIMV: 80% FiO2 at enrollment, mean: 0.305 Apgar score at enrollment, median: 8 at 5 min **Donn 1994** Gestational age in weeks, mean PTV: 29.5; TCPL: 29.3 Age at start of ventilation in hours, mean: PTV: 3.3; TCPL: 3 Birthweight in grams, mean PTV: 1285; TCPL: 1282 **Inclusion criteria** **Of relevant studies:** **Baumer 2000** Preterm babies <32 weeks gestational age Age at start of ventilation: <72 hours **Beresford 2000**		analysed until point of withdrawal **Craft 2003** Attrition unclear. Study terminated at adhoc interim analysis **D'Angio 2005** Complete data present **Donn 1994** All trial participants reported **Statistical analysis**	**Parental satisfaction** Not included in review. Not reported in any of the primary paper of RCTs included	review all objective outcomes **D'Angio 2005** low risk: unblinded, however outcome measures of interest for review all objective outcomes **Donn 1994** low risk: unblinded, however outcome measures of interest for review all objective outcomes **Attrition bias** **Baumer 2000** low risk **Beresford 2000** low risk: unblinded, however outcome measures of interest for review all objective outcomes **Bernstein 1996** low risk **Courtney 2002** Unclear risk: 10 babies from HFOV and 4 babies from CV withdrawn from study **Craft 2003** Unclear risk: attrition unclear as study

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Preterm babies 1000-2000g Age at start of ventilation: <24 hours **Bernstein 1996** Preterm babes >500g Age at start of ventilation: <36 hours FiO2 inclusion criteria at enrollment: >0.4 **Courtney 2002** Preterm babies 601-1200g Age at start of ventilation: <4 hours Apgar score of >3 at 5 min **Craft 2003** Preterm babies 23-34 weeks gestational age **D'Angio 2005** Preterm babies >24 weeks gestational age Age at start of ventilation: <6 hours **Donn 1994** Preterm babies 1.1-1.5kg **Exclusion criteria Of relevant studies:** **Baumer 2000** Not ventilated for more than 6 hours at randomisation Major congenital malformation or inhalational pneumonitis **Beresford 2000**				terminated at ad-hoc analysis **D'Angio 2005** Low risk **Donn 1994** low risk **Reporting bias** **Baumer 2000** unclear risk: protocol not available for review **Beresford 2000** unclear risk: protocol not available for review **Bernstein 1996** unclear risk: protocol not available for review **Courtney 2002** unclear risk: protocol not available for review **Craft 2003** unclear risk: protocol not available for review **D'Angio 2005** unclear risk: protocol not available for review **Donn 1994** unclear risk: protocol not available for review **Other sources of bias** **Courtney 2002**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Major malformations, congenital heart disease, MAS **Bernstein 1996** Infants with airleak, seizures, IVH grade III or IV, neuromuscular disease affecting respiration, major malformations including chromosomal abnormalities, CDH, CHD (except PDA), lung hypoplasia, septic shock or severe skin disease **Courtney 2002** Apgar at 5 min <4; a base deficit of 15 or more prior to study Severe hypotension Chromosomal or genetic abnormalities Congenital heart disease Known neuromuscular disease **Craft 2003** None stated **D'Angio 2005** None stated **Donn 1994** None stated				high risk: cross-over - 10% in HFOV; 19% in CV **D'Angio 2005** unclear risk: different trigger modes in VTV and SIMV
Full citation	**Sample size**	**Interventions**	**Details**	**Results**	**Limitations** See Johnson 2002

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Greenough, A., Peacock, J., Zivanovic, S., Alcazar-Paris, M., Lo, J., Marlow, N., Calvert, S., United Kingdom Oscillation Study: long-term outcomes of a randomised trial of two modes of neonatal ventilation, Health Technology Assessment (Winchester, England), 18, v-xx, 1-95, 2014 **Ref Id** 445618 **Country/ies where the study was carried out** Multicentre **Study type** Randomised controlled trial **Aim of the study** To determine the long-term outcomes of children at 11-14 years of age who had been recruited into UKOS **Study dates** See Johnson 2002	Randomised to original RCT: n=797 (HFOV: 400; TCPL: 397) Survivors from original RCT: n=592 (HFOV: 300; TCPL: 292) Follow-up at 11-14 years: n= 319 (HFOV: 160; TCPL: 159) **Characteristics** Birthweight in grams (SD in parentheses): HFOV= 867 (209); TCPL= 923 (206) Gestational age in weeks (SD in parentheses): HFOV= 26.7 (1.45); TCPL= 27 (1.18) Postnatal steroids: HFOV= 48/157; TCPL= 36/157 **Inclusion criteria** See Johnson 2002 **Exclusion criteria** See Johnson 2002	See Johnson 2002	No details regarding the definitions of moderate and severe learning difficulties **Randomisation** See Johnson 2002 **Blinding** See Johnson 2002 **Attrition** High rate of attrition 47% **Statistical analysis** See Johnson 2002	**Critical outcomes** **Mortality before discharge** NMA outcome **BPD (oxygen dependency at 36 weeks corrected gestation or 28 days of age** NMA outcome **Neurodevelopmental outcomes at ≥18 months** ***Follow-up at 11-14 years of age*** <u>Severe learning difficulty (undefined)</u> TCPL: 1/108; HFOV: 3/116 <u>Moderate learning difficulty (undefined)</u> TCPL: 19/108; HFOV: 19/116 **Important outcomes** **Pneumothorax**	**Other information** **Selection bias** See Johnson 2002 **Performance bias** See Johnson 2002 **Detection bias** Unclear risk as study unblended and no details as whether the assessors for learning difficulty were blinded **Attrition bias** High risk of bias as high level of attrition at 47% **Reporting bias** Low risk of bias: all outcomes noted in the methods were reported in the results

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding NIHR Health Technology Assessment programme				See Johnson 2002 **Other sources of bias**	
Full citation Guven,S., Bozdag,S., Saner,H., Cetinkaya,M., Yazar,A.S., Erguven,M., Early neonatal outcomes of volume guaranteed ventilation in preterm infants with respiratory distress syndrome, Journal of Maternal-Fetal and Neonatal Medicine, 26, 396-401, 2013 **Ref Id** 282244 **Country/ies where the study was carried out** **Study type** **Aim of the study** **Study dates**	**Sample size** Please see Klingenberg 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 Johnson, A. H., Peacock, J. L., Greenough, A., Marlow, N., Limb, E. S., Marston, L., Calvert, S. A., United Kingdom Oscillation Study, Group, High-frequency oscillatory ventilation for the prevention of chronic lung disease of prematurity, The New England journal of medicine, 347, 633-42, 2002 **Ref Id** 510504 **Country/ies where the study was carried out** **Study type** **Aim of the study** **Study dates** **Source of funding**	**Sample size** Please see Cools 2015 Cochrane systematic review **Characteristics** **Inclusion criteria** **Exclusion criteria**	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Kirpalani, H., Millar, D., Lemyre, B., Yoder, B. A., Chiu, A., Roberts, R. S., Nippv Study Group, A trial comparing noninvasive ventilation strategies in preterm infants, New England Journal of MedicineN Engl J Med, 369, 611-20, 2013 **Ref Id** 561768 **Country/ies where the study was carried out** US **Study type** Multi-centre RCT **Aim of the study** The aim of the study was to reduce the risk of BPD in extremely low birth weight babies by introducing the early use of less invasive forms of positive airway pressure. **Study dates** May 2007 - June 2011	**Sample size** n randomised= 1009 nasal IPPV= 504 nasal CPAP= 505 n analysed= 1007 nasal IPPV= 504 nasal CPAP= 503 **Characteristics** NIPPV, n= 504 Gestational age, inclusion criteria, weeks= < 30 Gestational age, weeks, mean (SD)= 26.1 (1.5) Birthweight, grams, mean (SD)= 802 (131) Intubated at birth, %= 51.0 NCPAP, n= 503 Gestational age, inclusion criteria, weeks= < 30 Gestational age, weeks, mean (SD)= 26.2 (1.5) Birthweight, grams, mean (SD)= 805 (127) Intubated at birth, %= 49.3 **Inclusion criteria** • BW < 1000g	**Interventions** Intervention 1: Nasal IPPV included any technique that combines nasal CPAP with an intermittent increase in applied pressure. Those assigned to nasal IPPV and whose condition was stable for 7 days after extubation could be switched to nasal CPAP. Intervention 2: CPAP. Babies on CPAP were not permitted to receive nasal IPPV. No devices were specified and centers could use any standard equipment. Synchronisation was permitted but not	**Details** **Randomisation** Enrollment and treatment assignments were performed with the use of a secure study website after verification of eligibility and consent status. Treatment assignments (in a 1:1 ratio) were based on a prespecified randomized sequence (with a random block size of 2 or 4), with stratification according to center and two infant characteristics: birth weight (<750 g or 750 to 999 g) and status with respect to prior intubation (reflecting the duration and timing of intubation). **Blinding** Blinding was not completed	**Results** **Critical outcomes** **Mortality before discharge** Mortality prior to discharge Nasal IPPV, n/total: 37/504 Nasal CPAP, n/total: 45/503 **BPD (oxygen dependency at 36 weeks corrected gestation or 28 days of age** Survival with BPD Nasal IPPV, n/total: 157/463 Nasal CPAP, n/total: 139/449 **Important outcomes** **Failed non-invasive ventilation** Nasal IPPV, n/total: 294/504	**Limitations** **Other information** **Selection bias** Low risk: "Enrollment and treatment assignments were performed with the use of a secure study website after verification of eligibility and consent status. For all infants in the prior-intubation stratum, randomization was performed at the time of the first decision to use non-invasive support." **Performance bias** Low risk: "Our interventions did not permit blinding, leaving a potential for bias, despite guidelines for weaning, extubation, and reintubation."

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding Canadian Institutes of Health Research	• GA < 30 weeks • Candidates for non-invasive respiratory support **Exclusion criteria** • Infants expected to die • Congenital abnormalities • Required surgery • Neuromuscular disorder	mandated. Babies whose condition could not be maintained with the assigned method of non-invasive respiratory support were reintubated, and the originally assigned intervention was resumed after extubation.	**Attrition** The sample-size calculation was based on an anticipated rate of death or bronchopulmonary dysplasia of 46%, a value derived from a trial33 that was conducted at many of the centers participating in the current study. We estimated that with a sample of 1000 infants, the study would have 80% power to detect a relative risk reduction of 20% in the primary outcome with nasal IPPV as compared with nasal CPAP, at a two-tailed type I error rate of 0.05. This was more conservative than the relative risk reduction of 27% (relative risk, 0.73; 95% confidence interval [CI], 0.49 to 1.07) reported in Cochrane meta-analyses of previous trials	Nasal CPAP, n/total: 297/503	**Detection bias** Low risk: "The study team was not informed of interim results." The study had guidelines for weaning, extubation, and reintubation. **Attrition bias** High risk: "Twenty infants (7 in the nasal-IPPV group and 13 in the nasal-CPAP group) did not undergo a required oxygen-reduction test (typically owing to early transfer) and were thus not included in the primary analysis." **Reporting bias** Low risk: all outcomes reported in methods shown in results **Other sources of bias**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			comparing nasal IPPV with nasal CPAP. **Statistical analysis** Prespecified subgroup analyses for birth-weight stratum, prior-intubation status, and the effects of synchronized or nonsynchronized forms of nasal IPPV were performed with the use of logistic regression by incorporating an additional treatment-by-subgroup interaction term. Two-sided P values of less than 0.05 were considered to indicate statistical significance. Formal interim analyses of efficacy were carried out by the safety and efficacy monitoring committee when 25%, 50%, and 75% of the outcome data were available.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Klingenberg,C., Pettersen,M., Hansen,E.A., Gustavsen,L.J., Dahl,I.A., Leknessund,A., Kaaresen,P.I., Nordhov,M., Patient comfort during treatment with heated humidified high flow nasal cannulae versus nasal continuous positive airway pressure: a randomised cross-over trial, Archives of Disease in Childhood Fetal and Neonatal Edition, 99, F134-F137, 2014 **Ref Id** 319453 **Country/ies where the study was carried out** Norway **Study type** Randomised cross over trial **Aim of the study** The aim of the study was to compare comfort in preterm babies treated with HHHFNC vs NCPAP. **Study dates**	**Sample size** n=20 **Characteristics** n= 20 Gestational age, weeks, mean (SD)= 29.3 (1.7) Age at start of ventilation, days, median (IQR)= 6 (4-10) Birthweight, grams, mean (SD)= 1234 (353) **Inclusion criteria** • < 34 weeks GA • Mild respiratory illness (treatment with CPAP for < 72 hr if PMA < 29 wks and < 24hr if 29-33 weeks) • FiO2 < 0.3 • Last PCO2 < 8 kPa **Exclusion criteria** • > 34 weeks GA	**Interventions** "After parental consent, the patients were randomised to continue with NCPAP for 24 h and then switch to HHHFNC for the next 24 h, or to immediately switch to HHHFNC for 24 h and then back to NCPAP for 24 h. After the 48 h study period (2 X 24 h epochs) further respiratory support was at the discretion of the clinical team." HHHFNC= "Gas flow was set at 6 L/min for infants weighing >1500 g and at 5 L/min if <1500 g." SiPAP= "The nasal interface was either a mask or binasal prongs at the discretion of the nurse. We aimed for a	**Details** **Randomisation** "Infants were block (blocks of 4) randomised, using sealed opaque envelopes, to start with either HHHFNC or CPAP." **Blinding** Study was unblinded **Attrition** Method for managing attrition not reported **Statistical analysis** "Paired t test was used to compare continuous data and proportions were compared using $\chi 2$ test. A $p<0.05$ was considered statistically significant."	**Results** **Important outcomes** **Parental satisfaction** Échelle Douleur Inconfort Nouveau-Né, neonatal pain and discomfort scale (EDIN scale) (lower scores are better) **Child satisfied** HHHFNC, mean (SD)= 8.6 (1.1) NCPAP, mean (SD)= 6.9 (1.6) **Contact and interaction** HHHFNC, mean (SD)= 9.0 (1.1) NCPAP, mean (SD)= 6.7 (1.6) **Possibility to take part in care** HHHFNC, mean (SD)= 9.1 (1.2) NCPAP, mean (SD)= 8.0 (1.6)	**Limitations** **Other information** **Selection bias** Unclear risk: "Infants were block (blocks of 4) randomised, using sealed opaque envelopes, to start with either HHHFNC or CPAP." **Performance bias** High risk: "It is challenging for parents to assess their preference for types of medical support in an unblinded study as their opinions may be influenced by caregivers and other external factors." **Detection bias** High risk: "It is challenging for parents

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
2012 to 2013 **Source of funding** Not reported	• Congenital abnormalities • Needed higher concentrations of supplemental O2 • Considered to need of frequent blood samples due to infection, hypoglycaemia or other intercurrent conditions	NCPAP of 4–5 cmH2O."			to assess their preference for types of medical support in an unblinded study as their opinions may be influenced by caregivers and other external factors." **Attrition bias** Unclear risk: method for managing attrition not reported **Reporting bias** Low risk: All outcomes stated in methods reported in results **Other sources of bias** Unclear risk: Cross-over nature of study could have biased results as the study was not controlled
Full citation	**Sample size** n randomised= 84 n analysed= 84	**Interventions**	**Details**	**Results**	**Limitations**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Kugelman,, Nasal Synchronized Intermittent Positive Pressure Ventilation (NSIPPV) Versus Nasal Continuous Positive Airway Pressure (NCPAP) for Respiratory Distress Syndrome (RDS): a Randomized, Controlled, Prospective Study, Pediatric academic society, http://www.abstracts2view.com/pas/ , 2007 **Ref Id** 667040 **Country/ies where the study was carried out** Israel **Study type** Single-centre RCT **Aim of the study** The aim of the study was to assess whether nasal intermittent mandatory ventilation compared with nasal continuous positive airway pressure would decrease the need for endotracheal ventilation in the treatment of preterm infants with RDS.	NCPAP= 41 NIMV= 43 **Characteristics** NCPAP, n= 41 Gestational age, wks, mean (SD)= 30.6 (3.0 Birthweight, grams, mean (SD)= 1533 (603) Apgar score at 1 minute, median (IQR)= 8 (1-10) Apgar score at 5 minutes, median (IQR)= 9 (2-10) NIMV, n= 43 Gestational age, wks, mean (SD)= 31.1 (2.3) Birthweight, grams, mean (SD)= 1616 (494) Apgar score at 1 minute, median (IQR)= 8 (4-10) Apgar score at 5 minutes, median (IQR)= 9 (7-10) **Inclusion criteria** • GA 24-34 and 6/7 weeks • RDS and needed nasal respiratory support	NCPAP= NCPAP was set at 6 to 7 cm H2O NIMV= NIMV was set at a synchronized mode, rate of 12 to 30 breaths/min (according to PaCO2), inspiratory time of 0.3 seconds, positive end expiratory pressure (PEEP) of 6 to 7 cm H2 O, and positive peak inspiratory pressure of 14 to 22 cm H2 O according to chest excursion and the infant's weight. FiO2 was adjusted to keep oxygen saturation by pulse oximetry between 88% to 92%	**Randomisation** The randomization was performed with a system of randomly prepared cards in sealed nontransparent envelopes containing group assignments **Blinding** Medical team was not blinded to treatment assignment. **Attrition** "Two infants in the NCPAP group were switched by the medical team to NIMV in violation of the study protocol but were included in the intention-to-treat analysis according to their primary assignment"	**Critical outcomes** **BPD (oxygen dependency at 36 weeks corrected gestation or 28 days of age** O2 dependency at 36 weeks nCPAP, n/total= 7/41 NIMV, n/total= 1/43 **Failed non-invasive ventilation** nCPAP, n/total= 20/41 NIMV, n/total= 11/43 **Pneumothorax** nCPAP, n/total= 1/41 NIMV, n/total= 1/43	**Other information** **Selection bias** Unclear risk: The randomization was performed with a system of randomly prepared cards in sealed nontransparent envelopes containing group assignments **Performance bias** Low risk: Blinding not possible; set criteria for failure of nasal support **Detection bias** Unclear risk: lack of blinding unlikely to affect outcome assessment. Unclear whether criteria for failure of nasal support was met **Attrition bias** Low risk: ITT

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates 2004 to 2006 **Source of funding** Not reported	**Exclusion criteria** • Significant morbidity apart from RDS, including cardiac disease, congenital malformation, cardiovascular or respiratory instability because of sepsis, anemia, or severe IVH		**Statistical analysis** Two-sample unpaired t-tests were used for continuous variables with normal distribution and Wilcoxon rank-sum test was used where distribution was skewed. Differences for categorical variables were tested by use of 2 analysis. For the primary outcome measure (need for endotracheal ventilation) we used a multivariate regression model to correct for birth weight and gestational age. For all tests the level of significance was set at P < .05.		**Reporting bias** Low risk: all outcomes stated in methods reported in results **Other sources of bias** Unclear risk: "Two infants in the NCPAP group were switched by the medical team to NIMV in violation of the study protocol but were included in the intention-to-treat analysis according to their primary assignment"
Full citation Kugelman, A., Riskin, A., Said, W., Shoris, I., Mor, F., Bader, D., A randomized pilot study comparing heated humidified high-flow nasal cannulae with NIPPV for RDS,	**Sample size** n randomised= 76 n analysed= 76 NIPPV= 38 HHHFNC= 38	**Interventions** Humidified high-flow nasal cannula: flows were started on 1L/min and increased at	**Details** **Randomisation** System of randomly prepared cards in	**Results** **Critical outcomes** **Mortality before discharge**	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Pediatric pulmonology, 50, 576-83, 2015 **Ref Id** 667049 **Country/ies where the study was carried out** Israel **Study type** Single-centre RCT **Aim of the study** The aim of the study was to compare the requirement for endotracheal ventilation in preterm babies treated with heated, humidified high-flow nasal cannula with those treated with nasal intermittent positive pressure ventilation. **Study dates** Not reported **Source of funding** No external funding	**Characteristics** NIPPV, n=38 Gestational age, wks, median (IQR)= 32.7 (27.0-34.9) Birthweight, grams, mean (SD)= 1835 (530) Apgar score at 1 minute, median (IQR)= 8 (3-10) Apgar score at 5 minutes, median (IQR)= 9 (7-10) HHFNC, n= 38 Gestational age, wks, median (IQR)= 32.5 (27.5-34.7) Birthweight, grams, mean (SD)= 1759 (488) Apgar score at 1 minute, median (IQR)= 8 (1-9) Apgar score at 5 minutes, median (IQR)= 9 (6-10) **Inclusion criteria** • GA < 35 weeks • Birth weigh > 1000g • With RDS who needed NRS as initial therapy **Exclusion criteria**	intervals of 0.5-1 L/min per baby's weight and as needed according to clinical condition, hemodynamic, ventilation, and oxygenation. Leak was created/allowed by using the nasal prongs no larger than 1/2 diameter of the nares and no chin strap was allowed. Nasal intermittent positive pressure ventilation: set at a synchronized mode, rate of 12-30 breaths/min. Though not encouraged, babies were able to cross between interventions according to the attending physician after optimizing each mode ventilatory settings.	sealed non-transparent envelopes containing group assignment. Envelopes were stratified for infants or >1,500 g. **Blinding** Medical team was not blinded to treatment assignment. **Attrition** Intention to treat analysis used **Statistical analysis** Sample size calculations for primary outcome (need for endotracheal ventilation) was based on the authors' previous study. Two-sample unpaired t-test (student's t) was used for continuous variables with normal distribution and Mann–Whitney rank-sum test where	HHHFNC, n/total= 0/38 NIPPV, n/total= 0/38 **BPD (oxygen dependency at 36 weeks corrected gestation or 28 days of age** Oxygen dependency at 36 weeks post-conceptual age HHHFNC, n/total= 1/38 NIPPV, n/total= 2/38 **Important outcomes** **Number of days on invasive ventilation** N/A Duration of mechanical ventilation, days, median (range) NIPPV= 4.0 (0.5-16.0) HHHFNC= 3.0 (0.01-14.0) p-value= 0.95 **Failed non-invasive ventilation** Failed nasal support NIPPV, n/total= 13/38 HHHFNC, n/total= 12/38	**Selection bias** Unclear risk: Randomised through a system of randomly prepared cards in sealed non-transparent envelopes containing group assignment. Treatment allocation was not blinded. **Performance bias** Low risk: Blinding could not be performed. **Detection bias** Low risk: Medical team were not blinded, but unlikely to affect outcome assessment. Criteria for failure of nasal support were stated. **Attrition bias** Low risk: ITT analysis used; all patients accounted for in outcome assessment

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	• Significant morbidity apart from RDS including: cardiac disease or cardiovascular or respiratory instability because of sepsis, anemia or severe IVH • Unavailability of suitable ventilator/device		distribution was skewed. Differences for categorical variables were tested by using x2 analysis or Fisher-exact test when appropriate. For the primary outcome measure we also used a multi-variate stepwise regression model.	**Pneumothorax** Air leak NIPPV, n/total= 0/38 HHHFNC, n/total= 2/38	**Reporting bias** Low risk: all outcomes stated in methods reported in results **Other sources of bias** High risk: Babies were able to cross between interventions according to the attending physician after optimizing each mode's ventilatory settings.
Full citation Lavizzari, A., Colnaghi, M., Ciuffini, F., Veneroni, C., Musumeci, S., Cortinovis, I., Mosca, F., Heated, Humidified High-Flow Nasal Cannula vs Nasal Continuous Positive Airway Pressure for Respiratory Distress Syndrome of Prematurity: A Randomized Clinical Noninferiority Trial, JAMA Pediatrics, 08, 08, 2016 **Ref Id**	**Sample size** n randomised= 316 n analysed= 316 HHHFNC= 158 nCPAP/BiPAP= 158 **Characteristics** HHHFNC, n=158 Gestational age, weeks, mean (SD)= 33.1 (1.9) Birthweight, grams, mean (SD)= 1968 (581)	**Interventions** HHHFNC= flow was started at 4 to 6 L/min and increased to a maximum of 6 L/min if the FIO2 was increased greater than 0.1 of the starting value or for intensification of respiratory distress as	**Details** **Randomisation** Block randomisation with 4 blocks stratified by GA. Clinicians were given sequentially numbered, sealed, opaque, envelopes with treatment allocation.	**Results** **Critical outcomes** **Mortality before discharge** HHHFNC, n/total= 0/158 nCPAP/BiPAP, n/total= 1/158	**Limitations** **Other information** **Selection bias** Unclear risk: did not state whether computer-generated random assignment was used

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
653949 **Country/ies where the study was carried out** Italy **Study type** Single centre RCT **Aim of the study** The aim of the study is to assess whether HHHFNC provides respiratory support noninferior to nCPAP or BiPAP as a primary approach to RDS. **Study dates** 2012 to 2014 **Source of funding** Not reported	Apgar score at 5 minutes, median (IQR)= 9 (8-9) NCPAP/BiPAP, n=158 Gestational age, weeks, mean (SD)= 33.0 (2.1) Birthweight, grams, mean (SD)= 1908 (528) Apgar score at 5 minutes, median (IQR)= 9 (8-9) **Inclusion criteria** • GA 29+0 weeks to 36+6 weeks • Mild to moderate RDS requiring non-invasive respiratory support • FiO2 > 0.3 **Exclusion criteria** • Severe RDS requiring early intubation • Major congenital anomalies • Severe IVH	assessed by Silverman score." Nasal CPAP= 'The starting pressure was set at 4 to 6 cm H2O and the pressure was increased up to 6 cm H2O according to the same criteria for altering HHHFNC flow. Moreover, in the nCPAP group, infants were shifted to BiPAP in the case of more than 4 episodes of apnea per hour or more than 2 episodes per hour requiring positive pressure ventilation or if deemed by clinicians because of increased work of breathing. The BiPAP was set with a starting rate of 30 breaths/min, inspiratory time of 0.7 to 1 second,	**Blinding** Not blinded **Attrition** ITT analysis **Statistical analysis** 95% confidence intervals were used. Dichotomous outcomes were compared by χ2 tests. Continuous outcomes were compared by using Wilcoxon 2-sample test. A posteriori, a logistic model was applied to detect factors possibly affecting the probability of failure.	**BPD (oxygen dependency at 36 weeks corrected gestation or 28 days of age** O2 dependency at 36 weeks HHHFNC, n/total= 7/158 nCPAP/BiPAP, n/total= 8/158 **Important outcomes** **Number of days on invasive ventilation** Duration of mechanical ventilation, days, median (IQR) HHHFNC= 3.2 (1.2-5.0) nCPAP/BiPAP= 3.0 (1.2-6.0) 95% CI (-1.25 to 2.25) p-value= 0.72 **Failed non-invasive ventilation** **Mechanical ventilation within 72 hours** **29+0 to 32+6 weeks** HHHFNC, n/total= 10/71	**Performance bias** Low risk: study could not be blinded. Criteria for intubation and mechanical ventilation were stated. **Detection bias** Unclear risk: lack of blinding unlikely to affect outcome assessment. Unclear whether criteria for intubation and mechanical ventilation were met **Attrition bias** Low risk: ITT used, all patients accounted for in outcome assessment **Reporting bias** Low risk: All outcomes stated in methods were reported in results

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
		and a mean airway pressure of 6 to 8 cm H2O.'		nCPAP/BiPAP, n/total= 8/73 **33+0 to 34+6 weeks** HHHFNC, n/total= 2/53 nCPAP/BiPAP, n/total= 4/53 **35+0 to 36+6 weeks** HHHFNC, n/total= 5/34 nCPAP/BiPAP, n/total= 3/32 **Pneumothorax** Air leaks HHHFNC, n/total= 3/158 nCPAP/BiPAP, n/total= 4/158	**Other sources of bias** N/A
Full citation Lemyre, Brigitte, Laughon, Matthew, Bose, Carl, Davis, Peter G, Early nasal intermittent positive pressure ventilation (NIPPV) versus early nasal continuous positive airway pressure (NCPAP) for preterm infants, Cochrane Database of Systematic Reviews, 2016 **Ref Id**	**Sample size** **Of relevant studies:** **Bisceglia 2007** n randomised= 88 (n= 46 NCPAP); n= 42 NIPPV) **Wood 2013** n randomised= 120 (n= 60 CPAP; n= 60 SiPAP) **Characteristics** **Of relevant studies**	**Interventions** **Of relevant studies** **Bisceglia 2007** NCPAP= administered at 4-6 cmH2O NIPPV= administered with PIP 14-20 cmH2O at 40 breaths per minute and end expiratory	**Details** **Randomisation** **Of relevant studies:** **Bisceglia 2007** Randomisation through an online statistical program to generate treatment allocation **Wood 2013**	**Results** **Critical outcomes** **Mortality before discharge** **Of relevant studies:** **Bisceglia 2007** NIPPV, n/total= 0/42 NCAPA, n/total= 0/46 **Wood 2013**	**Limitations** **Quality of Cochrane SR:** Systematic review assessed using AMSTAR checklist. Total score: 15/16 All checklist items addressed, with the exception of: Checklist item 2: Did the report contain an explicit statement that

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
653961 **Country/ies where the study was carried out** **Study type** Cochrane systematic review **Aim of the study** The aim of the study was to assess the risks and benefits of early NIPPV vs early NCPAP alone for preterm infants at risk of or with RDS within the first hours after birth. **Study dates** Search dates from 1966 to September 28, 2015 **Source of funding** NIH grant; Eunice Kennedy Shriver National Institute of Child Health and Human Development; National Institute for Health Research	**Bisceglia 2007** Not reported **Wood 2013 (extracted from conference abstract)** CPAP, n= 60 Gestational age, weeks, mean (SD)= 29.7 (1.2) Birthweight, grams, mean (SD)= 1325 (335) CRIB score, mean (SD)= 4.3 (2.4) SiPAP, n= 60 Gestational age, weeks, mean (SD)= 29.8 (1.1) Birthweight, grams, mean (SD)= 1324 (300) CRIB score, mean (SD)= 4.8 (2.3) **Inclusion criteria** **Of relevant studies** **Bisceglia 2007** -24-37 weeks GA -Mild to moderate RDS (defined as need for FiO2 < 0.4 and chest x-ray positive for early hyaline membrane disease) **Wood 2013** -GA 28+0 to 31+6 -Inborn -< 6 hours old -No prior intubation	pressure 4-6 cmH2O. NIPPV was nonsynchronized. **Wood 2013** SiPAP (BiPhasic Tr); settings unspecified CPAP delivered by the Infant Flow SiPAP device	Randomisation was stratified by centre and gestation **Blinding** **Of relevant studies:** **Bisceglia 2007** No blinding **Wood 2013** NR **Attrition** **Of relevant studies:** **Bisceglia 2007** NR **Wood 2013** NR **Statistical analysis** **Of relevant studies:** **Bisceglia 2007** NR **Wood 2013** To detect a 50% reduction in failure (power 80%, α = 0.05, 2 tailed), 116 participants were required. Analyses were by intention-to-treat.	CPAP, n/total= 2/60 SiPAP, n/total= 0/60 **BPD (oxygen dependency at 36 weeks corrected gestation or 28 days of age** **Need for O2 at 36 weeks in surviving infants** **Of relevant studies:** **Bisceglia 2007** NIPPV, n/total= 2/42 NCAPA, n/total= 4/46 **Wood 2013** CPAP, n/total= 7/60 SiPAP, n/total= 5/60 **Important outcomes** **Failed non-invasive ventilation** **Of relevant studies:** **Bisceglia 2007** Respiratory failure NIPPV, n/total= 1/42 NCAPA, n/total= 1/46 Need for intubation NIPPV, n/total= 1/42 NCAPA, n/total= 1/46 **Wood 2013**	the review methods were established a priori? No details provided. **Other information** **Quality of individual studies:** Risk of bias assessment taken from Cochrane systematic review (Cochrane risk of bias tool) **Selection bias** **Of relevant studies:** **Bisceglia 2007** Low risk: Online statistical program used to generate sequence of interventions. Allocation sequence was concealed from practitioners. **Wood 2013** Unclear risk: Method for randomisation and allocation unclear **Performance bias** **Of relevant studies:**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	-No major congenital disorders **Exclusion criteria Of relevant studies** **Bisceglia 2007** Not reported **Wood 2013** -No prior intubation -No major congenital disorders			Failure of non-invasive respiratory support, necessitating intubation and ventilation in the first 72 hrs CPAP, n/total= 7/60 SiPAP, n/total= 8/60 **Pneumothorax** **Of relevant studies:** **Bisceglia 2007** NIPPV, n/total= 0/42 NCPAP, n/total= 0/46 **Wood 2013** CPAP, n/total= 0/60 SiPAP, n/total= 4/60	**Bisceglia 2007** Unclear risk: blinding not possible; unclear whether set criteria utilised for failure of nasal support **Wood 2013** Unclear risk: blinding not possible; unclear whether set criteria utilised for failure of nasal support **Detection bias** **Of relevant studies:** **Bisceglia 2007** Unclear risk: lack of blinding unlikely to affect outcome assessment; however, unclear whether set criteria used for failure of nasal support **Wood 2013** Unclear risk: lack of blinding unlikely to affect outcome assessment; however, unclear whether set criteria used for failure of nasal support

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					Attrition bias **Of relevant studies:** **Bisceglia 2007** Low risk: no missing data **Wood 2013** Low risk: no missing data **Reporting bias** **Of relevant studies:** **Bisceglia 2007** Unclear risk: unclear from information provided **Wood 2013** Unclear risk: unclear from information provided **Other sources of bias** **Of relevant studies:** N/A
Full citation Lista,G., Castoldi,F., Bianchi,S., Battaglioli,M., Cavigioli,F., Bosoni,M.A., Volume guarantee versus high-frequency ventilation:	**Sample size** Please see Cools 2015 Cochrane systematic review	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Lung inflammation in preterm infants, Archives of Disease in Childhood: Fetal and Neonatal Edition, 93, F252-F256, 2008 **Ref Id** 174463 **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 Lista, G, Castoldi, F, Fontana, P, Daniele, I, Cavigioli, F, Rossi, S, Mancuso, D, Reali, R, Nasal continuous positive airway pressure (CPAP) versus bi-level nasal CPAP in preterm babies with respiratory distress syndrome: a randomised control trial, Archives of disease in	**Sample size** n= 40 NCPAP= 20 Bi-level NCPAP= 20 **Characteristics** NCPAP, n=20	**Interventions** NCPAP= CPAP level 6 cm H2O. Weaning occurred following NICU protocols with the progressive reduction of the set CPAP level.	**Details** **Randomisation** "All infants enrolled in the study were sequentially numbered after birth and were	**Results** **Critical outcomes** **Mortality before discharge** NCPAP, n/total= 0/20	**Limitations** **Other information** **Selection bias**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
childhood. Fetal and neonatal edition, 95, F85-9, 2010 **Ref Id** 667166 **Country/ies where the study was carried out** Italy **Study type** Single-centre RCT **Aim of the study** The aim of the study was to assess the clinical course, respiratory outcomes, and markers of inflammation in preterm babies with moderate RDS assigned from birth to NCPAP or bi-level NCPAP. **Study dates** 2007-2008 **Source of funding** Not reported	Gestational age, weeks, mean (SD)= 30.3 (2) Birthweight, grams, mean (SD)= 1429 (545) Bilevel nCPAP, n=20 Gestational age, weeks, mean (SD)= 30.2 (2) Birthweight, grams, mean (SD)= 1411 (560) **Inclusion criteria** • 28-34 weeks GA • Inborn • Affected by moderate RDS **Exclusion criteria** • Lethal congenital anomalies or requiring muscle relaxant, severe IVH, chorioamnionitis, sepsis, suspected infection	Bi-level NCPAP= Lower CPAP level of 4.5 cm H2O with Thigh set at 0.5-0.7s with a pressure exchange rate of 30 times/min to start. Weaning occurred following NICU protocols with progressive reduction of the set pressure exchange rate.	randomised at 1 h of life to the NCPAP group (group A) or bi-level NCPAP group (group B) using a table of random numbers and using a stratified randomisation for gestational age (GA 28–31 weeks; GA 32–34 weeks)." **Blinding** Staff in the NICU were not blinded. The laboratory staff who checked the cytokine levels were blinded to the ventilatory strategy used, however, and the results communicated at the end of the study. **Attrition** All patients in initial randomisation were accounted for in outcome assessment. **Statistical analysis**	Bi-level NCPAP, n/total= 0/20 **BPD (oxygen dependency at 36 weeks corrected gestation or 28 days of age** BPD (O2 dependency at 28 days) NCPAP, n/total= 0/20 Bi-level NCPAP, n/total= 0/20 **Important outcomes** **Pneumothorax** NCPAP, n/total= 1/20 Bi-level NCPAP, n/total= 0/20	High risk: "All infants enrolled in the study were sequentially numbered after birth and were randomised at 1 h of life to the NCPAP group (group A) or bi-level NCPAP group (group B) using a table of random numbers and using a stratified randomisation for gestational age (GA 28–31 weeks; GA 32–34 weeks)."Allocation and blinding procedure were not reported. **Performance bias** High risk: NICU staff were not blinded **Detection bias** Low risk: "All cytokine samples were analysed in duplicate by laboratory staff unaware of the ventilatory strategies, and the results were communicated to the

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			"Normally distributed data were compared with use of the unpaired Student t test and non-parametric outcomes with use of the χ2 test. Data within each group were compared by analysis of variance (ANOVA; Bonferroni post hoc). Statistical signifi cance was at the p<0.05 level."		investigators at the end of the analysis." **Attrition bias** Low risk: All randomised babies were accounted for in outcome assessment. **Reporting bias** Low risk: all outcomes stated in methods reported in results **Other sources of bias**
Full citation Lista, G., Colnaghi, M., Castoldi, F., Condo, V., Reali, R., Compagnoni, G., Mosca, F., Impact of targeted-volume ventilation on lung inflammatory response in preterm infants with respiratory distress syndrome (RDS), Pediatric Pulmonology, 37, 510-514, 2004 **Ref Id**	**Sample size** Please see Klingeberg 2017 Cochrane systematic review **Characteristics** **Inclusion criteria**	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
653974 **Country/ies where the study was carried out** **Study type** **Aim of the study** **Study dates** **Source of funding**	**Exclusion criteria**				
Full citation Marlow, N., Greenough, A., Peacock, J. L., Marston, L., Limb, E. S., Johnson, A. H., Calvert, S. A., Randomised trial of high frequency oscillatory ventilation or conventional ventilation in babies of gestational age 28 weeks or less: respiratory and neurological outcomes at 2 years, Archives of Disease in Childhood Fetal & Neonatal EditionArch Dis Child Fetal Neonatal Ed, 91, F320-6, 2006	**Sample size** Randomised to original RCT: n=797 (HFOV: 400; TCPL: 397) Survivors from original RCT: n=592 (HFOV: 300; TCPL: 292) Participants returned questionnaire: n=428 (HFOV: 211; TCPL: 217) Questionnaires returned with assessments done in the pre-sepcified 22-28 month window: n=373 (HFOV: 176; TCPL: 197)	**Interventions** See Johnson 2002	**Details** Neurodevelopmental outcomes Parents were mailed a questionnaire that included questions in 3 areas; non-verbal vognitive development (dervived from items in the Bayleys scales of infant development) and vocabulary and language (derived from the MacArthur language scales).	**Results** **Critical outcomes** **Mortality before discharge** NMA outcome **BPD (oxygen dependency at 36 weeks corrected**	**Limitations** See Johnson 2002 **Other information** See Johnson 2002 **Selection bias** See Johnson 2002 **Performance bias** See Johnson 2002

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ref Id 667252 **Country/ies where the study was carried out** Multicentre **Study type** Randomised controlled trial **Aim of the study** To evaluate respiratory and neurodevelopmental outcomes for children at 2 years entered into the UK oscillation study **Study dates** Not reported **Source of funding** Medical research council, London.	23-25 weeks gestation: n=102 (HFOV: 53; TCPL: 49) 26-28 weeks gestation: n=271 (HFOV: 123; TCPL: 148) **Characteristics** Birthweight in grams (SD in parentheses): HFOV = 882 (208); TCPL = 914 (210) Gestational age in weeks (SD in parentheses): HFOV = 26.7 (1.4); TCPL = 26.8 (1.3) Postnatal steroids: HFOV = 54/174; TCPL = 52/195 **Inclusion criteria** See Johnson 2002 **Exclusion criteria** See Johnson 2002		Questionnaire ws validated in a term population and modified for this study to incorporate better sensitivity at lower developmental scores. A score of <49 achievied 81% sensitivity and 81% specificity for a Bayley scale mental developmental index of ≤70 **Randomisation** See Johnson 2002 **Blinding** See Johnson 2002 **Attrition** High rate of attrition = 37% **Statistical analysis** See Johnson 2002	**gestation or 28 days of age** NMA outcome **Neurodevelopmental outcomes at ≥18 months** Profound hearing loss despite aids HFOV: 2/170; TCPL: 0/189 Parental report of visual problems; reduced vision HFOV: 5/163; TCPL: 14/189 Cognitive development: parent report composite score <49 HFOV: 41/137: TCPL: 40/151 ***Parental questionnaire composite score of non-verbal development, sentence complexity, and vocabulary; 49 is the cut off for cognitive delay equivalent to Bayley mental***	**Detection bias** High risk for cognitive development as parents were not blinded and subjective outcome **Attrition bias** High risk as high rate of attrition of 37% **Reporting bias** Low risk all outcomes in the methods reported in the results **Other sources of bias**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				development index ≤70 **Important outcomes** **Pneumothorax** See Johnson 2002	
Full citation Moriette, G., Paris-Llado, J., Walti, H., Escande, B., Magny, J. F., Cambonie, G., Thiriez, G., Cantagrel, S., Lacaze-Masmonteil, T., Storme, L., Blanc, T., Liet, J. M., Andre, C., Salanave, B., Breart, G., Prospective randomized multicenter comparison of high-frequency oscillatory ventilation and conventional ventilation in preterm infants of less than 30 weeks with respiratory distress syndrome, Pediatrics, 107, 363-72, 2001 **Ref Id** 654066 **Country/ies where the study was carried out** **Study type**	**Sample size** Please see Cools 2015 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 Nafday, S. M., Green, R. S., Lin, J., Brion, L. P., Ochshorn, I., Holzman, I. R., Is there an advantage of using pressure support ventilation with volume guarantee in the initial management of premature infants with respiratory distress syndrome? A pilot study, Journal of perinatology, 25, 193-7, 2005 **Ref Id** 667455 **Country/ies where the study was carried out** **Study type** **Aim of the study**	**Sample size** Please see Klingeberg 2017 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 Nair, G, Karna, P, Comparison of the Effects of Vapotherm and Nasal CPAP in Respiratory Distress in Preterm Infants, Pediatric academic societies annual meeting; 2005 may 14-17; washington DC, united states, 2005 **Ref Id** 667459 **Country/ies where the study was carried out** **Study type** **Aim of the study** **Study dates**	**Sample size** Please see Wilkinson 2016 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 Ogawa,Y., Miyasaka,K., Kawano,T., Imura,S., Inukai,K., Okuyama,K., Oguchi,K., Togari,H., Nishida,H., Mishina,J., A multicenter randomized trial of high frequency oscillatory ventilation as compared with conventional mechanical ventilation in preterm infants with respiratory failure, Early Human Development, 32, 1-10, 1993 **Ref Id** 225778 **Country/ies where the study was carried out** **Study type** **Aim of the study** **Study dates**	**Sample size** Please see Cools 2015 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 Oncel, M. Y., Arayici, S., Uras, N., Alyamac-Dizdar, E., Sari, F. N., Karahan, S., Canpolat, F. E., Oguz, S. S., Dilmen, U., Nasal continuous positive airway pressure versus nasal intermittent positive-pressure ventilation within the minimally invasive surfactant therapy approach in preterm infants: a randomised controlled trial, Archives of Disease in Childhood Fetal & Neonatal EditionArch Dis Child Fetal Neonatal Ed, 101, F323-8, 2016 **Ref Id** 654136 **Country/ies where the study was carried out** Turkey **Study type** Single centre RCT **Aim of the study**	**Sample size** n randomised= 100 n analysed= 200 NCPAP= 100 NPPV= 100 **Characteristics** NCPAP, n=100 Gestational age, weeks, mean (SD)= 29.1 (1.6) Birthweight, grams, mean (SD)= 175 (214) Apgar score at 1 minute, median (IQR)= 6 (3-7) Apgar score at 5 minutes, median (IQR)= 8 (5-9) NIPPV, n=100 Gestational age, weeks, mean (SD)= 29.2 (1.7) Birthweight, grams, mean (SD)= 1180 (206) Apgar score at 1 minute, median (IQR)= 6 (3-8) Apgar score at 5 minutes, median (IQR)= 8 (5-10) **Inclusion criteria**	**Interventions** "All of the infants were started on prophylactic caffeine within 1 h of birth. NCPAP or NIPPV was started within 30 min of birth immediately after randomisation. Both NCPAP and NIPPV were delivered by a neonatal ventilator." NCPAP= NCPAP pressure was set at 5–6 cm H2O, and NIPPV was set in a non-synchronised mode at 20–30 bpm, with positive end-expiratory pressure of 5–6 cm H2O and peak inspiratory	**Details** **Randomisation** "Each infant was randomly assigned to NCPAP or NIPPV. Sequential numbers were generated at the NICU's computer centre with a 1:1 allocation ratio and were concealed in opaque, sequentially numbered, sealed envelopes. Two neonatologists followed the instructions in the envelopes." **Blinding** Medical team was not blinded to treatment allocation **Attrition** ITT analysis was used	**Results** **Critical outcomes** **Mortality before discharge** All infants NCPAP, n/total= 6/100 NIPPV, n/total= 4/100 Babies < 30 weeks GA NCPAP, n/total= 5/60 NIPPV, n/total= 3/55 **BPD (oxygen dependency at 36 weeks corrected gestation or 28 days of age** Moderate-to-severe BPD among survivors to discharge NCPAP, n/total= 10/100 NIPPV, n/total= 6/100 Babies < 30 weeks GA NCPAP, n/total= 10/60 NIPPV, n/total= 6/55	**Limitations** **Other information** "The initial mode of nasal support (NIPPV or NCPAP) was continued until the patient was weaned from it in accordance with our NICU practice. Infants supported with NCPAP were not allowed to be switched to NIPPV when the severity of their respiratory symptoms increased." **Selection bias** Low risk: "Each infant was randomly assigned to NCPAP or NIPPV. Sequential numbers were generated at the NICU's computer centre with a 1:1 allocation

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
To assess the efficacy of NCPAP and NIPPV as the initial respiratory support within the MIST approach in preterm babies with RDS. **Study dates** 2012 to 2013 **Source of funding** Not reported	• GA 26-32 weeks • Showed signs of RDS • Did not require intubation in the delivery room **Exclusion criteria** • Major congenital malformations	pressure of 15–20 cm H2O. FiO2 was titrated at 0.21–0.50 to maintain an oxygen saturation level of 90%–95%, as measured via pulse oximeter. NIPPV=	**Statistical analysis** "We used the independent-samples t test to compare continuous variables, the Mann–Whitney U test to compare independent groups (because of their lack of normality) and χ2 test for categorical variables. Continuous variables are presented as median (and minimum–maximum), and categorical variables are presented as number and percentage. In addition to the p value of the primary outcomes, results were given as differences and 95% CIs. The multivariate analysis using logistic regression was used to control for NCPAP/NIPPV support, gestational age, birthweight, male gender, antenatal steroids, Apgar score at	**Important outcomes** **Number of days on invasive ventilation** Duration of invasive ventilation, median (IQR), days All babies NCPAP= 3 (1-25) NIPPV= 2 (1-7) p-value= 0.34 Babies < 30 weeks GA NCPAP, n/total= 2 (1-25) NIPPV, n/total= 2 (1-7) p-value= 0.37 **Failed non-invasive ventilation** Needed invasive ventilation in the first 72 hours of life, n/total All infants NCPAP= 29/100 NIPPV= 13/100 Babies < 30 weeks GA NCPAP= 19/60 NIPPV= 11/55 Required surfactant, n/total All infants NCPAP= 60/100	ratio and were concealed in opaque, sequentially numbered, sealed envelopes. Two neonatologists followed the instructions in the envelopes." **Performance bias** Low risk: Study could not be blinded; set intubation criteria **Detection bias** Unclear risk: Set intubation criteria, unclear if criteria was met **Attrition bias** Low risk: ITT analysis was used; all infants accounted for in outcome assessment **Reporting bias** Low risk: all outcomes stated in methods reported in results

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			5 min and SNAP-II, as these are all important clinical factors. Factors affecting the need for invasive ventilation, a surfactant requirement, BPD and death were assessed via multivariate logistic regression analysis with OR and 95% CI. A p value <0.05 was considered statistically significant."	NIPPV= 38/100 Babies < 30 weeks GA NCPAP= 38/60 NIPPV= 24/55 Overall rate of intubation, n/total All infants NCPAP= 37/100 NIPPV= 20/100 Babies < 30 weeks GA NCPAP= 24/60 NIPPV= 15/55 **Pneumothorax** All babies NCPAP, n/total= 3/100 NIPPV, n/total= 5/100 Babies < 30 weeks GA NCPAP, n/total= 0/60 NIPPV, n/total= 2/55	**Other sources of bias**
Full citation Piotrowski, A., Bernas, S., Fendler, W., A randomised trial comparing two synchronised ventilation modes in neonates with respiratory distress syndrome, Anestezjologia Intensywna Terapia, 39, 58-63, 2007 **Ref Id**	**Sample size** Please see Klingeberg 2017 Cochrane systematic review **Characteristics** **Inclusion criteria**	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
667655 **Country/ies where the study was carried out** **Study type** **Aim of the study** **Study dates** **Source of funding**	**Exclusion criteria**				
Full citation Piotrowski,A., Sobala,W., Kawczynski,P., Patient-initiated, pressure-regulated, volume-controlled ventilation compared with intermittent mandatory ventilation in neonates: a prospective, randomised study, Intensive Care Medicine, 23, 975-981, 1997 **Ref Id** 225800	**Sample size** Please see Klingeberg 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 Ramanathan, R., Sekar, K. C., Rasmussen, M., Bhatia, J., Soll, R. F., Nasal intermittent positive pressure ventilation after surfactant treatment for respiratory distress syndrome in preterm infants <30 weeks' gestation: A randomized, controlled trial, Journal of perinatology, 32, 336-343, 2012 **Ref Id** 667710 **Country/ies where the study was carried out**	**Sample size** n randomised= 110 n analysed= 110 NCPAP= 57 NIPPV= 53 **Characteristics** NIPPV, n=53 Gestational age, weeks, mean (SD)=27.8 (0.9) Birthweight, grams, mean (SD)= 1052 (223) Apgar score at 1 minute, median= 6 Apgar score at 5 minutes, median= 8	**Interventions** NCPAP= 5 cm H2O and remained on NCPAP for 72h or for as long as there was need for supplemental oxygen during the first week of life. NCPAP levels were increased to a max of 8cm H2O. Provided with short binasal prongs and bubble CPAP,	**Details** **Randomisation** "Randomization was stratified according to center and gestational age (26 0/7 to 27 6/7 weeks and 28 0/7 or 29 6/7 weeks), and was performed by an independent statistician, who prepared sequentially	**Results** **Critical outcomes** **Mortality before discharge** NIPPV, n/total= 1/53 NCPAP, n/total= 1/57 **BPD (oxygen dependency at 36 weeks corrected gestation or 28 days of age**	**Limitations** **Other information** **Selection bias** Low risk: "Randomization was stratified according to center and gestational age (26 0/7 to 27 6/7 weeks and 28 0/7 or 29 6/7 weeks), and was performed by an

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
US **Study type** Multicenter RCT **Aim of the study** To compare the effect of early extubation to NIPPV vs NCPAP for the need for mechanical ventilation via endotracheal tube. **Study dates** 2006-2008 **Source of funding** Dey LP and Chiesi Farmaoeutici, SpA	NCPAP, n=57 Gestational age, weeks, mean (SD)= 27.8 (0.9) Birthweight, grams, mean (SD)= 1099 (201) Apgar score at 1 minute, median= 6 Apgar score at 5 minutes, median= 8 **Inclusion criteria** • 26+0/7 to 29+6/7 weeks gestation • Intubated for RDS **Exclusion criteria** • < 600 g birthweight • Postnatal age > 120 min • Infants not requiring intubation and surfactant within 60 min of birth • Out born infants • Apgar score of 0 at 1 min of age • Major congenital abnormalities	SiPAP with no back up rate or conventional ventilator CPAP.	numbered, sealed, opaque envelopes." **Blinding** Assignments to NIPPV or NCAP could not be blinded **Attrition** ITT analysis **Statistical analysis** "Statistical analyses were performed using Student's t test for continuous normally distributed variables and with the Wilcoxon rank sum test for non-parametric variables. Comparison of proportions and analysis of categorical variables was performed using 2-tailed Fisher's exact test and logistic regression analysis. A P-value of <0.05 was	BPD at 36 weeks GA NIPPV, n/total= 11/53 NCPAP, n/total= 22/57 **Important outcomes** **Number of days on invasive ventilation** Number of days on mechanical ventilation via endotracheal tube, days, mean (SD) NIPPV= 7.5 (12) NCPAP= 12 (11) **Failed non-invasive ventilation** On MVET at 7 days of age, n/total NIPPV, n/total= 9/53 NCPAP, n/total= 24/57 **Pneumothorax** NIPPV, n/total= 1/53 NCPAP, n/total= 2/57	independent statistician, who prepared sequentially numbered, sealed, opaque envelopes." **Performance bias** Low risk: "Limitations of our study include: assignments to NIPPV or NCAP could not be blinded." "In an attempt to minimize any bias, minimum extubation criteria were kept the same in both the groups." **Detection bias** Low risk: "In an attempt to minimize any bias, minimum extubation criteria were kept the same in both the groups." **Attrition bias** Low risk: ITT analysis; all patients accounted

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			considered statistically significant. Odds ratios with 95% CI and w2 tests were used to compare proportions between the two groups for the main dichotomous outcomes and multivariate logistic regression to control for potentially confounding effects of center, gender, BW, GA, antenatal steroid use and multiple births was done."		for in outcome assessment **Reporting bias** Low risk: All outcomes stated in methods reported in results **Other sources of bias**
Full citation Rettwitz-Volk, W., Veldman, A., Roth, B., Vierzig, A., Kachel, W., Varnholt, V., Schlosser, R., von Loewenich, V., A prospective, randomized, multicenter trial of high-frequency oscillatory ventilation compared with conventional ventilation in preterm infants with respiratory distress syndrome receiving surfactant, Journal of pediatrics, 132, 249-54, 1998 **Ref Id**	**Sample size** Please see Cools 2015 Cochrane systematic review **Characteristics** **Inclusion criteria** **Exclusion criteria**	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
667740 **Country/ies where the study was carried out** **Study type** **Aim of the study** **Study dates** **Source of funding**					
Full citation Reyes, Z, Tauscher, M, Claure, N, D'Ugard, C, Bancalari, E, Randomized, controlled trial comparing pressure support (PS) + synchronized intermittent mandatory ventilation (SIMV) with SIMV in preterm infants, Pediatric Research, 55, 79, 2004 **Ref Id** 667744	**Sample size** NMA outcome only for heterogeneity **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 Roberts, C. T., Owen, L. S., Manley, B. J., Froisland, D. H., Donath, S. M., Dalziel, K. M., Pritchard, M. A., Cartwright, D. W., Collins, C. L., Malhotra, A., Davis, P. G., Hipster Trial Investigators, Nasal High-Flow Therapy for Primary Respiratory Support in Preterm Infants, New England Journal of MedicineN Engl J Med, 375, 1142-51, 2016 **Ref Id** 561130	**Sample size** n randomised= 583 High-flow=289 CPAP= 294 n analysed= 564 High-flow= 278 CPAP= 286 **Characteristics** Hi Flow, n=278 Gestational age, wks, mean (SD)= 32.0 (2.1) Birthweight, grams, mean (SD)= 1737 (580) Apgar score at 5 minutes, median (IQR)= 8 (8-9)	**Interventions** High-flow= initial gas flow of 6 to 8 liters per minute. The size of the nasal cannulae was determined according to the manufacturers' instructions in order to maintain a leak at the nares. The maximum permissible gas flow was 8 liters per minute, as	**Details** **Randomisation** "A computer-generated randomization sequence with variable block sizes was used. Sequentially numbered, sealed, opaque envelopes containing the treatment assignment were opened as soon as both	**Results** **Critical outcomes** **Mortality before discharge** High flow, n/total= 1/278 CPAP, n/total= 1/286 **BPD (oxygen dependency at 36 weeks corrected**	**Limitations** **Other information** **Selection bias** Low risk: "A computer-generated randomization sequence with variable block sizes was used. Sequentially numbered, sealed, opaque envelopes containing the treatment

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out Australia **Study type** International, multicenter RCT **Aim of the study** The aim of the study was to assess the efficacy of high-flow therapy as the primary means of respiratory support for preterm babies with RDS. **Study dates** 2013 to 2015 **Source of funding** National Health and Medical Research Council, Royal Brisbane and Women's Hospital Foundation	CPAP, n= 286 Gestational age, wks, mean (SD)= 32.0 (2.2) Birthweight, grams, mean (SD)= 1751 (599) Apgar score at 5 minutes, median (IQR)= 9 (8-9) **Inclusion criteria** • 28 weeks + 0 to 36 weeks + 6 weeks gestation • < 24 hours old • Had not previously received endotracheal ventilation or surfactant treatment and if the attending clinician had decided to commence or continue non-invasive respiratory support **Exclusion criteria**	recommended by the manufacturer. CPAP= "Starting pressure was 6 to 8 cm of water, achieved with a ventilator, an underwater “bubble” system, or a variable-flow device. Treatment was delivered through either short binasal prongs or a nasal mask, according to the protocol at each participating center, with sizing determined according to the manufacturer’s recommendations. The maximum permissible pressure was 8 cm of water. Infants treated with CPAP who met the criteria for treatment failure were intubated and ventilated."	eligibility and consent criteria had been met." **Blinding** "Blinding of the intervention was not possible; therefore, to minimize bias, we used prespecified, objective criteria to determine the primary outcome." **Attrition** ITT analysis and per-protocol analysis **Statistical analysis** "For the primary outcome and dichotomous secondary outcomes, we calculated a risk difference (with a two-sided 95% confidence interval) in percentage points between treatment groups. We	**gestation or 28 days of age** Oxygen supplementation, respiratory support, or both at post-menstrual age of 36 weeks High flow, n/total= 17/140 CPAP, n/total= 17/149 **Important outcomes** **Failed non-invasive ventilation** **Primary ITT analysis** **Treatment failure within 72 hour** All infants, n/total High flow= 71/278 CPAP= 38/286 Gestational age < 32 wk, n/total High flow= 46/140 CPAP= 27/149 Gestational age ≥ 32 wk, n/total High flow= 25/138 CPAP= 11/137 **Intubation within 72 hour** All infants, n/total High flow= 43/278 CPAP= 33/286	assignment were opened as soon as both eligibility and consent criteria had been met." **Performance bias** Low risk: "Blinding of the intervention was not possible; therefore, to minimize bias, we used prespecified, objective criteria to determine the primary outcome." **Detection bias** Unclear risk: Unclear whether prespecified criteria were met **Attrition bias** Low risk **Reporting bias** Unclear risk: Some outcomes were only reported for infants at less than 32 weeks GA, and not all

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	• Urgent need for intubation and ventilation • Already met the criteria for treatment failure • Known major congenital abnormality or pneumothorax, or had received 4 hours or more of CPAP support		used chi-square tests to compare dichotomous outcomes and the appropriate parametric test (Student's t-test) or nonparametric test (difference in medians estimated by quantile regression) to compare continuous outcomes."	<u>Gestational age < 32 wk, n/total</u> High flow= 30/140 CPAP= 24/149 <u>Gestational age ≥ 32 wk, n/total</u> High flow= 13/138 CPAP= 9/137 **<u>Per-protocol analysis</u>** **Treatment failure within 72 hour, All infants** High flow= 64/264 CPAP= 36/279 **Intubation within 72 hour, All infants** High flow= 39/264 CPAP=33/279 **Pneumothorax** Pneumothorax or other air leak syndrome During assigned treatment High flow, n/total= 0/278 CPAP, n/total= 6/286 Any time during admission High flow, n/total= 10/278 CPAP, n/total= 8/286	**Other sources of bias** High risk: "Infants assigned to highflow therapy who met the criteria for treatment failure could receive CPAP as rescue therapy, initiated at 7 to 8 cm of water." "We acknowledge that the use of CPAP as rescue therapy may have influenced the rates of secondary outcomes in the high-flow group. Furthermore, over half of the infants assigned to this group had received CPAP for a brief period (median, 1.6 hours) before randomization, which may also have influenced the outcomes."

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Salvo, V, Lista, G, Lupo, E, Ricotti, A, Zimmermann, Lj, Gavilanes, Aw, Barberi, I, Colivicchi, M, Temporini, F, Gazzolo, D, Noninvasive ventilation strategies for early treatment of RDS in preterm infants: an RCT, Pediatrics, 135, 444-451, 2015 **Ref Id** 667855 **Country/ies where the study was carried out** Italy **Study type** Multi centre RCT **Aim of the study** The aim of the study was to assess the efficacy of NSIPPV and BiPAP for treating very low birth weight infants with RDS. **Study dates** 2010 to 2012	**Sample size** n randomised= 124 n analysed= 124 NSIPPV= 62 BiPAP= 62 **Characteristics** NSIPPV, n=62 Gestational age, weeks, mean (SD)= 28.6 (2.1) Birthweight, grams, mean (SD)= 1106 (276) Apgar score at 1 minute, mean (SD)= 7 (1) Apgar score at 5 minutes, mean (SD)= 8 (1) BiPAP, n=62 Gestational age, weeks, mean (SD)= 28.8 (2.2) Birthweight, grams, mean (SD)= 1165 (275) Apgar score at 1 minute, mean (SD)= 7 (1) Apgar score at 5 minutes, mean (SD)= 8 (1) **Inclusion criteria** • < 32 weeks GA • Birth weight < 1500 g **Exclusion criteria**	**Interventions** NSIPPV= "The initial ventilator parameters were positiveend expiratory pressure (PEEP) 4 to 6 cmH2O; peak inspiratory pressure (PIP) 15 to 20 cmH2O; inspiratory time 0.3 to 0.4 second; flow rate 6 to 10 L/minute; respiratory rate (RR) 40 breaths per minute with the lowest adjusted FIO2, to maintain an SaO2 of 88% to 93%. Respiratory settings (PIP maximum 25 cmH2O, PEEP maximum 7 cmH2O, RR maximum 60 breaths per minute) were adjusted to guarantee blood gas analysis	**Details** **Randomisation** Computer-generated random numbers **Blinding** Study not blinded **Attrition** Per-protocol analysis **Statistical analysis** "Parameters of the 2 groups were compared using Student t or Mann-Whitney U 2-sided tests for continuous variables and x2 or Fisher exact test for categorical variables. P < .05 was considered statistically significant, and all P values were based on 2-tailed tests."	**Results** **Critical outcomes** **Mortality before discharge** NSIPPV, n/total= 0/62 BiPAP, n/total= 2/62 **BPD (oxygen dependency at 36 weeks corrected gestation or 28 days of age** Moderate/severe BPD NSIPPV, n/total= 7/62 BiPAP, n/total= 7/60 **Important outcomes** **Failed non-invasive ventilation** NSIPPV, n/total= 10/62 BiPAP, n/total= 8/62 **Pneumothorax** NSIPPV, n/total= 2/62 BiPAP, n/total= 4/60	**Limitations** **Other information** **Selection bias** Low risk: Computer-generated random numbers **Performance bias** Low risk: Blinding not possible; set criteria for failure of nasal support **Detection bias** Unclear risk: lack of blinding unlikely to affect outcome assessment; unclear whether failure criteria were met **Attrition bias** Low risk: ITT analysis

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding No external funding	Not reported	within normal ranges. BiPAP= "The initial ventilator parameters were lower and higher, CPAP levels 4 to 6 cmH2O and 8 to 9 cmH2O, respectively; a timehigh of 1 second; and a pressure exchange rate of 20/minute, with the lowest adjusted FIO2 to maintain an SaO2 of 88% to 93%. Respiratory settings (CPAP lower maximum 7 cmH2O, CPAP higher maximum 10 cmH2O, pressure exchange rate max 30/minute) were adjusted to guarantee blood gas analysis within normal ranges."			**Reporting bias** Low risk: All outcomes stated in methods reported in results **Other sources of bias**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Salvo,V., Zimmermann,L.J., Gavilanes,A.W., Barberi,I., Ricotti,A., Abella,R., Frigiola,A., Giamberti,A., Florio,P., Tagliabue,P., Tina,L.G., Nigro,F., Temporini,F., Gazzolo,D., First intention high-frequency oscillatory and conventional mechanical ventilation in premature infants without antenatal glucocorticoid prophylaxis, Pediatric Critical Care Medicine, 13, 72-79, 2012 **Ref Id** 254066 **Country/ies where the study was carried out** **Study type** **Aim of the study** **Study dates** **Source of funding**	**Sample size** Please see Cools 2015 Cochrane systematic review **Characteristics** **Inclusion criteria** **Exclusion criteria**	**Interventions**	**Details** **Randomisation** **Blinding** **Attrition** **Statistical analysis**	**Results**	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Shin, J., Park, K., Lee, E. H., Choi, B. M., Humidified High Flow Nasal Cannula versus Nasal Continuous Positive Airway Pressure as an Initial Respiratory Support in Preterm Infants with Respiratory Distress: a Randomized, Controlled Non-Inferiority Trial, Journal of Korean medical science, 32, 650-655, 2017 **Ref Id** 668004 **Country/ies where the study was carried out** South Korea **Study type** Single centre RCT **Aim of the study** The aim of the study was to examine the efficacy and safety of HHFNC compared to nCPAP for the **Study dates** 2010 to 2013	**Sample size** n randomised= 87 HHFNC= 43 nCPAP= 44 n analysed= 85 HHFNC= 42 nCPAP= 43 **Characteristics** HHFNC, n=42 Gestational age, weeks, mean (SD)= 32.5 (1.5) Birthweight, grams, mean (SD)= 2058 (371) Apgar score at 1 minute, median (IQR)= 7 (6-8) NCPAP, n=43 Gestational age, weeks, mean (SD)= 33.0 (1.2) Birthweight, grams, mean (SD)= 1996 (374) Apgar score at 1 minute, median (IQR)= 7 (5-8) **Inclusion criteria** • Delivered at more than 30 wk and less than 35 wk GA • Did not meet the invasive respiratory	**Interventions** HHFNC= "flow of 5 L/min initially and it was adjusted between 3–7 L/min according to the infant's respiratory condition (to ensure blood gas analysis results within normal ranges). A fraction of inspired oxygen (FiO2) of 0.4 was initiated and it was adjusted until SpO2 of 88%–94% was maintained. Weaning was started with a progressive reduction of the set FiO2 (minimum 0.25), followed by a reduction of the flow to 3 L/min and then a reduction of FiO2 to 0.21." nCPAP = "positive end expiratory	**Details** **Randomisation** Computer-generated randomization and sequentially numbered sealed opaque envelopes containing group assignments **Blinding** Medical team not blinded to treatment assignment **Attrition** Per-protocol analysis **Statistical analysis** "For the primary outcome, we calculated risk difference and 95% confidence intervals (CIs). We used the χ2 test or Fisher exact test to compare categorical variables and the appropriate parametric	**Results** **Critical outcomes** **BPD (oxygen dependency at 36 weeks corrected gestation or 28 days of age** BPD at 36 weeks GA HHFNC, n/total= 1/42 nCPAP, n/total= 0/43 **Important outcomes** **Number of days on invasive ventilation** Received endotracheal intubation HHFNC, n/total= 13/42 nCPAP, n/total= 8/43 **Failed non-invasive ventilation** HHFNC, n/total= 16/42 nCPAP, n/total= 9/43 **Pneumothorax** HHFNC, n/total= 1/42 nCPAP, n/total= 0/43	**Limitations** **Other information** **Selection bias** Low risk: randomisation performed computer-generated random number generation and opaque, sealed envelopes **Performance bias** Moderate risk: "Our study limitation is that randomized mode of support could not be blinded to the medical team. Although we used the objective failure criteria and management protocols, the possibility of a bias might exist" **Detection bias**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding Not reported	support criteria after birth, but required non-invasive respiratory support for RDS within 24 hr after birth • Clinical signs of RDS • Need for prolonged positive pressure ventilation during neonatal resuscitation • > 1250g **Exclusion criteria** • GA < 30 wk GA • Birth weight < 1250g • Congenital abnormalities of the upper airway tract, major congenital or chromosomal abnormalities • Presence of air leak or cardiovascular instability	pressure (PEEP) of 5 cmH2O initially and it was adjusted between 4–7 cmH2O according to the infant's respiratory condition (to ensure blood gas analysis results within normal ranges). FiO2 of 0.4 was initiated and it was adjusted until SpO2 of 88%–94% was maintained."	test (Student's t-test) or nonparametric test (Mann-Whitney U 2-sided tests) to compare continuous variables. A ***P*** value below 0.05 was considered statistically significant."		Unclear risk: lack of blinding unlikely to affect outcome assessment; unclear whether objective criteria were met **Attrition bias** Low risk: Per-protocol analysis **Reporting bias** Low risk: All outcomes stated in methods reported in results **Other sources of bias**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Singh,, Volume control ventilation in extremely low birth weight infants ? a randomized controlled trial, European Journal of Pediatrics, 165, 2006 **Ref Id** 668012 **Country/ies where the study was carried out** **Study type** **Aim of the study** **Study dates** **Source of funding**	**Sample size** Please see Klingeberg 2017 Cochrane systematic review **Characteristics** **Inclusion criteria** **Exclusion criteria**	**Interventions**	**Details**	**Results**	**Limitations** **Other information**
Full citation Singh, J, Sinha, Sk, Alsop, E, Gupta, S, Mishra, A, Donn, Sm, Long term follow-up of very low birthweight infants from a neonatal	**Sample size** Number randomised: n=109 Survivors at 2 years: n=91 Number analysed: n=85 (VCV: 45; PLV: 40)	**Interventions** See Singh 2006	**Details** **Randomisation** See Singh 2006	**Results** **Critical outcomes**	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
volume versus pressure mechanical ventilation trial, Archives of disease in childhood. Fetal and neonatal edition, 94, F360-2, 2009 **Ref Id** 668018 **Country/ies where the study was carried out** UK **Study type** Randomised controlled trial **Aim of the study** To assess the outcomes of survival and respiratory and gross neurodevelopmental status at around 2 years of age as part of routine clinical follow up **Study dates** See Singh 2006 **Source of funding** See Singh 2006	**Characteristics** Birthweight in grams, mean (SD in parentheses): VCV =1018 (222); PLV = 1009 (243) Gestational age in weeks, mean (SD in parentheses): VCV = 27.3 (1.7); PLV: 27.7 (1.9) **Inclusion criteria** See Singh 2006 **Exclusion criteria** See Singh 2006		**Blinding** Blinding of participants and personnel: Unblinded Blinding of outome assessment: A questionnaire was used to determine neurodevelopmental follow-up. The questionnaire administer was masked to the original interventional group. **Attrition** 7% attrition,no reasons reported for loss to follow up **Statistical analysis** See Singh 2006	**Mortality before discharge** NMA outcome **BPD (oxygen dependency at 36 weeks corrected gestation or 28 days of age** NMA outcome **Neurodevelopmental outcomes at ≥18 months** <u>Cerebral Palsy</u> PLV: 6/40 VCV: 2/45 **Important outcomes** **Number of days on invasive ventilation** Reported in Singh 2006 **Failed non-invasive ventilation** Not reported	**Selection bias** See Singh 2006 **Performance bias** See Singh 2006 **Detection bias** Low risk: A questionnaire was used to determine neurodevelopmental follow-up. The questionnaire administer was masked to the original interventional group. **Attrition bias** Unclear risk: 7% attrition,no reasons reported for loss to follow up **Reporting bias** Low risk: all outcomes stated in the methods reported

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Pneumothorax Reported in Singh 2006 **Parental satisfaction** Not reported	**Other sources of bias**
Full citation Sinha, S. K., Donn, S. M., Gavey, J., McCarty, M., Randomised trial of volume controlled versus time cycled, pressure limited ventilation in preterm infants with respiratory distress syndrome, Archives of Disease in Childhood Fetal & Neonatal EditionArch Dis Child Fetal Neonatal Ed, 77, F202-5, 1997 **Ref Id** 668033 **Country/ies where the study was carried out** **Study type** **Aim of the study**	**Sample size** Please see Klingeberg 2017 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 Thome, U, Kössel, H, Lipowsky, G, Porz, F, Fürste, Ho, Genzel-Boroviczeny, O, Tröger, J, Oppermann, Hc, Högel, J, Pohlandt, F, Randomized comparison of high-frequency ventilation with high-rate intermittent positive pressure ventilation in preterm infants with respiratory failure, Journal of pediatrics, 135, 39-46, 1999 **Ref Id** 668237 **Country/ies where the study was carried out** **Study type** **Aim of the study**	**Sample size** Please see Cools 2015 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 Truffert, P., Paris-Llado, J., Escande, B., Magny, J. F., Cambonie, G., Saliba, E., Thiriez, G., Zupan-Simunekh, V., Blanc, T., Roze, J. C., Breart, G., Moriette, G., Neuromotor outcome at 2 years of very preterm infants who were treated with high-frequency oscillatory ventilation or conventional ventilation for neonatal respiratory distress syndrome, Pediatrics, 119, e860-e865, 2007 **Ref Id** 348078 **Country/ies where the study was carried out** France **Study type** Randomised controlled trial	**Sample size** Number randomised: n=292 (HFOV: 148; SIMV: 134) Survivors at 2 years: n=209 (HFOV: 105; SIMV: 104) Number analysed: n=192 (HFOV: 97; SIMV: 95) **Characteristics** Birthweight in grams (SD in parentheses): HFOV= 995 (234); SIMV: 1004 (252) Gestational age in weeks (SD in parentheses): HFOV= 27.6 (1.4); SIMV= 27.8 (1.5) **Inclusion criteria** See Moritette 2001	**Interventions** See Moriette 2001	**Details** **Randomisation** See Moriette 2001 **Blinding** See Moriette 2001 **Attrition** 8% attrition, no explanation for loss to follow up **Statistical analysis** See Moriette 2001	**Results** **Critical outcomes** **Mortality before discharge** NMA Outcome **BPD (oxygen dependency at 36 weeks corrected gestation or 28 days of age** NMA Outcome **Neurodevelopmental outcomes at ≥18 months** <u>Cerebral Palsy</u> SIMV: 16/95; HFOV: 4/97	**Limitations** See Moriette 2001 **Other information** **Selection bias** See Moriette 2001 **Performance bias** See Moriette 2001 **Detection bias** Low risk: standardised questionnaire was designed to minimise risk for ambigious answers, required a detailed physical and neurologic

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study Assessing neurodevelopmental outcome of infants who were randomly assinged to HFOV or conventional ventilation at 2 years of age **Study dates** See Moriette 2001 **Source of funding** Programme Hospitalier de Recherche Clinique and Assistance-Publique-Hopitaux de Paris	**Exclusion criteria** See Moriette 2001			**Important outcomes** **Number of days on invasive ventilation** See Moriette 2001 **Pneumothorax** See Moriette 2001	examinationthat assessed tone, reflexes, posture, and movements. Cerebral Palsy was defined according to the defintions of the European Collaborative Study Group. Correct classification of CP cases was checked by an investigator not informed about the ventilation group allocation. **Attrition bias** Unclear risk: 9% attrition with loss to follow up not explained **Reporting bias** Low risk: all outcomes specified in the methods were reported **Other sources of bias** Higher cerebral palsy rates in the SIMV group are speculative as infants may have been

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					more effectively stabilised on HFOV, with limited variations of PCO2 and blood pressure, but this was not detected in the initial study. However, more infants switched from conventional ventilation to HFOV, therefore identifying a subset of patients who randomly assigned to conventional ventilation and had a particularly severe respiratory outcome, possibly increasing the risk for cerebral palsy
Full citation Unal, S., Ergenekon, E., Aktas, S., Altuntas, N., Beken, S., Kazanci, E., Kulali, F., Gulbahar, O., Hirfanoglu, I. M., Onal, E., Turkyilmaz, C., Koc, E., Atalay, Y., Effects of Volume Guaranteed Ventilation Combined with Two Different Modes in Preterm Infants, Respiratory Care, 11, 11, 2017 **Ref Id**	**Sample size** NMA outcome only for heterogeneity **Characteristics** **Inclusion criteria** **Exclusion criteria**	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
668317 **Country/ies where the study was carried out** **Study type** **Aim of the study** **Study dates** **Source of funding**					
Full citation Van Reempts, P., Borstlap, C., Laroche, S., Van der Auwera, J. C., Early use of high frequency ventilation in the premature neonate, European Journal of Pediatrics, 162, 219-26, 2003 **Ref Id** 398306 **Country/ies where the study was carried out**	**Sample size** Please see Cools 2015 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 Vento, G., Matassa, P. G., Ameglio, F., Capoluongo, E., Zecca, E., Tortorolo, L., Martelli, M., Romagnoli, C., HFOV in premature neonates: effects on pulmonary mechanics and epithelial lining fluid cytokines. A randomized controlled trial, Intensive Care Medicine, 31, 463-70, 2005 **Ref Id** 668360 **Country/ies where the study was carried out** **Study type**	**Sample size** Please see Cools 2015 Cochrane systematic review **Characteristics** **Inclusion criteria** **Exclusion criteria**	**Interventions**	**Details**	**Results**	**Limitations**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study **Study dates** **Source of funding**					
Full citation Wilkinson, D., Andersen, C., O'Donnell, C. P., De Paoli, A. G., Manley, B. J., High flow nasal cannula for respiratory support in preterm infants, Cochrane Database of Systematic Reviews, 2, CD006405, 2016 **Ref Id** 668487 **Country/ies where the study was carried out** **Study type** Cochrane systematic review **Aim of the study**	**Sample size** **Of relevant studies:** **Nair 2005** n=67 randomised (n= 33 HFNC; n= 34 CPAP) **Yoder 2013** n=125 (n= 58 HHHFNC; n= 67 nCPAP) **Characteristics** **Of relevant studies:** **Nair 2005** Baseline data not available **Yoder 2013** Baseline data not available **Inclusion criteria** **Of relevant studies:** **Nair 2005**	**Interventions** **Of relevant studies:** **Nair 2005** HFNC: VapothermTM 5 to 6 L/min CPAP: bubble CPAP, Hudson prongs, 5 to 6 cmH2O **Yoder 2013** HFNC (various devices) starting at 3 to 5 L/min (increased as required to maximum of 3	**Details** **Randomisation** **Of relevant studies:** **Nair 2005** Permuted block randomisation **Yoder 2013** Opaque sealed envelopes in blocks of 10 by study site by using random-number generation **Blinding** **Of relevant studies:** **Ciuffini 2014** Not reported **Nair 2005**	**Results** **Critical outcomes** **Mortality before discharge** **Of relevant studies:** **Nair 2005** HFNC, n/total= 0/33 CPAP, n/total= 0/34 **Yoder 2013** 28-32 weeks GA HFNC, n/total= 0/20 CPAP, n/total= 0/17 ≥32 weeks HFNC, n/total= 0/38 CPAP, n/total= 0/50	**Limitations** **Quality of Cochrane SR:** Systematic review assessed using AMSTAR checklist. Total score: 15/16 All checklist items addressed, with the exception of: Checklist item 2: Did the report contain an explicit statement that the review methods were established a priori? No details **Other information** **Quality of individual studies:**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
To assess the efficacy of HFNC as compared to other non-invasive methods of respiratory support in preventing chronic lung injury and death. **Study dates** 1982 to January 1, 2016 **Source of funding** NHMRC, Australia; Eunice Kennedy Shriver National Institute of Child Health and Human Development National Institutes of Health	-RDS requiring CPAP -In the first 6 hours -27-24 weeks gestation **Yoder 2013** -Birthweight ≥1000g -GA ≥28 weeks -At the time of randomisation there was intention to manage the infant with either non-invasive respiratory support from birth initiated in the first 24 hours of life or non-invasive respiratory support at any age after a period of mechanical ventilation with an endotracheal tube **Exclusion criteria** **Of relevant studies:** **Nair 2005** -Not reported **Yoder 2013** -Birthweight < 1000g -GA < 28 weeks -Presence of active air leak syndrome -Concurrent participation in a study that prohibited HHHFNC -Abnormalities of upper and lower airpways	L/min above starting point) Nasal CPAP 5 to 6 cmH2O or equivalent to end expiratory pressure on ventilator (subsequently increased to maximum 8 cmH2O)	Not blinded **Yoder 2013** Not blinded **Attrition** **Of relevant studies:** **Ciuffini 2014** Not reported **Nair 2005** Not reported **Yoder 2013** Intention to treat analysis **Statistical analysis** **Of relevant studies:** **Ciuffini 2014** Statistics were calculated at the 95% CI level. Risk ratios using chi-squared tests and Fisher's test were used. Dichotomous variables were assessed with the Student's t-test. **Nair 2005** Not reported **Yoder 2013** X-squared or Fisher’s exact test were used for	**BPD (oxygen dependency at 36 weeks corrected gestation or 28 days of age** **Of relevant studies:** **Nair 2005** HFNC, n/total= 0/33 CPAP, n/total= 1/34 **Yoder 2013** 28-32 weeks GA HFNC, n/total= 3/20 CPAP, n/total= 1/17 ≥32 weeks HFNC, n/total= 2/38 CPAP, n/total= 0/50 **Neurodevelopmental outcomes at ≥18 months** N/A **Important outcomes** **Number of days on invasive ventilation** N/A	Risk of bias assessment taken from Cochrane systematic review (Cochrane risk of bias tool) **Selection bias** **Of relevant studies:** **Nair 2005** Unclear risk: method of randomisation and allocation unclear **Yoder 2013** Unclear risk: "random number generation" **Performance bias** **Of relevant studies:** **Nair 2005** Low risk: Blinding not possible; standardised criteria for respiratory failure **Yoder 2013** Low risk: Blinding not possible; prespecified criteria for intbuation **Detection bias** **Of relevant studies:**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	-Serious abdominal, cardiac, or respiratory malformations		all other categorical comparisons. Student's t test was used for analysis of normally distributed continuous data. Mann-Whitney U test was applied for ordinal data or continuous data that were not normally distributed. Two-sided p-values 0.05 were considered statistically significant, and no adjustments were made for multiple comparisons.	**Failed non-invasive ventilation** **Of relevant studies:** **Nair 2005** Treatment failure within 7 days of trial entry HFNC, n/total= 4/33 CPAP, n/total= 4/34 **Yoder 2013** Treatment failure within 7 days of trial entry 28-32 weeks GA HFNC, n/total= 0/20 CPAP, n/total= 2/17 ≥32 weeks HFNC, n/total= 6/38 CPAP, n/total= 7/50 Note: Treatment failure within 7 days of trial entry defined as: Intubation (or re-intubation) within 7 days of trial entry **Pneumothorax** **Of relevant studies:** **Nair 2005** HFNC, n/total= 0/33 CPAP, n/total= 2/34 **Yoder 2013** HFNC, n/total= 0/58	**Nair 2005** Unclear risk: standardised criteria for respiratory failure, though frequency of blood gases and recording of apnoea not blinded. **Yoder 2013** Unclear risk: Prespecified criteria for intbuation (however, did not report complicance with criteria) **Attrition bias** **Of relevant studies:** **Nair 2005** Unclear risk **Yoder 2013** ITT, all patients accounted for **Reporting bias** **Of relevant studies:** **Nair 2005** Unclear risk: protocol not registered **Yoder 2013** High risk: not all outcomes listed in

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				CPAP, n/total= 3/67 **Parental satisfaction** N/A	methods were reported in results **Other sources of bias Of relevant studies:** **Nair 2005** N/A **Yoder 2013** N/A
Full citation Wood, Fe, Gupta, S, Tin, W, Sinha, S, Randomised controlled trial of synchronised intermittent positive airway pressure (SiPAP) versus continuous positive airway pressure (CPAP) as a primary mode of respiratory support in preterm infants with respiratory distress syndrome, Archives of Disease in Childhood, 98, A1-117, 2013 **Ref Id** 668517 **Country/ies where the study was carried out** **Study type**	**Sample size** Please see Lemyre 2016 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 Yoder, Ba, Stoddard, Ra, Li, M, King, J, Dirnberger, Dr, Abbasi, S, Heated, humidified high-flow nasal cannula versus nasal CPAP for respiratory support in neonates, Pediatrics, 131, e1482-90, 2013 **Ref Id** 654508 **Country/ies where the study was carried out** **Study type** **Aim of the study** **Study dates**	**Sample size** Please see Wilkinson 2016 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 Klingenberg, C., Wheeler, K. I., McCallion, N., Morley, C. J., Davis, P. G., Volume-targeted versus pressure-limited ventilation in neonates, Cochrane Database of Systematic Reviews, 10, CD003666, 2017 **Ref Id** 758749 **Country/ies where the study was carried out** **Study type** Cochrane systematic review **Aim of the study** To determine whether volume targeted ventilation compared with pressure limited ventilation leads to reduced rates of death and death or BPD in newborn infants and to detemine whether use of volume targeted ventilation affected	**Sample size** **Of relevant studies:** **Chowdhury 2013** n=40 (VTV: 20; SIMV: 20) **Dunman 2012** n=45 (A/C: 22; A/C + VG: 23) **Guven 2013** n=72 (SIMV: 30; SIMV + VG: 42) **Lista 2004** n=53 (PSV: 23; PSV + VG: 30) **Nafday 2005** n=34 (SIMV: 18; PSV + VG: 16) **Piotrowski 1997** n=57 (IMV: 30; PRVC: 27) **Piotrowski 2007** n=56 (SIMV: 26; PRVC: 30) **Singh 2006** n=109 (A/C: 52; VCV: 57) **Sinha 1997** n=50 (A/C: 25; A/C + VG: 25)	**Interventions** **Of relevant studies:** **Chowdhury 2013** VTV vs SIMV Ventilator type: SLE5000. Both groups inflation time 0.3-0.4 sec, inflation rate 40-60/min, PEEP not reported Both groups: predefined weaning strategy, underlying trigger mode changed from SIMV to AC. **Dunman 2012** A/C vs A/C + VG Ventilator type: Drager Babylog 8000+. Initially in SIPPV(AC) mode and then switched to SIMV mode during weaning. Inflation time 0.3-	**Details** **Randomisation** **Of relevant studies:** **Chowdhury 2013** Random number table generation. Blinding of randomisation: sealed opaque envelopes **Dunman 2012** Block randomisation with random block sizes Blinding of randomisation: sealed opaque envelopes. **Guven 2013** Block randomisation with random block sizes Blinding of randomisation: not specified **Lista 2004** Random number sequencing, stratified by GA (25-28 weeks	**Results** **Critical outcomes** **Mortality before discharge** NMA outcome **BPD (oxygen dependency at 36 weeks corrected gestation or 28 days of age** NMA outcome **Neurodevelopmental outcomes at ≥18 months** Not included in the Cochrane review **Important outcomes**	**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) **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
outcomes in air leak, cranial ultrasound findings and neurodevelopment. **Study dates** Up to June 2017 **Source of funding** No sources of external support	**Characteristics Of relevant studies:** **Chowdhury 2013** Gestational age in weeks, mean VTV: 28; SIMV: 26 Age at start of ventilation in hours, median VTV: 5; SIMV: 4 Birthweight in grams, mean VTV: 1016; SIMV: 856 Antenatal steroid use VTV: 70%; SIMV: 55% FiO2 at enrollment VTV: 0.33; SIMV: 0.31 **Dunman 2012** Gestational age in weeks, mean A/C + VG: 27.8; A/C: 27.6 Birthweight in grams, mean A/C + VG: 1055; A/C: 975 Surfactant use: 100% Antenatal steroid use A/C + VG: 73%; A/C: 74% FiO2 at enrollment A/C + VG: 0.61; A/C: 0.7 **Guven 2013** Gestational age in weeks, mean SIMV + VG: 29.4; SIMV: 29.17 Birthweight in grams, mean	0.4 sec and PEEP 4-6 cmH20. During weaning, respiratory rate was gradually reduced to 18/min. Clear protocol for ventilation and weaning. Target PaCO2 40-60 mmHg **Guven 2013** SIMV vs SIMV + VG <u>Ventilator type:</u> Drager Babylog 8000+ in SIMV mode **Lista 2004** PSV vs PSV + VG <u>Ventilator type:</u> Draeger Babylog 8000+ with set backup rate 40/min, PEEP 3.5-4 cm H2O. Mean inflation time 0.4-0.5 sec (upper limit in PSV mode) Target: FiO2 to maintain SPO2 90-96%, pH > 7.25 50-75	and 29-32 weeks) and centre Blinding of randomisation: not specified **Nafday 2005** Block randomisation, stratified by weight (500-750 g, 751-1000 g, 1001-1250 g, 1251-1500 g) Blinding of randomisation: sealed envelopes. **Piotrowski 1997** Randomised, but no further information about randomisation procedure Blinding of randomisation: sealed envelopes. **Piotrowski 2007** Sequential numbers. Stratified by GA (24-28 weeks and 29-33 weeks) Blinding of randomisation: sealed envelopes. **Singh 2006**	**Number of days on invasive ventilation Of relevant studies:** **Chowdhury 2013** Duration of ventilation in days, survivors in mean (SD in parentheses) PLV: 20 (24.1); VTV: 7.9 (15.3) **Dunman 2012** Duration of ventilation in days, survivors in mean (SD in parentheses) A/C: 6.93 (7.23); A/C + VG: 4.06 (5.1) **Guven 2013** Duration of mechanical ventilation in days in mean (SD in parentheses) SIMV: 6.93 (7.81) SIMV + VG: 3.02 (6.76) **Lista 2004*** Length of ventilation in days, all in mean (SD in parentheses) PSV + VG: 8.8 (3); PSV: 12.3 (3) **Piotrowski 1997** Duration of ventilation in days, survivors in	**Selection bias** **Chowdhury 2013** Unclear risk: did not report if randomisation was computer generated **Dunman 2012** Unclear risk: did not report if randomisation was computer generated **Guven 2013** Unclear risk: did not report if randomisation was computer generated **Lista 2004** Unclear risk: did not report if randomisation was computer generated **Nafday 2005** Unclear risk: did not report if randomisation was computer generated **Piotrowski 1997** Unclear risk: did not report if randomisation was computer generated **Piotrowski 2007** Unclear risk: did not report if randomisation

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	SIMV + VG: 1352; SIMV: 1275 Surfactant use: 100% Antenatal steroid use SIMV + VG: 69%; SIMV: 73% Apgar score at enrollment, median SIMV + VG: 8.17 at 5 min; SIMV: 7.6 at 5 min **Lista 2004** Gestational age in weeks, mean PSV + VG: 28.5; PSV: 29.4 Age at start of ventilation in hours, mean: 3 Birthweight in grams, mean PSV + VG: 1125; PSV: 1197 Surfactant use: 100% Antenatal steroid use: 86% **Nafday 2005** Gestational age in weeks, mean PSV + VG: 27.9; SIMV: 27.4 Birthweight in grams, mean PSV + VG: 1198; SIMV: 1055 Surfactant use: 100% Antenatal steroid use PSV + VG: 63%; SIMV: 78% Apgar score at enrollment, median	mmHg, PaCO2 40-65 mmHg **Nafday 2005** SIMV vs PSV + VG <u>Ventilator type:</u> Drager Babylog 8000+. Ventilator rate adjusted to target blood gas values. Target: pH 7.25-7.35, PaCO2 45-55 mmHg, PaO2 50-70 mmHg, SpO2 88-95% ***Duration of intervention: 24 hrs*** **Piotrowski 1997** IMV vs PRVC <u>Ventilator type:</u> Different ventilator type for PRVC (Siemens Sevo 300) and IMV (Bear cub or sechrist). Both ventilated using PEEP 3-5 cmH20 and inflation time 0.5 sec Target: SpO2 88-95%, pCO2 <55 mmHg. Infants	Random block randomisation. Stratified by birthweight Blinding of randomisation: sealed, opaque envelopes. **Sinha 1997** Randomised, but no further information about randomisation procedure Blinding of randomisation: sealed envelopes. **Blinding** **Of relevant studies:** **Chowdhury 2013** Unblinded **Dunman 2012** Unblinded **Guven 2013** Unblinded **Lista 2004** Unblinded **Nafday 2005** Unblinded **Piotrowski 1997** Unblinded **Piotrowski 2007**	mean (SD in parentheses) IMV: 13 (15) ; PRVC: 6.7 (4.9) **Singh 2006** Duration of ventilation in days, survivors in mean (SD in parentheses) VC: 8.4 (12.6) vs A/C: 9.7 (14) **Sinha 1997** Duration of ventilation in days, all in mean (SD in parentheses) A/C: 6.7 (5.6) VC: 5.1 (2.7) *Extracted from the original paper by the NGA technical team **Failed non-invasive ventilation** Not reported **Pneumothorax** **Of relevant studies:** **Chowdhury 2013** PLV: 0/20; VTV: 2/20 **Dunman 2012*** A/C: 2/22; A/C + VG: 2/23	was computer generated **Singh 2006** Unclear risk: did not report if randomisation was computer generated **Sinha 1997** Unclear risk: did not report if randomisation was computer generated **Performance bias** **Chowdhury 2013** high risk: unblinded **Dunman 2012** high risk: unblinded **Guven 2013** high risk: unblinded **Lista 2004** high risk: unblinded **Nafday 2005** high risk: unblinded **Piotrowski 1997** high risk: unblinded **Piotrowski 2007** high risk: unblinded **Singh 2006** high risk: unblinded **Sinha 1997** high risk: unblinded

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	PSV + VG: 8 at 5 min; SIMV: 7.5 at 5 min **Piotrowski 1997** Gestational age in weeks, mean PRVC: 29; IMV: 30 Age at start of ventilation in hours, mean PRVC: 15.6; IMV: 12.1 Birthweight in grams, mean PRVC: 1239; IMV: 1137 FiO2 at enrollment, mean PRVC: 0.62; IMV: 0.68 Apgar score at enrollment, mean PRVC: 4.2 at 5 min; IMV: 5.5 at 5 min **Piotrowski 2007** Gestational age in weeks, median: 28 Birthweight in grams, median PRVC: 1050; SIMV: 1040 Surfactant use: PRVC: 50%; SIMV: 23% Antenatal steroid use PRVC: 30%; SIMV: 23% Apgar score at enrollment, median PRVC: 4 at 5 min; SIMV: 5 at 5 min **Singh 2006** Gestational age in weeks, median VCV: 27.1; A/C: 27.2	extubated once ventilator rate < 12/min, FiO2 <0.25, and after 30-60 min of ETT-CPAP **Piotrowski 2007** SIMV vs PRVC <u>Ventilator type:</u> PRVC group used Siemens Servo 300. SIMV group used 1 of the 4 different ventilators (depending on availability): Bear Cub (CEM)/ Bear 750 PSV, Sechrist Millenium, Draeger Babylog 8000+ or SLE 5000. Both groups: inflation time 0.4 sec, inflation rate 40/min, PEEP 3-5 cmH2O **Singh 2006** A/C vs VCV <u>Ventilator type:</u> Both groups used VIP Bird Gold **Sinha 1997** A/C vs A/C + VG	Unblinded **Singh 2006** Unblinded **Sinha 1997** Unblinded **Attrition** **Of relevant studies:** **Chowdhury 2013** Follow-up: complete to end of intervention. Secondary post intervention outcomes reported during period of primary admission **Dunman 2012** Follow-up: complete to end of intervention. Secondary post intervention outcomes reported during period of primary admission **Guven 2013** Follow-up: complete to end of intervention. **Lista 2004** Follow-up: complete to discharge. **Nafday 2005** Follow-up: complete to discharge. **Piotrowski 1997** Follow-up: complete. **Piotrowski 2007**	**Lista 2004*** PSV: 3/23; PSV + VG: 0/30 **Nafday 2005*** SIMV: 0/18; PSV + VG: 0/16 **Piotrowski 1997*** IMV: 6/30; PRVC: 2/27 **Piotrowski 2007** SIMV: 4/26; PRVC: 3/30 **Singh 2006** A/C: 4/52 VCV: 2/57 **Sinha 1997** A/C: 3/25; A/C + VG: 0/25 **Parental satisfaction** Not reported	**Detection bias** **Chowdhury 2013** low risk: unblinded, however outcome measures of interest for review all objective outcomes **Dunman 2012** low risk: unblinded, however outcome measures of interest for review all objective outcomes **Guven 2013** low risk: unblinded, however outcome measures of interest for review all objective outcomes **Lista 2004** low risk: unblinded, however outcome measures of interest for review all objective outcomes **Nafday 2005** low risk: unblinded, however outcome measures of interest for review all objective outcomes **Piotrowski 1997** low risk: unblinded, however outcome measures of interest for

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Birthweight in grams, mean VCV: 985; A/C: 976 Surfactant use: 100% Antenatal steroid use VCV: 96%; A/C: 94% Apgar score at enrollment, median: 9 at 5 min **Sinha 1997** Gestational age in weeks, mean A/C + VG: 31.2; A/C: 31.2 Age at start of ventilation in hours, mean A/C + VG: 8; A/C: 5 Birthweight in grams, mean A/C + VG: 1793; A/C: 1762 Surfactant use: 100% Antenatal steroid use: 44% **Inclusion criteria** **Of relevant studies:** **Chowdhury 2013** Preterm babies <34 weeks gestation age Age at start of ventilation: <24 hours **Dunman 2012** Preterm babies 23-31 weeks gestation age Age at start of ventilation: <24 hours **Guven 2013**	<u>Ventilator type:</u> Both groups used VIP Bird Gold in A/C mode with inflation time at 0.3-0.5 sec. Target: pH 7.27-7.40, PaCO2 4.5-6 kPa, PaO2 8-11 kPa	Follow-up: complete to discharge. **Singh 2006** Follow-up: complete to discharge. 85/91 (93%) infants eligible for follow-up were assessed at a median of 22 months' corrected age **Sinha 1997** Follow-up: complete. **Statistical analysis**		review all objective outcomes **Piotrowski 2007** low risk: unblinded, however outcome measures of interest for review all objective outcomes **Singh 2006** low risk: unblinded, however outcome measures of interest for review all objective outcomes **Sinha 1997** low risk: unblinded, however outcome measures of interest for review all objective outcomes **Attrition bias** **Chowdhury 2013** low risk **Dunman 2012** low risk **Guven 2013** low risk **Lista 2004** low risk **Nafday 2005** low risk **Piotrowski 1997** low risk

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Preterm babies <32 weeks gestation age Age at start of ventilation: <2 hours **Lista 2004** Preterm babies 25-32 weeks gestation age Age at start of ventilation: <24 hours **Nafday 2005** Preterm babies <1500g Age at start of ventilation: <12 hours **Piotrowski 1997** Preterm babies <2500g Age at start of ventilation: <72 hours **Piotrowski 2007** Preterm babies 24-32 weeks gestation age **Singh 2006** Preterm babies 24-31 weeks gestation age **Sinha 1997** Preterm babies >1200g **Exclusion criteria** **Of relevant studies:** **Chowdhury 2013** Major congenital anomalies **Dunman 2012** Major congenital anomalies **Guven 2013**				**Piotrowski 2007** low risk **Singh 2006** low risk **Sinha 1997** low risk **Reporting bias** **Chowdhury 2013** Unclear risk: trial registration submitted after completion of study **Dunman 2012** Unclear risk: protocol not available for review **Guven 2013** Unclear risk: protocol not available for review **Lista 2004** Unclear risk: protocol not available for review **Nafday 2005** Unclear risk: protocol not available for review **Piotrowski 1997** Unclear risk: protocol not available for review **Piotrowski 2007** Unclear risk: protocol not available for review **Singh 2006** Unclear risk: protocol not available for review

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Major congenital anomalies, prenatal asphyxia and meconium aspiration **Lista 2004** Lethal anomalies Receiving muscle relaxants at entry IVH grade ≥2 Actual or suspected sepsis **Nafday 2005** Major congenital malformations, congenital heart disease Confirmed/suspected sepsis Pneumothorax Other air leak Requiring paralysis/ heavy sedation **Piotrowski 1997** Sepsis/ pneumonia congenital malformation Pneumothorax or any airleak Meconium aspiration **Piotrowski 2007** Severe congenital malformation Pulmonary airleak on admission **Singh 2006** Severe congenital malformations **Sinha 1997** Confirmed/suspected sepsis/pneumonia				**Sinha 1997** Unclear risk: protocol not available for review **Other sources of bias** **Chowdhury 2013** Unclear risk: imbalance in baseline characteristics **Guven 2013** High risk: randomisation occured before patient consent **Lista 2004** High risk: imbalance in treatment arm numbers **Piotrowski 1997** High risk: different ventilators, modes, and synchronisation settings used in the treatment arms **Piotrowski 2007** High risk: different ventilators, modes, and synchronisation settings used in the treatment arms **Singh 2006** High risk: both arms weaned using the same treatment **Sinha 1997**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Congenital malformation Lack of arterial access				High risk: both arms weaned using the same treatment

Clinical evidence tables for question 3.7 What is the effectiveness of nitric oxide in preterm babies requiring invasive ventilation?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Ballard, R. A., Truog, W. E., Cnaan, A., Martin, R. J., Ballard, P. L., Merrill, J. D., Walsh, M. C., Durand, D. J., Mayock, D. E., Eichenwald, E. C., Null, D. R., Hudak, M. L., Puri, A. R., Golombek, S. G., Courtney, S. E., Stewart, D. L., Welty, S. E., Phibbs, R. H., Hibbs, A. M., Luan, X., Wadlinger, S. R., Asselin, J. M., Coburn, C. E., No Cld Study Group, Inhaled nitric oxide in preterm infants undergoing mechanical ventilation.[Erratum	**Sample size** See Cochrane systematic review Barrington 2017 **Characteristics** **Inclusion criteria** **Exclusion criteria**	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
appears in N Engl J Med. 2007 Oct 4;357(14):1444-5; PMID: 17914048], New England Journal of Medicine, 355, 343-53, 2006 **Ref Id** 433060 **Country/ies where the study was carried out** **Study type** **Aim of the study** **Study dates** **Source of funding**					
Full citation Barrington, Keith J, Finer, Neil, Pennaforte, Thomas, Inhaled nitric oxide for respiratory failure in preterm infants,	**Sample size** **Of relevant studies:** **Ballard 2006** n=582 randomised **Dani 2006:** n=40 randomised **EUNO 2009:**	**Interventions** **Of relevant studies:** **Ballard 2006** Infants < 1250 grams on assisted ventilation at 7-21	**Details** **Of relevant studies:** **Ballard 2006** Methods: Multi-centre trial Outcomes: Survival without BPD at 36 weeks' postmenstrual age.	**Results** Outcome: Mortality prior to discharge Studies with entry before 3 days based on oxygenation **Dani 2006**	**Limitations** **Quality of Cochrane SR:** Systematic review assessed using AMSTAR checklist. Total score: 13/16

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Cochrane Database of Systematic Reviews, 2017 **Ref Id** 619443 **Country/ies where the study was carried out** **Study type** Cochrane systematic review **Aim of the study** The aim of the review was to assess the effects of treating preterm babies with hypoxic respiratory failure on outcomes including BPD, IVH and other serious brain injury or adverse long-term neurodevelopmental outcomes. **Study dates** Search up to January 2016	n= 800 randomised **Hascoet 2005:** n randomised= 145 randomised (n=61 iNO; n=84 control) **INNOVO (Field) 2005:** n randomised= 108 (n=55 iNO; n=53 no iNO) **Kinsella 1999:** n randomised= 80 (n=48 iNO, n=52 placebo) **Kinsella 2006:** n randomised= 793 (n=398 iNO; n=395 no iNO) **Kinsella 2014:** n randomised= 124 **Mercier 1999:** n randomised= 85 (n= 40 iNO; n=45 control) **Schreiber 2003:** n randomised = 207 (n=105 iNO; n= 102 control) **Srisuparp 2002:** n randomised= 34 **Subhedar 1997:** n randomised= 42 (n=20 iNO; n=22 control) **Van Meurs 2005:** n randomised= 420 (n= 210 iNO; n=210 placebo) **Van Meurs 2007:** n randomised= 29	days (or, if < 800 grams, on CPAP) **Dani 2006:** iNO at 10 ppm for 4 hours followed by 6 ppm compared with no treatment. Weaning started at 72 hours or when the infant was extubated, or when FiO2 was < 0.3 with mean airway pressure < 8 cm H2O **EUNO 2009:** Inhaled NO at 5 ppm for at least 7 and a maximum of 21 days **Hascoet 2005:** Inhaled NO was started at 5 ppm, with adjustments allowed depending on response up to a maximum of 10 ppm. Participants were allowed to receive iNO in either group if they developed refractory hypoxaemia **INNOVO (Field) 2005:** Inhaled NO usually at 5 ppm up to 40 ppm (n = 55) or no	Secondary outcomes included duration of oxygen therapy and duration of hospitalisation. In addition, investigators prospectively evaluated the need for hospitalisation and respiratory support, including invasive ventilation, continuous positive airway pressure and oxygen supplementation at 40, 44, 52 and 60 weeks' postmenstrual age Neurodevelopmental outcomes at 22-26 months of age* (Walsh 2010): Cerebral palsy defined as unable to crawl or walk, palisano score of ≥2. Bilateral deafness requiring amplification. Bilateral blindness. **Dani 2006:** Methods: single-centre trial Outcomes: The primary endpoint was death or BPD. Bronchopulmonary dysplasia was defined as oxygen requirement at 36 weeks' postmenstrual age. Secondary endpoints were evaluation of ventilation changes during iNO	iNO= 4/20; Control=6/20 **Hascoet 2005** iNO=25/61; Control=26/84 **INNOVO (Field) 2005** iNO= 30/55; Control=34/53 **Kinsella 1999** iNO= 23/48; Control=17/32 **Mercier 1999** iNO= 11/40; Control=16/45 **Srisuparp 2002** iNO= 2/18; Control=2/16 **Van Meurs 2005** iNO= 109/210; Control=93/210 **Van Meurs 2007** iNO= 5/14; Control=4/15 Studies with entry after 3 days based on BPD risk **Ballard 2006** iNO= 16/294; control= 18/288 **Subhedar 1997** iNO= 10/20; control= 7/22 Studies of routine use in preterm infants on respiratory support	All checklist items addressed with the exception of: Checklist items: (1) did the research questions and inclusion criteria for the review included the components of PICO (the research question was not clearly stated) (3) Did the review authors explain their selection of the study designs for inclusion in the review? (authors did not explain why only RCTs or quasi-experimental studies were included) (8) Did the review authors describe the included studies in adequate detail? (authors did not describe the population in detail or the timeframe for follow-up) **Quality of individual studies:** Risk of bias assessment taken from Cochrane systematic

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments

Source of funding
Eunice Kennedy Shriver National Institute of Child Health and Human Development
	Characteristics Extracted from original studies
	Of relevant studies:
	Ballard 2006
	Setting: US
	Gestational age, weeks, mean (SD): iNO= 26 (1.5); control= 26 (1.5)
	Birth weight, g, mean (SD): iNO= 766 (161); control= 759 (155)
	Dani 2006:
	Setting: Italy
	Gestational age, weeks, mean (SD): iNO= 26.3 (2.6); control= 26.7 (1.9)
	Birth weight, g, mean (SD): iNO= 937 (298); control= 825 (299.3)
	Apgar score, 1st minute, median (IQR): iNO= 4 (1-8); control= 4 (2-8)
	Apgar score, 5th minute, median (IQR): iNO= 7 (2-9); control= 6 (2-9)
	EUNO 2009 (Mercier 2010):
	Setting: 9 countries in the EU
	Gestational age, weeks, mean (SD): iNO= 26.4 (1.3); control= 26.6 (1.3)
	Birth weight, g, mean (SD): iNO= 851(207); control= 864 (192)
		supplemental gas (n = 53)
		Kinsella 1999:
		Inhaled NO at 5 ppm (n = 48) or no supplemental gas (n = 32) for 7 days, after which "trials off" were allowed. Maximum treatment duration was 14 days
		Kinsella 2006:
		iNO at 5 ppm (n = 398) or no iNO (n = 395) for 21 days or until extubation
		Kinsella 2014:
		iNOat 10 ppm (to give effective concentration ≥ 5 ppm) or placebo, for at least 2 weeks and until 30 weeks' postmenstrual age
		Mercier 1999:
		10 ppm inhaled NO(n = 40) or control (n = 45). Open-label treatment with NO allowed in controls if OI > 30
		Schreiber 2003:
		Inhaled nitric oxide starting at 10 ppm for 1 day, then 5 ppm for
			therapy, duration of oxygen treatment, NCPAP and invasive ventilation, incidence of patent ductus arteriosus (PDA), pulmonary hypertension, intraventricular haemorrhage (IVH) , periventricular leukomalacia (PVL), retinopathy of prematurity (ROP), necrotising enterocolitis (NEC), sepsis and length of stay in the intensive care unit and in hospital
			EUNO 2006:
			Methods: multi-centre trial
			Outcomes: Primary outcome was survival without BPD at 36 weeks' postmenstrual age. Secondary outcome was survival without severe brain injury on head ultrasonography. Neurodevelopmental outcomes at 2 years of age*: Cerebral palsy using GMFCS classification, no score defined. Severe cognitive impairment using BSID-III <70. Moderate cognitie impairment using BSID-III 70-<85.
			Hascoet 2005:
				EUNO 2009
				iNO= 54/399; control= 41/401
				Kinsella 2006
				iNO= 78/398; control= 98/395
				Kinsella 2014
				iNO= 1/59; control= 2/65
				Schreiber 2003
				iNO= 16/105; control= 23/102
				
				Outcome: Bronchopulmanory dysplasia at 36 weeks corrected gestation
				Studies with entry before 3 days based on oxygenation
				Hascoet 2005*
				iNO=7/61;
				Control=15/84
				INNOVO (Field) 2005
				iNO= 26/55;
				Control=15/53
				Kinsella 1999*
				iNO= 15/48;
				Control=12/32
				Mercier 1999*
				iNO= 7/40;
				Control=8/45
				Van Meurs 2007*
				iNO= 3/14;
				Control=5/15
					review (Cochrane risk of bias tool)
					Ballard 2006:
					Random sequence generation: Unclear risk (Randomised in permuted blocks at study centre; computer-generated randomisation not specified)
					Allocation concealment: Low risk
					Blinding of outcome assessment: Low risk (ND: low risk [unclear if outcome assessment was blinded, however clear criteria for diagnosis of all ND outcomes])
					Incomplete outcome data: Low risk (ND: high risk [19% attrtion from initial sample randomised due to death and loss to follow up])
					Selective reporting: Low risk
					Other bias: Low risk
					Dani 2006:
					Random sequence generation: Unclear risk (not described)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Hascoet 2005: Setting: France Gestational age < 28 weeks, n/total: iNO= 30/61; control= 38/84 Birth weight > 750g, n/total: iNO= ; control= Birth weight 750-1500g, n/total: iNO= 41/61; control= 49/84 Birth weight > 1500g, n/total: iNO= 10/61; control= 16/84 Apgar score at 1 minute < 3, n/total: iNO= 12/61; control= 19/84 Apgar score at 1 minute 3-5, n/total: iNO= 21/61; control= 22/84 Apgar score at 1 minute > 5, n/total: iNO= 23/61; control= 40/84 **INNOVO (Field) 2005:** Setting: UK Gestational age, weeks, mean (SD): iNO= 27.4 (2.6); control= 26.3 (2.4) Birth weight, g, mean (SD): iNO= 1066 (395); control= 890 (343) **Kinsella 1999:** Setting: US Gestational age, weeks, mean (SD): iNO= 27.1 (2.5); control= 26.8 (2.5)	6 days; thereafter weaned by 1 ppm, stopped if extubated) vs control. HFOV (N=102) vs CMV (N = 105) **Srisuparp 2002:** iNO at 20 ppm or standard care, trial of weaning after 72 hours, maximum duration 7 days **Subhedar 1997:** iNO initially administered at 20 ppm and weaned if effective (n = 20) or control (n =22). Dexamethasone at 1 mg/kg/d for 3 days, followed by 0.5 mg/kg/d for 3 days (n = 21) (3 infants received a lower dose), or no steroids (n = 21) **Van Meurs 2005:** iNO initially at 5 ppm to 10 ppm (210) or placebo (210) (if no response at 10 ppm, study gas was stopped). Weaning ≥ 10 hours after initiation. Maximum	Methods: Multi-centre trial Outcomes: Primary outcome was survival to 28 days without death, need for oxygen, IVH > grade 1 or refractory hypoxaemia defined as need for 100% oxygen with PaO2 < 50. Secondary outcomes included incidence and severity of IVH and periventricular leukomalacia (PVL), BPD or steroid treatment and pulmonary haemorrhage, patent ductus arteriosus (PDA), necrotising enterocolitis and nosocomial infection **INNOVO (Field) 2005:** Methods: Multi-centre trial Outcomes: Primary outcomes were (1) death or severe disability at 1 year corrected postnatal age; and (2) death or continued oxygen need at expected date of birth Secondary outcomes included length of stay in hospital; length of time on supplemental oxygen; length of time on ventilatory support; pneumothorax; other pulmonary air leak; pulmonary haemorrhage;	Studies with entry after 3 days based on BPD risk **Ballard 2006*** iNO= 149/294; control= 164/288 **Subhedar 1997*** iNO= 10/20; control= 14/22 Studies of routine use in preterm infants on respiratory support **EUNO 2009*** iNO= 81/399; control= 96/401 **Kinsella 2006** iNO= 212/398; control= 210/395 **Kinsella 2014*** iNO= 24/59; control= 25/65 **Schreiber 2003*** iNO= 35/105; control= 42/102 Outcome: Neurodevelopmental outcomes at ≥ 18 months Outome: Cerebral Palsy at ≥ 18 months** Studies with entry before 3 days based on oxygenation	Allocation concealment: Low risk Blinding of outcome assessment: High risk (unmasked trial) Incomplete outcome data: Low risk Selective reporting: Unclear risk (protocol not available) Other bias: High risk (Study terminated after 40 infants enrolled. Initially planned to include 26 per group. Unplanned interim analysis was performed because of an impression that the results were significant. No evidence indicated that the analysis was adjusted to account for potential multiple looks at the data) **EUNO 2009:** Random sequence generation: Low risk (computer generated) Allocation concealment: Low risk Blinding of outcome assessment: Low risk (ND outcome: low risk (outcome assessors

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Birth weight, g, mean (SD): iNO= 1040 (461); control= 988 (387) **Kinsella 2006:** Setting: US Gestational age, weeks, mean (SD): iNO= 25.6 (1.7); control= 25.6 (1.8) Birth weight, g, mean (SD): iNO= 796 (190); control= 788 (185) Apgar score, 1st minute, median (IQR): iNO= 4 (0-9); control= 4 (0-9) Apgar score, 5th minute, median (IQR): iNO= 7 (0-9); control= 7 (1-10) **Kinsella 2014:** Setting: US Gestational age, weeks, mean (SD): iNO= 27.5 (1.6); control= 27.3 (1.8) Birth weight, g, mean (SD): iNO= 961 (186); control= 968 (159) Apgar score, 1st minute, median (IQR): iNO= 2 (1-4); control= 2 (1-3) Apgar score, 5th minute, median (IQR): iNO= 7 (1-9); control= 7 (2-9) **Mercier 1999:** Setting: France, Belgium	duration was 336 hours **Van Meurs 2007:** iNO initially at 5 ppm to 10 ppm (210) or placebo (210) (if no response at 10 ppm, study gas was stopped). Weaning ≥ 10 hours after initiation. Maximum duration was 14 days	major cerebral abnormality; necrotising enterocolitis; patent ductus arteriosus needing medical treatment; treatment of retinopathy of prematurity; infection; and age at which full oral feeding was established. Secondary outcomes at 1 year corrected age included disability and/or impairment of neuromotor development, vision and hearing; respiratory problems; seizures; growth; and hospital admissions Neurodevelopmental outcomes at 4-5 years of age* (Huddy 2008): Severe cognitive impairment using GCAS <50. Moderate cognitive impairment using GCAS 50-69. Moderate to severe disability of vision defined as sees light or gross movement only or no useful vision (blind). Moderate to severe disability of hearing or communication defined as some hearing loss not corrected by aids and/or uses formal methods of communication (signing);	**Van Meurs 2005 (Hintz 2007)** iNO= 18/90; Control=11/102 **Van Meurs 2007** iNO= 0/9; Control=0/8 Studies with entry after 3 days based on BPD risk **Ballard 2006** (Walsh 2010) iNO= 15/243; control= 12/234 **Subhedar 1997 (Bennett 2001)** iNO= 0/7; control= 2/14 Studies of routine use in preterm infants on respiratory support **EUNO 2009 (Durmeyer 2013)** iNO= 29/306; control= 29/324 **Schreiber 2003 (Mestan 2005)** iNO= 6/70; control= 7/68 Outcome: Severe cognitive impairment at ≥ 18 months** Studies with entry before 3 days based on oxygenation	blinded and clear criteria for ND outcomes) Incomplete outcome data: Low risk (ND: high risk [22% attrtion from initial sample randomised due to death and loss to follow up]) Selective reporting: Low risk Other bias: High risk (funded by industry (Ikaria)); initiated by investigators **Hascoet 2005:** Random sequence generation: Unclear risk (stratified, blocked central randomisation; unclear whether computer randomisation was used) Allocation concealment: Low risk Blinding of outcome assessment: High risk (no blinding of intervention or outcome assessment) Incomplete outcome data: Low risk

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Gestational age, weeks, median: iNO= 29.6; control= 29 Birth weight, g, median: iNO= 1200; control= 1150 5 minute Apgar score, ≤ 6, n/total: iNO= 15/40; control= 12/45 5 minute Apgar score, 7-9, n/total: iNO= 13/40; control= 19/45 5 minute Apgar score, 10, n/total: iNO= 8/40; control= 9/45 **Schreiber 2003:** Setting: US Gestational age, weeks, mean (SD): iNO= 27.4 (2.5); control= 27.0 (2.8) Birth weight, g, mean (SD): iNO= 1017 (369); control= 949 (387) Apgar score at 1 minute, median (IQR): iNO= 5 (3-6); control= 5 (3-6) Apgar score at 5 minutes, median (IQR): iNO= 7 (6-8); control= 7 (6-8) **Srisuparp 2002:** Setting: US Gestational age, weeks, mean (SD): iNO= 26.8 (0.5); control= 27.2 (0.5)		nouseful hearing and/or no formal communication. **Kinsella 1999:** Methods: Multi-centre trial Outcomes: Primary outcome was survival. Bronchopulmonary dysplasia, intraventricular haemorrhage and duration of ventilation were secondary outcomes **Kinsella 2006:** Methods: Multi-centre trial Outcomes: Primary outcome was death or bronchopulmonary dysplasia. Secondary outcomes included severe intraventricular haemorrhage, periventricular leukomalacia and ventriculomegaly **Kinsella 2014:** Methods: Multi-centre parallel-group randomised trial Outcomes: Death or BPD, IVH, retinopathy of prematurity, necrotising enterocolitis, treatment of infants with PDA **Mercier 1999:** Methods: Multi-centre parallel-group randomised trial	**INNOVO 2005 (Huddy 2008)** iNO= 3/22; control= 3/16 **Van Meurs 2005 (Hintz 2007)** MDI iNO= 37/86; control= 35/98 PDI iNO= 29/85; control= 32/99 **Van Meurs 2007** MDI iNO= 1/9; Control=2/8 PDI iNO= 0/9; Control=0/8 Studies of routine use in preterm infants on respiratory support **EUNO 2009 (Durmeyer 2013)** iNO= 7/306; control= 12/324 **Schreiber 2003 (Mestan 2005)** MDI iNO= 13/70; control= 24/68 PDI iNO= 9/70; control= 12/68	Selective reporting: Unclear risk (registration documents or protocol not found) Other bias: High risk (28 control infants received open-label iNO after the randomised intervention) **INNOVO (Field) 2005:** Random sequence generation: Unclear risk (central randomisation with minimisation; unclear whether computer randomisation was used) Allocation concealment: Low risk Blinding of outcome assessment: high risk (no blinding of intervention or outcome assessment) / (ND outcomes: low risk [assessors blinded to allocation and families were told not to reveal the allocation until after the assessment was over, clear definition of ND outcomes])

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Birth weight, g, mean (SD): iNO= 874 (70); control= 901 (73) Apgar score, 1st minute, mean (SD): iNO= 3.4 (0.5); control= 4.6 (0.6) Apgar score, 5th minute, mean (SD): iNO= 6.6 (0.3); control= 7.3 (0.3) **Subhedar 1997:** Setting: UK Gestational age, weeks, median (IQR): iNO= 27 (24-30); control= 27 (22-31) Birth weight, g, median (IQR): iNO= 882 (416-1354); control= 750 (520-1400) Apgar score at 5 minutes, median (IQR): iNO= 8 (2-10); control= 8 (3-10) **Van Meurs 2005:** Setting: US Gestational age, weeks, mean (SD): iNO= 26 (2); control= 26 (2) Birth weight, g, mean (SD): iNO= 840 (264); control= 837 (260) Apgar scores < 4 at 1 min, n/total: iNO= 92/210; control= 87/210 Apgar scores < 4 at 5 min, n/total: iNO= 27/210; control= 22/210 **Van Meurs 2007:**		Outcomes: Primary outcome was decrease in OI after 2 hours of therapy. **Schreiber 2003:** Methods: Factorial 2x2 single-centre trial Outcomes: Primary outcome was a decrease in death or BPD at 36 weeks Neurodevelopmental outcomes at 2 years of age* (Mestan 2005): Cerebral palsy defined as spastic hemiplegia, diplegia, hemiplegia quadraplegia. Severe cognitive impairment using BSID-II <70 (MDI and PDI). Blindness defined as corrected visual acuity <20/200. Hearing loss defined as impairment requiring hearing aid. **Srisuparp 2002:** Methods: Single-centre trial Outcomes: Primary outcome was severe intraventricular haemorrhage (grade 3 or 4) **Subhedar 1997:** Methods: Factorial 2x2 randomised single-centre trial Outcomes: Primary outcome was survival	Outcome: Moderate cognitive impairment at ≥ 18 months** Studies with entry before 3 days based on oxygenation **INNOVO 2005 (Huddy 2008)** iNO= 3/24; control= 3/19 **EUNO 2009 (Durmeyer 2013)** iNO= 51/338; control= 31/347 Outcome: Severe hearing impairment at ≥ 18 months** Studies with entry before 3 days based on oxygenation **INNOVO 2005 (Huddy 2008)** iNO= 3/22; control= 2/16 **Van Meurs 2005 (Hintz 2007)** iNO= 5/90; control= 5/102 **Van Meurs 2007** iNO= 0/9; Control=0/11 Studies with entry after 3 days based on BPD risk	Incomplete outcome data: Low risk (ND: high risk [75% attrtion from initial sample randomised due to death and loss to follow up]) Selective reporting: Low risk Other bias: Unclear risk (recruited half of planned sample size in the 2-year time frame) **Kinsella 1999:** Random sequence generation: Unclear risk (central stratified randomisation; unclear whether computer randomisation was used) Allocation concealment: Low risk Blinding of outcome assessment: Low risk Incomplete outcome data: Low risk Selective reporting: Unclear risk (no protocol or registration document found) Other bias: High risk (study terminated after first interim analysis

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Setting: US Gestational age, weeks, mean (SD): iNO= 31.1 (1.2); control= 31.4 (1.1) Birth weight, g, mean (SD): iNO= 1970 (391); control= 2168 (441) Apgar scores ≤ 3 at 1 min, n/total: iNO= 3/13; control= 3/14 Apgar scores ≤ 3 at 5 min, n/total: iNO= 0/13; control= 1/14 **Inclusion criteria Of relevant studies:** **Ballard 2006** Infants < 1250 grams on assisted ventilation at 7-21 days (or, if < 800 grams, on CPAP) **Dani 2006:** Preterm infants ventilated with severe RDS with FiO2 > 0.5 and arterial-alveolar oxygen ratio < 0.15, despite surfactant treatment **EUNO 2009:** Babies between 24 weeks' and 28 weeks' gestation and 6 days enrolled at less than 24 hours of age. If intubated, they had to have received		without bronchopulmonary dysplasia. Secondary outcomes included duration of ventilation, intraventricular haemorrhage and other neonatal complications Neurodevelopmental outcomes at 30 months of age* (Bennett 2001): Cerebral palsy defined as significant abnormalities or tone or movement. **Van Meurs 2005:** Methods: Multi-centre trial Outcomes: Primary outcome was reduced death or BPD at 36 weeks. Secondary outcomes were grade 3 or 4 intraventricular haemorrhage or periventricular leukomalacia, number of days of assisted ventilation and oxygen use, length of hospitalisation and threshold retinopathy of prematurity Neurodevelopmental outomes at 18-22 months of age* (Hinz 2007): Moderate to severe cerebral palsy defined as moderate if the child could sit independently or with	**Ballard 2006** (Walsh 2010) iNO= 8/243; control= 3/234 Studies of routine use in preterm infants on respiratory support **EUNO 2009 (Durmeyer 2013)** iNO= 7/306; control= 12/324 **Schreiber 2003 (Mestan 2005)** iNO= 0/70; control= 1/68 Outcome: Severe visual impairment at ≥ 18 months** Studies with entry before 3 days based on oxygenation **INNOVO 2005 (Huddy 2008)** iNO= 1/22; control= 1/16 **Van Meurs 2005 (Hintz 2007)** iNO= 2/90; control= 1/102 **Van Meurs 2007** iNO= 0/9; Control=0/11	due to little difference in outcomes being apparent) **Kinsella 2006:** Random sequence generation: Unclear risk (central stratified randomisation; unclear whether computer randomisation was used) Allocation concealment: Low risk Blinding of outcome assessment: Low risk Incomplete outcome data: Low risk Selective reporting: Low risk Other bias: Low risk **Kinsella 2014:** Random sequence generation: Low risk Allocation concealment: Low risk Blinding of outcome assessment: Low risk Incomplete outcome data: Low risk Selective reporting: Low risk Other bias: Low risk **Mercier 1999:** Random sequence generation: Unclear

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	surfactant and could be enrolled if on CPAP requiring > 30% oxygen **Hascoet 2005:** Babies < 32 weeks who developed hypoxic respiratory failure (i.e. need for invasive ventilation, FiO_2 > 0.40, and arterial alveolar O_2 ratio < 0.22 at 6 to 48 hours of age) **INNOVO (Field) 2005:** Preterm babies < 34 weeks gestational age less than 28 days of age, with "severe respiratory failure" **Kinsella 1999:** Preterm babies ≤ 34 weeks, < 7 days of age, with a/AO2 < 0.1 on 2 blood gases after surfactant treatment **Kinsella 2006:** Preterm babies < 34 weeks, respiratory failure needing assisted ventilation in first 48 hours **Kinsella 2014:** Preterm babies with birth weight of 500 to 1250 grams, receiving oxygen by non-invasive means at < 72 hours of age **Mercier 1999:** Preterm babies (< 33 weeks) with OI of 12.5 to 30 at < 7 days		support, but not independently ambulate, and severe if the child was unable to sit or walk even with support. Severe cognitive impairment using BSID-II <70 (MDI and PDI). Deaf no defintion. Blind no definition **Van Meurs 2007:** Methods: Multi-centre trial Outcomes: Primary outcome was reduced death or BPD at 36 weeks. Secondary outcomes were grade 3 or 4 intraventricular haemorrhage or periventricular leukomalacia, number of days of assisted ventilation and oxygen use, length of hospitalisation and threshold retinopathy of prematurity Neurodevelopmental outcomes at 18-22 months of age* : Moderate to severe cerebral palsy defined as moderate if the child could sit independently or with support, but not independently ambulate, and severe if the child was unable to sit or walk even	Studies with entry after 3 days based on BPD risk **Ballard 2006** (Walsh 2010) iNO= 9/243; control= 9/234 Studies of routine use in preterm infants on respiratory support **EUNO 2009 (Durmeyer 2013)** iNO= 7/306; control= 12/324 **Schreiber 2003 (Mestan 2005)** iNO= 0/70; control= 2/68 Outcome: Days on ventilation Studies with entry before 3 days based on oxygenation **INNOVO (Field) 2005**** iNO= 7.0 (2.0-26.0) n=55; control= 4.0 (1.0-9.0) n=53 (log rank: 3.6; p=0.24) **Subhedar 1997**** iNO= 11 (5-44) n=20; control= 19 (5-39) n=22 **Van Meurs 2005****	risk (centralised phone randomisation; unclear whether computer generated randomisation was used) Allocation concealment: Low risk Blinding of outcome assessment: High risk (unblinded trial) Incomplete outcome data:Low risk Selective reporting: Unclear risk (no protocol or registration found) Other bias: Unclear risk (trial stopped early because of slowing enrollment) **Schreiber 2003:** Random sequence generation: Unclear risk (stratified blocked randomisation; unclear whether computer generated randomisation was used) Allocation concealment: Low risk Blinding of outcome assessment: Low risk (ND outcome: low

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Schreiber 2003: Babies < 34 weeks, < 72 hours of age, intubated and ventilated for RDS, birth weight < 2000 grams **Srisuparp 2002:** Preterm infnants < 2000 grams, ventilated after surfactant with an arterial catheter at < 72 hours of age. Also required to satisfy a severity of illness criterion. OI > 4 for birth weight < 1000 grams, > 6 for birth weight 1001-1250 grams, > 8 for 1251-1500 grams, > 10 for 1501-1750 grams and > 12 for 1751-2000 grams **Subhedar 1997:** Preterm babies < 32 weeks' gestation with "high risk" of developing BPD **Van Meurs 2005:** Preterm babies < 34 weeks, OI ≥ 10 on 2 blood gases 30 minutes to 12 hours apart. ≥ 4 hours after surfactant **Van Meurs 2007:** Preterm babies < 34 weeks' gestation with birth weight > 1500 grams; ventilated with OI > 15 on 2 consecutive blood gases between 30 minutes and 12 hours apart		with support. Severe cognitive impairment using BSID-II <70 (MDI and PDI). Deaf defined as requiring hearing aids. Blind defined as no useful vision in either eye. *Data extracted from original RCT by NGA technical team	iNO= 39 (45) n=210; control= 47 (53) n= 210 **Van Meurs 2007**** iNO= 8.7 (5.4) n=14; control= 16.8 (13.9) n=15 Studies of routine use in preterm infants on respiratory support **Kinsella 2014**** iNO= 9.7 (29) n= 59; control= 8.4 (12) n=65 **Kinsella 1999*** iNO= 28 (3-89) n=25, control= 37 (8-395) n=15 p=0.046 Outcome: Severe intraventricular haemorrhage (grade 3 or 4) Studies with entry before 3 days based on oxygenation **Dani 2006** iNO= 2/20; Control=2/20 **Hascoet 2005** iNO=14/61; Control=116/84 **Kinsella 1999** iNO= 16/48; Control=10/32	risk (outcome assessors blinded and clear criteria for ND outcomes) Incomplete outcome data: Low risk (ND: high risk [33% attrtion from initial sample randomised due to death and loss to follow up]) Selective reporting: Unclear risk (no protocol or registration documents found) Other bias: Low risk **Srisuparp 2002:** Random sequence generation: Unclear risk (no details provided) Allocation concealment: Unclear risk (unclear whether allocation was blinded) Blinding of outcome assessment: High risk (unblinded trial) Incomplete outcome data: Low risk Selective reporting: Unclear risk (no registration or protocol found) Other bias: Low risk

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Exclusion criteria **Of relevant studies:** None noted except for **EUNO 2009:** If babies required more than 50% O_2 to maintain saturation over 85% on a mean airway pressure ≥ 8 cmH_2O			**Srisuparp 2002** iNO= 5/18; Control=4/16 **Van Meurs 2005** iNO= 69/210; Control=50/210 Studies of routine use in preterm infants on respiratory support **EUNO 2009** iNO= 45/399; control= 36/401 **Kinsella 2006** iNO= 49/398; control= 63/395 **Kinsella 2014** iNO= 2/59; control= 4/65 **Schreiber 2003** iNO= 13/105; control= 19/102 Outcome: Pulmonary haemorrhage Studies with entry before 3 days based on oxygenation **INNOVO (Field) 2005**** iNO= 4/55; control= 5/53 **Subhedar 1997**** iNO= 2/20; control=2/22	**Subhedar 1997:** Random sequence generation: Low risk Allocation concealment: Low risk Blinding of outcome assessment: High risk (no blinding of intervention or outcome measurement)/ (ND outcome: high risk [unclear whether observer who was blinded was the one that was undertaking all outcome assessments]) Incomplete outcome data: Low risk (ND: high risk [50% attrtion from initial sample randomised due to death and loss to follow up]) Selective reporting: Unclear risk (no registration or protocol found) Other bias: High risk (trial terminated early because frequency of adverse primary outcome was close to 100% in all groups) **Van Meurs 2005:**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Studies of routine use in preterm infants on respiratory support **Kinsella 2006**** iNO=24/398; control=26/395 **Schreiber 2003**** iNO=4/105; control= 7/102 **EUNO 2009 (Mercier 2010)**** < 26 weeks iNO= 5/133; control= 7/140 ≥ 26 weeks iNO= 9/264; control= 5/255 Outcome: Methaemoglbinaemia Studies with entry before 3 days based on oxygenation **Van Meurs 2005**** Methemoglobin level ≥4% iNO= 2/210; control= 2/210 Methemoglobin level ≥8% iNO= 1/210; control= 0/210	Random sequence generation: Unclear risk (stratified blocked central randomisation; unclear whether computer generated randomisation was used) Allocation concealment: Low risk Blinding of outcome assessment: Low risk (ND outcome: low risk (outcome assessors blinded and clear criteria for ND outcomes) Incomplete outcome data: Low risk (ND: high risk [55% attrtion from initial sample randomised due to death and loss to follow up]) Selective reporting: Low risk Other bias: High risk (trial ended early because of an increase in severe IVH in the intervention group) **Van Meurs 2007:** Random sequence generation: Unclear risk (central telephone

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				*N taken from the whole population and not just survivors **Extracted from original study by NGA systematic reviewer	randomisation, stratified and blocked; unclear whether computer generated randomisation was used) Allocation concealment: Low risk Blinding of outcome assessment: Low risk (ND outcome: low risk (outcome assessors blinded and clear criteria for ND outcomes) Incomplete outcome data: Low risk (ND: high risk [42% attrtion from initial sample randomised due to death and loss to follow up]) Selective reporting: Low risk Other bias: High risk (less than 15 babies in the treatment arm) **Other information**
Full citation	**Sample size**	**Interventions**	**Details**	**Results**	**Limitations**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Bennett, A. J., Shaw, N. J., Gregg, J. E., Subhedar, N. V., Neurodevelopmental outcome in high-risk preterm infants treated with inhaled nitric oxide, Acta Paediatrica, 90, 573-6, 2001 **Ref Id** 347052 **Country/ies where the study was carried out** **Study type** **Aim of the study** **Study dates** **Source of funding**	See Subhedar 1997 for study details **Characteristics** **Inclusion criteria** **Exclusion criteria**				**Other information**
Full citation	**Sample size** See Cochrane systematic review Barrington 2017	**Interventions**	**Details**	**Results**	**Limitations**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Dani, C., Bertini, G., Pezzati, M., Filippi, L., Cecchi, A., Rubaltelli, F. F., Inhaled nitric oxide in very preterm infants with severe respiratory distress syndrome, Acta Paediatrica, International Journal of Paediatrics, 95, 1116-1123, 2006 **Ref Id** 703175 **Country/ies where the study was carried out** **Study type** **Aim of the study** **Study dates** **Source of funding**	**Characteristics** **Inclusion criteria** **Exclusion criteria**				**Other information**
Full citation	**Sample size**	**Interventions**	**Details**	**Results**	**Limitations**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Durrmeyer, X., Hummler, H., Sanchez-Luna, M., Carnielli, V. P., Field, D., Greenough, A., Van Overmeire, B., Jonsson, B., Hallman, M., Mercier, J. C., Marlow, N., Johnson, S., Baldassarre, J., European Union Nitric Oxide Study, Group, Two-year outcomes of a randomized controlled trial of inhaled nitric oxide in premature infants, Pediatrics, 132, e695-703, 2013 **Ref Id** 763116 **Country/ies where the study was carried out** **Study type** **Aim of the study** **Study dates**	See Mercier 2010 (EUNO 2009) for study details **Characteristics** **Inclusion criteria** **Exclusion criteria**				**Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding					
Full citation Hamon, I., Fresson, J., Nicolas, M. B., Buchweiller, M. C., Franck, P., Hascoet, J. M., Early inhaled nitric oxide improves oxidative balance in very preterm infants, Pediatric Research, 57, 637-643, 2005 **Ref Id** 752432 **Country/ies where the study was carried out** France **Study type** RCT **Aim of the study** The aim of the study was to analyse the oxidative balance in premature infants who were	**Sample size** N= 76 iNO= 37 Control= 39 **Characteristics** Gestational age, weeks, mean (SD): iNO= 27.9 (0.4); control= 27.3 (0.4) Birth weight, g, mean (SD): iNO= 1102 (54); control= 1083 (58) CRIB score < 6, n/total: iNO= 23/39; control= 18/37 CRIB score 5-10, n/total: iNO= 11/39; control= 14/37 CRIB score > 10, n/total: iNO= 5/39; control= 4/37 **Inclusion criteria**	**Interventions** Inhaled nitric oxide (iNO) versus placebo (nitrogen dioxide) iNO: A dose of 5 ppm of iNO was used for the first hour, and then subsequent dosage was determined according to aAO2 response. As soon as the response was positive (defined as an aAO2 increase 0.22), iNO was decreased to 2 ppm for 2 h and then weaned according to blood gas examination; when the response was intermediate (aAO2 remaining 0.22 but increasing by at least 25%), iNO was left at 5 ppm for 2 h and the	**Details** Randomisation: not reported Blinding: "Randomization was stratified by GA (28 wk and 28–31 wk GA) and kept blind until 6 h of age with optimal care performed according to standardized written protocols" Follow up and outcomes: Events recorded since birth and by the 28th day of life. Incidence and severity of IVH, periventricular leukomalacia, prevalence of oxygen dependence on day 28. Statistical analysis: X^2 or Fischer exact tests for categorical variables. Two way ANOVAs for continuous variables. A p value < 0.05 was considered statistically significant.	**Results** Outcome: Oxygen dependency at 28 days of life iNO= 15/39; control=8/37	**Limitations** Risk of bias assessed by Cochrane risk of bias tool Random sequence generation: unclear risk (method of randomisation unclear) Allocation concealment: high risk "Because of the continuous monitoring of iNO and of NO_2 it was difficult to blind the administration of the gas with the design of the study. Blinding of outcome measures: high risk "randomization was kept blind until analysis" Incomplete outcome data: low risk Selective reporting: unclear risk (no published protocol available)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
exposed to low dose iNO compared to placebo (NO) and the relationship with their clinical outcome on day 28 of life. **Study dates** July 1999 to February 2001 **Source of funding** Not reported	• GA < 32 weeks at birth and < 48 hours of life **Exclusion criteria** • Initial refractory hypoxemia, thromboxytopenia < 50,000/mm^3 or the presence of major fetal abnormality	response was re-evaluated every 2 h thereafter. Finally, when the infants showed no response, iNO was increased up to 10 ppm for 2 h and then re-evaluated. In case of treatment failure, iNO was weaned after 4 h.			**Other information**
Full citation Hasan, S. U., Potenziano, J., Konduri, G. G., Perez, J. A., Van Meurs, K. P., Walker, M. W., Yoder, B. A., Newborns Treated With Nitric Oxide Trial, Group, Effect of Inhaled Nitric Oxide on Survival Without Bronchopulmonary Dysplasia in Preterm Infants: A Randomized Clinical Trial, JAMA	**Sample size** N= 451 iNO= 229; control= 222 **Characteristics** Gestational age, weeks, mean (SD): iNO= 25.6 (1.4); control= 25.6 (1.5) Birth weight, g, mean (SD): iNO= 724 (160); control= 750 (164) Apgar score 1, mean (range): iNO= 4 (0-9); control= 4 (0-9)	**Interventions** Inhaled nitric oxide (iNO) versus placebo (nitrogen) "Placebo (nitrogen) or inhaled nitric oxide was initiated at 20ppm and was decreased to 10ppm between 72 and 96 hours after starting treatment and then to 5 ppm on day 10 or 11. Infants remained on the 5ppm dose	**Details** Randomisation: Block randomisation in groups of 4 via an interactive voice response system Blinding: A metal face plate was placed over the nitrogen delivery system to blind personnel to treatment assignment Follow up and outcomes: Babies were assessed at 36 weeks PMA; neurodevelopmental assessments were performed at 18-24 months	**Results** Outcome: Neurodevelopmental impairment at 18-24 months PMA Severe, BSID-III cognitive score < 70 iNO=13/164; placebo= 12/167 Moderate, BSID-III cognitive score of 70-84 iNO= 26/167; placebo= 33/167 Moderate to severe CP	**Limitations** Risk of bias assessed using Cochrane risk of bias tool Random sequence generation: Low risk (Randomisation was generated with an interactive voice response system) Allocation concealment: Low risk (All staff providing direct care were blinded to treatment assignment)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Pediatrics, 171, 1081-1089, 2017 **Ref Id** 763175 **Country/ies where the study was carried out** US and Canada **Study type** Multi-centre RCT **Aim of the study** The aim of the study was to assess whether inhaled nitric oxide for preterm babies needing positive pressure respiratory support on postnatal days 5-14 improved the rate of survival without BPD. **Study dates** December 2009 to April 2014 **Source of funding**	Apgar score 5, mean (range): iNO= 6 (1-10); control= 6 (1-9) **Inclusion criteria** • GA < 30 weeks • Birth weight < 1250g • Postnatal age 5-14 days at study entry • Requirement of invasive ventilation or, for those weighing < 800g, positive pressure respiratory support **Exclusion criteria** • Presence of any life threatening cranial, cardiac, thoracic, or chromosomal anomalies • Congenital diaphragmatic hernia • Bilateral grade 4 IVH • Dependency on right to left shunting	until completion of therapy (24 days)."	PMA. Outcomes assessed at 12-months. Survival, somatic growth measurements (weight, length, and head circumference), vital signs, medical history review, complete physical examination, vision assessment, oxygen therapy at discharge home or follow-up visit, hospitalisation or emergency department visit history, medications, and respiratory syncytial virus prophylaxis. Neurodevelopmental outcomes were assessed at 18-24months' PMA using the Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III). Statistical analysis: Mixed-effects models with random intercepts were used to analyse continuous outcome variables. All models were adjusted for GA strata because GA was used to stratify randomisation. The Fisher exact test was used for between-group comparisons of AE	iNO= 7/180; placebo= 11/180 Outcome: BPD at 36 weeks PMA* iNO= 130/229; control= 137/222 Outcome: Days on ventilation* iNO=54 (42) n=229; control= 55 (40) n=222 *Number taken for whole population	Blinding of participants and personnel: Low risk (Staff calibrating iNO delivery system were unblinded; but staff providing direct care were blinded) Blinding of outcome assessment: Low risk (study was double blinded) Incomplete outcome data: Low risk (ITT analysis); ND: high risk [49% attrition from initial sample randomised due to death and loss to follow up] Selective reporting: Low risk (protocol included in published review; all outcomes stated in protocol reported in study) Other bias: None reported **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Mallinckrodt Pharmaceuticals	• Prior exposure to iNO therapy • Use of another investigational agent		incidences. A significance level of 2-sided P < .05 was set for all between-group comparisons. Intention-to-treat analyses were used.		
Full citation Hascoet, J. M., Fresson, J., Claris, O., Hamon, I., Lombet, J., Liska, A., Cantagrel, S., Al Hosri, J., Thiriez, G., Valdes, V., Vittu, G., Egreteau, L., Henrot, A., Buchweiller, M. C., Onody, P., The safety and efficacy of nitric oxide therapy in premature infants, Journal of Pediatrics, 146, 318-323, 2005 **Ref Id** 653785 **Country/ies where the study was carried out** **Study type**	**Sample size** See Cochrane systematic review Barrington 2017 **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 Hibbs,A.M., Walsh,M.C., Martin,R.J., Truog,W.E., Lorch,S.A., Alessandrini,E., Cnaan,A., Palermo,L., Wadlinger,S.R., Coburn,C.E., Ballard,P.L., Ballard,R.A., One-year respiratory outcomes of preterm infants enrolled in the Nitric Oxide (to prevent) Chronic Lung Disease trial, Journal of Pediatrics, 153, 525-529, 2008 **Ref Id** 210081	**Sample size** See Ballard 2006 for study details **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 Hintz, S. R., Van Meurs, K. P., Perritt, R., Poole, W. K., Das, A., Stevenson, D. K., Ehrenkranz, R. A., Lemons, J. A., Vohr, B. R., Heyne, R., Childers, D. O., Peralta-Carcelen, M., Dusick, A., Johnson, Y. R., Morris, B., Dillard, R., Vaucher, Y., Steichen, J., Adams-Chapman, I., Konduri, G., Myers, G. J., de Ungria, M., Tyson, J. E.,	**Sample size** See Van Meurs 2005 (PiNO 2005) **Characteristics** **Inclusion criteria** **Exclusion criteria**	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Higgins, R. D., Nichd Neonatal Research Network, Neurodevelopmental outcomes of premature infants with severe respiratory failure enrolled in a randomized controlled trial of inhaled nitric oxide, Journal of Pediatrics, 151, 16-22, 22.e1-3, 2007 **Ref Id** 336454 **Country/ies where the study was carried out** **Study type** **Aim of the study** **Study dates** **Source of funding**					
Full citation	**Sample size**	**Interventions**	**Details**	**Results**	**Limitations**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Huddy, C. L., Bennett, C. C., Hardy, P., Field, D., Elbourne, D., Grieve, R., Truesdale, A., Diallo, K., Innovo Trial Collaborating Group, The INNOVO multicentre randomised controlled trial: neonatal ventilation with inhaled nitric oxide versus ventilatory support without nitric oxide for severe respiratory failure in preterm infants: follow up at 4-5 years, Archives of Disease in Childhood Fetal & Neonatal EditionArch Dis Child Fetal Neonatal Ed, 93, F430-5, 2008 **Ref Id** 763196 **Country/ies where the study was carried out** **Study type** **Aim of the study**	See Field 2005 (INNOVO 2005) for study details **Characteristics** **Inclusion criteria** **Exclusion criteria**				**Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates **Source of funding**					
Full citation Kinsella, J. P., Cutter, G. R., Steinhorn, R. H., Nelin, L. D., Walsh, W. F., Finer, N. N., Abman, S. H., Noninvasive inhaled nitric oxide does not prevent bronchopulmonary dysplasia in premature newborns, The Journal of pediatrics, 165, 1104-1108.e1, 2014 **Ref Id** 510508 **Country/ies where the study was carried out** **Study type**	**Sample size** See Cochrane systematic review Barrington 2017 **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 Kinsella, J. P., Cutter, G. R., Walsh, W. F., Gerstmann, D. R., Bose, C. L., Hart, C., Sekar, K. C., Auten, R. L., Bhutani, V. K., Gerdes, J. S., George, T. N., Southgate, W. M., Carriedo, H., Couser, R. J., Mammel, M. C., Hall, D. C., Pappagallo, M., Sardesai, S., Strain, J. D., Baier, M., Abman, S. H., Early inhaled nitric oxide therapy in premature newborns with respiratory failure, The New England journal of medicine, 355, 354-64, 2006	**Sample size** See Cochrane systematic review Barrington 2017 **Characteristics** **Inclusion criteria** **Exclusion criteria**	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ref Id 510509 **Country/ies where the study was carried out** **Study type** **Aim of the study** **Study dates** **Source of funding**					
Full citation Kinsella, J. P., Walsh, W. F., Bose, C. L., Gerstmann, D. R., Labella, J. J., Sardesai, S., Walsh-Sukys, M. C., McCaffrey, M. J., Cornfield, D. N., Bhutani, V. K., Cutter, G. R., Baier, M., Abman, S. H., Inhaled nitric oxide in premature neonates with	**Sample size** See Cochrane systematic review Barrington 2017 **Characteristics** **Inclusion criteria**	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
severe hypoxaemic respiratory failure: a randomised controlled trial, Lancet, 354, 1061-5, 1999 **Ref Id** 433251 **Country/ies where the study was carried out** **Study type** **Aim of the study** **Study dates** **Source of funding**	**Exclusion criteria**				
Full citation Mercier, J. C., Early compared with delayed inhaled nitric oxide in moderately hypoxaemic neonates with respiratory failure: A randomised	**Sample size** See Cochrane systematic review Barrington 2017 **Characteristics**	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
controlled trial, Lancet, 354, 1066-1071, 1999 **Ref Id** 667328 **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 Mercier, J. C., Hummler, H., Durrmeyer, X., Sanchez-Luna, M., Carnielli, V., Field, D., Greenough, A., Van Overmeire, B., Jonsson, B., Hallman, M., Baldassarre, J., Euno Study Group, Inhaled	**Sample size** See Cochrane systematic review Barrington 2017 **Characteristics** **Inclusion criteria**	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
nitric oxide for prevention of bronchopulmonary dysplasia in premature babies (EUNO): a randomised controlled trial, Lancet, 376, 346-54, 2010 **Ref Id** 411157 **Country/ies where the study was carried out** **Study type** **Aim of the study** **Study dates** **Source of funding**	**Exclusion criteria**				
Full citation Mestan,K.K., Marks,J.D., Hecox,K., Huo,D., Schreiber,M.D., Neurodevelopmental	**Sample size** See Schreiber 2003 for study details	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
outcomes of premature infants treated with inhaled nitric oxide, New England Journal of Medicine, 353, 23-32, 2005 **Ref Id** 253292 **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 Patrianakos-Hoobler, A. I., Marks, J. D., Msall, M. E., Huo, D., Schreiber, M. D., Safety and efficacy of inhaled nitric	**Sample size** See Schreiber 2003 for study details **Characteristics**	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
oxide treatment for premature infants with respiratory distress syndrome: Follow-up evaluation at early school age, Acta Paediatrica, International Journal of Paediatrics, 100, 524-528, 2011 **Ref Id** 411385 **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 Schreiber, M. D., Gin-Mestan, K., Marks, J. D.,	**Sample size** See Cochrane systematic review Barrington 2017	**Interventions**	**Details**	**Results**	**Limitations**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Huo, D., Lee, G., Srisuparp, P., Inhaled Nitric Oxide in Premature Infants with the Respiratory Distress Syndrome, New England Journal of Medicine, 349, 2099-2107, 2003 **Ref Id** 411705 **Country/ies where the study was carried out** **Study type** **Aim of the study** **Study dates** **Source of funding**	**Characteristics** **Inclusion criteria** **Exclusion criteria**				**Other information**
Full citation Srisuparp, P., Heitschmidt, M., Schreiber, M. D., Inhaled	**Sample size** See Cochrane systematic review Barrington 2017	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
nitric oxide therapy in premature infants with mild to moderate respiratory distress syndrome, Journal of the Medical Association of Thailand, 85 Suppl 2, S469-78, 2002 **Ref Id** 668111 **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	**Sample size** Please see Barrington 2017 Cochrane systematic review	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
controlled trial of inhaled nitric oxide and early dexamethasone in high risk preterm infants, Archives of Disease in 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**	**Characteristics** **Inclusion criteria** **Exclusion criteria**				
Full citation Subhedar, N. V., Shaw, N. J., Changes in oxygenation and	**Sample size** See Subhedar 1997a for study details	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
pulmonary haemodynamics in preterm infants treated with inhaled nitric oxide, Archives of Disease in Childhood Fetal & Neonatal EditionArch Dis Child Fetal Neonatal Ed, 77, F191-7, 1997 **Ref Id** 758881 **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 Van Meurs, K. P., Hintz, S. R., Ehrenkranz, R. A.,	**Sample size** See Cochrane systematic review Barrington 2017	**Interventions**	**Details**	**Results**	**Limitations**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Lemons, J. A., Ball, M. B., Poole, W. K., Perritt, R., Das, A., Higgins, R. D., Stevenson, D. K., Inhaled nitric oxide in infants >1500 g and <34 weeks gestation with severe respiratory failure, Journal of Perinatology, 27, 347-352, 2007 **Ref Id** 654432 **Country/ies where the study was carried out** **Study type** **Aim of the study** **Study dates** **Source of funding**	**Characteristics** **Inclusion criteria** **Exclusion criteria**				**Other information**
Full citation	**Sample size**	**Interventions**	**Details**	**Results**	**Limitations**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Van Meurs, K. P., Wright, L. L., Ehrenkranz, R. A., Lemons, J. A., Ball, M. B., Poole, W. K., Perritt, R., Higgins, R. D., Oh, W., Hudak, M. L., Laptook, A. R., Shankaran, S., Finer, N. N., Carlo, W. A., Kennedy, K. A., Fridriksson, J. H., Steinhorn, R. H., Sokol, G. M., Konduri, G. G., Aschner, J. L., Stoll, B. J., D'Angio, C. T., Stevenson, D. K., Preemie Inhaled Nitric Oxide, Study, Inhaled nitric oxide for premature infants with severe respiratory failure, The New England journal of medicine, 353, 13-22, 2005 **Ref Id** 510569 **Country/ies where the study was carried out** **Study type**	See Cochrane systematic review Barrington 2017 **Characteristics** **Inclusion criteria** **Exclusion criteria**				**Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study **Study dates** **Source of funding**					
Full citation Walsh, M. C., Hibbs, A. M., Martin, C. R., Cnaan, A., Keller, R. L., Vittinghoff, E., Martin, R. J., Truog, W. E., Ballard, P. L., Zadell, A., Wadlinger, S. R., Coburn, C. E., Ballard, R. A., No Cld Study Group, Two-year neurodevelopmental outcomes of ventilated preterm infants treated with inhaled nitric oxide, Journal of Pediatrics, 156, 556-61.e1, 2010 **Ref Id** 339681	**Sample size** See Ballard 2006 for study details **Characteristics** **Inclusion criteria** **Exclusion criteria**	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

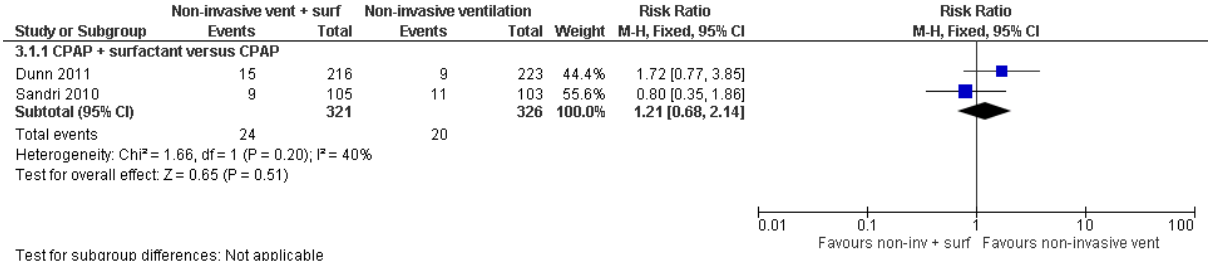
Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out **Study type** **Aim of the study** **Study dates** **Source of funding**					
Full citation Field, D., Elbourne, D., Truesdale, A., Grieve, R., Hardy, P., Fenton, A. C., Subhedar, N., Ahluwalia, J., Halliday, H. L., Stocks, J., Tomlin, K., Normand, C., Innovo Trial Collaborating Group, Neonatal Ventilation With Inhaled Nitric Oxide Versus Ventilatory Support Without Inhaled Nitric Oxide for Preterm Infants With Severe Respiratory	**Sample size** See Cochrane systematic review Barrington 2017 **Characteristics** **Inclusion criteria** **Exclusion criteria**	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Failure: the INNOVO multicentre randomised controlled trial (ISRCTN 17821339), Pediatrics, 115, 926-36, 2005 **Ref Id** 413812 **Country/ies where the study was carried out** **Study type** **Aim of the study** **Study dates** **Source of funding**					

Appendix E – Forest plots

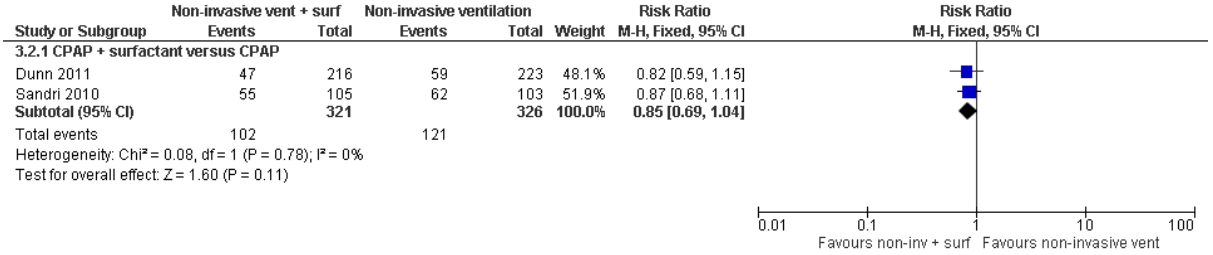
Forest plots for question 1.1 What respiratory support (excluding resuscitation) is the most effective for preterm babies before admission to the neonatal unit

Figure 13: Comparison 4.1 Non-invasive ventilation with surfactant versus non-invasive ventilation – Mortality prior to discharge



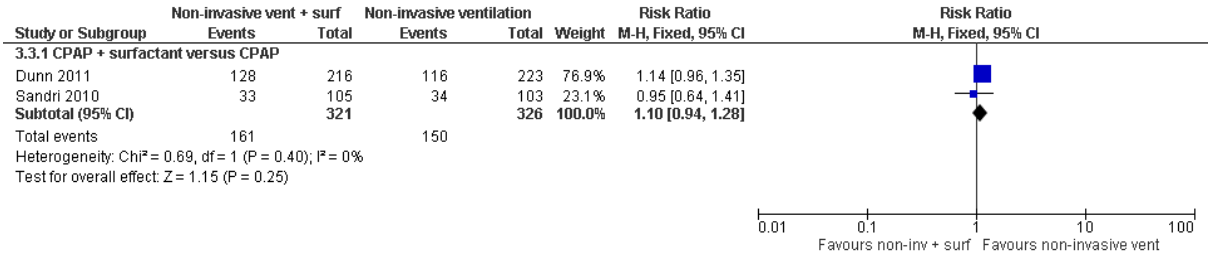
CI: confidence interval; CPAP: continuous positive airways pressure; M-H: Mantel-Haenszel; non-inv: non-invasive; Surf: surfactant; Vent: ventilation

Figure 14: Comparison 4.1 Non-invasive ventilation with surfactant versus non-invasive ventilation – Bronchopulmonary dysplasia at 36 weeks PMA



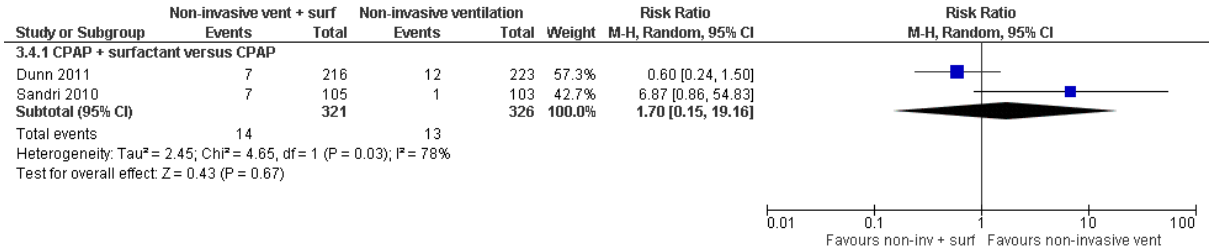
CI: confidence interval; CPAP: continuous positive airways pressure; M-H: Mantel-Haenszel; non-inv: non-invasive; Surf: surfactant; Vent: ventilation

Figure 15: Comparison 4.1 Non-invasive ventilation with surfactant versus non-invasive ventilation – Failed non-invasive ventilation



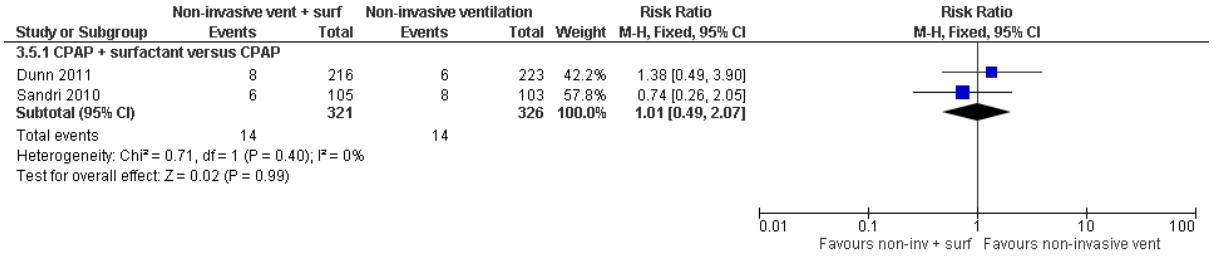
CI: confidence interval; CPAP: continuous positive airways pressure; M-H: Mantel-Haenszel; non-inv: non-invasive; Surf: surfactant; Vent: ventilation

Figure 16: Comparison 4.1 Non-invasive ventilation with surfactant versus non-invasive ventilation – Pneumothorax



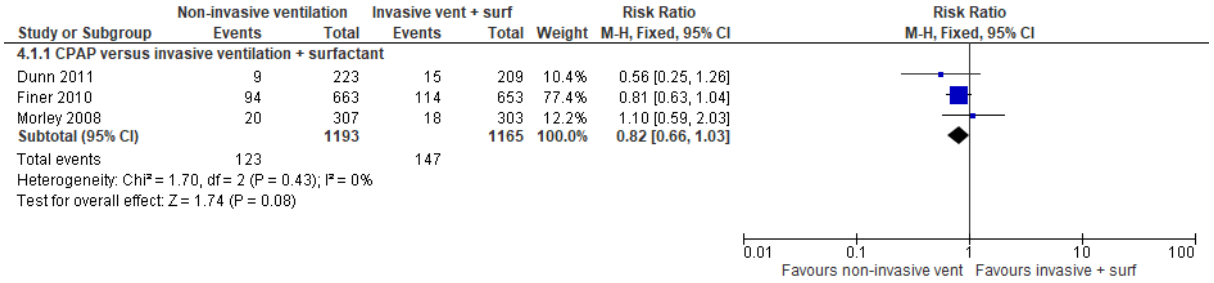
CI: confidence interval; CPAP: continuous positive airways pressure; M-H: Mantel-Haenszel; non-inv: non-invasive; Surf: surfactant; Vent: ventilation

Figure 17: Comparison 4.1 Non-invasive ventilation with surfactant versus non-invasive ventilation – Severe IVH (grade 3 or 4)



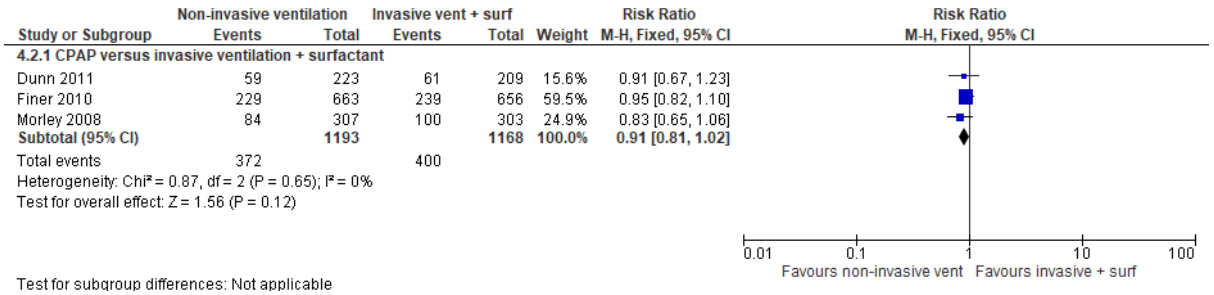
CI: confidence interval; CPAP: continuous positive airways pressure; M-H: Mantel-Haenszel; non-inv: non-invasive; Surf: surfactant; Vent: ventilation

Figure 18: Comparison 5.1 Non-invasive ventilation versus invasive ventilation with surfactant – Mortality prior to discharge



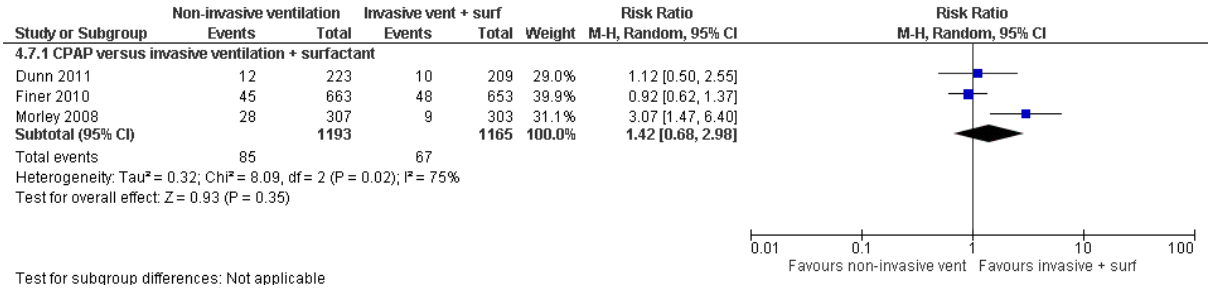
CI: confidence interval; CPAP: continuous positive airways pressure; M-H: Mantel-Haenszel; Surf: surfactant; Vent: ventilation

Figure 19: Comparison 5.1 Non-invasive ventilation versus invasive ventilation with surfactant – Bronchopulmonary dysplasia at 36 weeks PMA



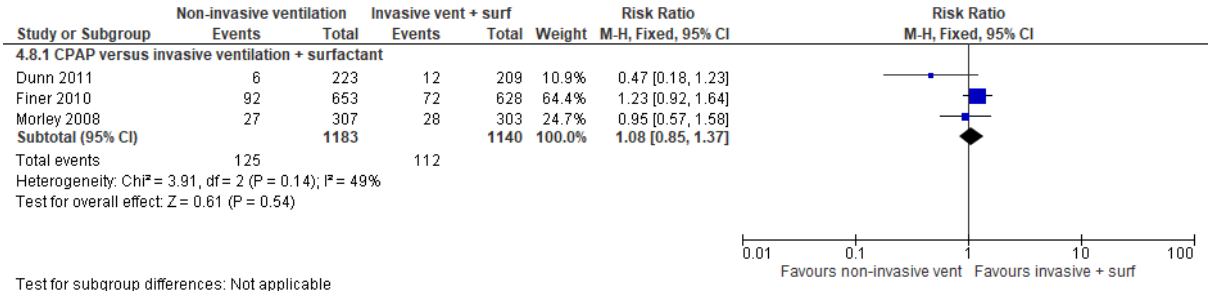
CI: confidence interval; CPAP: continuous positive airways pressure; M-H: Mantel-Haenszel; Surf: surfactant; Vent: ventilation

Figure 20: Comparison 5.1 Non-invasive ventilation versus invasive ventilation with surfactant – Pneumothorax



CI: confidence interval; CPAP: continuous positive airways pressure; M-H: Mantel-Haenszel; Surf: surfactant; Vent: ventilation

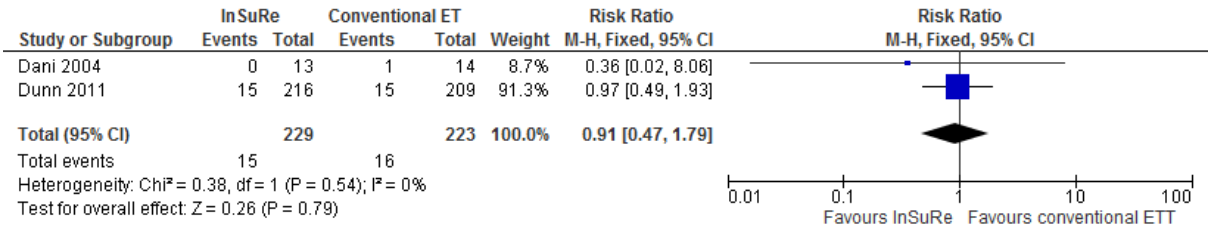
Figure 21: Comparison 5.1 Non-invasive ventilation versus invasive ventilation with surfactant – Severe IVH (grade 3 or 4)



CI: confidence interval; CPAP: continuous positive airways pressure; M-H: Mantel-Haenszel; Surf: surfactant; Vent: ventilation

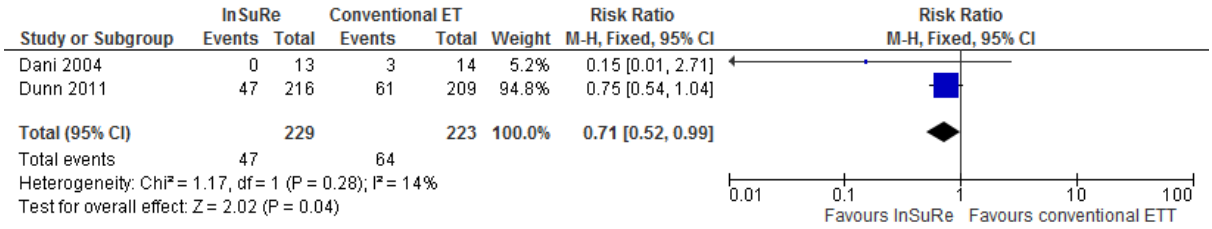
Forest plots for question 3.3 What is the most effective way of using surfactant in managing respiratory distress syndrome?

Figure 22: Comparison 1. Early extubation following administration of surfactant versus conventional endotracheal administration of surfactant – mortality prior to discharge



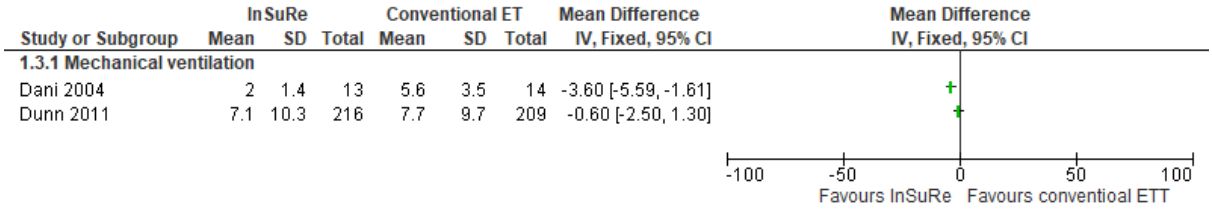
ETT: endotracheal tube; InSuRE: intubate, surfactant, extubate.

Figure 23: Comparison 1. Early extubation following administration of surfactant versus conventional endotracheal administration of surfactant – bronchopulmonary dysplasia at 36 weeks PMA



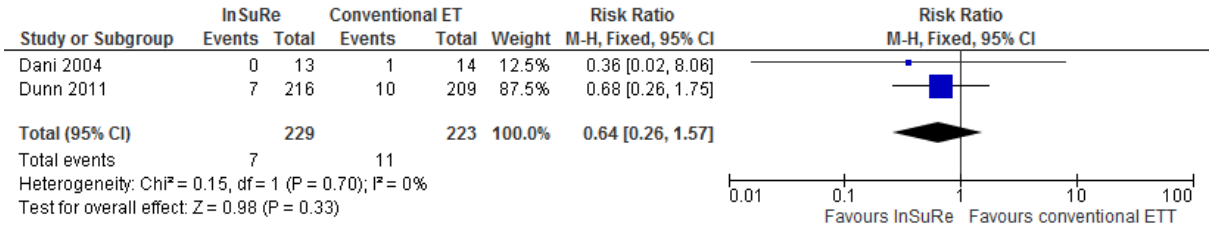
ETT: endotracheal tube; InSuRE: intubate, surfactant, extubate.

Figure 24: Comparison 1. Early extubation following administration of surfactant versus conventional endotracheal administration of surfactant – days on ventilation



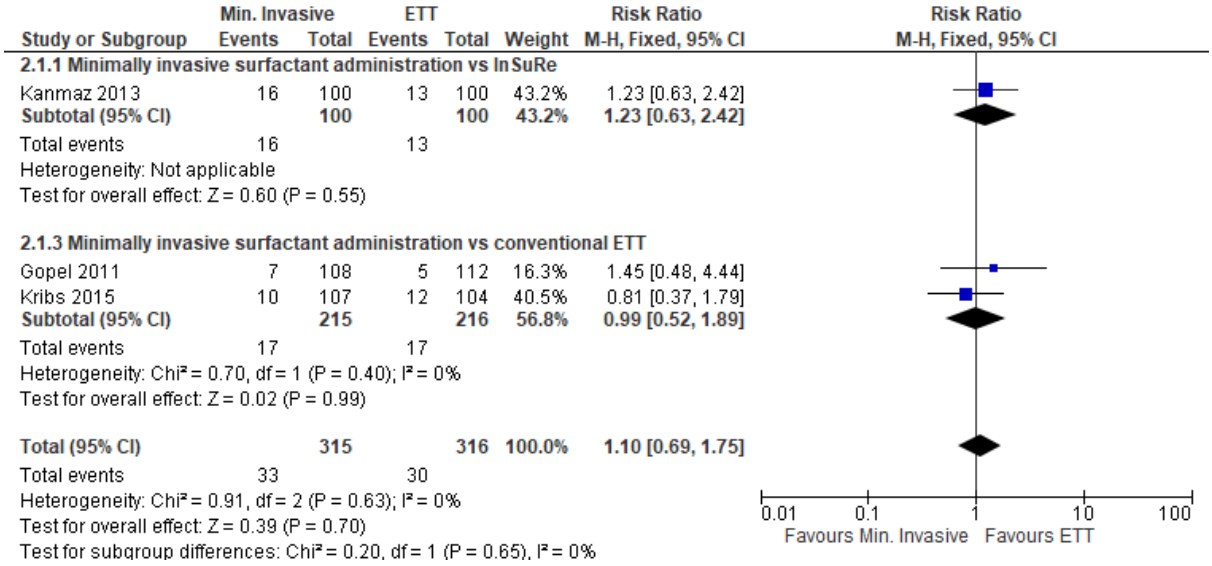
ETT: endotracheal tube; InSuRE: intubate, surfactant, extubate.

Figure 25: Comparison 1. Early extubation following administration of surfactant versus conventional endotracheal administration of surfactant – pneumothorax



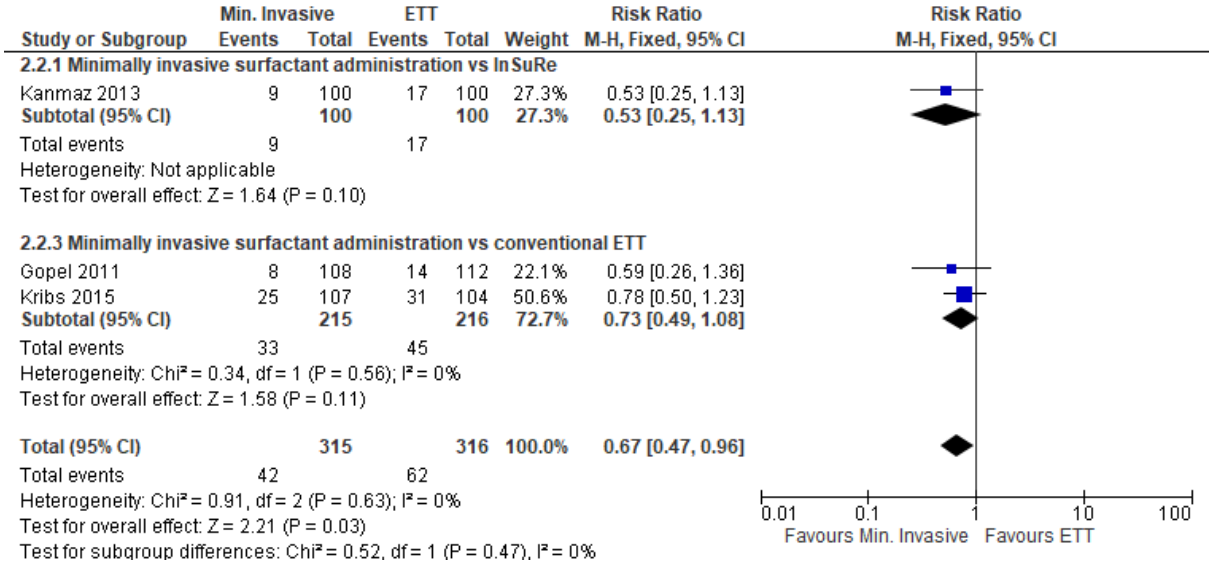
ETT: endotracheal tube; InSuRE: intubate, surfactant, extubate.

Figure 26: Comparison 2. Minimally invasive surfactant administration techniques versus endotracheal administration of surfactant – mortality prior to discharge



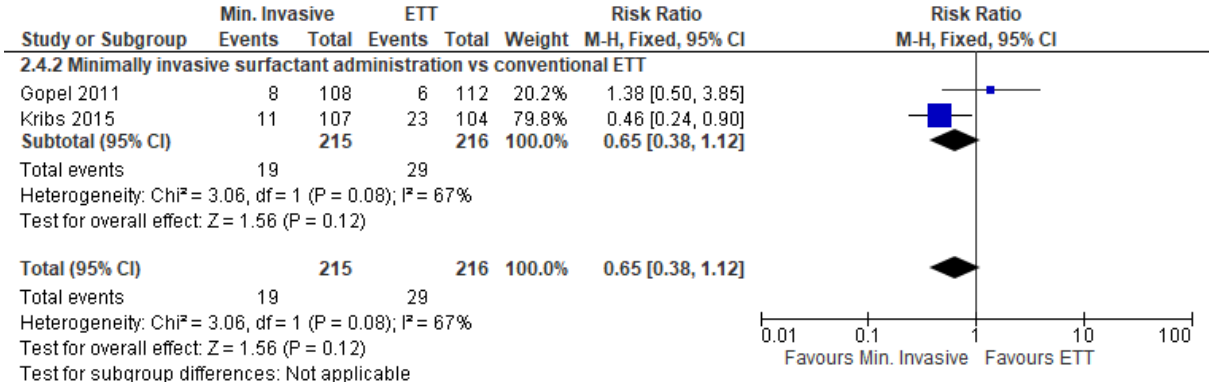
ETT: endotracheal tube; InSuRE: intubate, surfactant, extubate; Min. invasive: minimally invasive

Figure 27: Comparison 2. Minimally invasive surfactant administration techniques versus endotracheal administration of surfactant – bronchopulmonary dysplasia at 36 weeks PMA



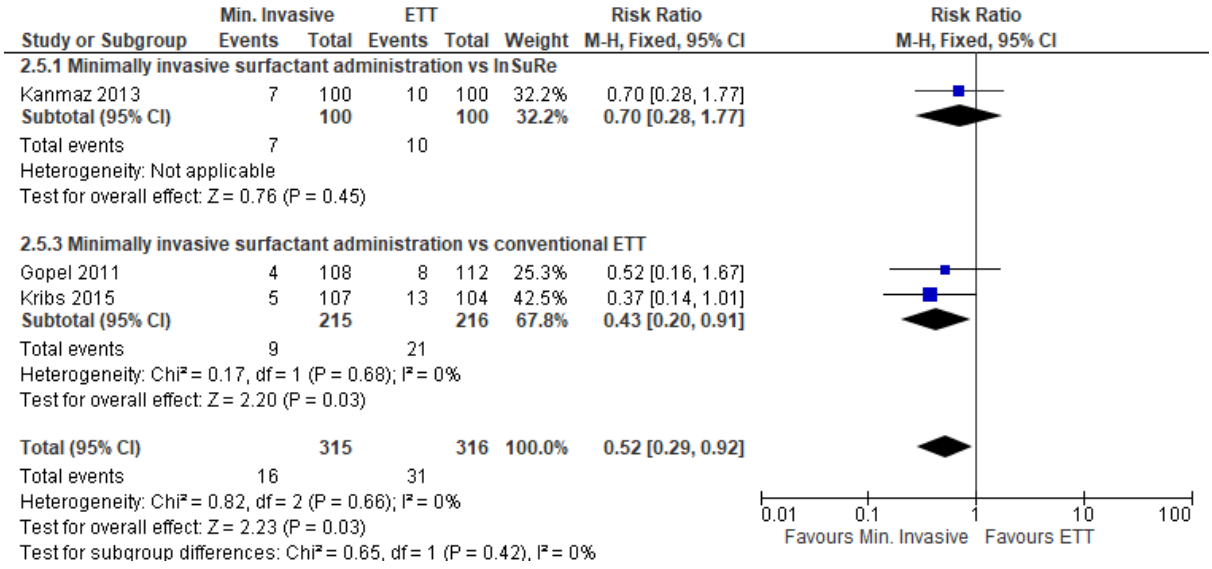
ETT: endotracheal tube; InSuRE: intubate, surfactant, extubate; Min. invasive: minimally invasive

Figure 28: Comparison 2. Minimally invasive surfactant administration techniques versus endotracheal administration of surfactant – severe intraventricular haemorrhage (grade 3 or 4)



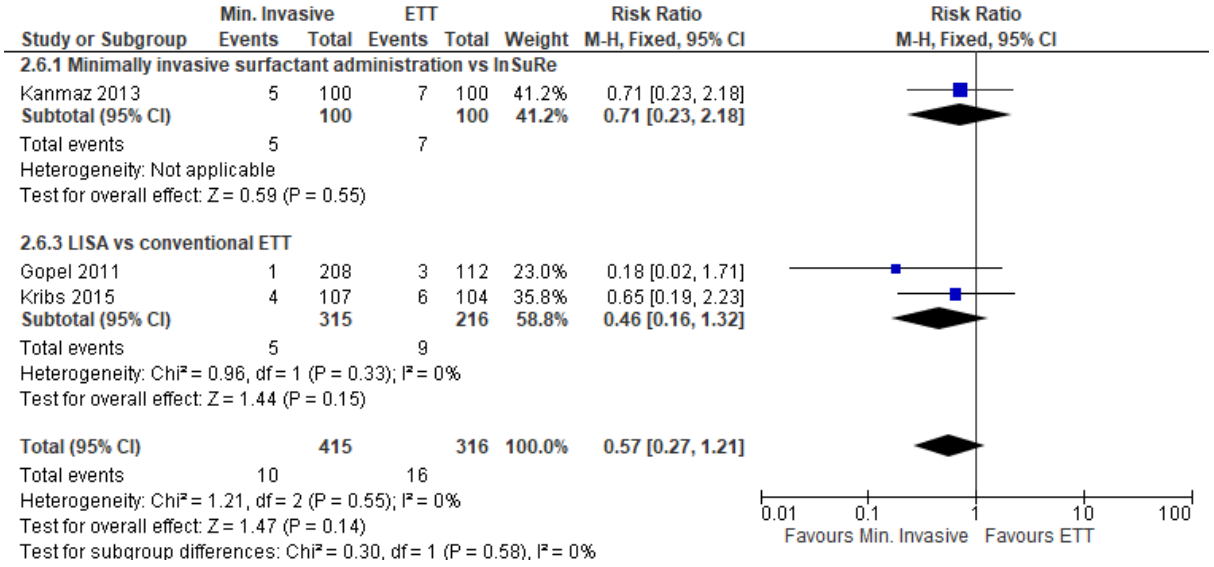
ETT: endotracheal tube; InSuRE: intubate, surfactant, extubate; Min. invasive: minimally invasive

Figure 29: Comparison 2. Minimally invasive surfactant administration techniques versus endotracheal administration of surfactant – pneumothorax



ETT: endotracheal tube; InSuRE: intubate, surfactant, extubate; Min. invasive: minimally invasive

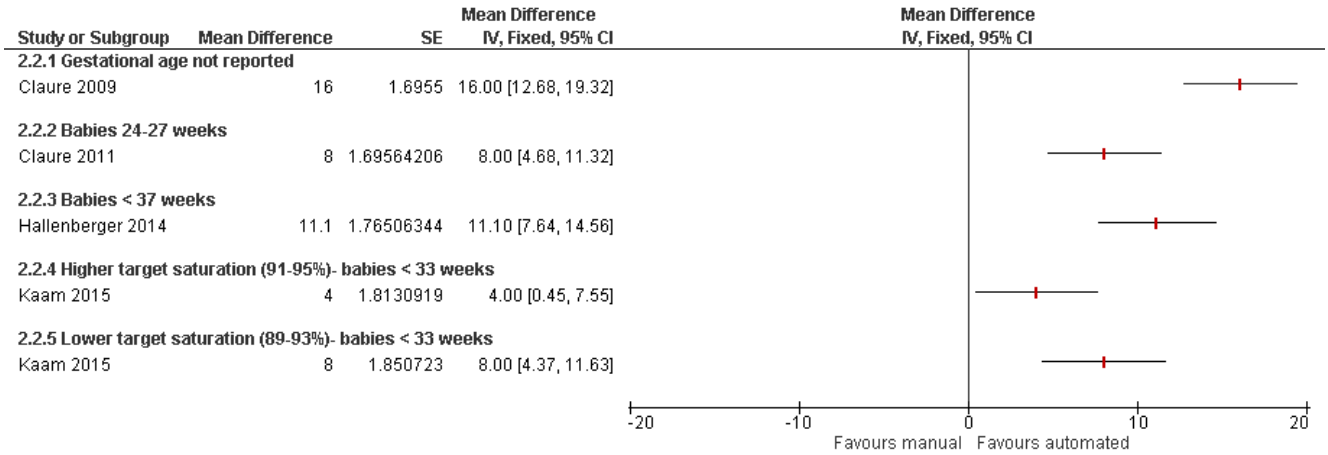
Figure 30: Comparison 2. Minimally invasive surfactant administration techniques versus endotracheal administration of surfactant – pulmonary haemorrhage



ETT: endotracheal tube; InSuRE: intubate, surfactant, extubate; Min. invasive: minimally invasive

Forest plots for question 3.1 What is the most effective way to administer oxygen during respiratory support?

Figure 31: Comparison 3: Automated versus manual titration – Proportion (percent) of time spent within optimal target limits

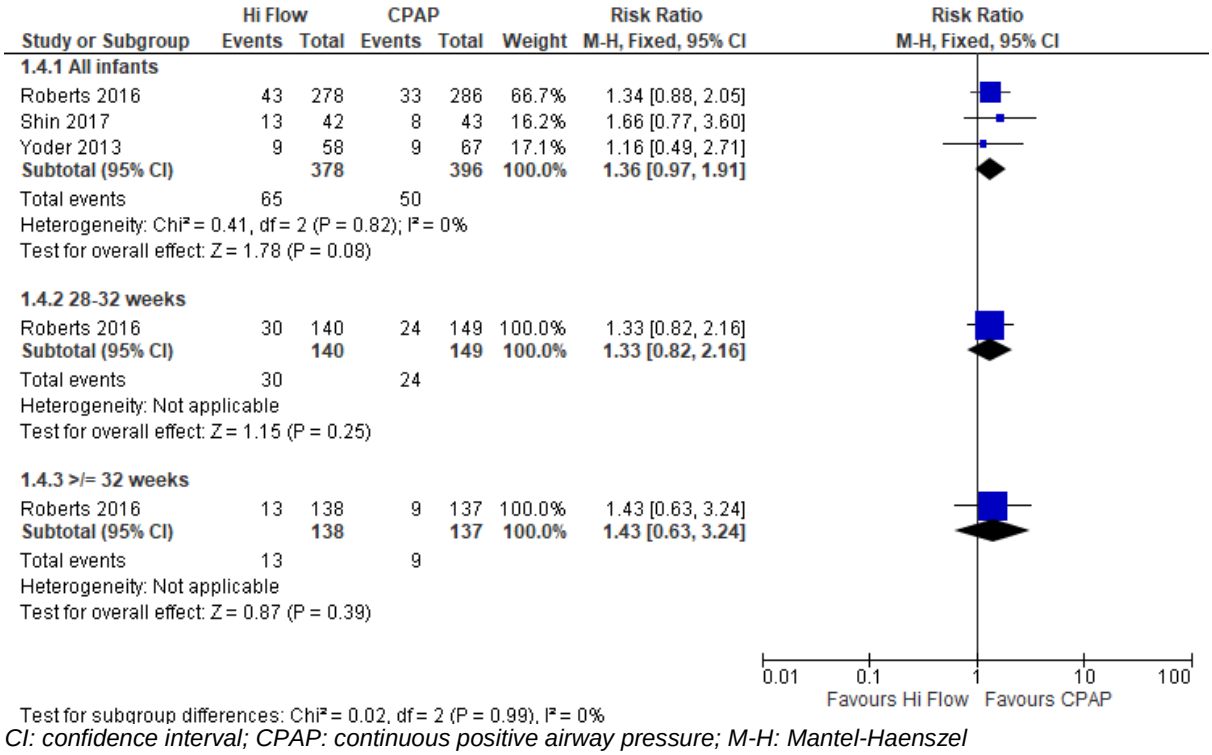


CI: confidence interval; IV: inverse variance; SE: standard error

Forest plots for question 3.2 What is the effectiveness and safety of the different assisted ventilation techniques in preterm babies?

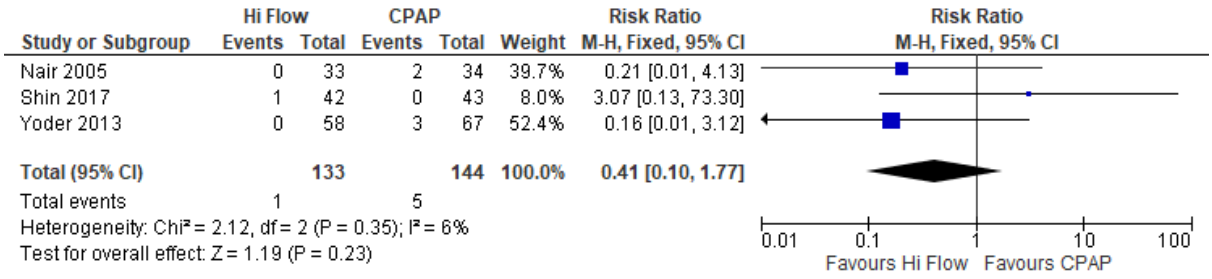
Non-invasive ventilation

Figure 32: Comparison 1. Hi Flow versus CPAP – Failed non-invasive ventilation



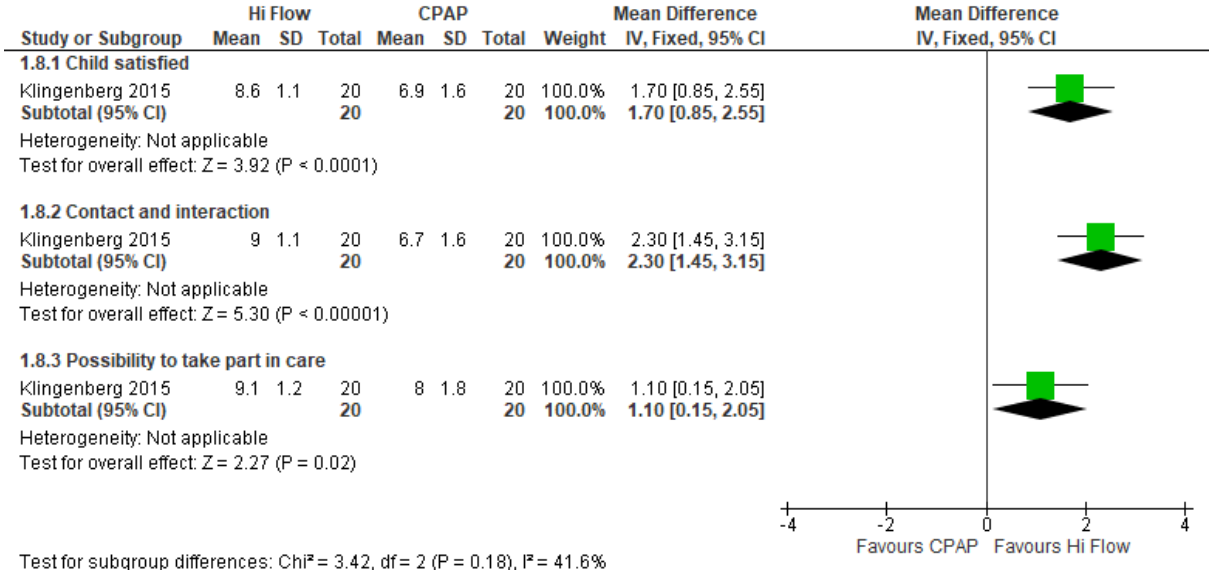
CI: confidence interval; CPAP: continuous positive airway pressure; M-H: Mantel-Haenszel

Figure 33: Comparison 1. Hi Flow versus CPAP – Pneumothorax



CI: confidence interval; CPAP: continuous positive airway pressure; M-H: Mantel-Haenszel

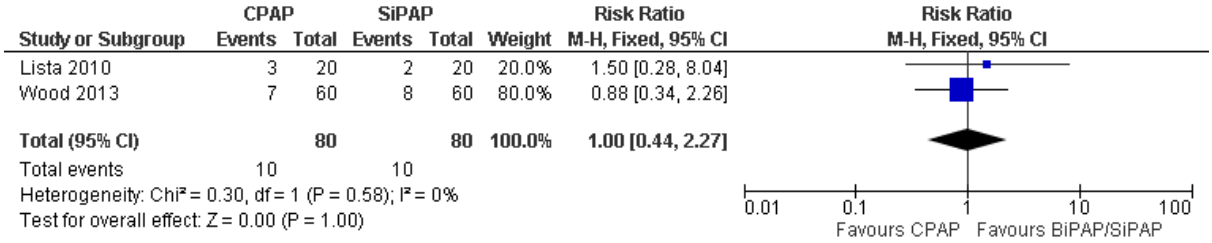
Figure 34: Comparison 1. Hi Flow versus CPAP – Parent satisfaction, response on a visual analogue scale 1-10**



**Klingenberg 2015 was a cross-over study, where 20 babies received 24hrs of one intervention followed by 24 hours of another intervention*
*** After each 24hr study period, parents were asked to respond to 3 questions regarding how satisfied they thought their baby was, how they assessed their contact and interaction with their baby and how they assessed their possibility to take part in nursing and care for their child on a visual analogue scale from 1-10. Better was indicated by higher scores*

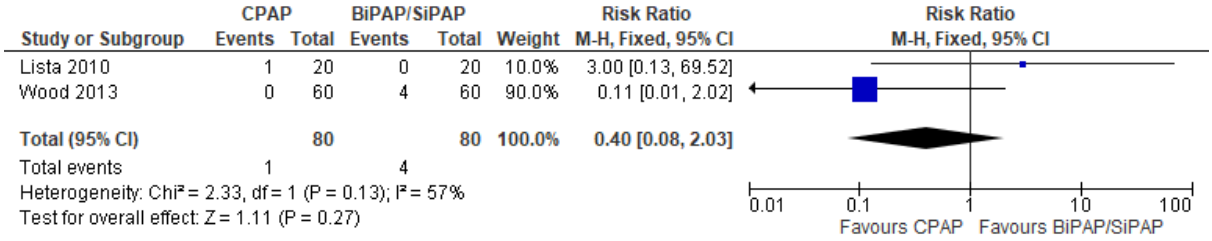
CI: confidence interval; CPAP: continuous positive airway pressure; M-H: Mantel-Haenszel

Figure 35: Comparison 2. CPAP versus BiPAP/SiPAP – Failed non-invasive ventilation



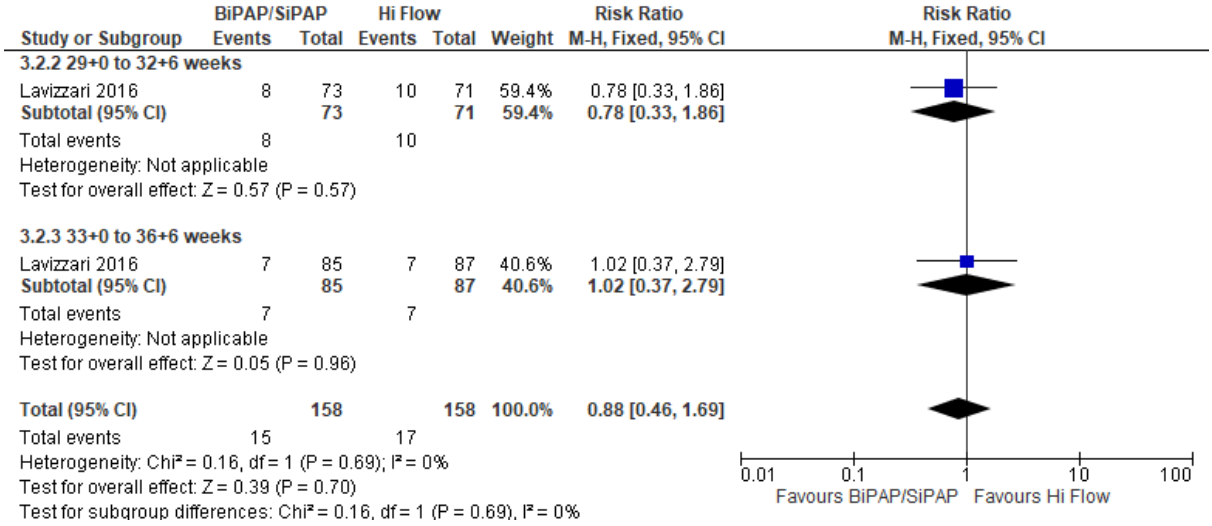
BiPAP: binasal positive airway pressure; CI: confidence interval; CPAP: continuous positive airway pressure; M-H: Mantel-Haenszel; SiPAP: synchronised positive airway pressure

Figure 36: Comparison 2. CPAP versus BiPAP/SiPAP – Pneumothorax



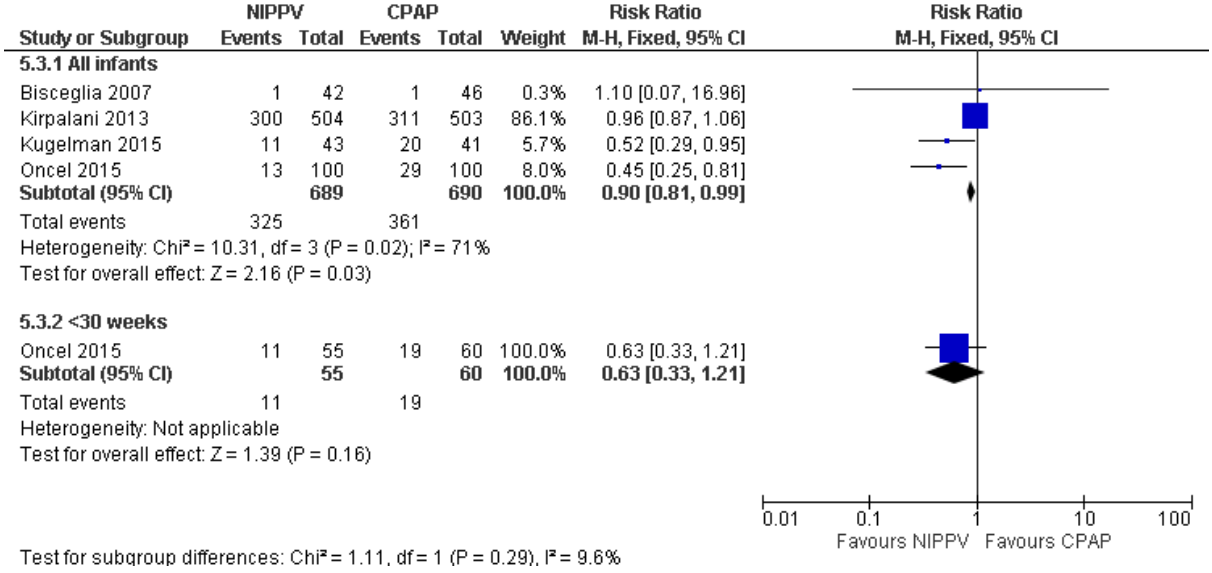
BiPAP: binasal positive airway pressure; CI: confidence interval; CPAP: continuous positive airway pressure; M-H: Mantel-Haenszel; SiPAP: synchronised positive airway pressure

Figure 37: Comparison 3. BiPAP/SiPAP versus Hi Flow – Failed non-invasive ventilation



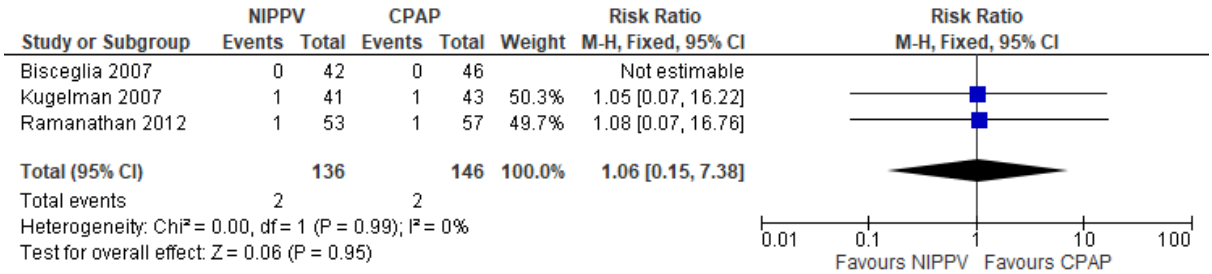
BiPAP: binasal positive airway pressure; CI: confidence interval; M-H: Mantel-Haenszel; SiPAP: synchronised positive airway pressure

Figure 38: Comparison 5. NIPPV versus CPAP – Failed non-invasive ventilation



CI: confidence interval; CPAP: continuous positive airway pressure; M-H: Mantel-Haenszel; NIPPV: nasal intermittent positive airway ventilation

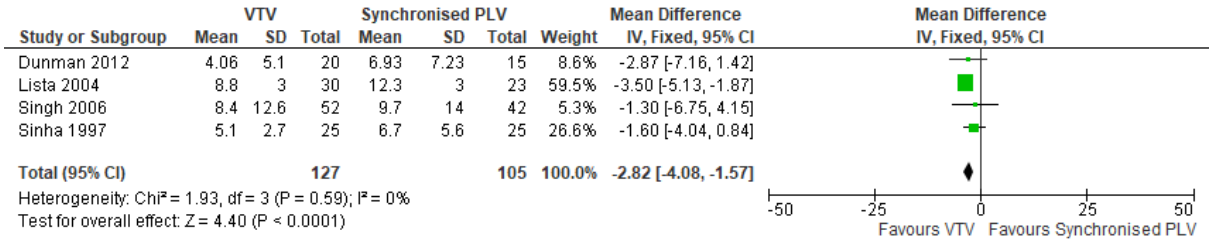
Figure 39: Comparison 5. NIPPV versus CPAP – Pneumothorax



CI: confidence interval; CPAP: continuous positive airway pressure; M-H: Mantel-Haenszel; NIPPV: nasal intermittent positive airway ventilation

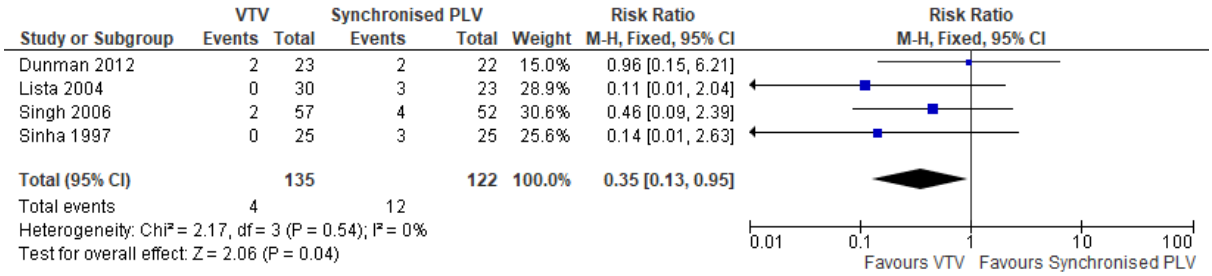
Invasive ventilation

Figure 40: Comparison 1. Volume targeted ventilation versus synchronised pressure limited ventilation – days on invasive ventilation



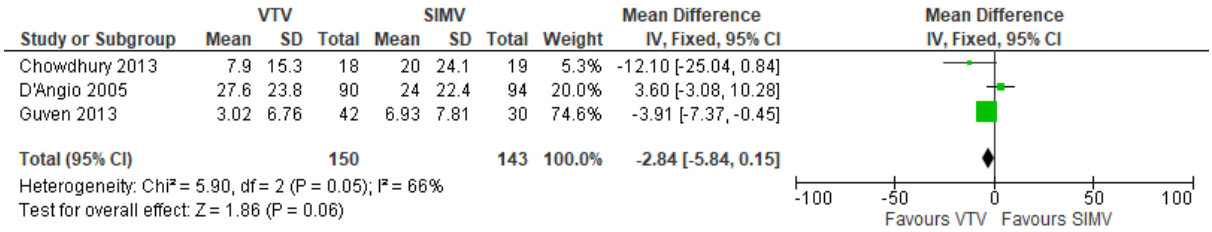
CI: confidence interval; I-V: inverse variance; PLV: pressure limited ventilation; VTV: volume targeted ventilation

Figure 41: Comparison 1. Volume targeted ventilation versus synchronised pressure limited ventilation - pneumothorax



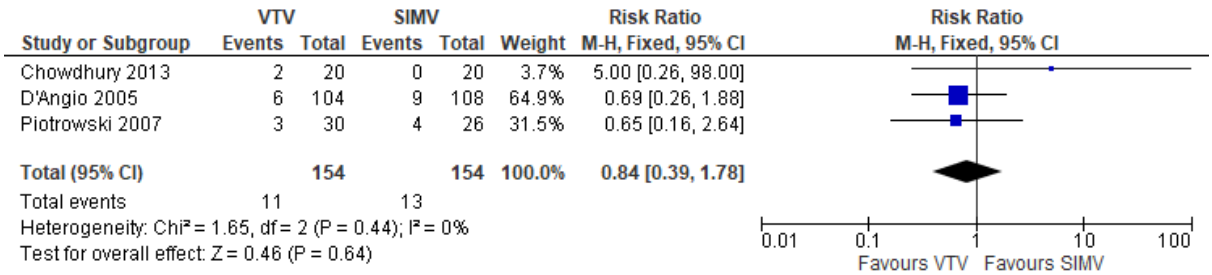
CI: confidence interval; M-H: Mantel-Haenszel; PLV: pressure limited ventilation; VTV: volume targeted ventilation

Figure 42: Comparison 3. Volume targeted ventilation versus synchronised intermittent mandatory ventilation – days on invasive ventilation



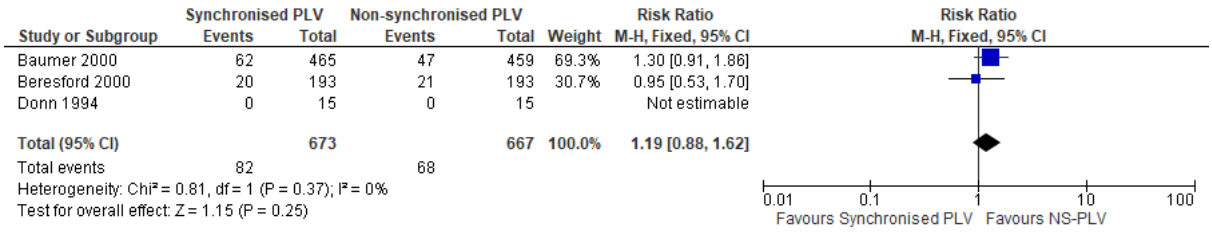
CI: confidence interval; I-V: inverse variance; SIMV: synchronised intermittent mandatory ventilation; VTV: volume targeted ventilation

Figure 43: Comparison 3. Volume targeted ventilation versus synchronised intermittent mandatory ventilation – pneumothorax



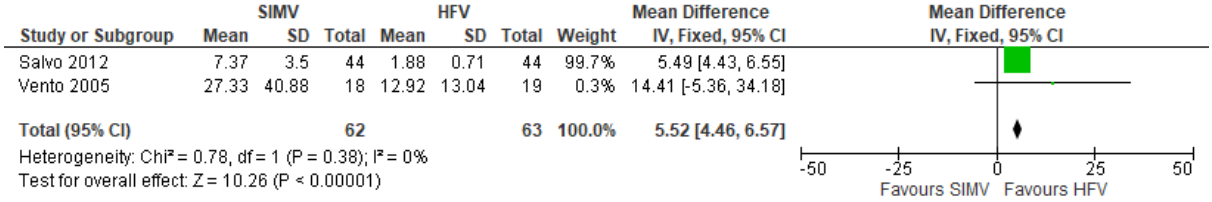
CI: confidence interval; M-H: Mantel-Haenszel; SIMV: synchronised intermittent mandatory ventilation; VTV: volume targeted ventilation

Figure 44: Comparison 5. Synchronised pressure limited ventilation versus non-synchronised pressure limited ventilation – pneumothorax



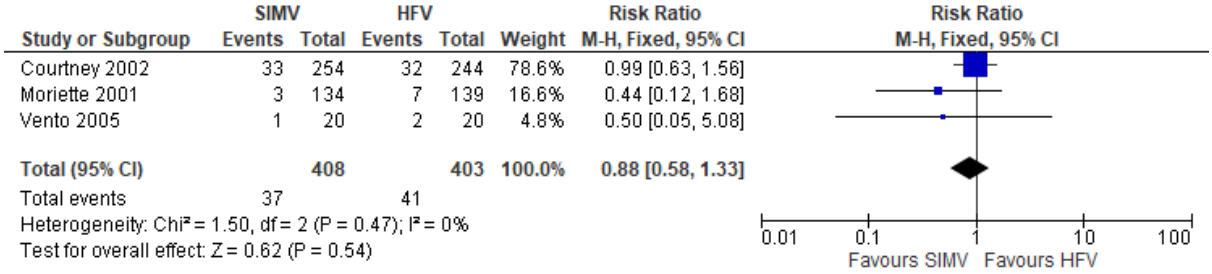
CI: confidence interval; M-H: Mantel-Haenszel; NS-PLV: non-synchronised pressure limited ventilation; PLV: pressure limited ventilation

Figure 45: Comparison 9. Synchronised intermittent mandatory ventilation versus high frequency ventilation – days on ventilation



CI: confidence interval; HFV: high frequency ventilation; I-V: inverse variance; SIMV: synchronised intermittent mandatory ventilation

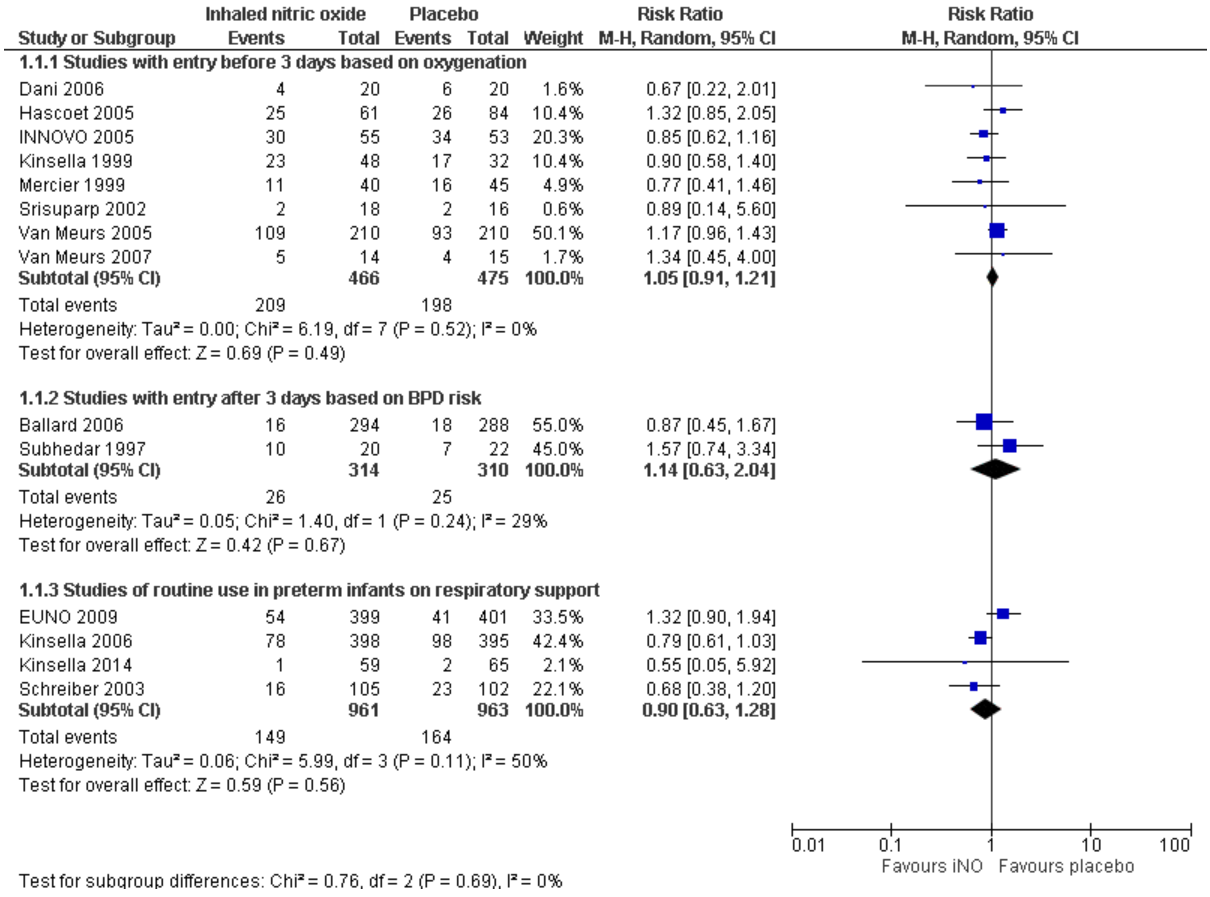
Figure 46: Comparison 9. Synchronised intermittent mandatory ventilation versus high frequency ventilation – pneumothorax



CI: confidence interval; HFV: high frequency ventilation; I-V: inverse variance; SIMV: synchronised intermittent mandatory ventilation.

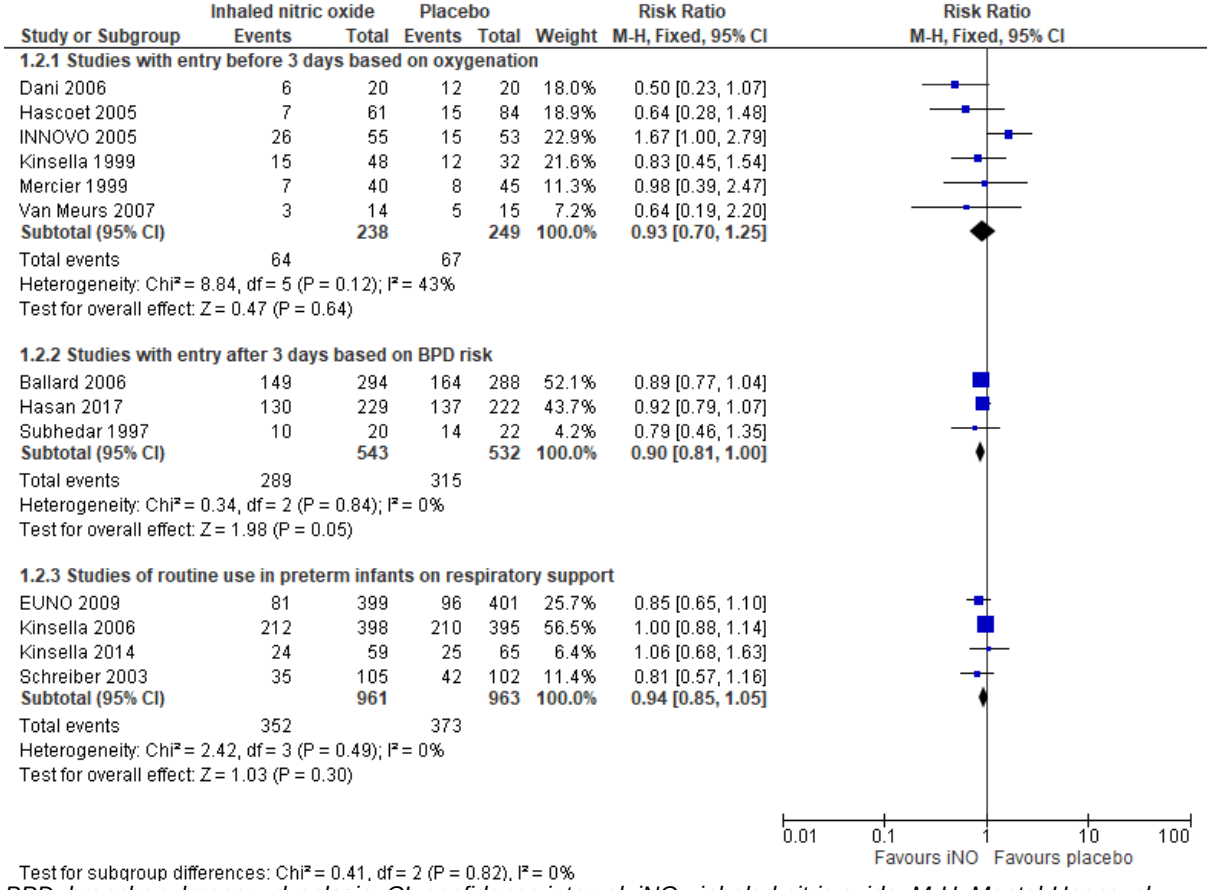
Forest plots for question 3.7 What is the effectiveness of nitric oxide in preterm babies requiring invasive ventilation?

Figure 47: Comparison 1: Nitric oxide versus placebo – Mortality prior to discharge



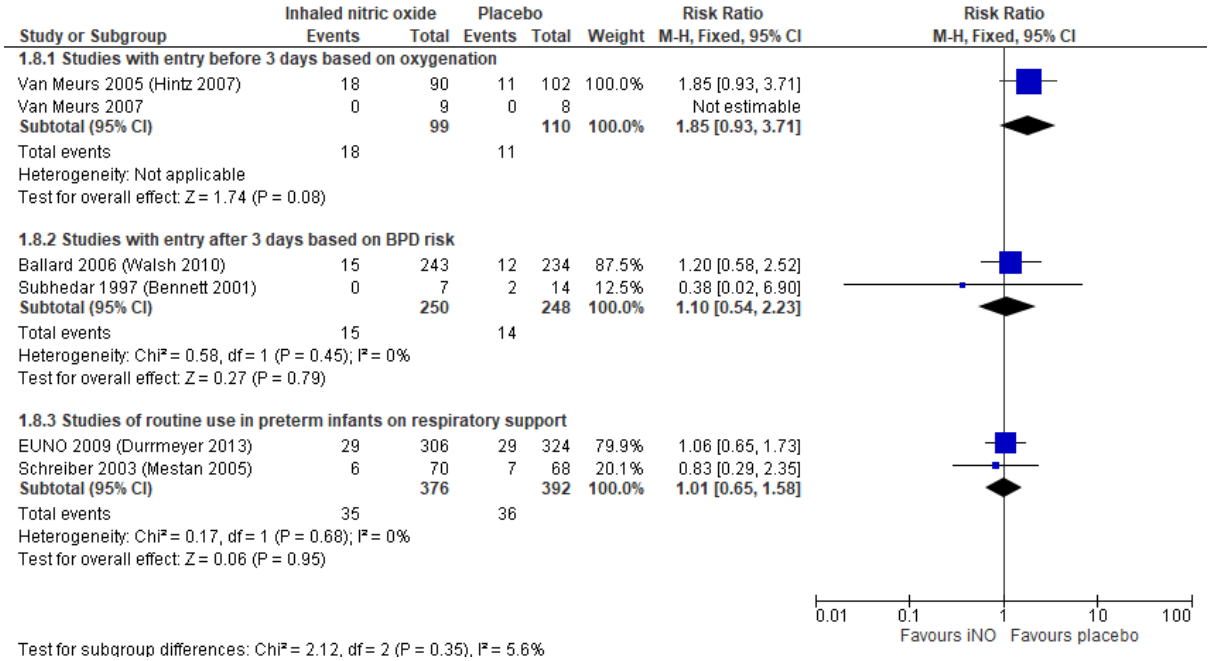
BPD: bronchopulmonary dysplasia; CI: confidence interval; iNO= inhaled nitric oxide; M-H: Mantel-Haenszel

Figure 48: Comparison 1: Nitric oxide versus placebo – BPD at 36 weeks



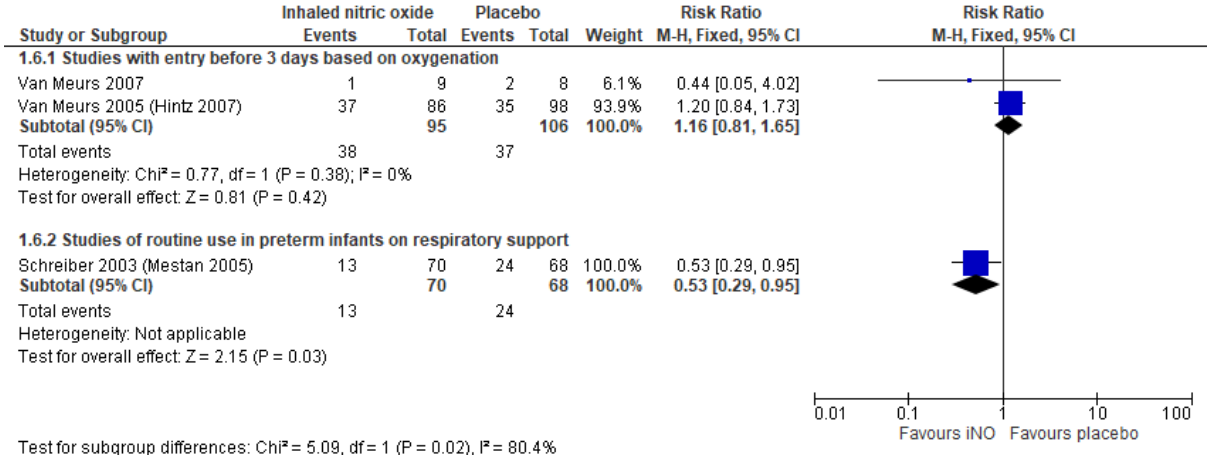
BPD: bronchopulmonary dysplasia; CI: confidence interval; iNO= inhaled nitric oxide; M-H: Mantel-Haenszel

Figure 49: Comparison 1: Nitric oxide versus placebo – Cerebral palsy at ≥ 18 months



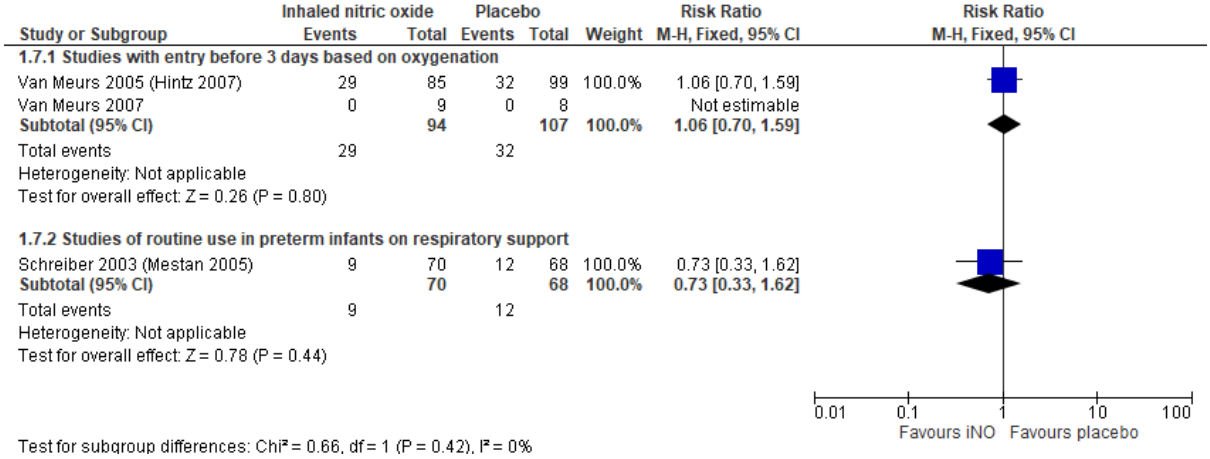
BPD: bronchopulmonary dysplasia; CI: confidence interval; M-H: Mantel-Haenszel

Figure 50: Comparison 1: Nitric oxide versus placebo – Severe cognitive impairment at ≥ 18 months, MDI



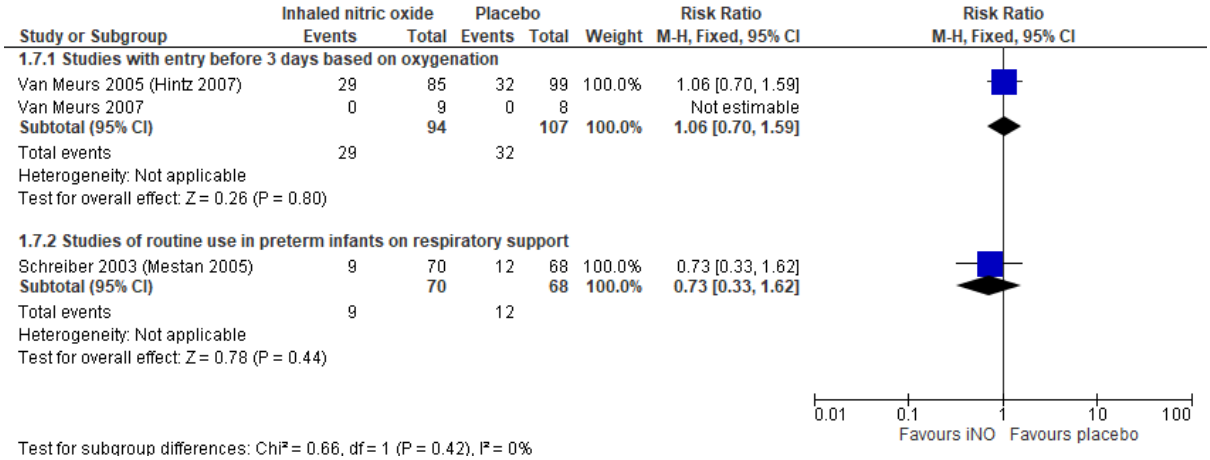
CI: confidence interval; MDI: Mental Developmental Index; iNO= inhaled nitric oxide; M-H: Mantel-Haenszel

Figure 51: Comparison 1: Inhaled nitric oxide versus placebo – Severe psychomotor impairment at ≥ 18 months, PDI



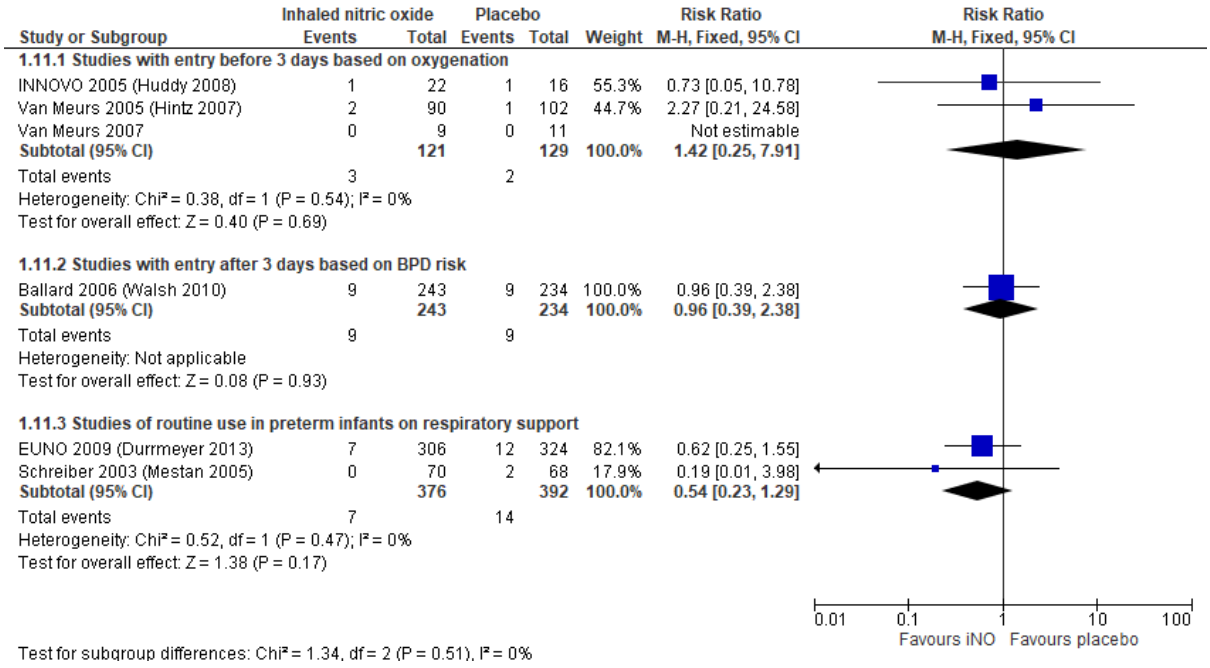
CI: confidence interval; iNO= inhaled nitric oxide; M-H: Mantel-Haenszel; PDI: Psychomotor Developmental Index

Figure 52: Comparison 1: Nitric oxide versus placebo – Severe hearing impairment at ≥ 18 months



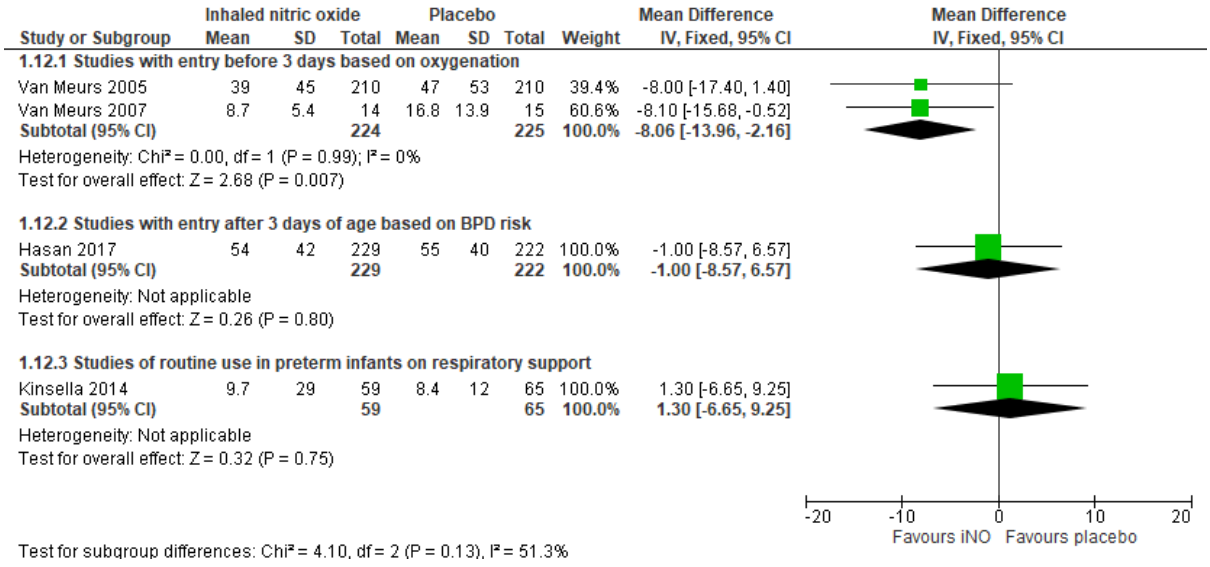
BPD: bronchopulmonary dysplasia; CI: confidence interval; iNO= inhaled nitric oxide; M-H: Mantel-Haenszel

Figure 53: Comparison 1: Nitric oxide versus placebo – Severe visual impairment at ≥ 18 months



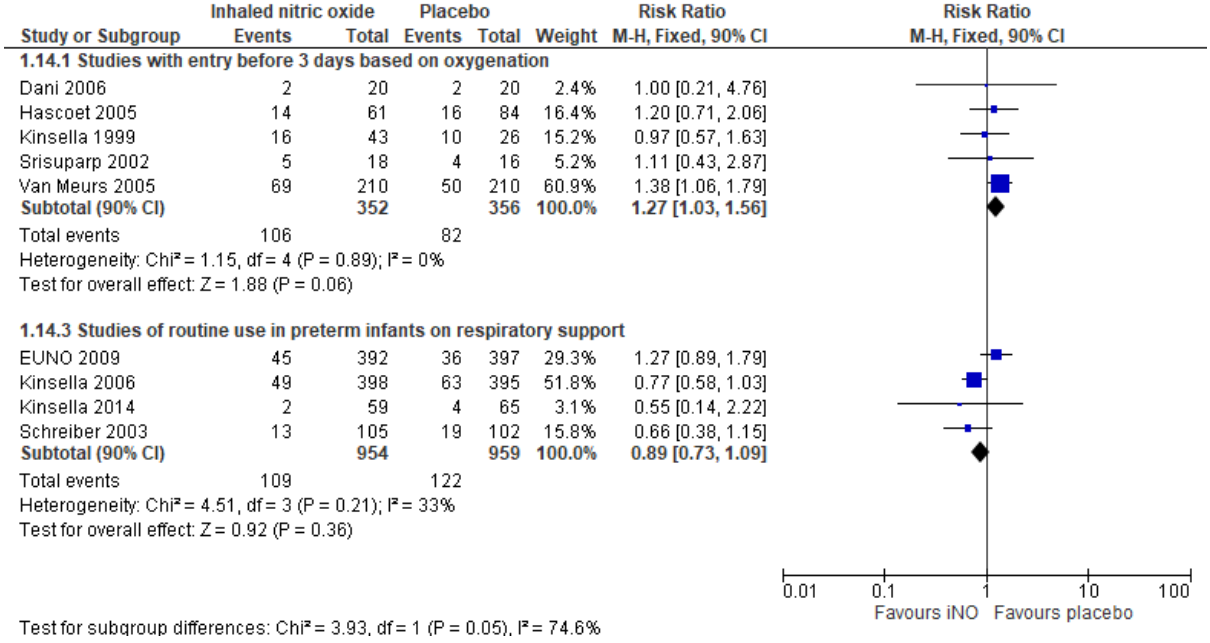
BPD: bronchopulmonary dysplasia; CI: confidence interval; iNO= inhaled nitric oxide; M-H: Mantel-Haenszel

Figure 54: Mean days on ventilation



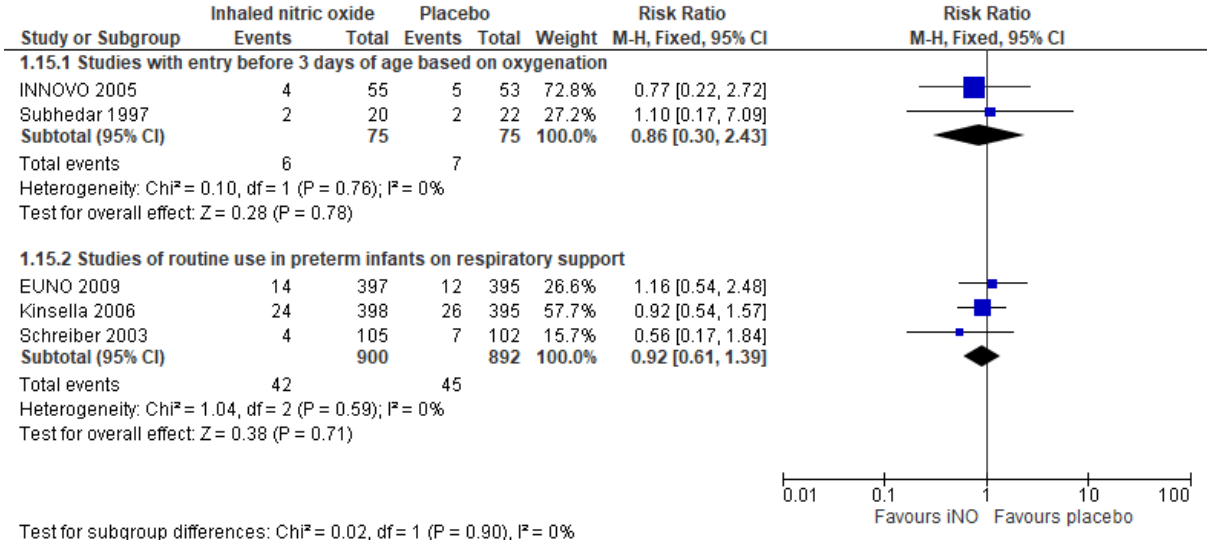
BPD: bronchopulmonary dysplasia; CI: confidence interval; iNO= inhaled nitric oxide; M-H: Mantel-Haenszel

Figure 55: Severe intraventricular haemorrhage



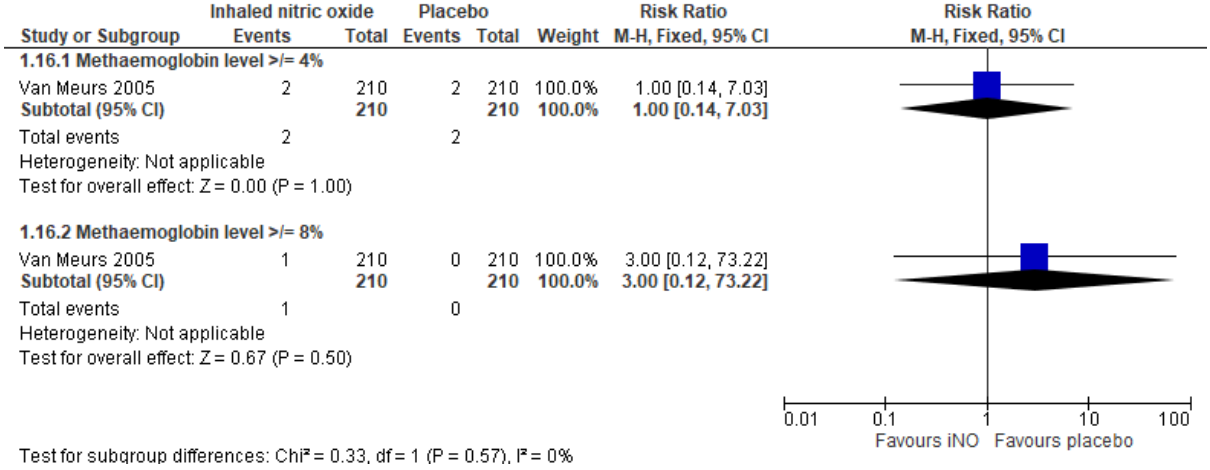
CI: confidence interval; iNO= inhaled nitric oxide; M-H: Mantel-Haenszel

Figure 56: Pulmonary haemorrhage



BPD: bronchopulmonary dysplasia; CI: confidence interval; iNO= inhaled nitric oxide; M-H: Mantel-Haenszel

Figure 57: Methaemoglobinaemia



BPD: bronchopulmonary dysplasia; CI: confidence interval; iNO= inhaled nitric oxide; M-H: Mantel-Haenszel

Appendix F – GRADE tables

GRADE tables for question 1.1 What respiratory support (excluding resuscitation) is the most effective for preterm babies before admission to the neonatal unit

Table 20: Clinical evidence profile: Comparison 1.1 CPAP versus no assisted ventilation

Quality assessment							Number of babies		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CPAP	No assisted ventilation	Relative (95% CI)	Absolute	Quality	Importance
Mortality prior to discharge - CPAP versus no assisted ventilation												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	4/115 (3.5%)	5/115 (4.3%)	RR 0.8 (0.22 to 2.9)	9 fewer per 1000 (from 34 fewer to 83 more)	LOW	CRITICAL
Bronchopulmonary dysplasia at 36 weeks PMA - CPAP versus no assisted ventilation												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	2/115 (1.7%)	1/115 (0.87%)	RR 2 (0.18 to 21.75)	9 more per 1000 (from 7 fewer to 180 more)	LOW	CRITICAL
Failed non-invasive ventilation - CPAP versus no assisted ventilation												
1	randomised trials	no serious risk of bias	no serious inconsistency	not calculable[2]	not calculable[2]	none	14/115	-	-	-	Not assessed[2]	IMPORTANT
Pneumothorax - CPAP versus no assisted ventilation												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	3/115 (2.6%)	3/115 (2.6%)	RR 1 (0.21 to 4.85)	0 fewer per 1000 (from 21 fewer to 100 more)	LOW	IMPORTANT
Severe IVH (grade 3 or 4) - CPAP versus non assisted ventilation												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	3/115 (2.6%)	1/115 (0.87%)	RR 3 (0.32 to 28.42)	17 more per 1000 (from 6 fewer to	LOW	IMPORTANT

Quality assessment							Number of babies		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CPAP	No assisted ventilation	Relative (95% CI)	Absolute		
										238 more)		

CI: confidence interval; CPAP: continuous positive airway pressure; IVH: intraventricular haemorrhage; RR: risk ratio
[1] The quality of evidence was downgraded by 2 as the 95% CI crosses 2 MIDs
[2] Not calculable because data were only available from one treatment arm

Table 21: Clinical evidence profile: Comparison 3.1 CPAP versus invasive ventilation (both ventilation techniques received surfactant)

Quality assessment							Number of babies		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CPAP	No assisted ventilation	Relative (95% CI)	Absolute		
Mortality prior to discharge - CPAP versus invasive ventilation												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	15/216 (6.9%)	15/209 (7.2%)	RR 0.97 (0.49 to 1.93)	2 fewer per 1000 (from 37 fewer to 67 more)	VERY LOW	CRITICAL
Bronchopulmonary dysplasia at 36 weeks PMA - CPAP versus invasive ventilation												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	47/216 (21.8%)	61/209 (29.2%)	RR 0.75 (0.54 to 1.04)	73 fewer per 1000 (from 134 fewer to 12 more)	LOW	CRITICAL
Failed non-invasive ventilation - CPAP versus invasive ventilation												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	not calculable[4]	none	128/216	-	-	-	Not assessed	IMPORTANT
Pneumothorax - CPAP versus invasive ventilation												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	7/216 (3.2%)	10/209 (4.8%)	RR 0.68 (0.26 to 1.75)	15 fewer per 1000 (from 35 fewer to 36 more)	VERY LOW	IMPORTANT
Severe IVH (grade 3 or 4) - CPAP versus invasive ventilation												

Quality assessment							Number of babies		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CPAP	No assisted ventilation	Relative (95% CI)	Absolute		
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	8/216 (3.7%)	12/209 (5.7%)	RR 0.65 (0.27 to 1.55)	20 fewer per 1000 (from 42 fewer to 32 more)	VERY LOW	IMPORTANT

CI: confidence interval; CPAP: continuous positive airway pressure; IVH: intraventricular haemorrhage; RR: risk
[1] The quality of evidence was downgraded by 1 because of unclear random sequence generation and allocation concealment
[2] The quality of evidence was downgraded by 2 as the 95% CI crosses 2 MIDs
[3] The quality of evidence was downgraded by 1 as the 95% CI crosses 1 MID
[4] Imprecision was not calculable because the uncertainty around the outcome was not available

Table 22: Clinical evidence profile: Comparison 4.1 CPAP with surfactant versus CPAP alone

Quality assessment							Number of babies		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CPAP + surfactant	CPAP alone	Relative (95% CI)	Absolute		
Mortality prior to discharge - CPAP + surfactant versus CPAP												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	24/321 (7.5%)	20/326 (6.1%)	RR 1.21 (0.68 to 2.14)	13 more per 1000 (from 20 fewer to 70 more)	LOW	CRITICAL
Bronchopulmonary dysplasia at 36 weeks PMA - CPAP + surfactant versus CPAP												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	102/321 (31.8%)	121/326 (37.1%)	RR 0.87 (0.68 to 1.11)	56 fewer per 1000 (from 115 fewer to 15 more)	MODERATE	CRITICAL
Failed non-invasive ventilation - CPAP + surfactant versus CPAP												
2	randomised trials	serious risk of bias[3]	no serious inconsistency	no serious indirectness	very serious[1]	none	161/321 (50.2%)	150/326 (46%)	RR 0.95 (0.64 to 1.41)	23 fewer per 1000 (from 166 fewer to 189 more)	VERY LOW	IMPORTANT
Pneumothorax - CPAP + surfactant versus CPAP												

Quality assessment							Number of babies		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CPAP + surfactant	CPAP alone	Relative (95% CI)	Absolute		
2	randomised trials	no serious risk of bias	serious inconsistency[4]	no serious indirectness	very serious[1]	none	14/321 (4.4%)	13/326 (4%)	RR 1.70 (0.15 to 19.16)	4 more per 1000 (from 19 fewer to 52 more)	VERY LOW	IMPORTANT
Severe IVH (grade 3 or 4) - CPAP + surfactant versus CPAP												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	14/321 (4.4%)	14/326 (4.3%)	RR 1.01 (0.49 to 2.07)	0 more per 1000 (from 22 fewer to 46 more)	LOW	IMPORTANT

CI: confidence interval; CPAP: continuous positive airway pressure; IVH: intraventricular haemorrhage; RR: risk
[1] The quality of evidence was downgraded by 2 as the 95% CI crosses 2 MIDs
[2] The quality of evidence was downgraded by 1 as the 95% CI crosses 1 MID
[3] The quality of the evidence was downgraded by 1 as the decision to initiate mechanical ventilation was at the discretion of the medical team (Dunn 2011)
[4] The quality of evidence was downgraded by 1 due to a high level of heterogeneity. Further subgroup analysis not possible as there were only 2 trials; random effects model used

Table 23: Clinical evidence profile: Comparison 5.1 CPAP alone versus invasive ventilation with surfactant

Quality assessment							Number of babies		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CPAP alone	Control	Relative (95% CI)	Absolute		
Mortality prior to discharge - CPAP versus invasive ventilation + surfactant												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	123/1193 (10.3%)	147/1165 (12.6%)	RR 0.82 (0.66 to 1.03)	23 fewer per 1000 (from 43 fewer to 4 more)	MODERATE	CRITICAL
Bronchopulmonary dysplasia at 36 weeks PMA - CPAP versus invasive ventilation + surfactant												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	372/1193 (31.2%)	400/1168 (34.2%)	RR 0.91 (0.81 to 1.02)	31 fewer per 1000 (from 65 fewer to 7 more)	HIGH	CRITICAL
Moderate or severe cerebral palsy at 18 months or older of age - CPAP versus invasive ventilation + surfactant												
1	randomised trials	no serious	no serious inconsistency	no serious indirectness	very serious[2]	none	21/511 (4.1%)	19/479 (4%)	RR 1.04 (0.56 to 1.9)	2 more per 1000 (from	LOW	CRITICAL

Quality assessment							Number of babies		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CPAP alone	Control	Relative (95% CI)	Absolute	Quality	Importance
		risk of bias								17 fewer to 36 more)		
Severe cognitive impairment at 18 months or older of age - CPAP versus invasive ventilation + surfactant												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	36/511 (7%)	36/479 (7.5%)	RR 0.94 (0.6 to 1.46)	5 fewer per 1000 (from 30 fewer to 35 more)	LOW	CRITICAL
Bilateral blindness - CPAP versus invasive ventilation + surfactant												
1	randomised trials	serious3	no serious inconsistency	no serious indirectness	very serious[2]	none	4/511 (0.78%)	7/479 (1.5%)	RR 0.54 (0.16 to 1.82)	7 fewer per 1000 (from 12 fewer to 12 more)	VERY LOW	CRITICAL
Hearing impairment - CPAP versus invasive ventilation + surfactant												
1	randomised trials	serious3	no serious inconsistency	no serious indirectness	serious[1]	none	17/511 (3.3%)	7/479 (1.5%)	RR 2.28 (0.95 to 5.44)	19 more per 1000 (from 1 fewer to 65 more)	LOW	CRITICAL
Failed non-invasive ventilation – CPAP versus invasive ventilation + surfactant												
1	randomised trials	serious4	no serious inconsistency	no serious indirectness	not calculable[5]	none	116/223	-	-	-	Not assessed	IMPORTANT
1	randomised trials	Serious6	no serious inconsistency	no serious indirectness	not calculable[5]	none	141/307	-	-	-	Not assessed	IMPORTANT
Pneumothorax - CPAP versus invasive ventilation + surfactant												
3	randomised trials	no serious risk of bias	serious[6]	no serious indirectness	very serious[2]	none	85/1193 (7.1%)	67/1165 (5.8%)	RR 1.42 (0.68 to 2.98)	14 more per 1000 (from 5 fewer to 40 more)	VERY LOW	IMPORTANT
Severe IVH (grade 3 or 4) - CPAP versus invasive ventilation + surfactant												
3	randomised trials	no serious risk of bias	serious[7]	no serious indirectness	serious[1]	none	125/1183 (10.6%)	112/1140 (9.8%)	RR 1.08 (0.85 to 1.37)	8 more per 1000 (from 15 fewer to 36 more)	LOW	IMPORTANT

CI: confidence interval; CPAP: continuous positive airway pressure; IVH: intraventricular haemorrhage; RR: risk

[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 evidence was downgraded by 1 because the parents were unblinded to the intervention and parental assessment was part of the the examination for hearing and visual impairment

[4] The quality of evidence was downgraded by 1 because of unclear random sequence generation and allocation concealment

[5] Imprecision was not calculable because the uncertainty around the outcome was not available

[6] The quality of evidence was downgraded by 1 as the study was unblinded and there was no strict criteria for intubation

[7] The quality of evidence was downgraded by 1 because of heterogeneity (I^2 = 75%). No predefined confounders identified; random effects model used.

GRADE tables for question 3.3 What is the most effective way of using surfactant in managing respiratory distress syndrome?

Table 24: Clinical evidence profile: Comparison 1. Early extubation following administration of surfactant versus conventional endotracheal administration of surfactant

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Early extubation following administration of surfactant	Conventional endotracheal administration of surfactant with mechanical ventilation	Relative (95% CI)	Absolute		
Mortality prior to discharge												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	15/229 (6.6%)	16/223 (7.2%)	RR 0.91 (0.47 to 1.79)	6 fewer per 1000 (from 38 fewer to 57 more)	VERY LOW	CRITICAL
Bronchopulmonary dysplasia at 36 weeks PMA												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	47/229 (20.5%)	64/223 (28.7%)	RR 0.71 (0.52 to 0.99)	83 fewer per 1000 (from 3 fewer to 138 fewer)	LOW	CRITICAL
Days on invasive ventilation (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	13	14	-	MD 3.60 lower (5.59 to 1.61 lower)	MODERATE	IMPORTANT
1	randomised trials	no serious risk of bias	no serious inconsistency	serious4	no serious imprecision	none	216	209	-	MD 0.60 lower (2.50 lower to 1.30 higher)	MODERATE	IMPORTANT
Pneumothorax												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	7/229 (3.1%)	11/223 (4.9%)	RR 0.64 (0.26 to 1.57)	18 fewer per 1000 (from 37	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Early extubation following administration of surfactant	Conventional endotracheal administration of surfactant with mechanical ventilation	Relative (95% CI)	Absolute	Quality	Importance
										fewer to 28 more)		
Pulmonary haemorrhage												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	7/216 (3.2%)	6/209 (2.9%)	RR 1.13 (0.39 to 3.3)	4 more per 1000 (from 18 fewer to 66 more)	VERY LOW	IMPORTANT

CI: confidence interval; MD: mean difference; PMA: postmenstrual age; RR: relative risk.
[1] The quality of evidence was downgraded by 1 because of unclear random sequence generation and allocation concealment
[2] The quality of the evidence was downgraded by 2 as the CI crosses 2 MIDs
[3] The quality of the evidence was downgraded by 1 as the CI crosses 1 MID
[4] The quality of the evidence was downgraded by 1 as the mode of mechanical ventilation was restricted to only high frequency oscillatory ventilation, other modes of conventional ventilation were not included in the analysis

Table 25: Clinical evidence profile: Comparison 2. Minimally invasive surfactant administration techniques versus endotracheal administration of surfactant

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Minimally invasive surfactant administration techniques	Endotracheal administration of surfactant	Relative (95% CI)	Absolute	Quality	Importance
Mortality prior to discharge												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	33/315 (10.5%)	30/316 (9.5%)	RR 1.1 (0.69 to 1.75)	9 more per 1000 (from 29 fewer to 71 more)	LOW	CRITICAL
Mortality prior to discharge - Minimally invasive surfactant administration versus InSuRE												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Minimally invasive surfactant administration techniques	Endotracheal administration of surfactant	Relative (95% CI)	Absolute		
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	16/100 (16%)	13/100 (13%)	RR 1.23 (0.63 to 2.42)	30 more per 1000 (from 48 fewer to 185 more)	LOW	CRITICAL
Mortality prior to discharge - Minimally invasive surfactant administration versus conventional ETT												
2	randomised trials	very serious[2]	no serious inconsistency	serious[3]	very serious[1]	none	17/215 (7.9%)	17/216 (7.9%)	RR 0.99 (0.52 to 1.89)	1 fewer per 1000 (from 38 fewer to 70 more)	VERY LOW	CRITICAL
Bronchopulmonary dysplasia at 36 weeks PMA												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	42/315 (13.3%)	62/316 (19.6%)	RR 0.67 (0.47 to 0.96)	65 fewer per 1000 (from 8 fewer to 104 fewer)	MODERATE	CRITICAL
Bronchopulmonary dysplasia at 36 weeks PMA - Minimally invasive surfactant administration versus InSuRE												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	9/100 (9%)	17/100 (17%)	0.53 (0.25 to 1.13)	80 fewer per 1000 (from 127 fewer to 22 more)	MODERATE	CRITICAL
Bronchopulmonary dysplasia at 36 weeks PMA - Minimally invasive surfactant administration versus conventional ETT												
2	randomised trials	serious[2]	no serious inconsistency	serious[3]	serious[4]	none	33/215 (15.3%)	45/216 (20.8%)	0.73 (0.49 to 1.08)	56 fewer per 1000 (from 106 fewer to 17 more)	VERY LOW	CRITICAL
Days on invasive ventilation - Minimally invasive surfactant administration versus InSuRE (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	n=100 Median (IQR) 35.6 hours (0 to 756)	n=100 Median= 64.1 hours Range= 0-489	-	Median 28.5 fewer hours (p=0.006)	MODERATE	IMPORTANT
Days on invasive ventilation - Minimally invasive surfactant administration versus conventional ETT (Better indicated by lower values)												
1	randomised trials	serious[2]	no serious inconsistency	serious[3]	serious[5]	none	n=108 Median (IQR) 0 days (0 to 3)	n=112 Median (IQR) 2 days (0 to 5)	-	Median 2 fewer days	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Minimally invasive surfactant administration techniques	Endotracheal administration of surfactant	Relative (95% CI)	Absolute	Quality	Importance
										(p not reported)		
Days on invasive ventilation - Minimally invasive surfactant administration versus conventional ETT (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	n=107 Median (IQR) 5 days (0 to 17)	n=104 Median (IQR) 7 days (2.5 to 19.5)	-	Median 2 fewer days (p= 0.031)	MODERATE	IMPORTANT
Intraventricular haemorrhage (grade 3 or 4) - Minimally invasive surfactant adminstration versus conventional ETT												
2	randomised trials	serious[2]	no serious inconsistency	serious[3]	serious[4]	none	19/215 (8.8%)	29/216 (13.4%)	RR 0.65 (0.38 to 1.12)	47 fewer per 1000 (from 83 fewer to 16 more)	VERY LOW	IMPORTANT
Pneumothorax												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	16/315 (5.1%)	31/316 (9.8%)	RR 0.52 (0.29 to 0.92)	47 fewer per 1000 (from 8 fewer to 70 fewer)	MODERATE	IMPORTANT
Pneumothorax - Minimally invasive surfactant administration versus InSuRE												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	7/100 (7%)	10/100 (10%)	RR 0.7 (0.28 to 1.77)	30 fewer per 1000 (from 72 fewer to 77 more)	LOW	IMPORTANT
Pneumothorax - Minimally invasive surfactant administration versus conventional ETT												
2	randomised trials	serious[2]	no serious inconsistency	serious[3]	serious[4]	none	9/215 (4.2%)	21/216 (9.7%)	RR 0.43 (0.2 to 0.91)	55 fewer per 1000 (from 9 fewer to 78 fewer)	VERY LOW	IMPORTANT
Pulmonary haemorrhage												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	10/415 (2.4%)	16/316 (5.1%)	RR 0.57 (0.27 to 1.21)	22 fewer per 1000 (from 37 fewer to 11 more)	MODERATE	IMPORTANT
Pulmonary haemorrhage - Minimally invasive surfactant administration versus InSuRE												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Minimally invasive surfactant administration techniques	Endotracheal administration of surfactant	Relative (95% CI)	Absolute		
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	5/100 (5%)	7/100 (7%)	RR 0.71 (0.23 to 2.18)	20 fewer per 1000 (from 54 fewer to 83 more)	LOW	IMPORTANT
Pulmonary haemorrhage - LISA versus conventional ETT												
2	randomised trials	serious[2]	no serious inconsistency	serious[3]	very serious[1]	none	5/315 (1.6%)	9/216 (4.2%)	RR 0.46 (0.16 to 1.32)	23 fewer per 1000 (from 35 fewer to 13 more)	VERY LOW	IMPORTANT

CI: confidence interval; ETT: endotracheal tube; InSuRE: intubate, surfactant, extubate; LISA: less invasive surfactant administration; MD: mean difference; PMA: postmenstrual age; RR: relative risk.

[1] The quality of evidence was downgraded by 2 because the CI crosses 2 MIDs

[2] The quality of evidence was downgraded as the criteria for surfactant was different in the intervention and control arm

[3] The quality of evidence was downgraded by 1 as not all the babies in the study received the intervention

[4] The quality of evidence was downgraded by 1 as the CI crosses 1 MID

[5] The quality of evidence was downgraded by 1 - imprecision was not calculable because the results were reported as medians

Table 26: Clinical evidence profile: Comparison 3. Laryngeal mask airway versus endotracheal administration of surfactant

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Laryngeal mask airway surfactant administration	Early extubation following administration of surfactant	Relative (95% CI)	Absolute		
Mortality prior to discharge												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	0/30 (0%)	0/30 (0%)	RD 0.00 (-0.06 to 0.06)	0 more per 1000 (from 60 fewer to 60 more)	LOW	CRITICAL
Bronchopulmonary dysplasia at 28 days of age or 36 weeks PMA												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Laryngeal mask airway surfactant administration	Early extubation following administration of surfactant	Relative (95% CI)	Absolute		
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	3/30 (10%)	2/30 (6.7%)	RR 1.5 (0.27 to 8.34)	33 more per 1000 (from 49 fewer to 489 more)	LOW	CRITICAL
Pneumothorax												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	6/30 (20%)	4/30 (13.3%)	RR 1.5 (0.47 to 4.78)	67 more per 1000 (from 71 fewer to 504 more)	LOW	IMPORTANT

CI: confidence interval; PMA: postmenstrual age; RD: risk difference; RR: relative risk.
[1] Imprecision was not calculable because the uncertainty around the outcome was not available
[2] The quality of evidence was downgraded by 2 as the CI crosses 2 MIDs
[3] The quality of evidence was downgraded by 2 as the CI of the risk difference includes both appreciable benefit and harm

Table 27: Clinical evidence profile: Comparison 6. Multiple dose of surfactant A versus single dose of surfactant A

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Single dose of surfactant	Multiple doses of surfactant	Relative (95% CI)	Absolute		
Mortality prior to discharge												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	none	37/176 (21%)	22/167 (13.2%)	RR 1.6 (0.98 to 2.59)	79 more per 1000 (from 3 fewer to 209 more)	LOW	CRITICAL
Bronchopulmonary dysplasia at 28 days of age												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	21/176 (11.9%)	22/167 (13.2%)	RR 0.91 (0.52 to 1.58)	12 fewer per 1000 (from 63 fewer to 76 more)	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Single dose of surfactant	Multiple doses of surfactant	Relative (95% CI)	Absolute		
Intraventricular haemorrhage (grade 3 or 4)												
1	randomised trials	serious	no serious inconsistency	no serious indirectness	very serious[3]	none	34/176 (19.3%)	38/167 (22.8%)	RR 0.85 (0.56 to 1.28)	34 fewer per 1000 (from 100 fewer to 64 more)	VERY LOW	IMPORTANT
Pneumothorax												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[2]	none	32/176 (18.2%)	15/167 (9%)	RR 2.02 (1.14 to 3.6)	92 more per 1000 (from 13 more to 234 more)	LOW	IMPORTANT
Pulmonary haemorrhage												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	4/176 (2.3%)	3/167 (1.8%)	RR 1.27 (0.29 to 5.57)	5 more per 1000 (from 13 fewer to 82 more)	VERY LOW	IMPORTANT

CI: confidence interval; RR: relative risk.
[1] The quality of the evidence was downgraded by 1 as the study dates were not reported
[2] The quality of evidence was downgraded by 1 as the CI crosses 1 MID
[3] The quality of the evidence was downgraded by 2 as the CI crosses 2 MIDs

GRADE tables for question 3.1 What is the most effective way to administer oxygen during respiratory support?

Table 28: Comparison 2. Nasal cannula versus incubator

Quality assessment							Number of babies		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nasal cannula	Incubator	Relative (95% CI)	Absolute		
Proportion of time spent within optimal target saturation limits, % (Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	25	25	-	MD 1 lower (6.27 lower	LOW	CRITICAL

Quality assessment							Number of babies		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nasal cannula	Incubator	Relative (95% CI)	Absolute		
										to 4.27 higher)		
Number of manual FiO2 adjustments per 24 hours (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	25	25	-	MD 0 higher (1.66 lower to 1.66 higher)	VERY LOW	IMPORTANT

CI: confidence interval; MD: mean difference
[1] The quality of the evidence was downgraded by 1 due to lack of blinding of participants and personnel, as well as of outcome assessment, which could have affected results (Travers 2018)
[2] The quality of evidence was downgraded by 1 because the CI crosses 1 MID
[3] The quality of evidence was downgraded by 2 because the CI crosses 2 MIDs

Table 29: Comparison 3. Automated versus manual titration

Quality assessment							Number of babies		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Automated	Manual	Relative (95% CI)	Absolute		
Number of days on respiratory support, median (IQR)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	N=42 Median 14 days (3 to 28)	N=42 Median 16 days (10 to 22)	-	Median 2 days lower (p-value not statistically significant)	VERY LOW	CRITICAL
Proportion of time spent within optimal target saturation limits, % - Gestational age not reported (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	16	16	-	MD 16 higher (12.68 to 19.32 higher)	VERY LOW	CRITICAL
Proportion of time spent within optimal target saturation limits, % - Babies 24-27 weeks (Better indicated by lower values)												

Quality assessment							Number of babies		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Automated	Manual	Relative (95% CI)	Absolute	Quality	Importance
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	32	32	-	MD 8 higher (4.68 to 11.32 higher)	LOW	CRITICAL
Proportion of time spent within optimal target saturation limits, % - Babies < 37 weeks (Better indicated by lower values)												
1	randomised trials	very serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	34	34	-	MD 11.1 higher (7.64 to 14.56 higher)	LOW	CRITICAL
Proportion of time spent within optimal target saturation limits, % - Higher target saturation (91-95%)- babies < 33 weeks (Better indicated by lower values)												
1	randomised trials	very serious[4]	no serious inconsistency	no serious indirectness	serious[3]	none	80	80	-	MD 4 higher (0.45 to 7.55 higher)	VERY LOW	CRITICAL
Proportion of time spent within optimal target saturation limits, % - Lower target saturation (89-93%)- babies < 33 weeks (Better indicated by lower values)												
1	randomised trials	very serious[4]	no serious inconsistency	no serious indirectness	serious[3]	none	80	80	-	MD 8 higher (4.37 to 11.63 higher)	VERY LOW	CRITICAL
Proportion of time within optimal target saturation limit, %, median (IQR)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	N=42 Median 62.0% (56.4 to 68.6)	N=42 Median 48.4% (41.5 to 56.4)	-	Median 13.6% higher (p<0.01)	VERY LOW	CRITICAL
Number of manual adjustments per 24 hours (Better indicated by lower values)												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	32	32	-	MD 102 lower (122.68 to 81.32 lower)	MODERATE	IMPORTANT
Number of manual adjustments per 24 hours, median (IQR) - Babies < 37 weeks												

Quality assessment							Number of babies		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Automated	Manual	Relative (95% CI)	Absolute		
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[5]	none	N=34 Median 52 (10 to 317)	N=34 Median 77 (0 to 224)	-	Median 25 lower (p<0.01)	VERY LOW	IMPORTANT
Number of manual adjustments per 24 hours, median (IQR) - Babies < 33 weeks												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[5]	none	N=80 Median 1 (0 to 3)	N=80 Median 102 (73 to 173)	-	Median 101 lower (p<0.01)	VERY LOW	IMPORTANT
Number of manual adjustments per 24 hours, median (IQR) - Babies < 33 weeks												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[5]	none	N=80 Median 1 (0 to 3)	N=80 Median 109 (79 to 156)	-	Median 108 lower (p<0.01)	VERY LOW	IMPORTANT

CI: confidence interval; IQR: inter-quartile range; MD: mean difference
[1] The quality of the evidence was downgraded by 1 due to lack of blinding of participants and personnel, as well as of outcome assessment, which could have affected results (Claure 2009; Claure 2011)
[2] The quality of evidence was downgraded by 2 because the CI crosses 2 MIDs
[3] The quality of evidence was downgraded by 1 because the CI crosses 1 MID
[4] The quality of the evidence was downgraded by 2 due to lack of blinding of participants and personnel, as well as of outcome assessment, which could have affected results. High attrition due to protocol non-adherence and lost data (Hallenberger 2014; Kaam 2015)
[5] The quality of evidence was downgraded by 1 as imprecision was not calculable because the outcome was reported using medians

GRADE tables for question 3.2 What is the effectiveness and safety of the different assisted ventilation techniques in preterm babies?

Non-invasive ventilation

Table 30: Clinical evidence profile: Comparison 1. Hi Flow versus CPAP

Quality assessment							Number of babies		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hi Flow	CPAP	Relative (95% CI)	Absolute		
Failed non-invasive ventilation requiring intubation - All infants												

Quality assessment							Number of babies		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hi Flow	CPAP	Relative (95% CI)	Absolute	Quality	Importance
3	randomised trials	very serious[1,2]	no serious inconsistency	no serious indirectness	serious[3]	none	65/378 (17.2%)	50/396 (12.6%)	RR 1.36 (0.97 to 1.91)	45 more per 1000 (from 4 fewer to 115 more)	VERY LOW	IMPORTANT
Failed non-invasive venitlation requiring intubation - 28-32 weeks												
1	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	30/140 (21.4%)	24/149 (16.1%)	RR 1.33 (0.82 to 2.16)	53 more per 1000 (from 29 fewer to 187 more)	VERY LOW	IMPORTANT
Failed non-invasive ventilation requiring intubation - ≥ 32 weeks												
1	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	13/138 (9.4%)	9/137 (6.6%)	RR 1.43 (0.63 to 3.25)	28 more per 1000 (from 24 fewer to 148 more)	VERY LOW	IMPORTANT
Pneumothorax												
3	randomised trials	very serious[1,2]	no serious inconsistency	no serious indirectness	very serious[4]	none	1/133 (0.75%)	5/144 (3.5%)	RR 0.41 (0.10 to 1.77)	26 fewer per 1000 (from 39 fewer to 34 more)	VERY LOW	IMPORTANT
Parent satisfaction - Child satisfied (VAS 1 to 10; Better indicated by higher values)												
1	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	20	20	-	MD 1.7 higher (0.85 to 2.55 higher)	LOW	IMPORTANT
Parent satisfaction - Contact and interaction (VAS 1-10; Better indicated by higher values)												
1	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	20	20	-	MD 2.3 higher (1.45 to 3.15 higher)	LOW	IMPORTANT
Parent satisfaction - Possibility to take part in care (VAS 1-10; Better indicated by higher values)												

Quality assessment							Number of babies		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hi Flow	CPAP	Relative (95% CI)	Absolute		
1	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	serious[3]	none	20	20	-	MD 1.1 higher (0.15 to 2.05 higher)	VERY LOW	IMPORTANT

CI: confidence interval; CPAP: continuous positive airway pressure, neonatal pain and comfort scale; MD: mean difference; RR: risk ratio; VAS: visual analogue scale
[1] The quality of evidence was downgraded by 2 because of unclear methods of randomisation, blinding and some studies not reporting all of the outcomes listed in the Methods (Nair 2005; Yoder 2013)
[2] The quality of evidence downgraded by 2 because cross-over was allowed and the decision to intubate was at the discretion of the clinical team (Roberts 2016)
[3] The quality of evidence was downgraded by 1 because the 95% CI crosses 1 MID
[4] The quality of evidence was downgraded by 2 because 95% CI crosses 2 MIDs
[5] The quality of evidence was downgraded by 2 because the study did not use computer generated randomisation, was unblinded, which could have affected subjective outcome assessment and was a cross-over study, which could have biased the treatment groups (Klingenberg 2014)

Table 31: Clinical evidence profile: Comparison 2. CPAP versus BiPAP/SiPAP

Quality assessment							Number of babies		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CPAP	BiPAP	Relative (95% CI)	Absolute		
Failed non-invasive ventilation requiring intubation												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	10/80 (12.5%)	10/80 (12.5%)	RR 1.00 (0.44 to 2.27)	0 fewer per 1000 (from 70 fewer to 159 more)	VERY LOW	IMPORTANT
Pneumothorax												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/80 (1.3%)	4/80 (5%)	RR 0.4 (0.08 to 2.03)	30 fewer per 1000 (from 46 fewer to 52 more)	VERY LOW	IMPORTANT

BiPAP: Bilevel positive airway pressure; CI: confidence interval; CPAP: continuous positive airway pressure; RR: risk ratio; SiPAP: synchronised positive airway pressure
[1] The quality of evidence was downgraded by 1 because it was unclear whether computer generated randomisation was used and it was unclear whether criteria for failure of nasal support was met (Lista 2010; Wood 2013)
[2] The quality of evidence was downgraded by 2 because the 95% CI crosses 2 MIDs

Table 32: Clinical evidence profile: Comparison 3. BiPAP/SiPAP versus Hi Flow

Quality assessment							Number of babies		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BiPAP	Hi Flow	Relative (95% CI)	Absolute		
Duration of invasive ventilation , days, median (IQR)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	N=158 Median 3.0 days (1.2 to 6.0)	158 Median 3.2 days (1.2 to 5.0)	-	Median 0.2 days lower (p=0.72)	LOW	IMPORTANT
Failed non-invasive ventilation requiring intubation - All infants												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	15/158 (9.5%)	17/158 (10.8%)	RR 0.88 (0.46 to 1.7)	13 fewer per 1000 (from 58 fewer to 75 more)	VERY LOW	IMPORTANT
Failed non-invasive ventilation requiring intubation - 29^{+0} to 32^{+6} weeks												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	8/73 (11%)	10/71 (14.1%)	RR 0.78 (0.33 to 1.86)	31 fewer per 1000 (from 94 fewer to 121 more)	VERY LOW	IMPORTANT
Failed non-invasive ventilation requiring intubation- 33^{+0} to 36^{+6} weeks												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	7/85 (8.2%)	7/87 (8%)	RR 1.02 (0.46 to 1.69)	2 more per 1000 (from 43 fewer to 56 more)	VERY LOW	IMPORTANT

BiPAP: Bilevel positive airway pressure; CI: confidence interval; CPAP: continuous positive airway pressure; IQR: inter-quartile range; MID: minimal important difference; RR: risk ratio; SiPAP: synchronised positive airway pressure

[1] The quality of evidence was downgraded by 1 because it was unclear whether computer generated random number generation was used and whether criteria for failure of nasal support was met

[2] The quality of evidence was downgraded by 1 as imprecision was not calculable because the outcome was reported using medians

[3] The quality of evidence was downgraded by 2 because the 95% CI crosses 2 MIDs

Table 33: Clinical evidence profile: Comparison 4. NIPPV versus BiPAP/SiPAP

Quality assessment							Number of babies		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NIPPV	BiPAP	Relative (95% CI)	Absolute		
Failed non-invasive ventilation requiring intubation												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	10/62 (16.1%)	8/62 (12.9%)	RR 1.25 (0.53 to 2.96)	32 more per 1000 (from 61 fewer to 253 more)	LOW	IMPORTANT
Pneumothorax												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	2/62 (3.2%)	4/62 (6.5%)	RR 0.5 (0.1 to 2.63)	32 fewer per 1000 (from 58 fewer to 105 more)	LOW	IMPORTANT

BiPAP: Bilevel positive airway pressure; CI: confidence interval; NIPPV: nasal intermittent positive pressure ventilation; MID: minimal important difference; RR: risk ratio; SiPAP: synchronised positive airway pressure

[1] The quality of evidence downgraded by 2 because the 95% CI crosses 2 MIDs

Table 34: Clinical evidence profile: Comparison 5. NIPPV versus CPAP

Quality assessment							Number of babies		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NIPPV	CPAP	Relative (95% CI)	Absolute		
Number of days on invasive ventilation via endotracheal tube, days (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	57	53	-	MD 4.5 lower (8.8 to 0.2 lower)	MODERATE	IMPORTANT
Duration of invasive ventilation, days, median (IQR) - All infants												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	n=100 Median2 days (1 to 7)	n=100 Median 3 days (1 to 25)	-	Median 1 day less (p=0.34)	MODERATE	IMPORTANT
Duration of invasive ventilation, days, median (IQR) - < 30 weeks												

Quality assessment							Number of babies		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**NIPPV**	**CPAP**	**Relative (95% CI)**	**Absolute**		
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	n=100 Median2 days (1 to 7)	n=100 Median 2 days (1 to 7)	-	Median 0 days less (p=0.37)	MODERATE	IMPORTANT
Failed non-invasive ventilation requiring intubation – All infants												
4	randomised trials	no serious risk of bias	very serious[3]	no serious indirectness	no serious imprecision	none	325/689 (47.2%)	361/690 (52.3%)	RR 0.90 (0.81 to 0.99)	52 fewer per 1000 (from 5 fewer to 99 fewer)	LOW	IMPORTANT
Failed non-invasive ventilation requiring intubation - <30 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	11/55 (20%)	19/60 (31.7%)	RR 0.63 (0.33 to 1.21)	117 fewer per 1000 (from 212 fewer to 67 more)	MODERATE	IMPORTANT
Pneumothorax												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	2/136 (1.5%)	2/146 (1.4%)	RR 1.06 (0.15 to 7.38)	1 more per 1000 (from 12 fewer to 87 more)	LOW	IMPORTANT

CI: confidence interval; CPAP: continuous positive airway pressure; IQR: inter-quartile range; MD: mean difference; MID: minimal important difference; NIPPV: nasal intermittent positive pressure ventilation; RR: risk ratio

[1] The quality of evidence was downgraded by 1 because the 95% CI crosses 1 MID

[2] Downgraded by 1 level - imprecision was not calculable because the outcome was reported using medians

[3] The quality of the evidence was downgraded by 2 because of a very high level of heterogeneity

[4] The quality of evidence was downgraded by 2 because 95% CI crosses 2 MIDs

Table 35: Clinical evidence profile: Comparison 6. NIPPV versus Hi Flow

Quality assessment							Number of babies		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NIPPV	Hi Flow	Relative (95% CI)	Absolute		
Duration of invasive ventilation , days, median (IQR)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	n=38 Median 4.0 days (0.5 to 16.0)	n=38 Median 3.0 (0.01 to 14.0)	-	Median 1 day more (p=0.95)	MODERATE	IMPORTANT
Failed non-invasive ventilation requiring intubation												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	13/38 (34.2%)	11/38 (28.9%)	RR 1.18 (0.61 to 2.30)	52 more per 1000 (from 113 fewer to 376 more)	LOW	IMPORTANT
Pneumothorax												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	0/38 (0%)	2/38 (5.3%)	RR 0.20 (0.01 to 4.03)	42 fewer per 1000 (from 52 fewer to 159 more)	LOW	IMPORTANT

CI: confidence interval; IQR: inter-quartile range; MID: minimal important difference;NIPPV: nasal intermittent positive pressure ventilation; RR: risk ratio
[1] Downgraded by 1 level - imprecision was not calculable because the outcome was reported using medians
[2] The quality of evidence was downgraded by 2 because the 95% CI crosses 2 MIDs

Invasive ventilation

Table 36: Clinical evidence profile: Comparison 1. Volume targeted ventilation versus synchronised pressure limited ventilation

Quality assessment							Number of babies		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Volume targeted ventilation	Synchronised pressure limited ventilation	Relative (95% CI)	Absolute		
Cerebral Palsy at 18 months or older of age												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/45 (4.4%)	6/40 (15%)	RR 0.3 (0.06 to 1.39)	105 fewer per 1000 (from 141	VERY LOW	CRITICAL

Quality assessment							Number of babies		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Volume targeted ventilation	Synchronised pressure limited ventilation	Relative (95% CI)	Absolute		
										fewer to 58 more)		
Days on invasive ventilation (Better indicated by lower values)												
4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	127	105	-	MD 2.82 lower (4.08 to 1.57 lower)	LOW	IMPORTANT
Pneumothorax												
4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	4/135 (3%)	12/122 (9.8%)	RR 0.35 (0.13 to 0.95)	64 fewer per 1000 (from 5 fewer to 86 fewer)	LOW	IMPORTANT

CI: confidence interval; MD: mean difference; MID: minimal important difference; RR: risk ratio
[1] The quality of evidence was downgraded by 1 as healthcare professionals and parents were unblinded to the intervention
[2] The quality of evidence was downgraded by 2 as the 95% CI crosses 2 MIDs
[3] The quality of evidence was downgraded by 1 as the 95% CI crosses 1 MID

Table 37: Clinical evidence profile: Comparison 2. Volume targeted ventilation versus non-synchronised pressure limited ventilation

Quality assessment							Number of babies		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Volume targeted ventilation	Non-synchronised pressure limited ventilation	Relative (95% CI)	Absolute		
Days on invasive ventilation (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	23	22	-	MD 6.3 lower (12.88 lower to 0.28 higher)	LOW	IMPORTANT
Pneumothorax												

Quality assessment							Number of babies		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Volume targeted ventilation	Non-synchronised pressure limited ventilation	Relative (95% CI)	Absolute		
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/27 (7.4%)	6/30 (20%)	RR 0.37 (0.08 to 1.68)	126 fewer per 1000 (from 184 fewer to 136 more)	VERY LOW	IMPORTANT

CI: confidence interval; MD: mean difference; MID: minimal important difference; RR: risk ratio
[1] The quality of evidence was downgraded by 1 as healthcare professionals and parents were unblinded to the intervention
[2] The quality of evidence was downgraded by 1 as the 95% CI crosses 1 MID
[3] The quality of evidence was downgraded by 2 as the 95% CI crosses 2 MIDs

Table 38: Clinical evidence profile: Comparison 3: Volume targeted ventilation versus synchronised intermittent mandatory ventilation

Quality assessment							Number of babies		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Volume targeted ventilation	Synchronised intermittent mandatory ventilation	Relative (95% CI)	Absolute		
Days on invasive ventilation (Better indicated by lower values)												
3	randomised trials	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	150	143	-	MD 2.84 lower (5.84 lower to 0.15 higher)	LOW	IMPORTANT
Pneumothorax												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	11/154 (7.1%)	13/154 (8.4%)	RR 0.84 (0.39 to 1.78)	14 fewer per 1000 (from 51 fewer to 66 more)	VERY LOW	IMPORTANT

CI: confidence interval; MD: mean difference; MID: minimal important difference; RR: risk ratio

[1] *The quality of evidence was downgraded by 1 as healthcare professionals and parents were unblinded to the intervention*
[2] *The quality of evidence was downgraded by 1 because of a high level of heterogeneity*
[3] *The quality of evidence was downgraded by 2 as the 95% CI crosses 2 MIDs*

Table 39: Clinical evidence profile: Comparison 5: Synchronised pressure limited ventilation versus non-synchronised pressure limited ventilation

Quality assessment							Number of babies		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Synchronised pressure limited ventilation	Non-synchronised pressure limited ventilation	Relative (95% CI)	Absolute	Quality	Importance
Days on invasive ventilation (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	n=465 Median 6 days (3 to 15)	n=459 Median 6 days (3 to 15)	-	No difference (p not reported)	LOW	IMPORTANT
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	n=193 Median 3 days (1 to 42)	n=193 Median 4 days (1 to 150)	-	Median 1 day less (p not reported)	LOW	IMPORTANT
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	15	15	-	MD 6.33 lower (39.54 lower to 26.88 higher)	VERY LOW	IMPORTANT
Pneumothorax												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	82/673 (12.2%)	68/667 (10.2%)	RR 1.19 (0.88 to 1.62)	19 more per 1000 (from 12 fewer to 63 more)	LOW	IMPORTANT

CI: confidence interval; MD: mean difference; MID: minimal important difference; RR: risk ratio
[1] *The quality of evidence was downgraded by 1 as healthcare professionals and parents were unblinded to the intervention*
[2] *Downgraded by 1 level - imprecision was not calculable because the outcome was reported using medians*
[3] *The quality of evidence was downgraded by 1 as the 95% CI crosses 1 MID*
[4] *The quality of evidence was downgraded by 2 as the 95% CI crosses 2 MIDs*

Table 40: Clinical evidence profile: Comparison 8: Synchronised intermittent mandatory ventilation versus non-synchronised pressure limited ventilation

Quality assessment							Number of babies		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Synchronised intermittent mandatory ventilation**	**Non-synchronised pressure limited ventilation**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Days on invasive ventilation (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	n=178 Median 4.3 days (3.9 to 4.9)	172 Median 5 days (4.2 to 5.9)	-	Median 0.7 days less (p not reported)	LOW	IMPORTANT

CI: confidence interval;
[1] The quality of evidence was downgraded by 1 as healthcare professionals and parents were unblinded to the intervention
[2] The quality of evidence was downgraded by 1 as imprecision was not calculable because the outcome was reported using medians

Table 41: Clinical evidence profile: Comparison 9: Synchronised intermittent mandatory ventilation versus high frequency ventilation

Quality assessment							Number of babies		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Synchronised intermittent mandatory ventilation**	**High frequency ventilation**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Cerebral palsy at 18 months or more of age												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	16/95 (16.8%)	4/97 (4.1%)	RR 4.08 (1.42 to 11.77)	127 more per 1000 (from 17 more to 444 more)	MODERATE	CRITICAL
Days on invasive ventilation (Better indicated by lower values)												
2	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	62	63	-	MD 5.52 higher (4.46 to 6.57 higher)	MODERATE	IMPORTANT
Pneumothorax												

Quality assessment							Number of babies		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Synchronised intermittent mandatory ventilation	High frequency ventilation	Relative (95% CI)	Absolute		
3	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	37/408 (9.1%)	41/403 (10.2%)	RR 0.88 (0.58 to 1.33)	12 fewer per 1000 (from 43 fewer to 34 more)	VERY LOW	IMPORTANT

CI: confidence interval; MD: mean difference; MID: minimal important difference; RR: risk ratio
[1] The quality of evidence was downgraded by 2 as the parents and babies were unblinded to the intervention and more in infants were switched from conventional ventilation to high frequency ventilation due to failure, therefore identifying a particular severe subset of babies possibly increasing the risk of cerebral palsy
[2] The quality of evidence was downgraded by 1 as healthcare professionals and parents were unblinded to the intervention
[3] The quality of evidence was downgraded by 2 as the 95% CI crosses 2 MIDs

Table 42: Clinical evidence profile: Comparison 10: Non-synchronised pressure limited ventilation versus high frequency ventilation

Quality assessment							Number of babies		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Non-synchronised pressure limited ventilation	High frequency ventilation	Relative (95% CI)	Absolute		
Moderate cognitive impairment at 18 months or older of age - Moderate learning difficulty at 11-14 years of age												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	19/108 (17.6%)	19/116 (16.4%)	RR 1.07 (0.6 to 1.92)	11 more per 1000 (from 66 fewer to 151 more)	VERY LOW	CRITICAL
Severe cognitive impairment at 18 months or older of age - Severe learning difficulty at 11-14 years of age												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/108 (0.93%)	3/116 (2.6%)	RR 0.36 (0.04 to 3.39)	17 fewer per 1000 (from 25 fewer to 62 more)	VERY LOW	CRITICAL
Severe cognitive impairment at 18 months or older of age - Parent composite score of <49 at 2 years of age												
1	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	very serious[2]	none	40/151 (26.5%)	41/137 (29.9%)	RR 0.89 (0.61 to 1.28)	33 fewer per 1000 (from 117	VERY LOW	CRITICAL

Quality assessment							Number of babies		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Non-synchronised pressure limited ventilation	High frequency ventilation	Relative (95% CI)	Absolute	Quality	Importance
										fewer to 84 more)		
Neurosensory impairment at 18 months or older of age - Profound hearing loss despite aids at 2 years of age												
1	randomised trials	very serious[4]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/189 (0%)	2/170 (1.2%)	RR 0.18 (0.01 to 3.72)	10 fewer per 1000 (from 12 fewer to 32 more)	VERY LOW	CRITICAL
Neurosensory impairment at 18 months or older of age - Parental report of visual problems at 2 years of age												
1	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	serious[5]	none	14/189 (7.4%)	5/163 (3.1%)	RR 2.41 (0.89 to 6.56)	43 more per 1000 (from 3 fewer to 171 more)	VERY LOW	CRITICAL
Days on invasive ventilation (Better indicated by lower values)												
1	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	serious[7]	none	n=61 Median (IQR) ≤1kg: 53.7 days (28.4 to 103) >1kg: 4.5 days (3 to 6.1)	64 Median(IQR): ≤1kg: 24.7 days (3.7 to 61.4) >1kg: 4.1 days (1.7 to 6)	-	≤1kg: Median 29 days more (p not reported) >1kg Median 0.4 days more (p not reported)	LOW	IMPORTANT
1	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	serious[7]	none	n=397 Median (IQR) 7 days (2 to 20)	n=400 Median (IQR) 7 days (3-21)	-	Median 0 days more (p = 0.58)	LOW	IMPORTANT
Pneumothorax												
1	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/20 (5%)	2/20 (10%)	RR 0.5 (0.05 to 5.08)	50 fewer per 1000 (from 95 fewer to	VERY LOW	IMPORTANT

Quality assessment							Number of babies		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Non-synchronised pressure limited ventilation	High frequency ventilation	Relative (95% CI)	Absolute	Quality	Importance
										408 more)		

CI: confidence interval; MID: minimal important difference; RR: risk ratio
[1] The quality of evidence was downgraded by 2 as the study was unblinded, unclear as whether outcome assessors were blinded and there was a high level of attrition
[2] The quality of evidence was downgraded by 2 as the 95% CI crosses 2 MIDs
[3] The quality of evidence was downgraded by 2 as the study was unblinded,outcome assessors were unblinded and there was a high level of attrition
[4] The quality of evidence was downgraded by 2 as the study was unblinded and there was a high level of attrition
[5] The quality of evidence was downgraded by 1 as the 95% CI crosses 1 MID
[6] The quality of evidence was downgraded by 1 as healthcare professionals and parents were unblinded to the intervention
[7] The quality of evidence was downgraded by 1 as imprecision was not calculable because the outcome was reported using medians

GRADE tables for question 3.7 What is the effectiveness of nitric oxide in preterm babies requiring invasive ventilation?

Table 43: Clinical evidence profile: Comparison 1 – Inhaled nitric oxide versus placebo

Quality assessment							Number of babies		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Inhaled nitric oxide	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Mortality prior to discharge - Studies with entry before 3 days based on oxygenation												
8	randomised trials	very serious[1,2,3,4,5]	no serious inconsistency[6]	no serious indirectness	no serious imprecision	none	209/466 (44.8%)	198/475 (41.7%)	RR 1.06 (0.92 to 1.22)	25 more per 1000 (from 33 fewer to 92 more)	LOW	CRITICAL
Mortality prior to discharge - Studies with entry after 3 days based on BPD risk												
2	randomised trials	serious[1]	no serious inconsistency[7]	no serious indirectness	very serious[8]	none	26/314 (8.3%)	25/310 (8.1%)	RR 1.06 (0.64 to 1.74)	5 more per 1000 (from 29 fewer to 60 more)	VERY LOW	CRITICAL
Mortality prior to discharge - Studies of routine use in preterm infants on respiratory support												

Quality assessment							Number of babies		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Inhaled nitric oxide	Placebo	Relative (95% CI)	Absolute		
4	randomised trials	no serious risk of bias	serious[9]	no serious indirectness	very serious[8]	none	149/961 (15.5%)	164/963 (17%)	RR 0.9 (0.63 to 1.28)	17 fewer per 1000 (from 44 fewer to 17 more)	VERY LOW	CRITICAL
Bronchopulmanory dysplasia at 36 weeks postmenstrual age - Studies with entry before 3 days based on oxygenation												
6	randomised trials	very serious[1,2,3,4,5]	no serious inconsistency	no serious indirectness	very serious[8]	none	64/238 (26.9%)	67/249 (26.9%)	RR 0.93 (0.7 to 1.25)	19 fewer per 1000 (from 81 fewer to 67 more)	VERY LOW	CRITICAL
Bronchopulmanory dysplasia at 36 weeks postmenstrual age- Studies with entry after 3 days based on BPD risk												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	289/543 (53.2%)	315/532 (59.2%)	RR 0.9 (0.81 to 1)	59 fewer per 1000 (from 112 fewer to 0 more)	HIGH	CRITICAL
Bronchopulmanory dysplasia at 36 weeks postmenstrual age - Studies of routine use in preterm infants on respiratory support												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	352/961 (36.6%)	373/963 (38.7%)	RR 0.94 (0.85 to 1.05)	23 fewer per 1000 (from 58 fewer to 19 more)	HIGH	CRITICAL
Bronchopulmanory dysplasia at 28 days of life - Studies with entry before 3 days of age based on oxygenation												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[10]	none	15/39 (38.5%)	8/37 (21.6%)	RR 1.78 (0.86 to 3.69)	169 more per 1000 (from 30 fewer to 582 more)	MODERATE	CRITICAL
Cerebral palsy at ≥ 18 months - Studies with entry before 3 days based on oxygenation												

Quality assessment							Number of babies		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Inhaled nitric oxide	Placebo	Relative (95% CI)	Absolute	Quality	Importance
2	randomised trials	very serious[1,5,12]	no serious inconsistency	no serious indirectness	serious[10]	none	18/99 (18.2%)	11/110 (10%)	RR 1.85 (0.93 to 3.71)	85 more per 1000 (from 7 fewer to 271 more)	VERY LOW	CRITICAL
Cerebral palsy at ≥ 18 months - Studies with entry after 3 days based on BPD risk												
2	randomised trials	very serious[1,12]	no serious inconsistency	no serious indirectness	very serious[8]	none	15/250 (6%)	14/248 (5.6%)	RR 1.1 (0.54 to 2.23)	6 more per 1000 (from 26 fewer to 69 more)	VERY LOW	CRITICAL
Cerebral palsy at ≥ 18 months - Studies of routine use in preterm infants on respiratory support												
2	randomised trials	serious[12]	no serious inconsistency	no serious indirectness	very serious[8]	none	35/376 (9.3%)	36/392 (9.2%)	RR 1.01 (0.65 to 1.58)	1 more per 1000 (from 32 fewer to 53 more)	VERY LOW	CRITICAL
Moderate to severe cerebral palsy at 18-24 months - Study entry after 3 days of age based on BPD risk												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[8]	none	7/180 (3.9%)	11/180 (6.1%)	RR 0.64 (0.25 to 1.6)	22 fewer per 1000 (from 46 fewer to 37 more)	LOW	CRITICAL
Severe neurodevelopmental delay at ≥ 18 months PMA, BSID-III cognitive score < 70 - Entry after 3 days based on BPD risk												
2	randomised trials	very serious[3,12]	no serious inconsistency	no serious indirectness	very serious[8]	none	16/186 (8.6%)	15/183 (8.2%)	RR 1.02 (0.52 to 1.99)	2 more per 1000 (from 39 fewer to 81 more)	VERY LOW	CRITICAL
Severe neurodevelopmental delay at ≥ 18 months PMA, BSID-III cognitive score < 70 - Studies of routine use in preterm infants on respiratory support												
1	randomised trials	serious[12]	no serious inconsistency	no serious indirectness	very serious[8]	none	7/306 (2.3%)	12/324 (3.7%)	RR 0.62 (0.25 to 1.55)	14 fewer per 1000 (from 28	VERY LOW	CRITICAL

Quality assessment							Number of babies		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Inhaled nitric oxide	Placebo	Relative (95% CI)	Absolute	Quality	Importance
										fewer to 20 more)		
Moderate neurodevelopmental delay at ≥ 18 months PMA, BSID-III cognitive score 70-84 - Entry after 3 days based on BPD risk												
3	randomised trials	very serious[3,12]	no serious inconsistency	no serious indirectness	very serious[8]	none	10/204 (11.3%)	14/199 (8.2%)	RR 0.67 (0.31 to 1.47)	30 more per 1000 (from 4 fewer to 79 more)	VERY LOW	CRITICAL
Moderate neurodevelopmental delay at ≥ 18 months PMA, BSID-III cognitive score 70-84 – Studies of routine use in preterm infants on respiratory support												
1	randomised trials	serious[12]	no serious inconsistency	no serious indirectness	serious[10]	none	51/338 (15.1%)	31/347 (8.9%)	RR 1.69 (1.11 to 2.57)	62 more per 1000 (from 10 more to 140 more)	LOW	CRITICAL
Severe cognitive impairment at ≥ 18 months (MDI) - Studies with entry before 3 days based on oxygenation												
2	randomised trials	very serious[1,5,12]	no serious inconsistency	no serious indirectness	serious[10]	none	38/95 (40%)	37/106 (34.9%)	RR 1.16 (0.81 to 1.65)	56 more per 1000 (from 66 fewer to 227 more)	VERY LOW	CRITICAL
Severe cognitive impairment at ≥ 18 months (MDI) - Studies of routine use in preterm infants on respiratory support												
1	randomised trials	serious[12]	no serious inconsistency	no serious indirectness	serious[10]	none	13/70 (18.6%)	24/68 (35.3%)	RR 0.53 (0.29 to 0.95)	166 fewer per 1000 (from 18 fewer to 251 fewer)	LOW	CRITICAL
Severe psychomotor impairment at ≥ 18 months (PDI) - Studies with entry before 3 days based on oxygenation												
2	randomised trials	very serious[1,5,12]	no serious inconsistency	no serious indirectness	very serious[8]	none	29/94 (30.9%)	32/107 (29.9%)	RR 1.06 (0.7 to 1.59)	18 more per 1000 (from 90 fewer to	VERY LOW	CRITICAL

Quality assessment							Number of babies		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Inhaled nitric oxide	Placebo	Relative (95% CI)	Absolute	Quality	Importance
										176 more)		
Severe psychomotor impairment at ≥ 18 months (PDI) - Studies of routine use in preterm infants on respiratory support												
1	randomised trials	serious[12]	no serious inconsistency	no serious indirectness	very serious[8]	none	9/70 (12.9%)	12/68 (17.6%)	RR 0.73 (0.33 to 1.62)	48 fewer per 1000 (from 118 fewer to 109 more)	VERY LOW	CRITICAL
Severe hearing impairment at ≥ 18 months - Studies with entry before 3 days based on oxygenation												
3	randomised trials	very serious[1,3,5,12]	no serious inconsistency	no serious indirectness	very serious[8]	none	8/121 (6.6%)	7/129 (5.4%)	RR 1.12 (0.42 to 2.98)	7 more per 1000 (from 31 fewer to 107 more)	VERY LOW	CRITICAL
Severe hearing impairment at ≥ 18 months - Studies with entry after 3 days based on BPD risk												
1	randomised trials	serious[12]	no serious inconsistency	no serious indirectness	very serious[8]	none	8/243 (3.3%)	3/234 (1.3%)	RR 2.57 (0.69 to 9.56)	20 more per 1000 (from 4 fewer to 110 more)	VERY LOW	CRITICAL
Severe hearing impairment at ≥ 18 months - Studies of routine use in preterm infants on respiratory support												
2	randomised trials	serious[12]	no serious inconsistency	no serious indirectness	very serious[8]	none	7/376 (1.9%)	13/392 (3.3%)	RR 0.58 (0.24 to 1.41)	14 fewer per 1000 (from 25 fewer to 14 more)	VERY LOW	CRITICAL
Severe visual impairment at ≥ 18 months - Studies with entry before 3 days based on oxygenation												
3	randomised trials	very serious[1,3,5,12]	no serious inconsistency	no serious indirectness	very serious[8]	none	3/121 (2.5%)	2/129 (1.6%)	RR 1.42 (0.25 to 7.91)	7 more per 1000 (from 12 fewer to	VERY LOW	CRITICAL

Quality assessment							Number of babies		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Inhaled nitric oxide	Placebo	Relative (95% CI)	Absolute	Quality	Importance
										107 more)		
Severe visual impairment at ≥ 18 months - Studies with entry after 3 days based on BPD risk												
1	randomised trials	serious[12]	no serious inconsistency	no serious indirectness	very serious[8]	none	9/243 (3.7%)	9/234 (3.8%)	RR 0.96 (0.39 to 2.38)	2 fewer per 1000 (from 23 fewer to 53 more)	VERY LOW	CRITICAL
Severe visual impairment at ≥ 18 months - Studies of routine use in preterm infants on respiratory support												
2	randomised trials	serious[12]	no serious inconsistency	no serious indirectness	very serious[8]	none	7/376 (1.9%)	14/392 (3.6%)	RR 0.54 (0.23 to 1.29)	16 fewer per 1000 (from 28 fewer to 10 more)	VERY LOW	CRITICAL
Mean days on ventilation - Studies with entry before 3 days based on oxygenation (Better indicated by lower values)												
2	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	224	225	-	MD 8.06 lower (13.96 to 2.16 lower)	MODERATE	IMPORTANT
Mean days on ventilation - Studies with entry after 3 days of age based on BPD risk (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	229	222	-	MD 1 lower (8.57 lower to 6.57 higher)	HIGH	IMPORTANT
Mean days on ventilation - Studies of routine use in preterm infants on respiratory support (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[8]	none	59	65	-	MD 1.3 higher (6.65 lower to 9.25 higher)	LOW	IMPORTANT
Median days on ventilation for survivors - Studies with entry before 3 days based on oxygenation												

Quality assessment							Number of babies		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Inhaled nitric oxide**	**Placebo**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[13]	none	n= 25 Median (IQR) 28 days (3 to 89)	15 Median (IQR) 37 days (8 to 395)	-	Median 9 days less (p= 0.046)	LOW	IMPORTANT
Median days on ventilation - Studies with entry before 3 days based on oxygenation												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[13]	none	n=55 Median (IQR) 7.0 days (2.0 to 26.0)	n=53 Median (IQR) 4.0 days (1.0 to 9.0)	-	Median 3 days more (p=0.24)	LOW	IMPORTANT
Median days on ventilation - Studies with entry after 3 days based on BPD risk												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[13]	none	n=20 Median (IQR) 11 days (5 to 44)	n=22 Median (IQR) 19 days (5 to 39)	-	Median 8 days less (p-value not reported)	LOW	IMPORTANT
Severe intraventricular haemorrhage (IVH) - Studies with entry before 3 days based on oxygenation												
5	randomised trials	very serious[1,2,3,4]	no serious inconsistency	no serious indirectness	serious[10]	none	106/352 (30.1%)	82/356 (23%)	1.27 (1.03 to 1.56)	62 more per 1000 (from 7 more to 129 more)	VERY LOW	IMPORTANT
Severe intraventricular haemorrhage (IVH) - Studies of routine use in preterm infants on respiratory support												
4	randomised trials	no serious risk of bias	no serious inconsistency [14]	no serious indirectness	serious[10]	none	109/954 (11.4%)	122/959 (12.7%)	0.89 (0.73 to 1.09)	14 fewer per 1000 (from 34 fewer to 11 more)	MODERATE	IMPORTANT

Quality assessment							Number of babies		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Inhaled nitric oxide	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Pulmonary haemorrhage - Studies with entry before 3 days of age based on oxygenation												
2	randomised trials	serious[1,3]	no serious inconsistency	no serious indirectness	very serious[8]	none	6/75 (8%)	7/75 (9.3%)	RR 0.86 (0.29 to 2.3)	13 fewer per 1000 (from 66 fewer to 121 more)	VERY LOW	IMPORTANT
Pulmonary haemorrhage - Studies of routine use in preterm infants on respiratory support												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[8]	none	42/900 (4.7%)	45/892 (5%)	RR 0.92 (0.61 to 1.39)	4 fewer per 1000 (from 20 fewer to 20 more)	LOW	IMPORTANT
Methaemoglobineamia - Methaemoglobin level ≥ 4%												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[8]	none	2/210 (0.95%)	2/210 (0.95%)	RR 1 (0.14 to 7.03)	0 fewer per 1000 (from 8 fewer to 57 more)	VERY LOW	IMPORTANT
Methaemoglobineamia - Methaemoglobin level ≥ 8%												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[8]	none	1/210 (0.48%)	0/210 (0%)	RR 3 (0.12 to 73.22)	not estimable[15]	VERY LOW	IMPORTANT

BSID-III: Bayley Scales of Infant Development, third edition; BPD: bronchopulmonary dysplasia; CI: confidence interval; MD: mean difference; MDI: Mental Developmental Index; PDI: Psychomotor Developmental Index; PMA: post-menstrual age; RR: risk ratio

[1] Quality of evidence downgraded by 1 because study terminated early due to lack of difference between outcomes, slowing enrollment, and/or an increase in adverse outcomes in one or both arms (Ballard 2006; Kinsella 1999; Mercier 1999; Subhedar 1997; Van Meurs 2005)

[2] Quality of evidence downgraded by 1 because unplanned interim analysis performed becaue of an impression that the results were significant (Dani 2006)

[3] Quality of evidence downgraded by 1 because of methods of randomisation, allocation andblinding were not specified (Field 2005; Srisuparp 2002)

[4] Quality of evidence downgraded by 1 because some control infants received open-label iNO after randomisation (Hascoet 2005)

[5] Quality of evidence downgraded by 1 because there were < 15 babies in each arm (Van Meurs 2007)

[6] I^2= 0% not downgraded for heterogeneity; fixed effects model used for meta-analysis

[7] I^2= 29% not downgraded for heterogeneity; fixed effects model used for meta-analysis

[8] Quality of evidence downgraded by 2 because CI crosses 2 MIDs

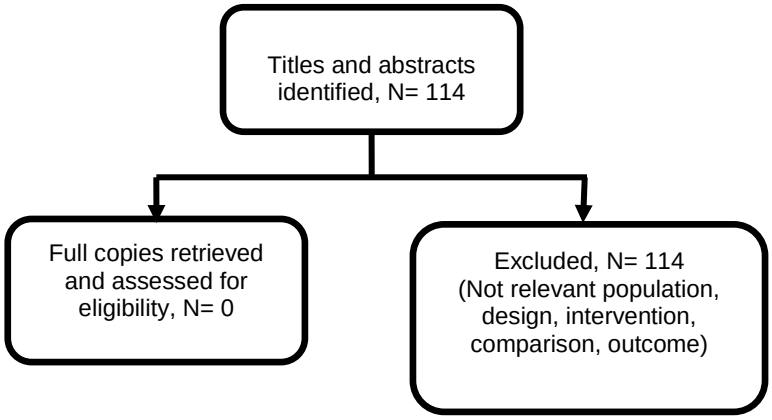
[9] Quality of evidence downgraded by 1 because of heterogeneity (I^2= 50%). The EUNO 2009 trial reported an increased risk with nitric oxide whereas the others reported a decrease, random effects model used.

[10] Quality of evidence downgraded by 1 because the CI crosses 1 MID

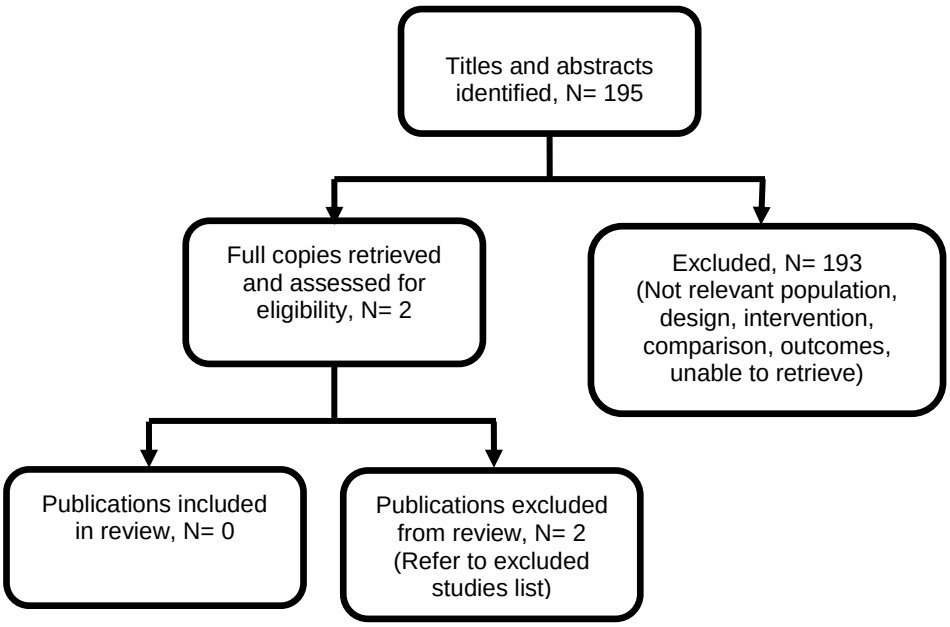
[11] *I^2= 43% not downgraded for heterogeneity; fixed effects model used for meta-analysis*
[12] *Quality of evidence downgraded by 1 because of attrition from initial sample randomised due to death and loss to follow up (Ballard 2006 (Walsh 2010); EUNO 2009 (Durrmeyer 2013); Hasan 2017; INNOVO 2005 (Huddy 2008); Schreiber 2003 (Mestan 2005); Subhedar 1997 (Bennett 2001); Van Meurs 2005 (Hintz 2007); Van Meurs 2007)*
[13] *Downgraded by 1 level as imprecision could not be assessed due to results being presented as medians*
[14] *I^2= 33% The EUNO 2009 trial reported an increased risk with nitric oxide whereas the others reported a decrease; not downgraded for heterogeneity; fixed effects model used for meta-analysis*
[15] *Unable to estimate due to 0 events in the control arm*

Appendix G – Economic evidence study selection

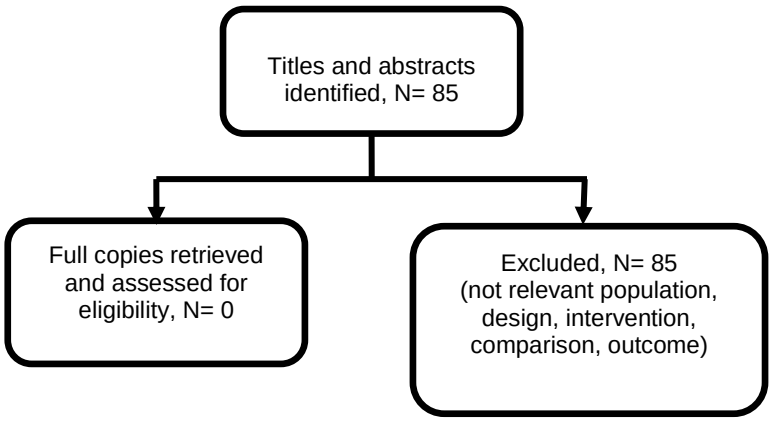
Economic evidence study selection for question 1.1 What respiratory support (excluding resuscitation) is the most effective for preterm babies before admission to the neonatal unit



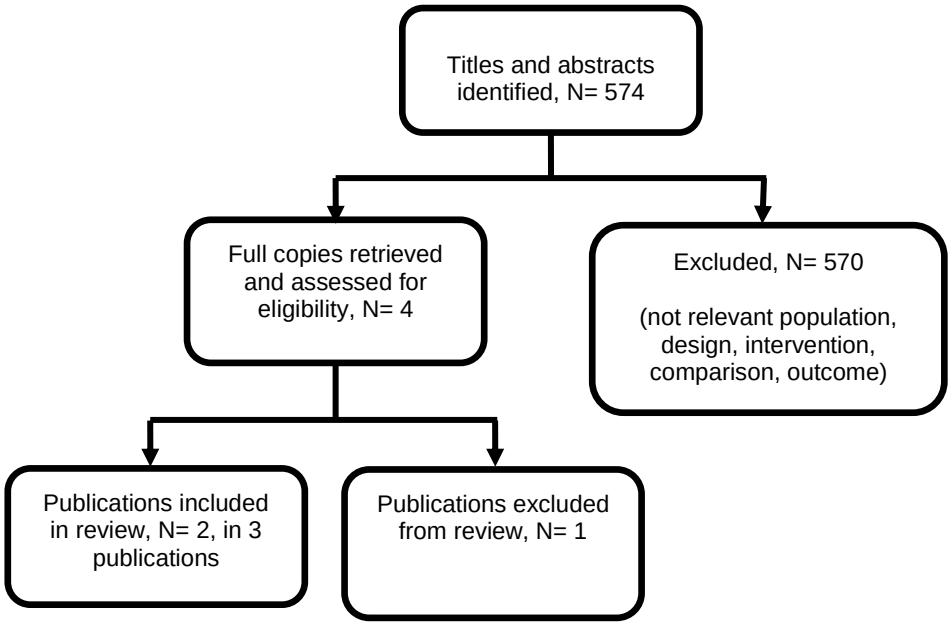
Economic evidence study selection for question 3.3 What is the most effective way of using surfactant in managing respiratory distress syndrome?



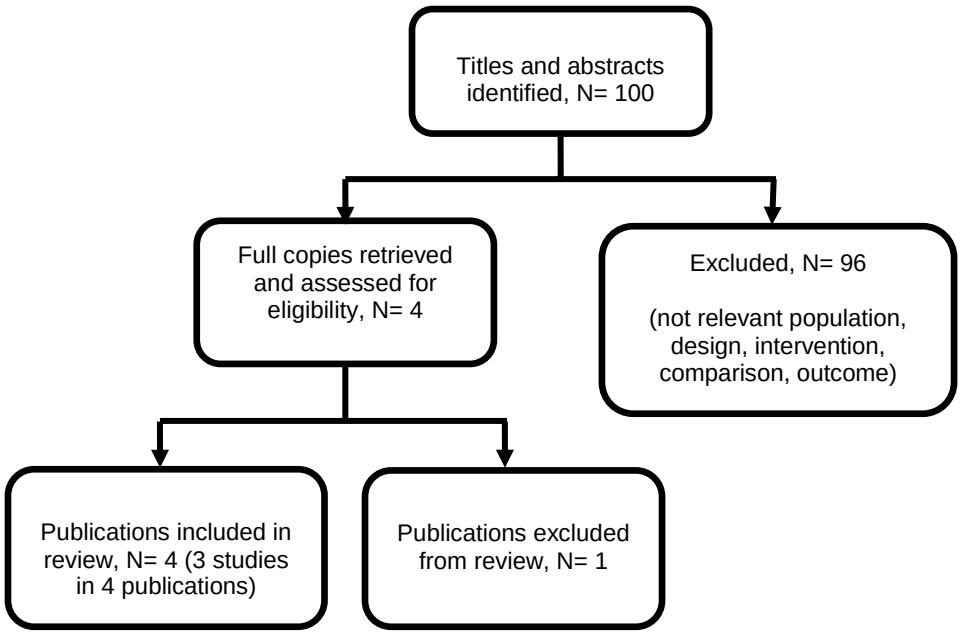
Economic evidence study selection for question 3.1 What is the most effective way to administer oxygen during respiratory support?



Economic evidence study selection for question 3.2 What is the effectiveness and safety of the different assisted ventilation techniques in preterm babies?



Economic evidence study selection for question 3.7 What is the effectiveness of nitric oxide in preterm babies requiring invasive ventilation?



Appendix H – Economic evidence tables

Economic evidence tables for question 1.1 What respiratory support (excluding resuscitation) is the most effective for preterm babies before admission to the neonatal unit

No economic evidence was identified for this review.

Economic evidence tables for question 3.3 What is the most effective way of using surfactant in managing respiratory distress syndrome?

No economic evidence was identified for this review.

Economic evidence tables for question 3.1 What is the most effective way to administer oxygen during respiratory support?

No economic evidence was identified for this review.

Economic evidence tables for question 3.2 What is the effectiveness and safety of the different assisted ventilation techniques in preterm babies?

Reference to the included studies:

1. Huang L, Roberts CT, Manley BJ, Owen LS, Davis PG, Dalziel KM. Cost-Effectiveness Analysis of Nasal Continuous Positive Airway Pressure Versus Nasal High Flow Therapy as Primary Support for Infants Born Preterm, The Journal of Pediatrics, 196, 58-64, 2018
2. Mowitz ME, Zupancic JA, Millar D, Kirpalani H, Gaulton JS, Roberts RS, Mao W, Dukhovny D. Prospective economic evaluation alongside the non-invasive ventilation trial, Journal of Perinatology, 37, 61-66, 2017

Hi Flow vs. nasal continuous positive airway pressure ventilation

Study Country Study type	Intervention details	Study population Study design Data sources	Costs: description and values Outcomes: description and values	Results: Cost-effectiveness	Comments
Huang 2018 Australia	Interventions: Hi Flow compared with nasal continuous positive	Infants ≥28 weeks gestation who required non-invasive ventilation	Costs: patient admission prior to discharge (imaging, pathology, nursing, medical, pharmacy, theater, allied services and neonatal intensive care unit stay); treatment-specific consumable equipment	The ICER of CPAP when compared with:	Perspective: healthcare payer Currency: Australian dollars

Study Country Study type	Intervention details	Study population Study design Data sources	Costs: description and values Outcomes: description and values	Results: Cost-effectiveness	Comments
Cost-effectiveness analysis Conflict of interest: None	airway pressure (CPAP) Hi Flow was stratified according to whether rescue CPAP was allowed To deliver High Flow, either Optiflow Junior or the Precision Flow (Vapotherm) system was used. Majority of babies were on Optiflow Junior.	RCT (Huang 2018) Source of clinical effectiveness data: RCT (n= 435) Source of resource use data: RCT (n= 435) Source of unit costs: from local sources (that is, cost data provided by the participating tertiary centres)	(circuits and the interfaces); and consumable equipment used for invasive ventilation. Mean cost per baby: CPAP: $43,453 (95% CI: $38,071; $48,834) Hi Flow (with CPAP rescue): $40,311 (95% CI: $35,643; $44,978) Hi Flow (without CPAP rescue): $42,620 The difference (CPAP vs. Hi Flow with CPAP rescue): $3,142, p =0.39 The difference (CPAP vs. Hi Flow without CPAP rescue): $833, p =0.82 Primary outcome measure: Treatment failure defined as the need for intubation and invasive ventilation Treatment failures: CPAP: 0.17 Hi Flow (with CPAP rescue): 0.19 Hi Flow (without CPAP rescue): 0.29 The difference (CPAP vs. Hi Flow with rescue): 0.02, p =0.57 The difference (CPAP vs. Hi Flow with rescue): 0.12, p =0.006	High Flow with CPAP rescue): $179,000 per additional failure avoided. At a willingness-to-pay (WTP) of $179,000 per additional case of failure avoided the probability that CPAP was cost effective was <50%. High Flow without CPAP rescue: $7,000 per additional failure avoided. At a willingness-to-pay (WTP) of >$23,000 per additional case of failure avoided the probability that CPAP was cost effective was >70%. Sensitivity analyses: CPAP when compared with Hi Flow without CPAP rescue remained cost effective under alternative scenarios explored.	Cost year: 2015 Time horizon: unclear (death or first discharge from hospital) Discounting: NA Applicability: Partially applicable Quality: Minor methodological limitations Bootstrapping was undertaken to assess uncertainty in costs and outcomes

Study Country Study type	Intervention details	Study population Study design Data sources	Costs: description and values Outcomes: description and values	Results: Cost-effectiveness	Comments
				The cost effectiveness of CPAP when compared with Hi Flow with CPAP rescue remained uncertain under alternative scenarios explored. Overall, sensitivity analyses indicated that cost effectiveness of CPAP was not affected by the use of data from non-lead centres (as opposed to lead centres), the use of treatment specific consumable equipment, the use of dataset with imputed cost data, using imputed non-tertiary costs, changes to Hi Flow consumable costs, and the use of CPAP ventilator costs (as opposed to bubble CPAP costs).	

Nasal continuous positive pressure vs. nasal intermittent positive pressure ventilation

Study Country Study type	Intervention details	Study population Study design Data sources	Costs: description and values Outcomes: description and values	Results: Cost-effectiveness	Comments
Mowitz 2017 US Cost-effectiveness analysis Conflict of interest: none	Interventions: Nasal continuous positive pressure (CPAP) compared with nasal intermittent positive pressure ventilation (NIPPV)	Infants <30 weeks gestation and 1000g at birth who required non-invasive ventilation RCT (Mowitz 2017) (NIPPV [n=497]; CPAP [n =490]) Source of clinical effectiveness data: RCT Source of resource use data: RCT Source of unit costs: unclear	Costs: hospital (hospital stay, ventilation, cannula), physician, medication (antibiotics, antifungals, surfactant, indomethacin, ibuprofen, caffeine, furosemide, thiazide, corticosteroids, vitamin A, parenteral nutrition, nitric oxide), procedure (packed red blood cell transfusions, chest x-ray, abdominal x-ray, echocardiogram, surgery for necrotising enterocolitis, PDA ligation, laser surgery eye) Mean cost per baby: CPAP: $140,404 (95% CI: $133,906; $146,902) NIPPV: $143,745 (95% CI: $137,323; $150,167) The difference: $3,341 (95% CI: −$5,783; $12,466) Primary outcome measure: Survival without BPD at 36 weeks corrected gestational age Percent of babies surviving and without BPD: CPAP: 0.633 NIPPV: 0.616 The difference: -0.017, p = 0.56	CPAP is dominant Sensitivity analyses: Even at a high willingness to pay threshold of $300,000 per survivor without BPD the probability of NIPPV being cost-effective was only 23.5%. The results were robust to changes in cost estimates	Perspective: healthcare payer Currency: USD Cost year: 2013 Time horizon: up to 44 weeks PMA Discounting: NA Applicability: Partially applicable Quality: Minor methodological limitations Bootstrapping was undertaken to assess uncertainty in costs and outcomes

Economic evidence tables for question 3.7 What is the effectiveness of nitric oxide in preterm babies requiring invasive ventilation?

References to the included studies:

1. Field D, Elbourne D, Truesdale A, Grieve R, Hardy P, Fenton AC, Subhedar N, Ahluwalia J, Halliday HL, Stocks J, Tomlin K. Neonatal ventilation with inhaled nitric oxide versus ventilatory support without inhaled nitric oxide for preterm infants with severe respiratory failure: the INNOVO multicentre randomised controlled trial (ISRCTN 17821339), Pediatrics, 115, 926-936, 2005 **AND** Huddy CL, Bennett CC, Hardy P, Field D, Elbourne D, Grieve R, Truesdale A, Diallo K. The INNOVO multicentre randomised controlled trial: neonatal ventilation with inhaled nitric oxide versus ventilatory support without nitric oxide for severe respiratory failure in preterm infants: follow up at 4–5 years, Archives of Disease in Childhood-Fetal and Neonatal Edition, 93, F430-435, 2008
2. Watson RS, Clermont G, Kinsella JP, Kong L, Arendt RE, Cutter G, Linde-Zwirble WT, Abman SH, Angus DC. Clinical and economic effects of iNO in premature newborns with respiratory failure at 1 year, Pediatrics, 124, 1333-1343, 2009
3. Zupancic JA, Hibbs AM, Palermo L, Truog WE, Cnaan A, Black DM, Ballard PL, Wadlinger SR, Ballard RA. Economic evaluation of inhaled nitric oxide in preterm infants undergoing mechanical ventilation, Pediatrics, 124, 1325-1332, 2009

Study **Country** **Study type**	**Intervention details**	**Study population** **Study design** **Data sources**	**Costs: description and values** **Outcomes: description and values**	**Results: Cost-effectiveness**	**Comments**
Field 2005 AND Huddy 2008 UK Cost-effectiveness analysis Conflict of interest: One author has been a paid speaker and has received support from	Interventions: iNO versus no iNO The suggested starting dose was 5 ppm, doubling to 10 ppm in no response achieved; if necessary, the dose was doubled again to 20 ppm and then again if required to 40 ppm.	Infants of <34 weeks' gestation, <28 days old and with severe respiratory failure requiring respiratory support RCT (Field 2005; INNOVO) Source of clinical effectiveness data: RCT (N=108 at 1 year follow up; N=38 at 4-5 years)	Costs: iNO, initial hospitalisation, subsequent hospitalisation, outpatient, GP and community and personal costs Mean cost per participant at year 1: iNO: £35,306 (SD £35,941) No iNO: £20,391 (SD £26,680)	The ICER of iNO (versus no iNO): £2.4 million per additional death or severe disability avoided; £155,365 per additional death avoided; £932,187 per additional death or case of BPD avoided However, these are based on non-	Perspective: NHS and PSS Currency: UK£ Cost year: 2002/2003 Time horizon: 1 year; 4 years Discounting: NA Applicability: Directly applicable Quality: Minor limitations Comments: confidence intervals around costs

Study Country Study type	Intervention details	Study population Study design Data sources	Costs: description and values Outcomes: description and values	Results: Cost-effectiveness	Comments
British Ino Therapeutics and another author received educational support from Ino Therapeutics.		Source of resource use data: RCT (N=108 at 1 year follow up; N=38 at 4-5 years) Source of unit costs: national sources	The difference: £14,915 (95% CI: £2,803; £27,026) Mean cost per participant at year 4 (over preceding 12 months): iNO: £2,638 (SD: £9,454) No iNO: £2,416 (SD £5,604) The difference: £223 (95% CI: -£5,159 to £5,605) Primary outcome measures: Field et al., death or severe disability; death; death or supplemental oxygen at 36 weeks PMA Huddy et al., proportion of children with disability; cognitive functioning; neuromotor, sensory and communication; and abnormal behaviour	significant differences in the primary outcomes. There were no significant differences in costs in year 4 between the groups Sensitivity analysis (on results at 1 year) The results were robust to variations in the unit cost of iNO and hospitalisation costs.	were estimated using bootstrapping.

Study Country Study type	Intervention details	Study population Study design Data sources	Costs: description and values Outcomes: description and values	Results: Cost-effectiveness	Comments
			Proportion of babies dead or with severe disability at 1 year follow-up: iNO: 0.673 No iNO: 0.679 The difference: -0.006; p = ns Proportion of babies dead at 1 year follow-up: iNO: 0.545 No iNO: 0.642 The difference: -0.096, p = ns Proportion of babies dead or on supplemental oxygen at 36 weeks PMA: iNO: 0.890 No iNO: 0.906 The difference: -0.016, p = ns There were no significant differences between the groups in any of the clinical		

Study Country Study type	Intervention details	Study population Study design Data sources	Costs: description and values Outcomes: description and values	Results: Cost-effectiveness	Comments
			outcomes at a long term follow-up		

Study Country Study type	Intervention details	Study population Study design Data sources	Costs: description and values Outcomes: description and values	Results: Cost-effectiveness	Comments
Watson 2009 US Cost-utility analysis Conflict of interest: funded by manufacturer (Ikaria, formerly iNO therapeutics)	Interventions: iNO versus no iNO (placebo) The suggested dose was 5 ppm, doubling to 10 ppm	Infants of ≤34 weeks' gestation, weighed 500 to 1250 g, were <48 hours old and required invasive ventilation RCT (Watson 2005) Source of clinical effectiveness data: RCT (N=793) Source of resource use data: RCT (N=631 inpatient data; N=512 post-discharge data) Source of unit costs: local and national sources (billing information, cost reports, Medicare fee schedule)	Costs: iNO, initial hospitalisation, physician, re-hospitalisation, medication, emergency department visits, outpatient visits andlost work Mean cost per participant: iNO: $285,200 No iNO: $260,700 The difference: $24,400 Primary outcome measure: QALYs (utility weights from various published studies) Mean QALYs per participant: iNO: 0.604	The ICER of iNO (versus no iNO): $2.25 million per QALY gained The probability of iNO being cost effective at a WTP of $500,000 per QALY gained was 12.9% Sensitivity analysis: The findings were robust to the cost of iNO, medication costs and utilities. The results were sensitive to physician reimbursement and post-discharge costs.	Perspective: health care payer plus indirect costs Currency: USD Cost year: likely 2005 Time horizon: under 1 year Discounting: NA Applicability: Partially applicable Quality: Minor limitations Comments: confidence intervals around costs were estimated using bootstrapping.

Study Country Study type	Intervention details	Study population Study design Data sources	Costs: description and values Outcomes: description and values	Results: Cost-effectiveness	Comments
			No iNO: 0.593 The difference: 0.011, SD 0.026	The inclusion of indirect costs did not impact the conclusions. Sub-group analysis: Among babies in the 750-999 g stratum, the ICER was $102,500 per QALY gained, with an 81.2% probability at a WTP of $500,000 per QALY gained	

Study Country Study type	Intervention details	Study population Study design Data sources	Costs: description and values Outcomes: description and values	Results: Cost-effectiveness	Comments
Zupancic 2009 Cost-effectiveness analysis US Conflict of interest: one author received reimbursement for participation in an Ikaria expert advisory panel and internal	Interventions: iNO versus no iNO iNO was administered at weekly decreasing doses, beginning at 20 ppm, for a minimum of 24 days.	Preterm infants ≤34 weeks GA, 500-1250g and who required respiratory support RCT (Hibbs 2008) Source of clinical effectiveness data: RCT (n=582) Source of resource use data: RCT and	Costs: iNO, hospital stay, physician fees, invasive ventilation, CPAP, oxygen Mean cost for infants initiated between 7-21 days): iNO: $194,702 No iNO: $193,125 The difference: $1,576	In infants initiated between 7 and 21 days the ICER of iNO: $21,297 per additional survivor without BPD The probability that iNO reduces costs and improves outcomes was 43%	Perspective: health care payer Currency: USD Cost year: 2006 Time horizon: under 1 year (up to discharge) Discounting: NA Applicability: Partially applicable Quality: Minor limitations

Study Country Study type	Intervention details	Study population Study design Data sources	Costs: description and values Outcomes: description and values	Results: Cost-effectiveness	Comments
presentation. Another 2 authors received support from Ikaria to fund completion of 24-month follow-up and data analysis. One author received reimbursement for travel to investigators meetings.		database for a similar group of infants in 1 NICU (N=582) Source of unit costs: national sources (Medicare fee schedule)	Mean cost for infant initiated between 7-14 days): iNO: $181,525 No iNO: $187,407 The difference: -$5,882 Primary outcome measure: survival without BPD Proportion of infants surviving without BPD: iNO initiated between 7-21 days iNO: 0.439 No iNO: 0.365 The difference: 0.074, p = 0.04 iNO initiated between 7-14 days iNO: 0.491 No iNO: 0.270 The difference: 0.221, p = 0.0004	In infants initiated between 7 and 14 days iNO was dominant The probability that iNO reduces costs and improves outcomes was 71% The probability of iNO being cost effective was above 70% at any WTP values Sensitivity analyses: For infants initiated on iNO between 7-21 days iNO was cost savings through a cost of approximately $10,000 per course and $17,000 for infants initiated on iNO between 7 and 14 days (base case $12,000 per course) When varying hospital costs 50-150% around their base case values the ICER of iNO was $80,889 and -$36,479, respectively.	Comments: confidence intervals around costs were estimated using bootstrapping

Study Country Study type	Intervention details	Study population Study design Data sources	Costs: description and values Outcomes: description and values	Results: Cost-effectiveness	Comments
				When varying physician costs 50-150% around their base case values the ICER of iNO was $7,485 and $36,925, respectively. When varying non-iNO costs 50-150% around their base case values the ICER of iNO was $95,610 and -$51,199, respectively.	

Appendix I – Economic evidence profiles

Economic evidence profiles for question 1.1 What respiratory support (excluding resuscitation) is the most effective for preterm babies before admission to the neonatal unit

No economic evidence was identified for this review.

Economic evidence profiles for question 3.3 What is the most effective way of using surfactant in managing respiratory distress syndrome?

No economic evidence was identified for this review.

Economic evidence profiles for question 3.1 What is the most effective way to administer oxygen during respiratory support?

No economic evidence was identified for this review.

Economic evidence profiles for question 3.2 What is the effectiveness and safety of the different assisted ventilation techniques in preterm babies?

Hi Flow vs. nasal continuous positive airway pressure ventilation

Study and country	Limitations	Applicability	Other comments	Incremental costs	Incremental effects	ICER	Uncertainty
Huang 2018 Australia	Minor limitations[1]	Partially applicable[2]	Type of economic analysis: cost effectiveness analysis Comparison: CPAP (vs. Hi Flow without and with CPAP rescue)	CPAP vs. Hi Flow with CPAP rescue: $3,142 CPAP vs. Hi Flow without CPAP rescue: $833	CPAP vs. Hi Flow with CPAP rescue: -0.02 CPAP vs. Hi Flow without CPAP rescue: -0.12	$179,000 per additional failure avoided $7000 per additional failure avoided	CPAP vs. Hi Flow with CPAP rescue: The difference in costs and outcomes was not significant. At a willingness-to-pay (WTP) of $179,000 per additional case of failure avoided the probability that CPAP was cost effective was <50. CPAP vs. Hi Flow without CPAP rescue:

Study and country	Limitations	Applicability	Other comments	Incremental costs	Incremental effects	ICER	Uncertainty
			Primary measure of outcome: survivors without BPD				The difference in costs not significant; the difference in outcomes was significant (p=0.006). At a WTP of >$23,000 per additional case failure avoided the probability that CPAP was cost effective was >70%. CPAP vs. Hi Flow without CPAP rescue remained more cost effective under alternative scenarios. The cost effectiveness of CPAP when compared with Hi Flow (with CPAP rescue) remained uncertain under alternative scenarios explored. Cost effectiveness was not affected by the use of data from non-lead centres (as opposed to lead centres), the use of treatment specific consumable equipment, the use of dataset with imputed cost data, using imputed non-tertiary costs, changes Hi Flow consumable costs, and the use of CPAP ventilator costs (as opposed to bubble CPAP).

1. Short time horizon; local unit cost data
2. Non-UK study; no QALYs

Nasal continuous positive pressure vs. nasal intermittent positive pressure ventilation

Study and country	Limitations	Applicability	Other comments	Incremental costs	Incremental effects	ICER	Uncertainty
Mowitz 2017	Minor limitations[1]	Partially applicable[2]	Type of economic analysis: cost effectiveness analysis	$3,341	-0.017	CPAP dominant	The difference in costs and outcomes was not significant.

Study and country	Limitations	Applicability	Other comments	Incremental costs	Incremental effects	ICER	Uncertainty
US			Comparison: NIPPV (vs. CPAP) Primary measure of outcome: survivors without BPD				Results robust to changes in cost estimates. Bootstrapping indicated that even at very high levels of willingness to pay threshold per survivor without BPD the probability of NIPPV being cost effective was low (i.e. 23.5%).

1. Short time horizon; unclear source of unit costs
2. Non-UK study; no QALYs, however this was not a problem since CPAP was found to be dominant

Economic evidence profiles for question 3.7 What is the effectiveness of nitric oxide in preterm babies requiring invasive ventilation?

Inhaled nitric oxide versus no inhaled nitric oxide

Study and country	Limitations	Applicability	Other comments	Incremental costs	Incremental effects	ICER	Uncertainty
Field 2005 AND Huddy 2008 UK	Minor limitations[1]	Directly applicable[2]	Cost effectiveness analysis Outcome: death or severe disability; death; death or supplemental oxygen at 36 weeks PMA – year 1 Proportion of children with disability; cognitive functioning; neuromotor, sensory and communication; and abnormal behaviour - year 4 Time horizon: up to 4 years	£14,915 (at 1 year) £223 (in year 4)	Year 1 -0.006 (babies dead or with severe disability) -0.096 babies dead -0.016 babies dead or on supplemental oxygen at 36 weeks PMA Year 4 No difference in clinical outcomes	Year 1 £2.4 million per additional death or severe disability avoided £155,365 per additional death avoided £932,187 per additional death or case of BPD avoided	Year 1, the difference in mean costs 95% CI £2,803; £27,026 Year 4, the difference in mean costs 95% CI: -£5,159 to £5,605 The results at year 1 were robust to variations in the unit cost of iNO and

Study and country	Limitations	Applicability	Other comments	Incremental costs	Incremental effects	ICER	Uncertainty
							hospitalisation costs
Watson 2009 US	Minor limitations[3]	Partially applicable[4]	Cost-utility analysis Outcome: QALYs Time horizon: 1 year	$24,400	0.011	$2.25 million	The probability of iNO being cost effective at a WTP of $500,000 per QALY was 12.9% The findings were robust to the cost of iNO, medication costs and utilities. The results were sensitive to physician reimbursement and post-discharge costs.
Zupancic 2009 US	Minor limitations[5]	Partially applicable[6]	Cost-effectiveness analysis Outcome: survival without BPD Time horizon: 1 year (until discharge)	$1,576 (infant initiated on iNO 7-21 days) -$5,882 (infant initiated on iNO 7-14 days)	0.074 (infant initiated on iNO 7-21 days) 0.221 (infant initiated on iNO 7-14 days	$21,297 per additional survivor without BPD (initiated on iNO 7-21 days) iNO dominant (initiated on iNO 7-14 days)	Initiated on iNO 7-21 days The probability that iNO reduces costs and improves outcomes was 43% Initiated on iNO 7-14 days

Study and country	Limitations	Applicability	Other comments	Incremental costs	Incremental effects	ICER	Uncertainty
							The probability that iNO reduces costs and improves outcomes was 71% The probability of iNO being cost effective was above 70% at any WTP values For infants initiated on iNO 7-21 days iNO was cost savings through a cost of approximately $10,000 per course and $17,000 for infants initiated on iNO between 7 and 14 days (base case $12,000 per course). When varying hospital costs 50%-150% around their base case values the ICER of iNO was $80,889 and -

Study and country	Limitations	Applicability	Other comments	Incremental costs	Incremental effects	ICER	Uncertainty
							$36,479, respectively. When varying physician costs 50-150% around their base case values the ICER of iNO was $7,485 and $36,925, respectively. When varying non-iNO costs 50-150% around their base case values the ICER of iNO was $95,610 and -$51,199, respectively.

1. At 1 year assessment outpatient and community costs were extrapolated from an initial sampling period over 4-weeks. However, this doesn't matter since these costs accounted only for a small proportion of total costs. In year 4 costs were estimated based on preceding 12 months.
2. UK study, no QALYs
3. Unit costs were from local and national sources
4. US study, estimated QALYs with utility weights based on published literature derived using various measures from other paediatric and adult populations
5. Unit costs from various sources including a tertiary care NICU centre, national sources and other published sources
6. US study, no QALYs. However, iNO was found to be dominant in babies initiated on iNO at 7-14 days

Appendix J – Economic analysis

Economic analysis for question 1.1 What respiratory support (excluding resuscitation) is the most effective for preterm babies before admission to the neonatal unit

No economic analysis was undertaken for this review.

Economic analysis for question 3.3 What is the most effective way of using surfactant in managing respiratory distress syndrome?

No economic analysis was undertaken for this review.

Economic analysis for question 3.1 What is the most effective way to administer oxygen during respiratory support?

No economic analysis was undertaken for this review.

Economic analysis for question 3.2 What is the effectiveness and safety of the different assisted ventilation techniques in preterm babies?

Non-invasive ventilation techniques

Introduction

In the NMA for the outcome of mortality prior to discharge and BPD at 36 weeks PMA there was no evidence to suggest a difference between between CPAP, NIPPV, BiPAP/SiPAP, or Hi Flow. Similarly, pairwise analyses did not identify any meaningful differences between non-invasive ventilation techniques.

The committee acknowledged two existing non-UK economic evaluations comparing CPAP with NIPPV and Hi Flow, respectively. However, these analyses did not include all non-invasive ventilation techniques of interest.

Given the lack of differences in the clinical effectiveness between non-invasive ventilation techniques and the lack of existing economic evidence the committee considered it important to compare the costs of the techniques to aid considerations of cost effectiveness. Generally the NHS Reference Costs (DHSC, 2018) is the recommended source of unit cost data that should be used to aid considerations of cost effectiveness. However, the committee explained that the neonatal activity payments are based on the level of activity (that is, intensive care, high dependency and special care) rather than procedures. As a result, costings of non-invasive ventilation techniques were undertaken to aid considerations of cost effectiveness and included equipment acquisition costs, maintenanece costs and consumable costs.

Intervention assessed

According to the committee, there are different types of CPAP including bubble CPAP, ventilator-based CPAP and flow drive CPAP. However, bubble CPAP and ventilator-based CPAP is uncommon in the NHS and as a result these types of CPAP were not considered in the costings.

The committee explained that there are two different types of Hi Flow including Optiflow and Vapotherm. The costings considered both types of Hi Flow and also ventilator-based Hi Flow.

In addition to CPAP and Hi Flow the costs for NIPPV, BiPAP and SiPAP were also estimated.

Methods

Non-invasive ventilation equipment incur a capital cost, requiring an up-front payment. There are 2 aspects to capital costs: 1) Opportunity cost – this is the money spent on equipment that could have been invested in another venture. This cost is calculated by applying an interest rate on the sum invested in the capital. 2) Depreciation cost – the equipment has a certain lifespan and depreciates over time and will eventually need to be replaced. The usual practice for economic evaluation is to calculate an 'annual equivalent cost'. This is calculated by annuitising the initial capital outlay (including training costs) over the expected life of the equipment. Calculating the equivalent annual cost means making allowance for the differential timing of costs by discounting.

The formula for calculating the equivalent annual cost is: E = (K+T) / A(n,r)

Where:

- E = equivalent annual cost
- K = purchase price of the device
- T = training
- A(n,r) = annuity factor (n years at interest rate r)
- r = discount (interest) rate
- n = equipment lifespan (years)

Using this formula the equivalent annual cost of equipment was estimated. In all cases, it was assumed that that equipment should last for at least 7 years before it needs to be replaced. In addition to the capital outlay, each mode is associated with consumables mainly circuit, prongs, masks and bonnets. For the purposes of costings, it was assumed that circuits need to be changed every 7 days and the mean duration of non-invasive ventilation is approximately 10 days. This was based on the duration of non-invasive ventilation reported in the RCTs included in the guideline systematic review. It was further assumed that equipment will be used at a full capacity. So for example, to apportion equipment and maintenance costs it was assumed that approximately 37 babies will use the same equipment per annum (that is, 365 days divided by an average duration of non-invasive ventilation of 10 days). For each technique the overall costs per preterm infant are reported and include capital equipment costs, consumable costs and equipment maintenance costs.

According to the committee the frequency of circuit changes for Hi Flow (Vapotherm) varies from 7 to 30 days. Costings were undertaken assuming both frequencies of circuit changes.

Results – intervention costs

CPAP (Flow drive)

According to the committee, FABIAN is a commonly used system to deliver CPAP in the UK. Inspiration Healthcare was approached to provide accurate costing information on CPAP system.

There are different FABIAN systems available to the NHS. For example, the FABIAN

Therapy Evolution is a 2-in-1 device that offers CPAP and Hi Flow; the FABIAN plus CPAP is a 3-in-1 device that offers CPAP and Hi Flow plus standard invasive ventilation modes; and FABIAN HFOVi is a 4-in-1 device that offers CPAP and Hi Flow plus standard invasive ventilation modes plus invasive High Frequency Oscillation Ventilation.

According to Inspiration Healthcare, FABIAN equipment have an upfront cost of around £9,000 to £25,000, depending on the model; and all offer CPAP as a standard option. These costs can vary depending on what software options and accessories are required. For the purposes of costings only FABIAN Therapy Evolution and FABIAN HFOVi systems were considered.

Table 44 and Table 45 below presents the parameters used to calculate the equivalent annual costs.

Table 44: Equivalent annual cost of CPAP based on a FABIAN 2-in-1 device

Parameter	Value	Source
K = purchase price	£9,000	Inspiration Healthcare
T = training	£0	Committee assumption that training would be minimal
r = discount	3.5%	NICE
n = equipment lifespan	7	Assumption informed by committee
A (n, r) = annuity factor (n years at interest rate r)	6.33	Calculated
E = equivalent annual cost	£1,422.13	Calculated

Table 45: Equivalent annual cost of CPAP based on a FABIAN HFOVi

Parameter	Value	Source
K = purchase price	£25,000	Inspiration Healthcare
T = training	£0	Committee assumption that training would be minimal
r = discount	3.5%	NICE
n = equipment lifespan	7	Assumption informed by committee
A (n, r) = annuity factor (n years at interest rate r)	6.33	Calculated
E = equivalent annual cost	£3,950.35	Calculated

According to Inspiration Healthcare for the consumables there are several options depending on whether the aim is wean to CPAP from a standard invasive ventilation mode or to wean from CPAP to a Hi Flow option. However, for CPAP only option the consumables required are outlined in Table 46. The consumables are the same irrespective of the device used.

Table 46: The consumables associated with CPAP FABIAN system

Consumable	Price	Cost per infant	Source
FABIAN Delivery Circuit and INSPIRE Generator complete with 3 x nasal prongs	£645/20 units	£64.50	Inspiration Healthcare
INSPIRE Bonnet	£54	£5.40	Inspiration Healthcare

Consumable	Price	Cost per infant	Source
Total cost of consumables per infant	NA	£69.90	Calculated

In addition to the capital outlay and consumable costs the committee advised that equipment would need to be serviced annually. Inspiration Healthcare explained that in the UK hospitals have two options. One is to attend a recognised service course to allow their own BioMedical Engineers to undertake routine servicing and repairs, or secondly to place the equipment on contract with Inspiration Healthcare. The annual servicing costs are approximately £628 for FABIAN Therapy Evolution and £1,113 for FABIAN HFOVi. These estimates exclude spare parts that maybe used on a case-by-case basis.

Based on the above the mean cost of CPAP was estimated to be £127 per preterm infant based on FABIAN 2-in-1 device and £211per preterm infant based on FABIAN HFOVi device.

Hi Flow (Vapotherm)

According to the committee, Vapotherm (Solus Medical Ltd.) is a commonly used equipment to provide Hi Flow in the UK. The manufacturer was approached on a several occasions. However, no response was received to a request to provide accurate costings on Vapotherm system. Consequently, the costings are mainly based on the committee expert opinion. It was estimate that Vapotherm has an upfront capital cost of £5,571 (NHS Supply Chain, 2017).

Table 47 below presents the parameters used to calculate the equivalent annual cost.

Table 47: Equivalent annual cost of Hi Flow (Vapotherm)

Parameter	Value	Source
K = purchase price	£5,571	NHS Supply Chain, 2017
T = training	£0	Committee assumption that training would be minimal
r = discount	3.5%	NICE
n = equipment lifespan	7	Assumption informed by committee
A (n, r) = annuity factor (n years at interest rate r)	6.33	Calculated
E = equivalent annual cost	£880.36	Calculated

The consumables required were estimated assuming circuit changes every 7 and 30 days and are outlined in Table 48 and Table 49 below, respectively.

Table 48: The consumables associated with Hi Flow (Vapotherm) assuming circuit changes every 7 days (that is, 2 circuits per baby over a mean duration of 10 days on non-invasive ventilation)

Consumable	Price	Cost per infant	Source
Disposable circuit Low Flow Infant/Neonate 1-8lpm - with water path-vapour transfer cartridge-delivery tube- use with Vapotherm System only	£487.50/5 units	£195.00	NHS Supply Chain, 2017

Consumable	Price	Cost per infant	Source
High flow therapy single prong nasal cannula Prem/Neonate/Infant	£153.06/25 units	£6.12	NHS Supply Chain, 2017
Total cost of consumables per infant	NA	£201.12	Calculated

Table 49: The consumables associated with Hi Flow (Vapotherm) assuming circuit changes every 30 days (that is, 1 circuit per baby over a mean duration of 10 days on non-invasive ventilation)

Consumable	Price	Cost per infant	Source
Disposable circuit Low Flow Infant/Neonate 1-8lpm - with water path-vapour transfer cartridge-delivery tube- use with Vapotherm System only	£487.50/5 units	£97.50	NHS Supply Chain, 2017
High flow therapy single prong nasal cannula Prem/Neonate/Infant	£153.06/25 units	£6.12	NHS Supply Chain, 2017
Total cost of consumables per infant	NA	£103.62	Calculated

In addition to the capital outlay and consumable costs the committee advised that equipment would need to be serviced annually. Maintenenace costs for Vapotherm system could not be identified. Consequently, the committee advised that servicing costs would be similar to the other available Hi Flow system (that is, Optiflow, Fisher & Paykel). However, it was noted that since the equipment costs are higher (when compared with Optiflow) it is very likely that servicing costs are also likely to be higher. Nethertheless, given the lack of better estimates, the annual maintenance costs of approximately £374.42 were assumed (Fisher & Paykel, Optiflow system).

Based on the above estimates the cost of Hi Flow (Vapotherm) was estimated to be £236 and £138 per preterm infant assuming circuit changes every 7 and 30 days, respectively.

Hi Flow (Optiflow)

According to the Committee, Optiflow (Fisher & Paykel) is another commonly used equipment to provide Hi Flow in the UK. Fisher & Paykel was approached to provide accurate information on the cost of equipment, consumables and maintenance costs. According to Fisher & Paykel, Optiflow has an upfront capital cost of £2,475.

Table 50 below presents the parameters used to calculate the equivalent annual cost.

Table 50: Equivalent annual cost of Hi Flow (Optiflow)

Parameter	Value	Source
K = purchase price	£2,475	Fisher & Paykel
T = training	£0	Committee assumption that training would be minimal
r = discount	3.5%	NICE

Parameter	Value	Source
n = equipment lifespan	7	Assumption informed by committee
A (n, r) = annuity factor (n years at interest rate r)	6.33	Calculated
E = equivalent annual cost	£391.08	Calculated

The consumables required are outlined in Table 51 below.

Table 51: The consumables associated with Hi Flow (Optiflow)

Consumable	Price	Cost per infant	Source
Heated circuit and chamber for Optiflow Junior	£385.00/10 units	£77.00	Fisher & Paykel (RT330)
Optiflow Junior interface - premature	£525/20 units	£26.25	Fisher & Paykel (OPT312)
Total cost of consumables per infant	NA	£103.25	Calculated

Fisher & Paykel explained that the wiggle pads are required too. However, these are not needed on initial set-up of Optiflow, as the interface will already come with these already attached. Sometimes they become dirty with mucus and they are then changed without having to change the full interface. However, the costs of these are negligible and were not considered.

In addition to the capital outlay and consumable costs the committee advised that equipment would need to be serviced annually. Fisher & Paykel advised that there are various options available to hospitals in the UK. However, generally the annual cost is approximately £374 per annum including major overhaul every 5 years.

Based on the above estimates the cost of Hi Flow (Optiflow) was estimated to be £125 per preterm infant.

Hi Flow (SLE)

According to SLE, SLE 6000HFO SLHF equipment can be used to deliver Hi Flow in addition to a number of other respiratory support modes including invasive, BiPAP and NIPPV modes. The equivalent annual cost of equipment is the same as outlined for NIPPV in Table 53 and is equivalent to £4,235.41 using SLE6000HFO SLHF ventilator.

The consumables are summarised in Table 52 below.

Table 52: The consumables associated with Hi Flow, SLE6000 ventilator

Consumable	Price	Cost per infant	Source
SLE6000 Single use Neonatal/Infant breathing circuit – 10/15mm tubing, dual heated wire. Includes humidification chamber	£194.00/7 units	£55.43	SLE
SLE6000 Premature nasal cannula & adaptor Kit Qty 20 for O2 Therapy mode. Max. Flow	£390/20 units	£19.50	SLE

Consumable	Price	Cost per infant	Source
Rate 6L/min. Contains 20x nasal cannula & 20x 7.5mm connector			
Total cost of consumables per infant	NA	£74.93	Calculated

Similarly, the servicing costs are the same as outlined for NIPPV mode. For the purposes of the costings a lower estimate of £590 per annum was used.

Based on the above estimates the cost of Hi Flow (SLE) was estimated to be £209 per preterm infant.

NIPPV

According to the committee, SLE devices are commonly used to provide NIPPV in the UK. SLE was approached to provide accurate information on the cost of equipment, consumables and servicing costs. RCTs included in the clinical review and the committee was referring to SLE2000 and SLE5000 models. However, SLE explained that even though SLE2000 and SLE5000 are capable of delivering NIV using dual-limb patient interfaces such as Miniflow as well as older, less popular, patient interfaces such as Inca or Argyle prongs. There are only a few SLE2000 machines still in use in the UK and the majority of centres are using the SLE5000 model and the new SLE6000 model that is capable of delivering all types of NIV modes. Moreover, the new ventilators are capable of delivering also invasive ventilation modes.

For NIPPV SLE 6000HFO SLHF or SLE6000c SL equipment could be used. SLE 6000HFO SLHF is also capable of providing all invasive modes, HFO, CPAP and Hi Flow in addition to NIPPV mode. Model SLE6000c SL is capable of providing CPAP in addition to all invasive modes and NIPPV mode.

SLE6000c SL has an upfront capital cost of £19,304 and SLE6000HFO SLHF £26,804.

Table 53 and Table 54 below presents the parameters used to calculate the equivalent annual costs.

Table 53: Equivalent annual cost of NIPPV, SLE6000c SL

Parameter	Value	Source
K = purchase price	£19,304	SLE
T = training	£0	Committee assumption that training would be minimal
r = discount	3.5%	NICE
n = equipment lifespan	7	Assumption informed by committee
A (n, r) = annuity factor (n years at interest rate r)	6.33	Calculated
E = equivalent annual cost	£3,050.30	Calculated

Table 54: Equivalent annual cost of NIPPV, SLE6000HFO SLHF

Parameter	Value	Source
K = purchase price	£26,804	SLE
T = training	£0	Committee assumption that training would be minimal

Parameter	Value	Source
r = discount	3.5%	NICE
n = equipment lifespan	7	Assumption informed by committee
A (n, r) = annuity factor (n years at interest rate r)	6.33	Calculated
E = equivalent annual cost	£4,235.41	Calculated

The consumables required are the same irrespective of the SLE6000 model and are outlined in Table 55 below.

Table 55: The consumables associated with NIPPV, SLE6000 ventilator

Consumable	Price	Cost per infant	Source
SLE6000 Single use Neonatal/Infant breathing circuit – 10/15mm tubing, dual heated wire. Includes humidification chamber	£194.00/7 units	£55.43	SLE
SLE Miniflow CPAP driver for use with SLE ventilators. Green	£230/20 units	£11.50	SLE
Nasal prong for SLE Miniflow or Medijet. Xsmall	£50.50/10 units	£5.05	SLE
Bonnet for SLE Miniflow-Medijet xxsmall. Green	£59.70/10 units	£5.97	SLE
Measuring tape for SLE Miniflow or Medijet bonnets (paper version single use)	£2.00/20 units	£0.10	SLE
Total cost of consumables per infant	NA	£78.05	Calculated

In addition to the capital outlay and consumable costs the committee advised that equipment would need to be serviced annually. Fisher & Paykel advised that there are 2 options available. Option 1 includes preventative servicing at £590 per annum and Option 2 includes comprehensive servicing at a cost of £1,282 per annum. For the purposes of costing a lower estimate of £590 was used.

Based on the above estimates the cost of NIPPV was estimated to range from £179 to £212 per preterm infant, using SLE6000c SL and SLE6000HFO SLHF, respectively.

BiPAP

SLE 6000HFO SLHF or SLE6000c SL equipment can be used to deliver BiPAP. The equivalent annual cost of equipment is the same as outlined for NIPPV in Table 53 and Table 54 and is equivalent to £3,050.30 and £4,235.41 using SLE6000c SL and SLE6000HFO SLHF ventilators, respectively. However, the consumables are slightly different and are summarised in Table 56 below.

Table 56: The consumables associated with BiPAP, SLE6000 ventilator

Consumable	Price	Cost per infant	Source
SLE6000 Single use Neonatal/Infant breathing circuit – 10/15mm tubing, dual	£194/7 units	£55.43	SLE

Consumable	Price	Cost per infant	Source
heated wire. Includes humidification chambe			
SLE1000 CPAP generator only (including 3 prongs - S, M, L	£349/10 units	£34.90	SLE
SLE1000 CPAP Bonnet - white, size 000	£59/10 units	£5.90	SLE
Cannulaide, size 0 for babies	£124/25 units	£4.96	SLE
Total cost of consumables per infant	NA	£101.19	Calculated

Similarly, just like for NIPPV the lower estimate of servicing costs of £590 per annum was used.

Based on the above estimates the cost of BiPAP was estimated to range from £202 to £235 per preterm infant, using SLE6000c SL and SLE6000HFO SLHF, respectively.

SiPAP

According to the Committee, Infant Flow (Carefusion) devices are commonly used to provide SiPPV in the UK. Carefusion was approached to provide accurate information on the cost of equipment, consumables and servicing costs. Infant Flow has an upfront capital cost of £7,250.

Table 57 below presents the parameters used to calculate the equivalent annual cost.

Table 57: Equivalent annual cost of SiPAP, Infant Flow

Parameter	Value	Source
K = purchase price	£7,250	Carefusion
T = training	£0	Committee assumption that training would be minimal
r = discount	3.5%	NICE
n = equipment lifespan	7	Assumption informed by committee
A (n, r) = annuity factor (n years at interest rate r)	6.33	Calculated
E = equivalent annual cost	£1,145.60	Calculated

The consumables required are outlined in Table 58.

Table 58: The consumables associated with SiPAP, Infant Flow

Consumable	Price	Cost per infant	Source
INFT Flow LP Generator, S, M, L Prongs, Size Guide and F&P RT132 Neonatal SingLelimb Heated Circuit F&P MR730 & MR850 - circuit and generator	£795.92/20 units	£79.59	Carefusion
INFT Flow LP Headgear single patient use extra small 1721 cm - LP headgear	£79.59/10 units	£7.96	SLE

Consumable	Price	Cost per infant	Source
INFT Flow LP Bonnet Single Patient Use; Size 000 White 18-20 cm - LP Bonnets	£67.35/10 units	£6.74	Carefusion
INFT FLOW LP nasal mask single patient use extra small - LP masks	£79.59/20 units	£3.98	Carefusion
INFT Flow LP nasal prong single patient use extra small - LP prongs	£51.43/10 units	£5.14	Carefusion
Total cost of consumables per infant	NA	£103.41	Calculated

In addition to the capital outlay and consumable costs the committee advised that equipment would need to be serviced annually. However, Carefusion could not provide cost estimates associated with the servicing of their equipment. As a result, it was assumed that the equipment servicing costs would be similar to those of other devices and for the purposes of costings £590 per annum was used (SLE).

Based on the above estimates the cost of SiPAP was estimated to be £152 per preterm infant using Infant Flow system.

Summary

Hi Flow (Optiflow) and CPAP FABIAN 2-in-1 device offering CPAP and Hi Flow results in lower intervention costs when compared with all other NIV techniques (Table 59). The cost of Hi Flow (Vapotherm) was sensitive to the frequency of circuit changes. When assuming that circuit is changed only every 30 days Hi Flow (Vapotherm) resulted in similar costs to Hi Flow (Optiflow) and CPAP. However, when assuming circuit changes every 7 days, like for other NIV techniques, Hi Flow (Vapotherm) resulted in the highest cost when compared with all other techniques due to high consumable costs. There seems to be little difference between NIPPV and BiPAP (SLE6000) modes with costs dependent on the equipment used. Although, SiPAP (Infant Flow) has also relatively low intervention costs when compared with other non-invasive ventilation modes.

Table 59: Summary of the findings

Mode	Cost per infant	Manufacturer/system	Other modes that can be delivered
Hi Flow (Optiflow)	£125	Optiflow, Fisher & Paykel	NA
CPAP (Flow drive)	£127	FABIAN, Inspire Healthcare	Hi Flow
Hi Flow (Vapotherm - circuit changed every 30 days)	£138	Vapotherm, Solus Medical	NA
SiPAP (Infant Flow)	£152	Infant Flow, Carefusion	NA
NIPPV (SLE)	£179	SLE6000c SL, SLE	Invasive, CPAP
BiPAP (SLE)	£202	SLE6000c SL, SLE	Invasive, CPAP, NIPPV
Hi Flow (SLE)	£209	SLE6000HFO SLHF, SLE	Invasive, HFO, CPAP, NIPPV

Mode	Cost per infant	Manufacturer/system	Other modes that can be delivered
CPAP (Flow drive)	£211	FABIAN, Inspire Healthcare	Hi Flow, Standard invasive ventilation modes, High Frequency Oscillation Ventilation
NIPPV (SLE)	£212	SLE6000HFO SLHF, SLE	Invasive, HFO, CPAP, Hi Flow
BiPAP (SLE)	£235	SLE6000HFO SLHF, SLE	Invasive, HFO, CPAP, NIPPV, Hi Flow
Hi Flow (Vapotherm - circuit changed every 7 days)	£236	Vapotherm, Solus Medical	NA

References

DHSC 2018

DHSC. NHS reference costs 2016/17. Department of Health and Social Care, 2018

NHS Supply Chain 2017

NHS Supply Chain, 2017. Available at: https://www.supplychain.nhs.uk/ Last accessed 25.07.2018

Economic analysis for question 3.7 What is the effectiveness of nitric oxide in preterm babies requiring invasive ventilation?

No economic analysis was undertaken for this review.

Appendix K – Excluded studies

Excluded studies for question 1.1 What respiratory support (excluding resuscitation) is the most effective for preterm babies before admission to the neonatal unit

Clinical studies

Study	Reason for Exclusion
Alallah, J., Nasal ventilation is not superior to nasal CPAP in extreme preterm infants, Journal of Clinical Neonatology, 2, 161-163, 2013	Inclusion criteria includes preterm babies within first 7 days of life, not in line with delivery room setting
Bahadue, F. L., Soll, R., Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome, Cochrane Database of Systematic Reviews, 11, CD001456, 2012	Comparison not of interest for review: early vs delayed surfactant administration
Bevilacqua, G., Parmigiani, S., Robertson, B., Caramia, G., Catalani, P., Chiappe, F., Rinaldi, G., Magaldi, R., Pantarotto, F., Spennati, G., Calo, S., Perotti, G. F., Gaioni, L., Compagnoni, G., Corbella, E., Tripodi, V., Grano, S., Cassata, N., Sulliotti, G., Gambini, L., Gancia, P., Serrao, P., Nicolo, A., Bonacini, G., Romagnoli, C., Gandolfo, M. T., De Nisi, G., Mazza, A., Uxa, F., Monici-Preti, P., Gardini, F., Prophylaxis of respiratory distress syndrome by treatment with modified porcine surfactant at birth: A multicentre prospective randomized trial, Journal of perinatal medicine, 24, 609-620, 1996	Study did not specify what type of respiratory support the baby received, only whether baby received surfactant or not
Conte, F., Orfeo, L., Gizzi, C., Massenzi, L., Fasola, S., Rapid systematic review shows that using a high-flow nasal cannula is inferior to nasal continuous positive airway pressure as first-line support in preterm neonates, Acta PaediatricaActa Paediatr, 11, 11, 2018	Inclusion criteria for systematic review did not specify if respiratory support was provided before admission to NICU; studies assessed individually
Finer, N, The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants? The SUPPORT Trial, Pediatric academic society, http://www.abstracts2view.com/pas/, 2010	Literature review
Finer, N., To intubate or not - That is the question: Continuous positive airway pressure versus surfactant and extremely low birthweight infants, Archives of Disease in Childhood: Fetal and Neonatal Edition, 91, F392-F394, 2006	Literature review
Finer, N. N., Carlo, W. A., Duara, S., Fanaroff, A. A., Donovan, E. F., Wright, L. L., Kandefer, S., Poole, W. K., National Institute of Child, Health, Human Development Neonatal Research, Network, Delivery room continuous positive airway pressure/positive end-expiratory pressure in extremely low birth weight infants: a feasibility trial, Pediatrics, 114, 651-7, 2004	Respiratory support included resuscitation as part of the interventions - not of interest for review

Goncalves-Ferri, W. A., Martinez, F. E., Caldas, J. P. S., Marba, S. T. M., Fekete, S., Rugolo, L., Tanuri, C., Leone, C., Sancho, G. A., Almeida, M. F. B., Guinsburg, R., Application of continuous positive airway pressure in the delivery room: A multicenter randomized clinical trial, Brazilian Journal of Medical and Biological Research, 47, 259-264, 2014	Country not of interest for review: Brazil not an OECD country
Gopel, W., Kribs, A., Hartel, C., Avenarius, S., Teig, N., Groneck, P., Olbertz, D., Roll, C., Vochem, M., Weller, U., Von Der Wense, A., Wieg, C., Wintgens, J., Preuss, M., Ziegler, A., Roth, B., Herting, E., Less invasive surfactant administration is associated with improved pulmonary outcomes in spontaneously breathing preterm infants, Acta Paediatrica, International Journal of Paediatrics, 104, 241-246, 2015	Inclusion criteria includes preterm babies within 12 hours of life, not explicitly in line with delivery room setting
Isayama, T., Iwami, H., McDonald, S., Beyene, J., Association of noninvasiveventilation strategies withmortality and bronchopulmonarydysplasiaamong preterm infants: A systematic review and meta-analysis, JAMA - Journal of the American Medical Association, 316, 611-624, 2016	Not all RCTs relevant for review, therefore checked for relevant RCTS and extracted from original RCTs instead
Jasani, B., Ismail, A., Rao, S., Patole, S., Effectiveness and safety of nasal mask versus binasal prongs for providing continuous positive airway pressure in preterm infants-A systematic review and meta-analysis, Pediatric PulmonologyPediatr Pulmonol, 23, 23, 2018	Intervention not before transfer to neonatal unit
Kraybill,E.N., Bose,C.L., Corbet,A.J., Garcia-Prats,J., Asbill,D., Edwards,K., Long,W., Double-blind evaluation of developmental and health status to age 2 years of infants weighing 700 to 1350 grams treated prophylactically at birth with a single dose of synthetic surfactant or air placebo, Journal of Pediatrics, 126, S33-S42, 1995	Synthetic surfactant not of interest for review
Lefort, S., Diniz, E. M., Vaz, F. A., Clinical course of premature infants intubated in the delivery room, submitted or not to porcine-derived lung surfactant therapy within the first hour of life, Journal of maternal-fetal & neonatal medicine, 14, 187-96, 2003	Comparison not of interest for review: both groups of babies received invasive ventilation
Lindner, W, Vossbeck, S, Hummler, H, Pohlandt, F, Delivery room management of extremely low birth weight infants: â spontaneous breathing or intubation?, Pediatrics, 103, 961-967, 1999	Study design not of interest for review: retrospective cohort study
Liu, Cj, Yang, Zy, Chen, Z, Shao, Xh, Combined use of pulmonary surfactants with continuous distending pressure is useful in the treatment of respiratory distress syndrome in very low birth weight infants, Zhongguo dang dai er ke za zhi [Chinese journal of contemporary pediatrics], 10, 451-454, 2008	Country not of interest for review: China not in OECD

Manley, B. J., Arnolda, G., Wright, I. M., Owen, L. S., Foster, J. P., Dalziel, K. M., Roberts, C. T., Clark, T. L., Fan, W. Q., Fang, A. Y. W., Marshall, I. R., Pszczola, R. J., Davis, P. G., Buckmaster, A. G., Nasal high-flow for early respiratory support of newborn infants in Australian non-tertiary special care nurseries (the hunter trial): A multicentre, randomised, non-inferiority trial, Journal of Paediatrics and Child Health, 54 (Supplement 1), 4, 2018	Full text is an abstract
Manuela, C, Mihaela, Sl, Marta, S, Monika, R, Carmen, G, Marcela, U, Mihaela, M, Efectiveness and safety of minimally inasive surfactant administration techniques on short term outcomes for preterm neonates born before 32 weeks of gestation, Archives of disease in childhood. Conference: 8th europaediatrics congress jointly with 13th national congress of romanian pediatrics society. Romania, 102, A32, 2017	Full text is an abstract
McMillan, D., Chernick, V., Finer, N., Schiff, D., Bard, H., Watts, J., Krzeski, R., Long, W., Effects of two rescue doses of synthetic surfactant in 344 infants with respiratory distress syndrome weighing 750 to 1249 grams: A double-blind, placebo-controlled multicenter Canadian trial, Journal of Pediatrics, 126, S90-S98, 1995	Synthetic surfactant not of interest for review
Rojas, M. A., Lozano, J. M., Rojas, M. X., Laughon, M., Bose, C. L., Rondon, M. A., Charry, L., Bastidas, J. A., Perez, L. A., Rojas, C., Ovalle, O., Celis, L. A., Garcia-Harker, J., Jaramillo, M. L., Very early surfactant without mandatory ventilation in premature infants treated with early continuous positive airway pressure: A randomized, controlled trial, Pediatrics, 123, 137-142, 2009	Country not of interest for review: Columbia not in OECD
Saigal, S., Robertson, C., Sankaran, K., Bingham, W., Casiro, O., MacMurray, B., Whitfield, M., Long, W., One-year outcome in 232 premature infants with birth weights of 750 to 1249 grams and respiratory distress syndrome randomized to rescue treatment with two doses of synthetic surfactant or air placebo, Journal of Pediatrics, 126, S61-S67, 1995	Synthetic surfactant not of interest for review
Schmolzer, G. M., Kumar, M., Aziz, K., Pichler, G., O'Reilly, M., Lista, G., Cheung, P. Y., Sustained inflation versus positive pressure ventilation at birth: A systematic review and meta-analysis, Archives of Disease in Childhood: Fetal and Neonatal Edition, 100, F361-F368, 2015	Intervention not of interest for review: sustained inflation
Schmolzer, G. M., Kumar, M., Pichler, G., Aziz, K., O'Reilly, M., Cheung, P. Y., Non-invasive versus invasive respiratory support in preterm infants at birth: systematic review and meta-analysis, BMJBmj, 347, f5980, 2013	No additional RCTs to Subramaniam 2016

Sell, M., Cotton, R., Hirata, T., Guthrie, R., LeBlanc, M., Mammel, M., Long, W., One-year follow-up of 273 infants with birth weights of 700 to 1100 grams after prophylactic treatment of respiratory distress syndrome with synthetic surfactant or air placebo, Journal of Pediatrics, 126, S20-S25, 1995	Synthetic surfactant not of interest for review
Shin, J, Park, K, Lee, Eh, Choi, Bm, Humidified High Flow Nasal Cannula versus Nasal Continuous Positive Airway Pressure as an Initial Respiratory Support in Preterm Infants with Respiratory Distress: a Randomized, Controlled Non-Inferiority Trial, Journal of Korean medical science, 32, 650-655, 2017	Study took place after babies were admitted to the NICU
Stevens, T. P., Blennow, M., Myers, E. W., Soll, R., Early surfactant administration with brief ventilation vs. selective surfactant and continued mechanical ventilation for preterm infants with or at risk for respiratory distress syndrome, Cochrane Database of Systematic Reviews, (4) (no pagination), 2007	Setting not of interest for review: NICU
Stevens, T. P., Finer, N. N., Carlo, W. A., Szilagyi, P. G., Phelps, D. L., Walsh, M. C., Gantz, M. G., Laptook, A. R., Yoder, B. A., Faix, R. G., Newman, J. E., Das, A., Do, B. T., Schibler, K., Rich, W., Newman, N. S., Ehrenkranz, R. A., Peralta-Carcelen, M., Vohr, B. R., Wilson-Costello, D. E., Yolton, K., Heyne, R. J., Evans, P. W., Vaucher, Y. E., Adams-Chapman, I., McGowan, E. C., Bodnar, A., Pappas, A., Hintz, S. R., Acarregui, M. J., Fuller, J., Goldstein, R. F., Bauer, C. R., O'Shea, T. M., Myers, G. J., Higgins, R. D., Respiratory outcomes of the surfactant positive pressure and oximetry randomized trial (SUPPORT), Journal of Pediatrics, 165, 240-249.e4, 2014	No outcomes of interest for review
Tapia, J. L., Urzua, S., Bancalari, A., Meritano, J., Torres, G., Fabres, J., Toro, C. A., Rivera, F., Cespedes, E., Burgos, J. F., Mariani, G., Roldan, L., Silvera, F., Gonzalez, A., Dominguez, A., South American Neocosur, Network, Randomized trial of early bubble continuous positive airway pressure for very low birth weight infants, Journal of Pediatrics, 161, 75-80.e1, 2012	Countries not of interest for review: out of 5 countries only 1 was an OECD member
Thomas, A. N., Hagan, J. L., Lingappan, K., Noninvasive ventilation strategies: Which to choose?, Journal of Perinatology, 38, 447-450, 2018	Inclusion criteria includes preterm babies within 24 hours of life, not explicitly in line with delivery room setting.
Tooley, J., Dyke, M., Randomized study of nasal continuous positive airway pressure in the preterm infant with respiratory distress syndrome, Acta PaediatricaActa Paediatr, 92, 1170-4, 2003	Setting unclear whether NICU or delivery room
Vaucher, Ye, Harker, L, Merritt, Ta, Hallman, M, Gist, K, Bejar, R, Heldt, Gp, Edwards, D,	Inclusion criteria for babies not of interest for review: 38 weeks of gestation

Pohjavuori, M, Outcome at twelve months of adjusted age in very low birth weight infants with lung immaturity: a randomized, placebo-controlled trial of human surfactant, Journal of Pediatrics, 122, 126-132, 1993	
Walther, F. J., Mullett, M., Schumacher, R., Sundell, H., Easa, D., Long, W., One-year follow-up of 66 premature infants weighing 500 to 699 grams treated with a single dose of synthetic surfactant or air placebo at birth: Results of a double-blind trial, Journal of Pediatrics, 126, S13-S19, 1995	Synthetic surfactant not of interest for review
White, A, Marcucci, G, Andrews, E, Edwards, K, Long, W, Antenatal steroids and neonatal outcomes in controlled clinical trials of surfactant replacement. The American Exosurf Neonatal Study Group I and The Canadian Exosurf Neonatal Study Group, American Journal of Obstetrics and Gynecology, 173, 286-290, 1995	Synthetic surfactant not of interest for review
Winter, J., Kattwinkel, J., Chisholm, C., Blackman, A., Wilson, S., Fairchild, K., Ventilation of Preterm Infants during Delayed Cord Clamping (VentFirst): A Pilot Study of Feasibility and Safety, American Journal of Perinatology, 34, 111-116, 2017	Non-comparative

NICU: neonatal intensive care unit; OECD: Organisation for Economic Co-operation and Development; RCT: randomised controlled trial

Economic studies

All economic studies were excluded at the initial title and abstract screening stage.

Excluded studies for question 3.3 What is the most effective way of using surfactant in managing respiratory distress syndrome?

Clinical studies

Study	Reason for Exclusion
Two-year follow-up of infants treated for neonatal respiratory distress syndrome with bovine surfactant, Journal of Pediatrics, 124, 962-7, 1994	Study dates not of interest for review: pre-1990
Early surfactant for neonates with mild to moderate respiratory distress syndrome: a multicenter randomized trial, Journal of Pediatrics, 144, 804-808, 2004	Comparison not of interest for review: early vs selective surfactant management
Abdel-Latif, Mohamed E, Osborn, David A, Pharyngeal instillation of surfactant before the first breath for prevention of morbidity and mortality in preterm infants at risk of respiratory distress syndrome, Cochrane Database of Systematic Reviews, 2011	Systematic review did not identify any RCTs
Abdel-Latif, Mohamed E, Osborn, David A, Laryngeal mask airway surfactant administration for prevention of morbidity and mortality in preterm infants with or at risk of respiratory distress syndrome, Cochrane Database of Systematic Reviews, 2011	No studies included on comparisons of interest for review: laryngeal mask airway surfactant administration vs no surfactant
Aldana-Aguirre, J. C., Pinto, M., Featherstone, R. M., Kumar, M., Less invasive surfactant administration versus intubation	Not all studies in the systematic review are relevant for review,

Study	Reason for Exclusion
for surfactant delivery in preterm infants with respiratory distress syndrome: A systematic review and meta-analysis, Archives of Disease in Childhood: Fetal and Neonatal Edition, 102, F17-F23, 2017	data extracted from primary studies
Ali, E., Abdel Wahed, M., Alsalami, Z., Abouseif, H., Gottschalk, T., Rabbani, R., Zarychanski, R., Abou-Setta, A. M., New modalities to deliver surfactant in premature infants: a systematic review and meta-analysis, Journal of Maternal-Fetal and Neonatal Medicine, 29, 3519-3524, 2016	No additional studies relevant to review than most recent systematic review by Aldara-Aguirre 2017
Attridge, J, Stewart, C, Kattwinkel, J, A pilot randomized controlled trial evaluating surfactant administration by laryngeal mask airway, Unpublished, 2010	Unavailable from the British Library
Bao, Y., Zhang, G., Wu, M., Ma, L., Zhu, J., A pilot study of less invasive surfactant administration in very preterm infants in a Chinese tertiary center, BMC Pediatrics, 15, 21, 2015	Country not of interest for study: China
Barbosa, R. F., Simoes, E. Silva A. C., Silva, Y. P., A randomized controlled trial of the laryngeal mask airway for surfactant administration in neonates, Jornal de Pediatria, 93, 343-350, 2017	Country not of interest for review: Brazil
Berry, D. D., Pramanik, A. K., Phillips, Iii J. B., Buchter, D. S., Kanarek, K. S., Easa, D., Kopelman, A. E., Edwards, K., Long, W., Comparison of the effect of three doses of a synthetic surfactant on the alveolar-arterial oxygen gradient in infants weighing ≥ 1250 grams with respiratory distress syndrome, Journal of pediatrics, 124, 294-301, 1994	Study dates not of interest for review: pre-1990
Chen, C., Tian, T., Liu, L., Zhang, J., Fu, H., Gender-related efficacy of pulmonary surfactant in infants with respiratory distress syndrome: A STROBE compliant study, MedicineMedicine (Baltimore), 97, e0425, 2018	Country not of interest for review: China
Corbet, A., Gerdes, J., Long, W., Avila, E., Puri, A., Rosenberg, A., Edwards, K., Cook, L., Stevenson, D., Goldman, S., Walther, F., Boros, S., Mammel, M., Thompson, T., Bucciarelli, R., Burchfield, D., Mullett, M., Cotton, R., Sundell, H., Double-blind, randomized trial of one versus three prophylactic doses of synthetic surfactant in 826 neonates weighing 700 to 1100 grams: Effects on mortality rate, Journal of Pediatrics, 126, 969-978, 1995	Study dates not of interest for review: pre-1990
Corbet, A., Long, W., Schumacher, R., Gerdes, J., Cotton, R., Double-blind developmental evaluation at 1-year corrected age of 597 premature infants with birth weights from 500 to 1350 grams enrolled in three placebo-controlled trials of prophylactic synthetic surfactant, Journal of Pediatrics, 126, S5-S12, 1995	Comparison not of interest in this analysis for the review: surfactant vs placebo
Corrine, Stewart, Joshua, Attridge John Kattwinkel, An,, N, Massaro, Randomized Controlled Trial of Surfactant Administration by Laryngeal Mask Airway (LMA) Massage and Kinesthetic Stimulation (Exercise) Improves Weight Gain in Very Low Birth Weight (VLBW) Preterm Infants; Results from a Randomized Controlled Trial, American pediatric society/society for pediatric research abstract, 2008	No full-text available only abstract
Dani, C., Surfactant replacement in preterm infants with respiratory distress syndrome, Acta Bio-Medica de l Ateneo ParmenseActa Biomed Ateneo Parmense, 83 Suppl 1, 17-20, 2012	Study design not of interest for review: narrative review

Study	Reason for Exclusion
Fiori, R. M., Diniz, E. M., Lopes, J. M., Goncalves, A. L., da Costa, M. T., Marino, W. T., Abdallah, V. O., Segre, C. A., de Carvalho, M., Guimaraes, W. M., Margotto, P. R., Bevilacqua, G., Surfactant replacement therapy: a multicentric trial comparing two dosage approaches, Acta Bio-Medica de l Ateneo ParmenseActa Biomed Ateneo Parmense, 68 Suppl 1, 55-63, 1997	Unavailable from the British Library
Fischer, H., Buhrer, C., Avoiding mechanical ventilation to prevent bronchopulmonary dysplasia: A meta-analysis, European Respiratory Journal. Conference: European Respiratory Society Annual Congress, 42, 2013	No additional studies relevant to review than most recent systematic review by Aldara-Aguirre 2017
Gerdes, J., Gerdes, M., Beaumont, E., Cook, L., Dhanireddy, R., Kopleman, A., Jarrett, R., Long, W., Health and neurodevelopmental outcome at 1-year adjusted age in 508 infants weighing 700 to 1100 grams who received prophylaxis with one versus three doses of synthetic surfactant, Journal of Pediatrics, 126, S26-S32, 1995	Timeframe around Neurodevelopmental outcomes not of interest for review: 1-year follow-up
Gopel, W., Kribs, A., Hartel, C., Avenarius, S., Teig, N., Groneck, P., Olbertz, D., Roll, C., Vochem, M., Weller, U., von der Wense, A., Wieg, C., Wintgens, J., Preuss, M., Ziegler, A., Roth, B., Herting, E., German Neonatal, Network, Less invasive surfactant administration is associated with improved pulmonary outcomes in spontaneously breathing preterm infants, Acta PaediatricaActa Paediatr, 104, 241-6, 2015	Study design not of interest for review: prospective cohort study
Halliday, H. L., Tarnow-Mordi, W. O., Corcoran, J. D., Patterson, C. C., Multicentre randomised trial comparing high and low dose surfactant regimens for the treatment of respiratory distress syndrome (the Curosurf 4 trial), Archives of disease in childhood, 69, 276-280, 1993	Dosing regimen not of interest for review: 3 doses vs 5 doses
Heidarzadeh, M., Mirnia, K., Hoseini, M. B., Sadeghnia, A., Akrami, F., Balila, M., Ghojazadeh, M., Shafai, F., Surfactant administration via thin catheter during spontaneous breathing: Randomized controlled trial in alzahra hospital, Iranian Journal of Neonatology, 4, 5-9, 2013	Country not of interest for review: Iran
Hentschel, R, Jorch, G, Acute side effects of surfactant treatment, Journal of perinatal medicine, 30, 143-148, 2002	Study design not of interest for review: narrative review
Herting, E, Tubman, R, Halliday, Hl, Harms, K, Speer, Cp, Curstedt, T, Robertson, B, Effect of 2 different dosages of a porcine surfactant on pulmonary gas exchange of premature infants with severe respiratory distress syndrome, Monatsschrift Kinderheilkunde, 141, 721-727, 1993	No outcomes of interest for review: pulmonary mechanics
Herting, E., Kribs, A., Roth, B., Hartel, C., Gopel, W., 2 Year outcome of very low birth weight infants following less invasive surfactant administration (LISA), Journal of Neonatal-Perinatal Medicine, 6 (2), 194-195, 2013	No full-text available
Isayama, T., Chai-Adisaksopha, C., McDonald, S. D., Noninvasive ventilation with vs without early surfactant to prevent chronic lung disease in preterm infants: A systematic review and meta-analysis, JAMA Pediatrics, 169, 731-739, 2015	No additional studies relevant to review than most recent systematic review by Aldara-Aguirre 2017
Isayama, T., Iwami, H., McDonald, S., Beyene, J., Association of Noninvasive Ventilation Strategies With Mortality and Bronchopulmonary Dysplasia Among Preterm Infants: A	No additional studies relevant to review than most recent systematic review by Aldara-Aguirre 2017

Study	Reason for Exclusion
Systematic Review and Meta-analysis, JAMAJama, 316, 611-24, 2016	
Karadag, A., Ozdemir, R., Degirmencioglu, H., Uras, N., Dilmen, U., Bilgili, G., Erdeve, O., Cakir, U., Atasay, B., Comparison of Three Different Administration Positions for Intratracheal Beractant in Preterm Newborns with Respiratory Distress Syndrome, Pediatrics and neonatology, 57, 105-112, 2016	Comparison not of interest for review: comparisons of intratracheal positioning for surfactant administration
Lau, C. S. M., Chamberlain, R. S., Sun, S., Less Invasive Surfactant Administration Reduces the Need for Mechanical Ventilation in Preterm Infants: A Meta-Analysis, Lobal Pediatric HealthGlob, 4, 2333794X17696683, 2017	Only 1 study in the systematic review met the inclusion criteria for the review, data extracted from primary study
Li, X. F., Cheng, T. T., Guan, R. L., Liang, H., Lu, W. N., Zhang, J. H., Liu, M. Y., Yu, X., Liang, J., Sun, L., Zhang, L., Effects of different surfactant administrations on cerebral autoregulation in preterm infants with respiratory distress syndrome, Journal of Huazhong University of Science and Technology. Medical SciencesJ Huazhong Univ Sci Technolog Med Sci, 36, 801-805, 2016	Country not of interest for review: China
Mario, Augusto Rojas, Md,, Mpha,, Juan, Manuel Lozano, Md,, Mscb,, Very Early Surfactant Without Mandatory Ventilation in Premature Infants Treated With Early Continuous Positive Airway Pressure: A Randomized, Controlled Trial, Pediatrics, 123, 137?142, 2009	Country not of interest for review: Columbia
Mirzarahimi, M., Barak, M., Comparison efficacy of Curosurf and Survanta in preterm infants with respiratory distress syndrome, Pakistan Journal of Pharmaceutical Sciences, 31, 469-472, 2018	Country not of interest for review: Iran
Mohammadizadeh, M., Ardestani, A. G., Sadeghnia, A. R., Early administration of surfactant via a thin intratracheal catheter in preterm infants with respiratory distress syndrome: Feasibility and outcome, Journal of Research in Pharmacy Practice, 4, 31-36, 2015	Country not of interest for review: Iran
More, K., Sakhuja, P., Shah, P. S., Minimally invasive surfactant administration in preterm infants: A meta-narrative review, JAMA Pediatrics, 168, 901-908, 2014	No additional studies relevant to review than most recent systematic review by Aldara-Aguirre 2017
Mosayebi, Z., Kadivar, M., Taheri-Derakhsh, N., Nariman, S., Marashi, S. M., Farsi, Z., A randomized trial comparing surfactant administration using INSURE technique and the minimally invasive surfactant therapy in preterm infants (28 to 34 weeks of gestation) with respiratory distress syndrome, Journal of Comprehensive Pediatrics, 8 (4) (no pagination), 2017	Country not of interest for review: Iran
Nayeri, F. S., Esmaeilnia Shirvani, T., Aminnezhad, M., Amini, E., Dalili, H., Bijani, F. M., Comparison of INSURE method with conventional mechanical ventilation after surfactant administration in preterm infants with respiratory distress syndrome: Therapeutic challenge, Acta medica Iranica, 52, 596-608, 2014	Country not of interest for review: Iran
Rigo, V., Lefebvre, C., Broux, I., Surfactant instillation in spontaneously breathing preterm infants: a systematic review and meta-analysis, European Journal of Pediatrics, 175, 1933-1942, 2016	No additional studies relevant to review than most recent systematic review by Aldara-Aguirre 2017

Study	Reason for Exclusion
Roberts, K., Lampland, A., Leone, T., Tipnis, J., Stepka, E., Kessel, J., Rich, W., Brown, R., Rudser, K., Merritt, T., Finer, N., Mammel, M., Laryngeal mask airway for surfactant administration in neonates, European Journal of Pediatrics, 175 (11), 1491, 2016	Comparison not of interest for review: LMA with surfactant vs CPAP without surfactant
Sadeghnia, A., Beheshti, B. K., Mohammadizadeh, M., The Effect of Inhaled Budesonide on the Prevention of Chronic Lung Disease in Premature Neonates with Respiratory Distress Syndrome, International Journal of Preventive MedicineInt J Prev Med, 9, 15, 2018	Country not of interest for review: Iran
Sadeghnia, A., Tanhaei, M., Mohammadizadeh, M., Nemati, M., A comparison of surfactant administration through i-gel and ET-tube in the treatment of respiratory distress syndrome in newborns weighing more than 2000 grams, Advanced Biomedical ResearchAdv, 3, 160, 2014	Country not of interest for review: Iran
Soll, R. F., Multiple versus single dose natural surfactant extract for severe neonatal respiratory distress syndrome, Cochrane database of systematic reviews (Online), CD000141, 2000	Superseded by Soll 2009
Shepherd, Emily, Salam, Rehana A, Middleton, Philippa, Han, Shanshan, Makrides, Maria, McIntyre, Sarah, Badawi, Nadia, Crowther, Caroline A, Neonatal interventions for preventing cerebral palsy: an overview of Cochrane Systematic Reviews, Cochrane Database of Systematic Reviews, 2018	Surfactant studies have no comparison between different surfactant regimes
Soll, Roger, Özek, Eren, Multiple versus single doses of exogenous surfactant for the prevention or treatment of neonatal respiratory distress syndrome, Cochrane Database of Systematic Reviews, 2009	1 study that meets inclusion criteria for review, data extracted from primary paper
Thomas, A. N., Hagan, J. L., Lingappan, K., Noninvasive ventilation strategies: Which to choose?, Journal of Perinatology, 38, 447-450, 2018	Summarises a previously excluded study (Isayama et al., 2016)
Trevisanuto, D, Grazzina, N, Ferrarese, P, Micaglio, M, Verghese, C, Zanardo, V, Laryngeal mask airway as a delivery channel for administration of surfactant in preterm infants with RDS, Biology of the neonate, 87, 217-20, 2005	Study design not an RCT: narrative review
Tsakalidis, C., Giougki, E., Karagianni, P., Dokos, C., Rallis, D., Nikolaidis, N., Is there a necessity for multiple doses of surfactant for respiratory distress syndrome of premature infants?, Turkish Journal of Pediatrics, 54, 368-75, 2012	Study design not of interest for review: retrospective observational study
van den Berg, E., Lemmers, P. M., Toet, M. C., Klaessens, J. H., van Bel, F., Effect of the "InSurE" procedure on cerebral oxygenation and electrical brain activity of the preterm infant, Archives of Disease in Childhood Fetal & Neonatal EditionArch Dis Child Fetal Neonatal Ed, 95, F53-8, 2010	Study design not of interest for review: prospective observational study
Wanous, A. A., Wey, A., Rudser, K. D., Roberts, K. D., Feasibility of Laryngeal Mask Airway Device Placement in Neonates, Neonatology, 111, 222-227, 2017	No outcomes of interest relevant for the review
Wu, W., Shi, Y., Li, F., Wen, Z., Liu, H., Surfactant administration via a thin endotracheal catheter during spontaneous breathing in preterm infants, Pediatric Pulmonology, 52, 844-854, 2017	No additional studies relevant to review than most recent systematic review by Aldara-Aguirre 2017
Yan, C., Dong, Y., Sun, B., Chen, C., Gao, X., Mu, J., Xiao, Y., Li, J., Liu, C., Qian, M., Lin, X., Huang, J., Yang, C., Yang, B.,	Country not of interest for review: China

Study	Reason for Exclusion
Chen, W., Lin, Z., Wu, B., Zhu, W., Tan, N., Hou, Z., Xie, Y., Gong, X., Qi, J., Yu, F., Kang, Y., Jang, K., Shi, X., Sun, Y., Feng, W., Hu, Y., Qiu, Y., Shi, L., Zhao, F., Yan, B., Zhang, Y., Lin, G., Wei, Q., Cheng, R., Feng, Y., Wu, Y., Zou, Y., Guo, Y., Que, Q., Zhao, L., Qian, L., Xie, J., Xiong, H., Sun, H., He, S., Zhong, J., Zhuang, D., Chen, A., He, Z., Sun, F., Chu, Y., Yang, J., Xiang, J., Yue, H., Han, L., Chen, D., He, Y., Wang, S., Yang, Z., Zhou, J., Gu, X., Shan, R., Sun, L., Zheng, J., Liu, L., Wang, W., Xiao, Z., Ding, X., Chen, X., Li, M., Lu, F., Song, X., Liu, F., Guo, Z., Du, Z., Mu, D., Xiong, Y., Wang, H., Wu, Z., Xiao, S., Zhou, X., Huang, H., Gao, P., Gan, X., Hou, L., Liu, M., Shi, Y., Wang, L., Yi, B., Gao, H., Liu, X., Gao, D., Qi, L., Li, X., Tian, Q., Han, S., Wu, D., Liu, Z., Chen, Y., Zhang, Q., Lu, H., Kang, H., Lei, H., Yang, X., Cheng, D., Zheng, Y., Yu, M., Wang, X., Chu, Q., Tu, W., Shi, B., Yao, G., Wang, Y., Liang, K., Zhong, Q., Yue, S., Liao, Z., Huang, Y., Li, Y., Chen, J., Ni, L., Zhang, L., Zhang, J., AnZeng, J., Fu, Y., Zhao, Y., Zha, P., Jiang, Y., Bai, X., Cao, Y., Pan, J., Lv, Y., Li, L., Bao, J., Surfactant reduced the mortality of neonates with birth weight 3/41500 g and hypoxemic respiratory failure: A survey from an emerging NICU network, Journal of Perinatology, 37, 645-651, 2017	
Zola, E. M., Gunkel, J. H., Chan, R. K., Lim, M. O., Knox, I., Feldman, B. H., Denson, S. E., Stonestreet, B. S., Mitchell, B. R., Wyza, M. M., Bennett, K. J., Gold, A. J., Comparison of three dosing procedures for administration of bovine surfactant to neonates with respiratory distress syndrome, Journal of Pediatrics, 122, 453-459, 1993	Comparison not of interest for review: administration procedure of surfactant

Economic studies

Study	Reason for Exclusion
Guardia CG, Moya FR, Sinha S, Simmons PD, Segal R, Greenspan JS. A pharmacoeconomic analysis of in-hospital costs resulting from reintubation in preterm infants treated with lucinactant, beractant, or poractant alfa. The Journal of Pediatric Pharmacology and Therapeutics. 2012 Dec;17(3):220-7.	Comparison not of interest for review: one surfactant versus another and not regimen or dosing.
Marsh W, Smeeding J, York JM, Ramanathan R, Sekar K. A cost minimization comparison of two surfactants—beractant and poractant alfa—based upon prospectively designed, comparative clinical trial data. The Journal of Pediatric Pharmacology and Therapeutics. 2004 Apr;9(2):117-25.	Comparison not of interest for review: one surfactant versus another and not regimen or dosing.

Excluded studies for question 3.1 What is the most effective way to administer oxygen during respiratory support?

Clinical studies

Study	Reason for Exclusion
Al-Alaiyan, S., Dawoud, M., Al-Hazzani, F., Positive distending pressure produced by heated, humidified high flow nasal cannula as compared to nasal continuous positive airway pressure in premature infants, Journal of Neonatal-Perinatal Medicine, 7, 119-24, 2014	Non-OECD country - Saudi Arabia
Ali, S. K. M., Jayakar, R. V., Marshall, A. P., Gale, T. J., Dargaville, P. A., Feasibility and safety of automated control of oxygen therapy in the delivery room for very preterm infants: A pilot study, Journal of Paediatrics and Child Health, 54 (Supplement 1), 6, 2018	Full text is an abstract
Bermudez Barrezueta, L., Garcia Carbonell, N., Lopez Montes, J., Gomez Zafra, R., Marin Reina, P., Herrmannova, J., Casero Soriano, J., High flow nasal cannula oxygen therapy in the treatment of acute bronchiolitis in neonates, Anales de Pediatria, 86, 37-44, 2017	Babies were not preterm
Clarke, A., Yeomans, E., Elsayed, K., Medhurst, A., Berger, P., Skuza, E., Tan, K., A randomised crossover trial of clinical algorithm for oxygen saturation targeting in preterm infants with frequent desaturation episodes, Neonatology, 107, 130-6, 2015	Compared 2 different manual titration modalities
Clarke, A., Yeomans, E., Elsayed, K., Medhurst, A., Berger, P., Skuza, E., Tan, K., A randomised crossover trial of dedicated nurse and clinical algorithm on oxygen saturation targeting in preterm infants, Journal of Paediatrics and Child Health, 49, 13-14, 2013	Full text is an abstract
Claure, N, Bencalari, E, Donn, Sm, D'Ugard, C, Hernandez, R, Nelin, L, Multicenter crossover trial of automated adjustment of inspired oxygen in preterm infants, American thoracic society international conference, may 15-20, 2009, san diego, A1566 [Poster #D41, 2009	Full text is an abstract
Collins, C. L., Barfield, C., Horne, R. S. C., Davis, P. G., A comparison of nasal trauma in preterm infants extubated to either heated humidified high-flow nasal cannulae or nasal continuous positive airway pressure, European Journal of Pediatrics, 173, 181-186, 2014	Comparison not of interest for review: hi-flow vs nCPAP
Collins, C. L., Holberton, J. R., Barfield, C., Davis, P. G., A randomized controlled trial to compare heated humidified high-flow nasal cannulae with nasal continuous positive airway pressure postextubation in premature infants, Journal of pediatrics, 162, 949-54.e1, 2013	Comparison not of interest for review: hi-flow vs nCPAP
Daish, H., Badurdeen, S., Heated humidified high-flow nasal cannula versus nasal continuous	Full text is an abstract

Study	Reason for Exclusion
positive airway pressure for postextubation ventilatory support in neonates: A meta-analysis, Journal of Maternal-Fetal and Neonatal Medicine, 27, 208, 2014	
Das, A., Mhanna, M., Teleron-Khorshad, A., Houdek, J., Kumar, N., Gunzler, D., Collin, M., A comparison of manual versus automated saturation of peripheral oxygenation in the neonatal intensive care unit, Journal of Maternal-Fetal & Neonatal MedicineJ Matern Fetal Neonatal Med, 29, 1631-5, 2016	Study assessed manual or automatic recording of oxygen saturation levels instead of manual or automatic administration of oxygen
Doctor, Tejas N, Foster, Jann P, Stewart, Alice, Tan, Kenneth, Todd, David A, McGrory, Lorraine, Heated and humidified inspired gas through heated humidifiers in comparison to non-heated and non-humidified gas in hospitalised neonates receiving respiratory support, Cochrane Database of Systematic ReviewsCochrane Database Syst Rev, 2017	Review protocol
Fassassi, M., Michel, F., Thomachot, L., Nicaise, C., Vialet, R., Jammes, Y., Lagier, P., Martin, C., Airway humidification with a heat and moisture exchanger in mechanically ventilated neonates : a preliminary evaluation, Intensive Care Medicine, 33, 336-43, 2007	< 15 babies in each arm
Fernandez-Alvarez, J. R., Gandhi, R. S., Amess, P., Mahoney, L., Watkins, R., Rabe, H., Heated humidified high-flow nasal cannula versus low-flow nasal cannula as weaning mode from nasal CPAP in infants <=28 weeks of gestation, European Journal of Pediatrics, 173, 93-98, 2014	Comparison not of interest for review: hi-flow vs low-flow
Fleeman, N., Mahon, J., Bates, V., Dickson, R., Dundar, Y., Dwan, K., Ellis, L., Kotas, E., Richardson, M., Shah, P., Shaw, B. N. J., The clinical effectiveness and cost-effectiveness of heated humidified high-flow nasal cannula compared with usual care for preterm infants: Systematic review and economic evaluation, Health Technology Assessment, 20, 2016	NICE health technology assessment - studies assessed individually
Gajdos, M., Waitz, M., Mendler, M., Braun, W., Hummler, H., Effects of automated closed loop control of inspired oxygen concentration on fluctuations of arterial and different regional organ tissue oxygen saturations in preterm infants, Monatsschrift fur Kinderheilkunde, 164 (2 Supplement), S157-S158, 2016	Full text is an abstract
Gupta, A., Abdelhamid, A. A., Harikumar, C., Gupta, S., Prolonged respiratory support for extreme preterm babies: HHFNC or NCPAP?, Archives of Disease in Childhood, 99, A497, 2014	Full text is an abstract
Hallenberger, A., Urschitz, M. S., Muller-Hansen, I., Miksch, S., Seyfang, A., Horn, W., Poets, C. F., Automatic control of the inspired	Full text is an abstract

Study	Reason for Exclusion
oxygen fraction in preterm infants. Preliminary results of a multicenter randomized cross-over trial, Archives of Disease in Childhood, 97, A117, 2012	
Heath Jeffery, R. C., Broom, M., Shadbolt, B., Todd, D. A., Increased use of heated humidified high flow nasal cannula is associated with longer oxygen requirements, Journal of Paediatrics & Child HealthJ Paediatr Child Health, 29, 29, 2017	Intervention not of interest - hi flow
Hegde, D., Mondkar, J., Panchal, H., Manerkar, S., Jasani, B., Kabra, N., Heated Humidified High Flow Nasal Cannula versus Nasal Continuous Positive Airway Pressure as Primary Mode of Respiratory Support for Respiratory Distress in Preterm Infants, Indian Pediatrics, 53, 129-33, 2016	Comparison not of interest hi-flow vs CPAP
Helder, O. K., Mulder, P. G., van Goudoever, J. B., Computer-generated versus nurse-determined strategy for incubator humidity and time to regain birthweight, JOGNN - Journal of Obstetric, Gynecologic, & Neonatal NursingJ Obstet Gynecol Neonatal Nurs, 37, 255-61, 2008	Intervention not relevant - Assessed automated or manual incubator humidity
Holleman-Duray, D., Kaupie, D., Weiss, M. G., Heated humidified high-flow nasal cannula: use and a neonatal early extubation protocol, Journal of Perinatology, 27, 776-81, 2007	Intervention not of interest: hi-flow
Iranpour, R., Sadeghnia, A., Hesaraki, M., High-flow nasal cannula versus nasal continuous positive airway pressure in the management of respiratory distress syndrome, Archives of Disease in Childhood, 97, A115-A116, 2012	Full text is an abstract
Jeffery, R. C. H., Todd, D. A., Heated humidified high-flow nasal cannula: Impact on neonatal outcomes, Respiratory Care, 61, 1428-1429, 2016	Editorial
Kim,S.M., Lee,E.Y., Chen,J., Ringer,S.A., Improved care and growth outcomes by using hybrid humidified incubators in very preterm infants, Pediatrics, 125, e137-e145, 2010	Outcomes not relevant
Klingenberg,C., Pettersen,M., Hansen,E.A., Gustavsen,L.J., Dahl,I.A., Leknessund,A., Kaaresen,P.I., Nordhov,M., Patient comfort during treatment with heated humidified high flow nasal cannulae versus nasal continuous positive airway pressure: a randomised cross-over trial, Archives of Disease in Childhood Fetal and Neonatal Edition, 99, F134-F137, 2014	Comparison not of interest: hi-flow vs CPAP
Kugelman, A., Riskin, A., Said, W., Shoris, I., Mor, F., Bader, D., A randomized pilot study comparing heated humidified high-flow nasal cannulae with NIPPV for RDS, Pediatric pulmonology, 50, 576-83, 2015	Comparison not of interest for review: hi flow vs NIPPV

Study	Reason for Exclusion
Kugelman,A., NCPAP vs. NIPPV vs. heated humidified high-flow nasal cannula (HHHFNC) for the treatment of premature infants with RDS, Journal of Maternal-Fetal and Neonatal Medicine, 27, 9-, 2014	Full text is an abstract
Ladlow, O., Marshall, A. P., Ali, S. K. M., Eastwood-Sutherland, C., Jayakar, R., Gale, T. J., Dargaville, P. A., Automated control of oxygen therapy in preterm infants on non-invasive respiratory support, Journal of Paediatrics and Child Health, 54 (Supplement 1), 29, 2018	Full text is an abstract
Lal, M. K., Sinha, S. K., Tin, W., Automated control of inspired oxygen in ventilated newborn infants: A randomised crossover study, Archives of Disease in Childhood, 99, A3, 2014	Full text is an abstract
Lampland,A.L., Plumm,B., Meyers,P.A., Worwa,C.T., Mammel,M.C., Observational study of humidified high-flow nasal cannula compared with nasal continuous positive airway pressure, Journal of Pediatrics, 154, 177-182, 2009	Study design not relevant - Comparative cohort study
Lyon, A. J., Oxley, C., HeatBalance, a computer program to determine optimum incubator air temperature and humidity. A comparison against nurse settings for infants less than 29 weeks gestation, Early human development, 62, 33-41, 2001	< 15 babies in each arm
Manley, B. J., Andersen, C. C., O'Donnell, C. P. F., De Paoli, A. G., Wilkinson, D., High-flow nasal cannulae for respiratory support of preterm infants: An updated systematic review and meta-analysis, Journal of Paediatrics and Child Health, 51, 81, 2015	Full text is an abstract
Manley, B. J., Owen, L. S., Doyle, L. W., Andersen, C. C., Cartwright, D. W., Pritchard, M. A., Donath, S. M., Davis, P. G., High-flow nasal cannulae in very preterm infants after extubation, New England journal of medicine, 369, 1425-1433, 2013	Comparison not of interest for review: hi-flow vs CPAP
Manley, B. J., Owen, L. S., Doyle, L. W., Andersen, C. C., Cartwright, D. W., Pritchard, M. A., Donath, S. M., Davis, P. G., High-flow nasal cannulae vs. nasal cpap for post-extubation respiratory support of very preterm infants: A multicentre, randomised non-inferiority trial, Journal of Paediatrics and Child Health, 49, 41, 2013	Full text is an abstract
Murki, S., Das, R. K., Sharma, D., Kumar, P., A Fixed Flow is More Effective than Titrated Flow during Bubble Nasal CPAP for Respiratory Distress in Preterm Neonates, Frontiers in PediatricsFront, 3, 81, 2015	Intervention not relevant - compared fixed flow to titrated flow for babies on CPAP
Murki, S., Singh, J., Khant, C., Kumar Dash, S., Oleti, T. P., Joy, P., Kabra, N. S., High-Flow	Comparison not of interest for review: hi-flow vs CPAP

Study	Reason for Exclusion
Nasal Cannula versus Nasal Continuous Positive Airway Pressure for Primary Respiratory Support in Preterm Infants with Respiratory Distress: A Randomized Controlled Trial, Neonatology, 235-241, 2018	
Osman, M., Elsharkawy, A., Abdel-Hady, H., Assessment of pain during application of nasal-continuous positive airway pressure and heated, humidified high-flow nasal cannulae in preterm infants, Journal of Perinatology, 35, 263-7, 2015	Comparison not of interest for review: hi-flow vs CPAP
Prentice, C. M., Heated humidified high flow nasal cannula compared to nasal continuous positive airway pressure for neonates: A systematic review and meta-analysis, Journal of Paediatrics and Child Health, 54 (Supplement 1), 102, 2018	Full text is an abstract
Roehr, C. C., Manley, B. J., Dold, S. K., Davis, P. G., High-flow nasal cannulae for respiratory support of preterm infants: A review of the evidence, Archives of Disease in Childhood, 97, A512-A513, 2012	Full text is an abstract
Rotta, A., Speicher, R., Shein, S., Speicher, D., High flow nasal cannula therapy in preterm infants: A pooled analysis, Critical Care Medicine, 1), A1541, 2014	Full text is an abstract
Ruegger, C. M., Lorenz, L., Kamlin, C. O. F., Manley, B. J., Owen, L. S., Bassler, D., Tingay, D. G., Donath, S. M., Davis, P. G., The Effect of Noninvasive High-Frequency Oscillatory Ventilation on Desaturations and Bradycardia in Very Preterm Infants: A Randomized Crossover Trial, Journal of Pediatrics, 2018	Comparison not of interest nHFOV vs CPAP
Sasi, A., Chandrakumar, N., Deorari, A., Paul, V. K., Shankar, J., Sreenivas, V., Agarwal, R., Neonatal self-inflating bags: achieving titrated oxygen delivery using low flows: an experimental study, Journal of Paediatrics & Child HealthJ Paediatr Child Health, 49, 671-7, 2013	Non-OECD country - India
Sasi, A., Malhotra, A., Patterns of respiratory outcomes in high flow nasal cannula (HFNC) treated neonates in a tertiary care nicu, Journal of Paediatrics and Child Health, 49, 133, 2013	Full text is an abstract
Sasi, A., Malhotra, A., High flow nasal cannula for continuous positive airway pressure weaning in preterm neonates: A single-centre experience, Journal of Paediatrics & Child HealthJ Paediatr Child Health, 51, 199-203, 2015	Non-OECD country - India
Shetty, S., Hickey, A., Rafferty, G. F., Peacock, J. L., Greenough, A., Work of breathing during CPAP and heated humidified high flow nasal cannula, Archives of Disease in Childhood, 101, A228, 2016	Full text is an abstract

Study	Reason for Exclusion
Shetty, S., Hunt, K., Douthwaite, A., Athanasiou, M., Dassios, T., Hickey, A., Greenough, A., HHFNC and NCPAP and full oral feeding in BPD infants, European journal of pediatrics, 175 (11), 1717, 2016	Full text is an abstract
Shetty, S., Hunt, K., Douthwaite, A., Athanasiou, M., Hickey, A., Greenough, A., High-flow nasal cannula oxygen and nasal continuous positive airway pressure and full oral feeding in infants with bronchopulmonary dysplasia, Archives of Disease in Childhood., 16, 2016	Comparison not of interest for review: hi-flow vs CPAP
Soonsawad, S., Swatesutipun, B., Limrungsikul, A., Nuntnarumit, P., Heated Humidified High-Flow Nasal Cannula for Prevention of Extubation Failure in Preterm Infants, Indian Journal of Pediatrics, 84, 262-266, 2017	Non-OECD country - Thailand
Soonsawad, S., Tongsawang, N., Nuntnarumit, P., Heated Humidified High-Flow Nasal Cannula for Weaning from Continuous Positive Airway Pressure in Preterm Infants: A Randomized Controlled Trial, Neonatology, 110, 204-9, 2016	Non-OECD country - Thailand
Sreenan,C., Lemke,R.P., Hudson-Mason,A., Osiovich,H., High-flow nasal cannulae in the management of apnea of prematurity: a comparison with conventional nasal continuous positive airway pressure, Pediatrics, 107, 1081-1083, 2001	Comparison not of interest for review: hi-flow vs CPAP
Taha, D. K., Kornhauser, M., Greenspan, J. S., Dysart, K. C., Aghai, Z. H., High Flow Nasal Cannula Use Is Associated with Increased Morbidity and Length of Hospitalization in Extremely Low Birth Weight Infants, Journal of Pediatrics, 173, 50-55.e1, 2016	Comparison not of interest for review: hi-flow vs CPAP
Tan, K., Lai, N. M., Berger, P., Ramsden, C. A., Automated delivery of oxygen to premature infants: A systematic review, Journal of Paediatrics and Child Health, 47, 110, 2011	Full text is an abstract
Urschitz, M. S., Horn, W., Seyfang, A., Hallenberger, A., Herberts, T., Miksch, S., Popow, C., Muller-Hansen, I., Poets, C. F., Automatic control of the inspired oxygen fraction in preterm infants a randomized: Crossover trial, American Journal of Respiratory and Critical Care Medicine, 170, 1095-1100, 2004	< 15 babies in each arm
Van zanten, H., Pauws, S., Kuypers, K., Stenson, B., Lopriore, E., Te Pas, A., The effect of implementing an automated oxygen system as standard care on oxygen saturation and apnoeas in preterm infants: An audit, European Journal of Pediatrics, 175 (11), 1570, 2016	Full text is an abstract
Wilinska, M., Bachman, T., Swietlinski, J., Kostro, M., Twardoch-Drozd, M., Automated FiO2-SpO2 control system in neonates requiring respiratory support: a comparison of a standard	Intervention not relevant - compared 2 different saturation ranges

Study	Reason for Exclusion
to a narrow SpO2 control range, BMC Pediatrics, 14, 130, 2014	
Wilinska, M., Bachman, T., Swietlinski, J., Wasko, A., Jakiel, G., Quicker response results in better SpO2 control - a comparison of 3 FiO2-titration strategies in ventilated preterm infants, Annals of Agricultural & Environmental MedicineAnn Agric Environ Med, 22, 708-12, 2015	< 15 babies in each arm
Wilinska, M., Skrzypek, M., Bachman, T., Swietlinski, J., Kostuch, M., Bierla, K., Czyzewska, M., Hajdar, R., Warakomska, M., Using the Automated Fio2- Spo2 Control in Neonatal Intensive Care Units in Poland. A Preliminary Report, Developmental period medicine, Part 1. 19, 263-270, 2015	Not comparative
Yoder,B.A., Stoddard,R.A., Li,M., King,J., Dirnberger,D.R., Abbasi,S., Heated, humidified high-flow nasal cannula versus nasal CPAP for respiratory support in neonates, Pediatrics, 131, e1482-e1490, 2013	Comparison not of interest for review: hi-flow vs CPAP
Zapata, J., Gomez, J. J., Araque Campo, R., Matiz Rubio, A., Sola, A., A randomised controlled trial of an automated oxygen delivery algorithm for preterm neonates receiving supplemental oxygen without mechanical ventilation, Acta PaediatricaActa Paediatr, 103, 928-33, 2014	< 15 babies in each arm

CPAP: continuous positive airway pressure; NIPPV: non-invasive positive pressure ventilation; OECD: Organisation for Economic Co-operation and Development

Economic studies

All economic studies were excluded at the initial title and abstract screening stage.

Excluded studies for question 3.2 What is the effectiveness and safety of the different assisted ventilation techniques in preterm babies?

Clinical studies

Study	Reason for Exclusion
Randomised study of high-frequency oscillatory ventilation in infants with severe respiratory distress syndrome, Journal of pediatrics, 122, 609-19, 1993	Study dates: pre-1990
Multicentre randomised controlled trial of high against low frequency positive pressure ventilation, Archives of Disease in Childhood, 66, 770-5, 1991	Study dates: pre-1990
Continuous Positive Airway Pressure versus Mechanical Ventilation on the First Day of Life in Very Low-Birth-Weight Infants, American Journal of Perinatology. 33 (10) (pp 939-944), 2016. Date of Publication: 01 Aug 2016., 2016	Study design not of interest: retrospective cohort study

Study	Reason for Exclusion
High-frequency oscillatory ventilation compared with conventional intermittent mechanical ventilation in the treatment of respiratory failure in preterm infants: neurodevelopmental status at 16 to 24 months of postterm age. The HIFI Study Group, Journal of Pediatrics, 117, 939-946, 1990	Study dates pre-1990
Randomized control trial comparing physiologic effects in preterm infants during treatment with nasal continuous positive airway pressure (NCPAP) generated by Bubble NCPAP and Ventilator NCPAP: A pilot study, Journal of perinatal medicine, 44, 655-661, 2016	No outcomes of interest for review and <15 in each arm
High-frequency oscillatory ventilation compared with conventional mechanical ventilation in the treatment of respiratory failure in preterm infants: assessment of pulmonary function at 9 months of corrected age. HiFi Study Group, Journal of Pediatrics, 116, 933-941, 1990	Study dates: pre-1990
Prophylactic nasal continuous positive airway pressure for preventing morbidity and mortality in very preterm infants, Cochrane Database of Systematic Reviews, CD001243, 2016	RCTs not relevant for review: included in review question 1.1
Abbasi, S., Bhutani, V. K., Spitzer, A. R., Fox, W. W., Pulmonary mechanics in preterm neonates with respiratory failure treated with high-frequency oscillatory ventilation compared with conventional mechanical ventilation, Pediatrics, 87, 487-493, 1991	Study dates: pre-1990
Abd El-Moneim, E. S., Fuerste, H. O., Krueger, M., Elmagd, A. A., Brandis, M., Schulte-Moenting, J., Hentschel, R., Pressure support ventilation combined with volume guarantee versus synchronized intermittent mandatory ventilation: A pilot crossover trial in premature infants in their weaning phase, Pediatric Critical Care Medicine, 6, 286-292, 2005	No outcomes of interest for review
Abdel-Hady, H, Shouman, B, Aly, H, Is it safe to use nasal cannula during weaning from nasal continuous positive airway pressure in preterm infants? A randomized controlled trial, Early human development., 86, S12-s13, 2010	Population not relevant for review: Post-nCPAP weaning
Abdel-Hady, H., Shouman, B., Aly, H., Early weaning from CPAP to high flow nasal cannula in preterm infants is associated with prolonged oxygen requirement: A randomized controlled trial, Early Human Development, 87, 205-208, 2011	Population not relevant for review: Post-CPAP weaning
Abubakar, K., Keszler, M., Effect of volume guarantee combined with assist/control vs synchronized intermittent mandatory ventilation, Journal of perinatology, 25, 638-42, 2005	<15 in each arm of study
Abubakar, Km, Keszler, M, Volume guarantee is more effective when combined with	<15 in each arm and intervention not of interest for review

Study	Reason for Exclusion
assist/control ventilation than with synchronized intermittent mandatory ventilation (SIMV), Pediatric Research, 55, 190, 2004	
Abyar, H, Ghafari, V, Nakhshab, M, Jafari, M, Rahimi, N, Asadpour, S, Nasal intermittent mandatory ventilation (NIMV) versus nasal continuous positive airway pressure (NCPAP) in weaning from mechanical ventilation in preterm infants, Journal of Mazandaran University of Medical Sciences, 21, 113-20, 2011	Population not relevant for review: Post-extubation respiratory support
Adegbite,M., Kalapurackal,M., Sankaran,K., Non invasive respiratory support in neonates: A review, Perinatology, 8, 46-52, 2006	Study design not relevant for review: Literature review
Afjeh, S. A., Sabzehei, M. K., Khoshnood Shariati, M., Shamshiri, A. R., Esmaili, F., Evaluation of Initial Respiratory Support Strategies in VLBW Neonates with RDS, Archives of Iranian Medicine, 20, 158-164, 2017	Country not of interest for review: Iran
Agarwal, S., Maria, A., Roy, M. K., Verma, A., A randomized trial comparing efficacy of bubble and ventilator derived nasal CPAP in very low birth weight neonates with respiratory distress, Journal of Clinical and Diagnostic Research, 10, SC09-SC12, 2016	Country not of interest for review: India
Aghai, Z. H., Saslow, J. G., Nakhla, T., Milcarek, B., Hart, J., Lawrysh-Plunkett, R., Stahl, G., Habib, R. H., Pyon, K. H., Synchronized nasal intermittent positive pressure ventilation (SNIPPV) decreases work of breathing (WOB) in premature infants with respiratory distress syndrome (RDS) compared to nasal continuous positive airway pressure (NCPAP), Pediatric pulmonology, 41, 875-81, 2006	No outcomes of interest for the review
Al Ethawi, Y., Volume-targeted versus Pressure-limited Ventilation for Preterm Infants: A Systematic Review and Meta-Analysis, Journal of Clinical Neonatology, 1, 18-20, 2012	Superseded by Klingenberg 2017
Al-Alaiyan, S., Dawoud, M., Al-Hazzani, F., Positive distending pressure produced by heated, humidified high flow nasal cannula as compared to nasal continuous positive airway pressure in premature infants, Journal of Neonatal-Perinatal Medicine, 7, 119-24, 2014	Country not of interest for review: Saudi Arabia
Alallah, J, Nasal ventilation is not superior to nasal CPAP in extreme preterm infants, Journal of Clinical Neonatology, 2, 161-3, 2013	Study design not of interest for review: narrative review
Amitay, M, Etches, Pc, Finer, Nn, Maidens, Jm, Synchronous mechanical ventilation of the neonate with respiratory disease, Critical Care Medicine, 21, 118-24, 1993	<15 in each arm of study
Anonymous,, Randomized study of high-frequency oscillatory ventilation in infants with severe respiratory distress syndrome. HiFO	Study dates: pre-1990

Study	Reason for Exclusion
Study Group, Journal of pediatrics, 122, 609-19, 1993	
Anonymous,, Multicentre randomised controlled trial of high against low frequency positive pressure ventilation. Oxford Region Controlled Trial of Artificial Ventilation OCTAVE Study Group, Archives of Disease in Childhood, 66, 770-5, 1991	Study dates: pre-1990
Anonymous,, High-frequency oscillatory ventilation compared with conventional intermittent mechanical ventilation in the treatment of respiratory failure in preterm infants: neurodevelopmental status at 16 to 24 months of postterm age. The HIFI Study Group, Journal of Pediatrics, 117, 939-46, 1990	Study dates: pre-1990
Anonymous,, High-frequency oscillatory ventilation compared with conventional mechanical ventilation in the treatment of respiratory failure in preterm infants: assessment of pulmonary function at 9 months of corrected age. HiFi Study Group, Journal of pediatrics, 116, 933-41, 1990	Study dates: pre-1990
Anonymous,, Elective high-frequency oscillatory ventilation versus conventional ventilation for acute pulmonary dysfunction in preterm infants, Neonatology, 103, 7-8; discussion 8-9, 2013	Superseded by Cools 2015
Armanian, A. M., Badiee, Z., Heidari, G., Feizi, A., Salehimehr, N., Initial treatment of respiratory distress syndrome with nasal intermittent mandatory ventilation versus nasal continuous positive airway pressure: A randomized controlled trial, International Journal of Preventive Medicine, 5, 1543-1551, 2014	Country not of interest for review: Iran
Armanian, A-M, Badiee, Z, Heidari, G, Feizi, A, Salehimehr, N, Initial treatment of respiratory distress syndrome with nasal intermittent mandatory ventilation versus nasal continuous positive airway pressure: A randomized controlled trial, International Journal of Preventive Medicine, 5, 1543-51, 2014	Country not of interest for review: Iran
Badiee, Z, Nekooie, B, Mohammadizadeh, M, Noninvasive positive pressure ventilation or conventional mechanical ventilation for neonatal continuous positive airway pressure failure, International Journal of Preventive Medicine, 5, 1045-53, 2014	Country not of interest for review: Iran
Badiee, Z., Naseri, F., Sadeghnia, A., Early versus delayed initiation of nasal continuous positive airway pressure for treatment of respiratory distress syndrome in premature newborns: A randomized clinical trial, Advanced Biomedical ResearchAdv, 2, 4, 2013	Country not of interest for review: Iran
Bahman-Bijari, B., Malekiyan, A., Niknafs, P., Baneshi, M. R., Bubble-CPAP vs. Ventilatory-CPAP in Preterm Infants with Respiratory	Country not of interest for review: Iran

Study	Reason for Exclusion
Distress, Iranian Journal of PediatricsIran, 21, 151-8, 2011	
Bai, X. M., Bian, J., Zhao, Y. L., Zhang, L., Darshana, S., Liu, Z. J., The application of nasal synchronized intermittent mandatory ventilation in primary apnea of prematurity, Turkish Journal of Pediatrics, 56, 150-3, 2014	Country not of interest for review: China
Barrington, Kj, Bull, D, Finer, Nn, Randomized trial of nasal synchronized intermittent mandatory ventilation compared with continuous positive airway pressure after extubation of very low birth weight infants, Pediatrics, 107, 638-641, 2001	Population not relevant for review: Post-extubation respiratory support
Bauer, K, Buschkamp, S, Marcinkowski, M, Kössel, H, Thome, U, Versmold, Ht, Postnatal changes of extracellular volume, atrial natriuretic factor, and diuresis in a randomized controlled trial of high-frequency oscillatory ventilation versus intermittent positive-pressure ventilation in premature infants <30 weeks gestation, Critical Care Medicine, 28, 2064-2068, 2000	No outcomes of interest for review
Baumer, J. H., Patient-triggered ventilation in premature neonates, Acta Paediatrica, International Journal of Paediatrics, Supplement, 90, 22-24, 2001	Review of RCTs
Bedi, P. K., Castro-Codesal, M. L., Featherstone, R., AlBalawi, M. M., Alkhaledi, B., Kozyrskyj, A. L., Flores-Mir, C., MacLean, J. E., Long-term Non-Invasive Ventilation in Infants: A Systematic Review and Meta-Analysis, Frontiers in PediatricsFront, 6, 13, 2018	Setting not of interest for review: outside acute care
Beker, F, Rogerson, Sr, Hooper, Sb, Wong, C, Davis, Pg, The effects of nasal continuous positive airway pressure on cardiac function in premature infants with minimal lung disease: A crossover randomized trial, Journal of pediatrics, 164, 726-9, 2014	No outcomes of interest
Bhandari,V., Gavino,R.G., Nedrelow,J.H., Pallela,P., Salvador,A., Ehrenkranz,R.A., Brodsky,N.L., A randomized controlled trial of synchronized nasal intermittent positive pressure ventilation in RDS, Journal of Perinatology, 27, 697-703, 2007	Comparison not of interest for review: invasive vs non-invasive ventilation
Bhat, P., Chowdhury, O., Shetty, S., Hannam, S., Rafferty, G. F., Peacock, J., Greenough, A., Volume-targeted versus pressure-limited ventilation in infants born at or near term, European Journal of Pediatrics, 175, 89-95, 2016	Population is mix of preterm and term infants
Bhatti, A., Khan, J., Murki, S., Sundaram, V., Saini, S. S., Kumar, P., Nasal Jet-CPAP (variable flow) versus Bubble-CPAP in preterm infants with respiratory distress: an open label,	Country not of interest for review: India

Study	Reason for Exclusion
randomized controlled trial, Journal of perinatology, 35, 935-40, 2015	
Bhuta, T., Henderson-Smart, D. J., Elective high frequency jet ventilation versus conventional ventilation for respiratory distress syndrome in preterm infants, Cochrane database of systematic reviews (Online), CD000328, 2000	Only 1 RCT that meets inclusion criteria for NMA and pairwise. RCT extracted from original paper.
Bhuta, Tushar, Henderson-Smart, David J, Elective high frequency jet ventilation versus conventional ventilation for respiratory distress syndrome in preterm infants, Cochrane Database of Systematic Reviews, 1998	Superseeded by Bhuta 2000
Bhuta,T., Henderson-Smart,D.J., Elective high-frequency oscillatory ventilation versus conventional ventilation in preterm infants with pulmonary dysfunction: systematic review and meta-analyses, Pediatrics, 100, E6-, 1997	Superseeded by Bhuta 1998
Bober,K., Swietlinski,J., Zejda,J., Kornacka,K., Pawlik,D., Behrendt,J., Gajewska,E., Czyzewska,M., Korbal,P., Witalis,J., Walas,W., Wilinska,M., Turzanska,A., Zielinski,G., Czeszynska,B., Bachman,T., A multicenter randomized controlled trial comparing effectiveness of two nasal continuous positive airway pressure devices in very-low-birth-weight infants, Pediatric Critical Care Medicine, 13, 191-196, 2012	Comparison not of interest for review: Non-invasive inter-group comparison
Bollen, C. W., Uiterwaal, C. S. P. M., Van Vught, A. J., Cumulative Metaanalysis of High-frequency Versus Conventional Ventilation in Premature Neonates, American Journal of Respiratory and Critical Care Medicine, 168, 1150-1155, 2003	Superseded by Cools 2015
Bollen, C. W., Uiterwaal, C. S. P. M., Van Vught, A. J., Meta-regression analysis of high-frequency ventilation vs conventional ventilation in infant respiratory distress syndrome, Intensive Care Medicine, 33, 680-688, 2007	Superseded by Cools 2015
Bollen, C. W., Uiterwaal, C. S. P. M., Van Vught, A. J., Van Der Tweel, I., Sequential meta-analysis of past clinical trials to determine the use of a new trial, Epidemiology, 17, 644-649, 2006	Superseded by Cools 2015
Buckmaster, A. G., Arnolda, G., Wright, I. M., Foster, J. P., Henderson-Smart, D. J., Continuous positive airway pressure therapy for infants with respiratory distress in non tertiary care centers: a randomized, controlled trial.[Erratum appears in Pediatrics.2008 Jun;121(6): 1301], Pediatrics, 120, 509-18, 2007	Population not relevant for review: mix of preterm and term neonates with no stratification for age in the outcomes
Calvert, S, Prophylactic high-frequency oscillatory ventilation in preterm infants, Acta paediatrica (oslo, norway), 91 Suppl, 16-18, 2002	Study design not of interest for review: narrative review

Study	Reason for Exclusion
Campbell, D. M., Shah, P. S., Shah, V., Kelly, E. N., Nasal continuous positive airway pressure from high flow cannula versus Infant Flow for preterm infants, Journal of perinatology, 26, 546-549, 2006	Study only relevant for NMA and no outcomes of interest for NMA
Caplan, M, MacKendrick, W, High-frequency jet ventilation in preterm infants, Pediatrics, 102, 158-159, 1998	Study design not of interest for review: Letter
Carlo, Wa, Siner, B, Chatburn, Rl, Robertson, S, Martin, Rj, Early randomized intervention with high-frequency jet ventilation in respiratory distress syndrome, Journal of pediatrics, 117, 765-770, 1990	Study dates: pre-1990
Carlo, Wa, Stark, Ar, Wright, Ll, Tyson, Je, Papile, La, Shankaran, S, Donovan, Ef, Oh, W, Bauer, Cr, Saha, S, Poole, Wk, Stoll, B, Minimal ventilation to prevent bronchopulmonary dysplasia in extremely-low-birth-weight infants, Journal of Pediatrics, 141, 370-374, 2002	Intervention not of interest for review: Study assesses different targets of carbon dioxide levels, not different ventilation strategies
Carlo,W.A., Siner,B., Chatburn,R.L., Robertson,S., Martin,R.J., Early randomized intervention with high-frequency jet ventilation in respiratory distress syndrome, Journal of Pediatrics, 117, 765-770, 1990	Study dates: Pre-1990
Chan, V, Greenough, A, Comparison of weaning by patient triggered ventilation or synchronous intermittent mandatory ventilation in preterm infants, Acta PaediatricaActa Paediatr, 83, 335-337, 1994	Population not relevant for review: Weaning from primary reispiratory support
Chan, V, Greenough, A, Neonatal patient triggered ventilators. Performance in acute and chronic lung disease, British Journal of Intensive Care, 3, 216-9, 1993	No outcomes of interest for the review
Chan, V., Greenough, A., Randomised controlled trial of weaning by patient triggered ventilation or conventional ventilation, European Journal of Pediatrics, 152, 51-54, 1993	Population not relevant for review: Weaning from primary respiratory support
Cheema, I. U., Ahluwalia, J. S., Feasibility of tidal volume-guided ventilation in newborn infants: A randomized, crossover trial using the volume guarantee modality, Pediatrics, 107, 1323-1328, 2001	No outcomes of interest for review
Cheema, I. U., Sinha, A. K., Kempley, S. T., Ahluwalia, J. S., Impact of volume guarantee ventilation on arterial carbon dioxide tension in newborn infants: a randomised controlled trial, Early Human Development, 83, 183-9, 2007	No outcomes of interest for review
Chen, J-W, Gao, W-W, Xu, F, Du, L-L, Zhang, T, Ling, X, Li, W-T, Comparison of clinical efficacy of heated humidified high flow nasal cannula versus nasal continuous positive airway pressure in treatment of respiratory distress syndrome in very low birth weight infants,	Country not of interest for review: China

Study	Reason for Exclusion
Chinese Journal of Contemporary Pediatrics, 17, 847-851, 2015	
Chen, L., Wang, L., Li, J., Wang, N., Shi, Y., Noninvasive Ventilation for Preterm Twin Neonates with Respiratory Distress Syndrome: A Randomized Controlled Trial, Scientific reports, 5, 14483, 2015	Country not of interest for review: China
Chen, X, Peng, Ws, Wang, L, Xu, Jl, Dong, Hf, Pan, Jh, A randomized controlled study of nasal intermittent positive pressure ventilation in the treatment of neonatal respiratory distress syndrome, Zhongguo Dang Dai Er Ke za Zhi [Chinese Journal of Contemporary Pediatrics], 15, 713-717, 2013	Country not of interest for review: China
Chen,J.Y., Ling,U.P., Chen,J.H., Comparison of synchronized and conventional intermittent mandatory ventilation in neonates, Acta Paediatrica Japonica, 39, 578-583, 1997	Country not of interest for review: China
Ciuffini, F., Pietrasanta, C., Lavizzari, A., Musumeci, S., Gualdi, C., Sortino, S., & Mosca, F., Comparison between two different modes of non-invasive ventilatory support in preterm newborn infants with respiratory distress syndrome mild to moderate: preliminary data, La Pediatria Medica e Chirurgica, 36, 8, 2014	Subset of babies, full sample reported in Lavizzarri 2016
Clark, R. H., Gerstmann, D. R., Null Jr, D. M., DeLemos, R. A., Prospective randomized comparison of high-frequency oscillatory and conventional ventilation in respiratory distress syndrome, Pediatrics, 89, 5-12, 1992	RCT study date pre-1990
Clark, R. H., Yoder, B. A., Sell, M. S., Prospective, randomized comparison of high-frequency oscillation and conventional ventilation in candidates for extracorporeal membrane oxygenation, Journal of pediatrics, 124, 447-54, 1994	Population not relevant for review: mixture of preterm and term neonates without stratification of outcomes
Cleary, J. P., Bernstein, G., Mannino, F. L., Heldt, G. P., Improved oxygenation during synchronized intermittent mandatory ventilation in neonates with respiratory distress syndrome: A randomized, crossover study, Journal of pediatrics, 126, 407-411, 1995	No outcomes of interest for review
Collins, C. L., Barfield, C., Davis, P. G., Horne, R. S. C., Randomized controlled trial to compare sleep and wake in preterm infants less than 32weeks of gestation receiving two different modes of non-invasive respiratory support, Early Human Development, 91, 701-704, 2015	No outcomes of interest for review
Collins, C. L., Holberton, J. R., Barfield, C., Davis, P. G., A randomized controlled trial to compare heated humidified high-flow nasal cannulae with nasal continuous positive airway pressure postextubation in premature infants, Journal of pediatrics, 162, 949-54.e1, 2013	Population not relevant for review: Post-extubation weaning

Study	Reason for Exclusion
Cools, F., Askie, L. M., Offringa, M., Asselin, J. M., Calvert, S. A., Courtney, S. E., Dani, C., Durand, D. J., Gerstmann, D. R., Henderson-Smart, D. J., Marlow, N., Peacock, J. L., Pillow, J. J., Soll, R. F., Thome, U. H., Truffert, P., Schreiber, M. D., Van Reempts, P., Vendettuoli, V., Vento, G., Pre, Vilig collaboration, Elective high-frequency oscillatory versus conventional ventilation in preterm infants: a systematic review and meta-analysis of individual patients' data, Lancet, 375, 2082-91, 2010	Superseded by Cools 2015
Cools, F., Askie, L. M., Offringa, M., tPrevention of Ventilator Induced Lung InjuryCollaborative Study, Group, Elective high-frequency oscillatory ventilation in preterm infants with respiratory distress syndrome: an individual patient data meta-analysis, BMC Pediatrics, 9, 33, 2009	Superseded by Cools 2015
Cvetnic, W. G., Shoptaugh, M., Sills, J. H., Intermittent mandatory ventilation with continuous negative pressure compared with positive end-expiratory pressure for neonatal hypoxemia, Journal of perinatology, 12, 316-24, 1992	Population not relevant for review: mixture of term and preterm neonates and no stratification for outcomes by age
Dani, C., Bertini, G., Pezzati, M., Filippi, L., Pratesi, S., Caviglioli, C., Rubaltelli, F. F., Effects of pressure support ventilation plus volume guarantee vs. high-frequency oscillatory ventilation on lung inflammation in preterm infants, Pediatric Pulmonology, 41, 242-9, 2006	<15 in each study arm
Davis, P. G., Lemyre, B., de Paoli, A. G., Nasal intermittent positive pressure ventilation (NIPPV) versus nasal continuous positive airway pressure (NCPAP) for preterm neonates after extubation, Cochrane database of systematic reviews (Online), CD003212, 2001	Superseeded by Davis 2003
Davis, Peter G, Henderson-Smart, David J, Nasal continuous positive airway pressure immediately after extubation for preventing morbidity in preterm infants, Cochrane Database of Systematic Reviews, 2003	Population not relevant for review: Post-extubation respiratory support
Davis,P., Henderson-Smart,D., Post-extubation prophylactic nasal continuous positive airway pressure in preterm infants: systematic review and meta-analysis, Journal of Paediatrics and Child Health, 35, 367-371, 1999	Population not relevant for review: Post-extubation respiratory support
De Paoli, A. G., Davis, P. G., Lemyre, B., Nasal continuous positive airway pressure versus nasal intermittent positive pressure ventilation for preterm neonates: a systematic review and meta-analysis, Acta PaediatricaActa Paediatr, 92, 70-5, 2003	Population not relevant for review: Post-extubation respiratory support
DeMauro, S. B., Millar, D., Kirpalani, H., Noninvasive respiratory support for neonates, Current Opinion in Pediatrics, 26, 157-62, 2014	No additional RCTs to other Cochrane systematic reviews included

Study	Reason for Exclusion
Dimitriou, G, Greenough, A, Giffin, F, Synchronous intermittent mandatory ventilation modes versus patient triggered ventilation during weaning of premature infants, Early Human Development, 41, 224, 1995	Population not relevant for review: Weaning from invasive ventilation
Dimitriou, G., Greenough, A., Griffin, F., Chan, V., Synchronous intermittent mandatory ventilation modes compared with patient triggered ventilation during weaning, Archives of Disease in Childhood Fetal & Neonatal EditionArch Dis Child Fetal Neonatal Ed, 72, F188-90, 1995	Population not relevant for review: Weaning from invasive ventilation
Doctor, T. N., Foster, J. P., Stewart, A., Tan, K., Todd, D. A., McGrory, L., Heated and humidified inspired gas through heated humidifiers in comparison to non-heated and non-humidified gas in hospitalised neonates receiving respiratory support, Cochrane Database of Systematic Reviews, 2017 (2) (no pagination), 2017	Protocol
Dunn, M. S., Kaempf, J., de Klerk, A., de Klerk, R., Reilly, M., Howard, D., Ferrelli, K., O'Conor, J., Soll, R. F., Vermont Oxford Network, D. R. M. Study Group, Randomized trial comparing 3 approaches to the initial respiratory management of preterm neonates, Pediatrics, 128, e1069-76, 2011	RCTs not relevant for review: included in review question 1.1
Durand,D.J., Asselin,J.M., Courtney,S.E., Weber,K.R., Meredith,K.S., Helm,J.F., Stoddard,R.A., Minton,S.D., Mountcastle,K., Lassen,G., Randomized study of high-frequency oscillatory ventilation in infants with severe respiratory distress syndrome, Journal of Pediatrics, 122, 609-619, 1993	Study dates: pre-1990
Erdemir, A., Kahramaner, Z., Turkoglu, E., Cosar, H., Sutcuoglu, S., Ozer, E. A., Effects of synchronized intermittent mandatory ventilation versus pressure support plus volume guarantee ventilation in the weaning phase of preterm infants, Pediatric Critical Care Medicine, 15, 236-41, 2014	Population not relevant for review: Weaning from mechanical ventilation
Esmaeilnia, T., Nayeri, F., Taheritafti, R., Shariat, M., Moghimpour-Bijani, F., Comparison of Complications and Efficacy of NIPPV and Nasal CPAP in Preterm Infants With RDS, Iranian Journal of PediatricsIran, 26, e2352, 2016	Country not of interest for review: Iran
Ethawi, Y. H., Abou Mehrem, A., Minski, J., Ruth, C. A., Davis, P. G., High frequency jet ventilation versus high frequency oscillatory ventilation for pulmonary dysfunction in preterm infants, Cochrane Database of Systematic Reviews, CD010548, 2016	No RCTs identified in the systematic review
Farhat, A. S., Mohammadzadeh, A., Saeidi, R., Noorizadeh, S., A comparison between nasal	Country not of interest for review: Iran

Study	Reason for Exclusion
intermittent positive pressure ventilation and nasal continuous positive airway pressure ventilation in the treatment of neonatal respiratory distress syndrome, Iranian Journal of Neonatology, 6, 1-6, 2015	
Finer, N. N., Carlo, W. A., Walsh, M. C., Rich, W., Gantz, M. G., Laptook, A. R., Yoder, B. A., Faix, R. G., Das, A., Poole, W. K., Donovan, E. F., Newman, N. S., Ambalavanan, N., Frantz, Iii I. D., Buchter, S., Sanchez, P. J., Kennedy, K. A., Laroia, N., Poindexter, B. B., Cotten, C. M., Van Meurs, K. P., Duara, S., Narendran, V., Sood, B. G., O'Shea, T. M., Bell, E. F., Bhandari, V., Watterberg, K. L., Higgins, R. D., Early CPAP versus surfactant in extremely preterm infants, New England Journal of Medicine, 362, 1970-1979, 2010	RCTs not relevant for review: included in review question 1.1
Firme, S. R. E., McEvoy, C. T., Alconcel, C., Tanner, J., Durand, M., Episodes of hypoxemia during synchronized intermittent mandatory ventilation in ventilator-dependent very low birth weight infants, Pediatric pulmonology, 40, 9-14, 2005	No outcomes of interest for review
Fleeman, N., Mahon, J., Bates, V., Dickson, R., Dundar, Y., Dwan, K., Ellis, L., Kotas, E., Richardson, M., Shah, P., Shaw, B. N. J., The clinical effectiveness and cost-effectiveness of heated humidified high-flow nasal cannula compared with usual care for preterm infants: Systematic review and economic evaluation, Health Technology Assessment, 20, 2016	Only 1 additional RCT identified in addition to the systematic review by Kotecha 2015. RCT extracted from original paper.
Friedlich,P., Lecart,C., Posen,R., Ramicone,E., Chan,L., Ramanathan,R., A randomized trial of nasopharyngeal-synchronized intermittent mandatory ventilation versus nasopharyngeal continuous positive airway pressure in very low birth weight infants after extubation, Journal of Perinatology, 19, 413-418, 1999	Population not of interest for review: Post-extubation weaning
Gerstmann, D. R., Wood, K., Miller, A., Steffen, M., Ogden, B., Stoddard, R. A., Minton, S. D., Childhood outcome after early high-frequency oscillatory ventilation for neonatal respiratory distress syndrome, Pediatrics, 108, 617-23, 2001	No outcomes of interest for review: Neurodevelopemental outcomes reported not of interest in review protocol
Gizzi, C, Papoff, P, Giordano, I, Massenzi, L, Barbàra, Cs, Campelli, M, Flow-Synchronized Nasal Intermittent Positive Pressure Ventilation for Infants <32 Weeks' Gestation with Respiratory Distress Syndrome, Critical care research and practice, 2012, 7 pages, 2012	Study design not of interest for review: retrospective cohort study
Gizzi, C., Montecchia, F., Panetta, V., Castellano, C., Mariani, C., Campelli, M., Papoff, P., Moretti, C., Agostino, R., Is synchronised NIPPV more effective than NIPPV and NCPAP in treating apnoea of prematurity (AOP)? A	No outcomes of interest for review

Study	Reason for Exclusion
randomised cross-over trial, Archives of Disease in Childhood: Fetal and Neonatal Edition, 100, F17-F23, 2015	
Glackin, S. J., O'Sullivan, A., George, S., Semberova, J., Miletin, J., High flow nasal cannula versus NCPAP, duration to full oral feeds in preterm infants: A randomised controlled trial, Archives of Disease in Childhood., 23, 2016	Population not of interest for review: Post-extubation respiratory support
Goncalves-Ferri, W. A., Martinez, F. E., Caldas, J. P. S., Marba, S. T. M., Fekete, S., Rugolo, L., Tanuri, C., Leone, C., Sancho, G. A., Almeida, M. F. B., Guinsburg, R., Application of continuous positive airway pressure in the delivery room: A multicenter randomized clinical trial, Brazilian Journal of Medical and Biological Research, 47, 259-264, 2014	Country not of interest: Brazil
Greenough, A., Dimitriou, G., Prendergast, M., Milner, A. D., Synchronized mechanical ventilation for respiratory support in newborn infants, Cochrane Database of Systematic Reviews, CD000456, 2008	Superseeded by Greenough 2016
Greenough, A., Limb, E., Marlow, N., Peacock, J. L., Calvert, S., Radiological outcome of very prematurely born infants randomised to high frequency oscillatory or conventional ventilation, European Journal of Pediatrics, 163, 671-4, 2004	No outcomes of interest for review
Greenough, A., Milner, A. D., Dimitriou, G., Synchronized mechanical ventilation for respiratory support in newborn infants, Cochrane Database of Systematic Reviews, CD000456, 2004	Superseeded by Greenough 2008
Gupta,, Pressure support ventilation in preterm babies ? a randomized crossover trial, European Journal of Pediatrics, 165, 2006	Abstract
Gupta, S., Janakiraman, S., Volume ventilation in neonates, Paediatrics and Child Health (United Kingdom), 28, 1-5, 2018	Study design not of interest for review: narrative review
Hallenberger, A., Poets, C. F., Horn, W., Seyfang, A., Urschitz, M. S., Miksch, S., Mueller-Hansen, I., Hummler, H., Schmid, M., Essers, J., Mendler, M., Hentschel, R., Freisinger, P., Schneider, H. C., Closed-loop automatic oxygen control (CLAC) in preterm infants: A randomized controlled trial, Pediatrics, 133, e379-e385, 2014	No interventions of interest for review
Hammer, J., Nasal CPAP in preterm infants - Does it work and how?, Intensive Care Medicine, 27, 1689-1691, 2001	Study design not of interest for review: Editorial
Hegde, D., Mondkar, J., Panchal, H., Manerkar, S., Jasani, B., Kabra, N., Heated Humidified High Flow Nasal Cannula versus Nasal Continuous Positive Airway Pressure as Primary Mode of Respiratory Support for Respiratory	Country not of interest for review: India

Study	Reason for Exclusion
Distress in Preterm Infants, Indian Pediatrics, 53, 129-33, 2016	
Heiring, C, Steensberg, J, Bjerager, M, Greisen, G, A Randomized Trial of Low-Flow Oxygen versus Nasal Continuous Positive Airway Pressure in Preterm Infants, Neonatology, 108, 259-265, 2015	Population not of interest for review: Weaning from primary respiratory support
Henderson-Smart, D. J., Bhuta, T., Cools, F., Offringa, M., Elective high frequency oscillatory ventilation versus conventional ventilation for acute pulmonary dysfunction in preterm infants, Cochrane Database of Systematic Reviews, CD000104, 2000	Superseeded by Henderson-Smart 2001
Henderson-Smart, D. J., Bhuta, T., Cools, F., Offringa, M., Elective high frequency oscillatory ventilation versus conventional ventilation for acute pulmonary dysfunction in preterm infants, Cochrane Database of Systematic Reviews, CD000104, 2003	Superseeded by Henderson-Smart 2007
Henderson-Smart, D. J., Bhuta, T., Cools, F., Offringa, M., Elective high frequency oscillatory ventilation versus conventional ventilation for acute pulmonary dysfunction in preterm infants, Cochrane Database of Systematic Reviews, CD000104, 2001	Superseeded by Henderson-Smart 2003
Henderson-Smart, D.J., Cools,F., Bhuta,T., Offringa,M., Elective high frequency oscillatory ventilation versus conventional ventilation for acute pulmonary dysfunction in preterm infants, Cochrane Database of Systematic Reviews, 2007. Article Number, -, 2007	Superseded by Cools 2015
Higgins, Rd, Richter, Se, Davis, Jm, Nasal continuous positive airway pressure facilitates extubation of very low birth weight neonates, Pediatrics, 88, 999-1003, 1991	Study dates: pre-1990
Hird,M.F., Greenough,A., Randomised trial of patient triggered ventilation versus high frequency positive pressure ventilation in acute respiratory distress, Journal of Perinatal Medicine, 19, 379-384, 1991	Study dates: Pre-1990
Ho, J. J., Subramaniam, P., Henderson-Smart, D. J., Davis, P. G., Continuous distending airway pressure for respiratory distress syndrome in preterm infants, Cochrane Database of Systematic Reviews, CD002271, 2000	No RCTs of interest for review
Imbulana, D. I., Manley, B. J., Dawson, J. A., Davis, P. G., Owen, L. S., Nasal injury in preterm infants receiving non-invasive respiratory support: a systematic review, Archives of Disease in Childhood, Fetal and neonatal edition. 103, F29-F35, 2018	No outcomes of interest for review: nasal injury
Iranpour, R, Sadeghnia, A, Hesaraki, M, High-flow nasal cannula versus nasal continuous positive airway pressure in the management of	Country not of interest: Persia (Iran)

Study	Reason for Exclusion
respiratory distress syndrome, Journal of Isfahan Medical School, 29, 2011	
Iscan, B., Duman, N., Tuzun, F., Kumral, A., Ozkan, H., Impact of Volume Guarantee on High-Frequency Oscillatory Ventilation in Preterm Infants: A Randomized Crossover Clinical Trial, Neonatology, 108, 277-282, 2015	Not outcomes of interest for review
Jain, D, Claure, N, D'Ugard, C, Bello, J, Bancalari, E, Volume Guarantee Ventilation: Effect on Preterm Infants with Frequent Hypoxemia Episodes, Neonatology, 110, 129-34, 2016	Not outcomes of interest for review
Jasani, B., Nanavati, R., Kabra, N., Rajdeo, S., Bhandari, V., Comparison of non-synchronized nasal intermittent positive pressure ventilation versus nasal continuous positive airway pressure as post-extubation respiratory support in preterm infants with respiratory distress syndrome: a randomized controlled trial, Journal of maternal-fetal & neonatal medicine, 29, 1546-51, 2016	Country not of interest for review: India
Joshi, V. H., Bhuta, T., Rescue high frequency jet ventilation versus conventional ventilation for severe pulmonary dysfunction in preterm infants, Cochrane database of systematic reviews (Online), CD000437, 2006	Superseded by Rojas-Reyes 2015
Kadivar, M. Md, Mosayebi, Z. Md, Razi, N. Md, Nariman, S. Md, Sangsari, R. Md, High Flow Nasal Cannulae versus Nasal Continuous Positive Airway Pressure in Neonates with Respiratory Distress Syndrome Managed with INSURE Method: A Randomized Clinical Trial, Iranian Journal of Medical Sciences, 41, 494-500, 2016	Country not of interest for review: Iran
Kahramaner, Z., Erdemir, A., Turkoglu, E., Cosar, H., Sutcuoglu, S., Ozer, E. A., Unsynchronized nasal intermittent positive pressure versus nasal continuous positive airway pressure in preterm infants after extubation, Journal of Maternal-Fetal and Neonatal Medicine, 27, 926-929, 2014	Population not of interest for review: Post-extubation weaning
Kang, W-Q, Xu, B-L, Liu, D-P, Zhang, Y-D, Guo, J, Li, Z-H, Zhou, Y-J, Xiong, H, Efficacy of heated humidified high-flow nasal cannula in preterm infants aged less than 32 weeks after ventilator weaning, Chinese Journal of Contemporary Pediatrics, 18, 488-491, 2016	Population not of interest for review: Post-extubation weaning
Keszler, M., Modanlou, H. D., Brudno, D. S., Clark, F. I., Cohen, R. S., Ryan, R. M., Kaneta, M. K., Davis, J. M., Multicenter controlled clinical trial of high-frequency jet ventilation in preterm infants with uncomplicated respiratory distress syndrome, Pediatrics, 100, 593-9, 1997	Cross-over study design attributing to significant incoherence and heterogeneity
Khorana,M., Paradeevisut,H., Sangtawesin,V., Kanjanapatanakul,W., Chotigeat,U.,	Country not of interest for review: Thailand

Study	Reason for Exclusion
Ayutthaya,J.K., A randomized trial of non-synchronized Nasopharyngeal Intermittent Mandatory Ventilation (nsNIMV) vs. Nasal Continuous Positive Airway Pressure (NCPAP) in the prevention of extubation failure in pre-term < 1,500 grams, Journal of the Medical Association of Thailand, 91 Suppl 3, S136-S142, 2008	
Komatsu, D. F. R., Diniz, E. M. A., Ferraro, A. A., Ceccon, M. E. J. R., Costavaz, F. A., Randomized controlled trial comparing nasal intermittent positive pressure ventilation and nasal continuous positive airway pressure in premature infants after tracheal extubation, Revista da Associacao Medica Brasileira, 62, 568-574, 2016	Country not of interest for review: Brazil
Kotecha, S. J., Adappa, R., Gupta, N., John Watkins, W., Kotecha, S., Chakraborty, M., Safety and efficacy of high-flow nasal cannula therapy in preterm infants: A meta-analysis, Pediatrics, 136, 542-553, 2015	Only 2 RCTs met the inclusion criteria for this review. The 2 RCTs were extracted from the original papers
Kugelman, A, Riskin, A, Said, W, Shoris, I, Mor, F, Bader, D, A randomized pilot study comparing heated humidified high-flow nasal cannulae with NIPPV for RDS, Pediatric pulmonology, 2014	Duplicate study with Kugelman 2015
Lemyre, B., Davis, P. G., De Paoli, A. G., Nasal intermittent positive pressure ventilation (NIPPV) versus nasal continuous positive airway pressure (NCPAP) for apnea of prematurity, Cochrane Database of Systematic Reviews, CD002272, 2000	Superseeded by Lemyre 2002
Lemyre, B., Davis, P. G., de Paoli, A. G., Nasal intermittent positive pressure ventilation (NIPPV) versus nasal continuous positive airway pressure (NCPAP) for apnea of prematurity, Cochrane Database of Systematic Reviews, CD002272, 2002	Superseeded by Lemyre 2014
Lemyre, B., Davis, P. G., De Paoli, A. G., Kirpalani, H., Nasal intermittent positive pressure ventilation (NIPPV) versus nasal continuous positive airway pressure (NCPAP) for preterm neonates after extubation, The Cochrane database of systematic reviews, 9, CD003212, 2014	Superseeded by Lemyre 2017
Li, W., Long, C., Zhangxue, H., Jinning, Z., Shifang, T., Juan, M., Renjun, L., Yuan, S., Nasal intermittent positive pressure ventilation versus nasal continuous positive airway pressure for preterm infants with respiratory distress syndrome: a meta-analysis and up-date, Pediatric pulmonology, 50, 402-9, 2015	No additional RCTs identified than Cochrane systematic reviews
Lin, C. H., Wang, S. T., Lin, Y. J., Yeh, T. F., Efficacy of nasal intermittent positive pressure ventilation in treating apnea of prematurity, Pediatric pulmonology, 26, 349-53, 1998	Country not of interest for review: China

Study	Reason for Exclusion
Liu, Cq, Xia, Yf, Xiao, M, A randomized, controlled study of nasal intermittent positive pressure ventilation vs. nasal continuous positive airway pressure for prevention of extubation failure in very low birth weight neonates, Journal of maternal-fetal & neonatal medicine, 27, 209-10, 2014	Country not of interest for review: China
Liu, Cz, Huang, By, Tan, By, Guan, Hf, Xu, Xh, Guo, Qy, Efficacy of volume-targeted ventilation for the treatment of neonatal respiratory distress syndrome, Zhongguo Dang Dai Er Ke za Zhi [Chinese Journal of Contemporary Pediatrics], 18, 6-9, 2016	Country not of interest for review: China
Luyt, K, Wright, D, Baumer, Jh, Randomised study comparing extent of hypocarbia in preterm infants during conventional and patient triggered ventilation, Archives of Disease in Childhood: Fetal and Neonatal Edition, 84, F14-f17, 2001	No outcomes of interest for review
Manley, B. J., Roberts, C. T., Froisland, D. H., Doyle, L. W., Davis, P. G., Owen, L. S., Refining the Use of Nasal High-Flow Therapy as Primary Respiratory Support for Preterm Infants, Journal of Pediatrics, 196, 65-70.e1, 2018	No outcomes of interest for review: clinical and demographic variables that predict high flow failure
Mazzella, M., Bellini, C., Calevo, M. G., Campone, F., Massocco, D., Mezzano, P., Zullino, E., Scopesi, F., Arioni, C., Bonacci, W., Serra, G., A randomised control study comparing the Infant Flow Driver with nasal continuous positive airway pressure in preterm infants, Archives of Disease in Childhood Fetal & Neonatal EditionArch Dis Child Fetal Neonatal Ed, 85, F86-90, 2001	Comparison only relevant for NMA and no outcomes of interest for NMA
McCallion, N, Lau, R, Morley, CJ, Dargaville, PA, Neonatal volume guarantee ventilation: effects of spontaneous breathing, triggered and untriggered inflations, Archives of disease in childhood. Fetal and neonatal edition, 93, F36-9, 2008	<15 participants in each arm
McCallion, N., Davis, P. G., Morley, C. J., Volume-targeted versus pressure-limited ventilation in the neonate, Cochrane database of systematic reviews (Online), CD003666, 2005	Superseded by Klingenberg 2017
Meneses, J, Bhandari, V, Alves, JG, Herrmann, D, Noninvasive ventilation for respiratory distress syndrome: a randomized controlled trial, Pediatrics, 127, 300-307, 2011	Country not of interest for review: Brazil
Millar, D, Lemyre, B, Kirpalani, H, Chiu, A, Yoder, Ba, Roberts, Rs, A comparison of bilevel and ventilator-delivered non-invasive respiratory support, Archives of disease in childhood. Fetal and neonatal edition, 101, F21-5, 2016	Comparison not of interest for review: Non-invasive inter-group comparison
Miller, S. M., Dowd, S. A., High-flow nasal cannula and extubation success in the premature infant: a comparison of two	Population not of interest for review: Post-extubation weaning

Study	Reason for Exclusion
modalities, Journal of perinatology, 30, 805-8, 2010	
Moriette, G, Paris-Llado, J, Escande, B, Magny, Jf, Cambonie, G, Thiriez, G, Lacaze-Masmonteil, T, Storme, L, Blanc, T, Liet, Jm, Breart, G, Truffert, P, Outcome at 2 years of age in preterm infants less than 30 weeks gestational age (GA) randomized to receive high-frequency oscillatory ventilation (HFOV) or conventional ventilation (CV) for treatment of RDS, Pediatric Research, 55, 81, 2004	Abstract
Morley, C. J., Davis, P., Doyle, L., Continuous positive airway pressure: randomized, controlled trial in Australia, Pediatrics, 108, 1383, 2001	Study design not of interest for review: Letter
Morley, Cj, Davis, Pg, Doyle, Lw, Brion, Lp, Hascoet, Jm, Carlin, Jb, Nasal CPAP or intubation at birth for very preterm infants, New England journal of medicine, 358, 700-708, 2008	RCTs not relevant for review: included in review question 1.1
Mukerji, A., Sarmiento, K., Lee, B., Hassall, K., Shah, V., Non-invasive high-frequency ventilation versus bi-phasic continuous positive airway pressure (BP-CPAP) following CPAP failure in infants <1250g: a pilot randomized controlled trial, Journal of perinatology, 37, 49-53, 2017	Interventions not of interest for review: non-invasive NIHFV not listed in protocol
Nasef, N, El-Gouhary, E, Schurr, P, Reilly, M, Beck, J, Dunn, M, Ng, E, High-flow nasal cannulae are associated with increased diaphragm activation compared with nasal continuous positive airway pressure in preterm infants, Acta PaediatricaActa Paediatr, 104, e337-43, 2015	No outcomes of interest for review
Osborn, D. A., Evans, N., Randomized trial of high-frequency oscillatory ventilation versus conventional ventilation: effect on systemic blood flow in very preterm infants, Journal of pediatrics, 143, 192-8, 2003	No outcomes of interest for review
Pardou, A., Vermeylen, D., Muller, M. F., Detemmerman, D., High-frequency ventilation and conventional mechanical ventilation in newborn babies with respiratory distress syndrome: A prospective, randomized trial, Intensive Care Medicine, 19, 406-410, 1993	Study dates: Pre-1990
Parmekar, S., Hagan, J., How does high-flow nasal cannulae compare to nasal CPAP for treatment of early respiratory distress?, Journal of Perinatology, 38, 23-25, 2018	Study design not of interest for review: narrative review
Peake, M., Dillon, P., Shaw, N. J., Randomized trial of continuous positive airways pressure to prevent reventilation in preterm infants, Pediatric pulmonology, 39, 247-250, 2005	Population not of interest for review: Post-extubation weaning
Peng, W, Zhu, H, Shi, H, Liu, E, Volume-targeted ventilation is more suitable than pressure-limited ventilation for preterm infants: a	Superseded by Klingenberg 2017

Study	Reason for Exclusion
systematic review and meta-analysis (Provisional abstract), Archives of disease in childhood. Fetal and neonatal edition, 99, F158-f165, 2014	
Plavka,R., Kopecky,P., Sebron,V., Svihovec,P., Zlatohlavkova,B., Janus,V., A prospective randomized comparison of conventional mechanical ventilation and very early high frequency oscillatory ventilation in extremely premature newborns with respiratory distress syndrome, Intensive Care Medicine, 25, 68-75, 1999	Ventilation technique used synchronised or non-synchronised TCPL, not possible to attribute effect to either technique as results not reported seperately
Pohlandt, F., Saule, H., Schroder, H., Leonhardt, A., Hornchen, H., Wolff, C., Bernsau, U., Oppermann, H. C., Obladen, M., Feilen, K. D., Decreased incidence of extra-alveolar air leakage or death prior to air leakage in high versus low rate positive pressure ventilation: Results of a randomised seven-centre trial in preterm infants, European Journal of Pediatrics, 151, 904-909, 1992	Study dates: Pre-1990
Ribeiro, S. N. S., Fontes, M. J. F., Bhandari, V., Resende, C. B., Johnston, C., Noninvasive Ventilation in Newborns ≤1,500 g after Tracheal Extubation: Randomized Clinical Trial, American Journal of Perinatology., 11, 2017	Country not of interest for review: Brazil
Roehr, C. C., Proquitte, H., Hammer, H., Wauer, R. R., Morley, C. J., Schmalisch, G., Positive effects of early continuous positive airway pressure on pulmonary function in extremely premature infants: results of a subgroup analysis of the COIN trial, Archives of Disease in Childhood, Fetal and neonatal edition. 96, F371-3, 2011	RCTs not relevant for review: included in review question 1.1
Rojas-Reyes, Maria Ximena, Orrego-Rojas, Paola A, Rescue high-frequency jet ventilation versus conventional ventilation for severe pulmonary dysfunction in preterm infants, Cochrane Database of Systematic Reviews, 2015	No RCTs met the inclusion for the review
Sadeghnia, A., Barekateyn, B., Badiei, Z., Hosseini, S. M., Analysis and comparison of the effects of N-BiPAP and Bubble-CPAP in treatment of preterm newborns with the weight of below 1500 grams affiliated with respiratory distress syndrome: A randomised clinical trial, Advanced Biomedical ResearchAdv, 5, 3, 2016	Country not of interest for review: Iran
Sadeghnia, A., Foroshani, M. Z., Badiei, Z., A Comparative Study of the Effect of Nasal Intermittent Positive Pressure Ventilation and Nasal Continuous Positive Airway Pressure on the Regional Brain Tissue Oximetry in Premature Newborns Weighing <1500 g, International Journal of Preventive Medicine, 8, 41, 2017	Country not of interest for review: Iran

Study	Reason for Exclusion
Sai Sunil Kishore, M., Dutta, S., Kumar, P., Early nasal intermittent positive pressure ventilation versus continuous positive airway pressure for respiratory distress syndrome, Acta PaediatricaActa Paediatr, 98, 1412-5, 2009	Country not of interest for review: India
Salama, G. S. A., Ayyash, F. F., Al-Rabadi, A. J., Alquran, M. L., Shakkoury, A. G., Nasal-imv versus nasal-CPAP as an initial mode of respiratory support for premature infants with RDS: A prospective randomized clinical trial, Rawal Medical Journal, 40, 197-202, 2015	Country not of interest for review: Jordan
Salvia,, Effect of volume guarantee combined with synchronized intermittent mandatory ventilation vs synchronized intermittent mandatory ventilation in the extreme premature, European Journal of Pediatrics, 165, 2006	Abstract
Sarafidis, K., Stathopoulou, T., Agakidou, E., Taparkou, A., Soubasi, V., Diamanti, E., Drossou, V., Comparable effect of conventional ventilation versus early high-frequency oscillation on serum CC16 and IL-6 levels in preterm neonates, Journal of perinatology, 31, 104-11, 2011	No outcomes of interest for review
Schmolzer, G. M., Kumar, M., Aziz, K., Pichler, G., O'Reilly, M., Lista, G., Cheung, P. Y., Sustained inflation versus positive pressure ventilation at birth: A systematic review and meta-analysis, Archives of Disease in Childhood: Fetal and Neonatal Edition, 100, F361-F368, 2015	Population not of interest for review: Resipiratory support during resuscitation
Schmolzer, G. M., Kumar, M., Pichler, G., Aziz, K., O'Reilly, M., Cheung, P. Y., Non-invasive versus invasive respiratory support in preterm infants at birth: systematic review and meta-analysis, BMJBmj, 347, f5980, 2013	RCTs not relevant for review: included in review question 1.1
Schulze,A., Gerhardt,T., Musante,G., Schaller,P., Claure,N., Everett,R., Gomez-Marin,O., Bancalari,E., Proportional assist ventilation in low birth weight infants with acute respiratory disease: A comparison to assist/control and conventional mechanical ventilation, Journal of Pediatrics, 135, 339-344, 1999	No outcomes of interest for review
Schulze,A., Rieger-Fackeldey,E., Gerhardt,T., Claure,N., Everett,R., Bancalari,E., Randomized crossover comparison of proportional assist ventilation and patient-triggered ventilation in extremely low birth weight infants with evolving chronic lung disease, Neonatology, 92, 1-7, 2007	Not outcomes of interest for review
Shefali-Patel, D., Murthy, V., Hannam, S., Lee, S., Rafferty, G. F., Greenough, A., Randomised weaning trial comparing assist control to pressure support ventilation, Archives of Disease in Childhood Fetal & Neonatal	Population not of interest for review: weaning study

Study	Reason for Exclusion
EditionArch Dis Child Fetal Neonatal Ed, 97, F429-33, 2012	
Shekhawat, P., George, V., Sasidharan, P., Randomized multicenter trial comparing synchronized and conventional intermittent mandatory ventilation in neonates, Journal of pediatrics, 129, 948-50, 1996	Study design not of interest for review: Letter to editor
Shetty, S, Hickey, A, Rafferty, Gf, Peacock, Jl, Greenough, A, Work of breathing during CPAP and heated humidified high-flow nasal cannula, Archives of Disease in Childhood: Fetal and Neonatal Edition, 101, F404-f407, 2016	No outcomes of interest for review
Shi, Y, Tang, S, Zhao, J, Hu, Z, Li, T, Efficiency of nasal intermittent positive pressure ventilation vs nasal continuous positive airway pressure on neonatal respiratory distress syndrome: a prospective, randomized, controlled study, Acta Academiae Medicinae Militaris Tertiae, 32, 1991-3, 2010	Country not of interest for review: China
Shi, Y, Tang, S, Zhao, J, Shen, J, A prospective, randomized, controlled study of NIPPV versus nCPAP in preterm and term infants with respiratory distress syndrome, Pediatric pulmonology, 49, 2013	Country not of interest for review: China
Shi, Y., Tang, S., Zhao, J., Shen, J., A prospective, randomized, controlled study of NIPPV versus nCPAP in preterm and term infants with respiratory distress syndrome, Pediatric pulmonology, 49, 673-678, 2014	Country not of interest for review: China
Silveira, C. S. T., Leonardi, K. M., Melo, A. P. C. F., Zaia, J. E., Brunherotti, M. A. A., Response of preterm infants to 2 noninvasive ventilatory support systems: Nasal CPAP and nasal intermittent positive-pressure ventilation, Respiratory Care, 60, 1772-1776, 2015	Country not of interest for review: Brazil
Singh, Sn Malik Gk Prashanth Gp Singh AKumar M, High frequency oscillatory ventilation versus synchronized intermittent mandatory ventilation in preterm neonates with hyaline membrane disease: a randomized controlled trial, Indian Pediatrics, 49, 405-8, 2012	Country not of interest for review: India
Soonsawad, S., Swatesutipun, B., Limrungsikul, A., Nuntnarumit, P., Heated Humidified High-Flow Nasal Cannula for Prevention of Extubation Failure in Preterm Infants, Indian Journal of Pediatrics, 84, 262-266, 2017	Population not of interest for review:Post-extubation weaning
Sreenan,C., Lemke,R.P., Hudson-Mason,A., Osiovich,H., High-flow nasal cannulae in the management of apnea of prematurity: a comparison with conventional nasal continuous positive airway pressure, Pediatrics, 107, 1081-1083, 2001	Population not of interest for review: No outcomes of interest for review
Stefanescu,B.M., Murphy,W.P., Hansell,B.J., Fuloria,M., Morgan,T.M., Aschner,J.L., A	Population not of interest for review: Post-extubation weaning

Study	Reason for Exclusion
randomized, controlled trial comparing two different continuous positive airway pressure systems for the successful extubation of extremely low birth weight infants, Pediatrics, 112, 1031-1038, 2003	
Stevens, T. P., Blennow, M., Soll, R. F., Early surfactant administration with brief ventilation vs selective surfactant and continued mechanical ventilation for preterm infants with or at risk for respiratory distress syndrome, Cochrane database of systematic reviews (Online), CD003063, 2004	Superseeded by Stevens 2007
Stevens, T. P., Blennow, M., Soll, R. F., Early surfactant administration with brief ventilation vs selective surfactant and continued mechanical ventilation for preterm infants with or at risk for RDS, Cochrane Database of Systematic Reviews, CD003063, 2002	Superseeded by Stevens 2004
Subramaniam, P., Henderson-Smart, D. J., Davis, P. G., Prophylactic nasal continuous positive airways pressure for preventing morbidity and mortality in very preterm infants, Cochrane database of systematic reviews (Online), CD001243, 2005	Superseeded by Subramaniam 2016
Subramaniam, P., Henderson-Smart, D. J., Davis, P. G., Prophylactic nasal continuous positive airways pressure for preventing morbidity and mortality in very preterm infants, Cochrane Database of Systematic Reviews, CD001243, 2000	Superseeded by Subramaniam 2005
Sukumar, M., Bommaraju, M., Fisher, J. E., Morin, F. C., 3rd, Papo, M. C., Fuhrman, B. P., Hernan, L. J., Leach, C. L., High-frequency partial liquid ventilation in respiratory distress syndrome: hemodynamics and gas exchange, Journal of Applied Physiology, 84, 327-34, 1998	No outcomes of interest for review
Sun, H., Cheng, R., Kang, W., Xiong, H., Zhou, C., Zhang, Y., Wang, X., Zhu, C., High-frequency oscillatory ventilation versus synchronized intermittent mandatory ventilation plus pressure support in preterm infants with severe respiratory distress syndrome, Respiratory Care, 59, 159-69, 2014	Country not of interest for review: China
Swamy, R, Gupta, S, Singh, J, Donn, Sm, Sinha, Sk, Tidal volume delivery and peak inspiratory pressure in babies receiving volume targeted or time cycled, pressure limited ventilation: a randomized controlled trial, Journal of Neonatal-Perinatal Medicine, 1, 239-243, 2008	No outcomes of interest for review
Tagare, A., Kadam, S., Vaidya, U., Pandit, A., Patole, S., Bubble CPAP versus ventilator CPAP in preterm neonates with early onset respiratory distress--a randomized controlled trial, Journal	Country not of interest for review: India

Study	Reason for Exclusion
of Tropical PediatricsJ Trop Pediatr, 59, 113-9, 2013	
Tagare,A., Kadam,S., Vaidya,U., Pandit,A., Patole,S., A pilot study of comparison of BCPAP vs. VCPAP in preterm infants with early onset respiratory distress, Journal of Tropical Pediatrics, 56, 191-194, 2010	Country not of interest for review: India
Tapia, J. L., Urzua, S., Bancalari, A., Meritano, J., Torres, G., Fabres, J., Toro, C. A., Rivera, F., Cespedes, E., Burgos, J. F., Mariani, G., Roldan, L., Silvera, F., Gonzalez, A., Dominguez, A., Randomized trial of early bubble continuous positive airway pressure for very low birth weight infants, Journal of pediatrics, 161, 75-80.e1, 2012	RCTs not relevant for review: included in review question 1.1
Tarnow-Mordi, W. O., Multicentre randomised controlled trial of high against low frequency positive pressure ventilation, Archives of Disease in Childhood, 66, 770-775, 1991	Study dates: Pre-1990
Thomas, M. R., Rafferty, G. F., Limb, E. S., Peacock, J. L., Calvert, S. A., Marlow, N., Milner, A. D., Greenough, A., Pulmonary function at follow-up of very preterm infants from the United Kingdom oscillation study, American Journal of Respiratory & Critical Care MedicineAm J Respir Crit Care Med, 169, 868-72, 2004	No outcomes of interest relevant for review
Thomas,C.W., Meinzen-Derr,J., Hoath,S.B., Narendran,V., Neurodevelopmental outcomes of extremely low birth weight infants ventilated with continuous positive airway pressure vs. mechanical ventilation, Indian Journal of Pediatrics, 79, 218-223, 2012	Study design not if interest: retrospective cohort study
Thome, U., Pohlandt, F., High-frequency oscillation and chronic lung disease in very low birth weight infants, Pediatrics, 108, 213-4, 2001	Study design not of interest for review: Letter to editor
Tooley, J, Dyke, M, Randomized study of nasal continuous positive airway pressure in the preterm infant with respiratory distress syndrome, Acta PaediatricaActa Paediatr, 92, 1170-1174, 2003	Comparison not of interest for review: invasive vs non-invasive ventilation technique
Trevisanuto, D., Grazzina, N., Doglioni, N., Ferrarese, P., Marzari, F., Zanardo, V., A new device for administration of continuous positive airway pressure in preterm infants: comparison with a standard nasal CPAP continuous positive airway pressure system, Intensive Care Medicine, 31, 859-64, 2005	Study only relevant for NMA and no outcomes of interest for NMA
Tsakalidis, C., Kourti, M., Karagianni, P., Rallis, D., Porpodi, M., Nikolaidis, N., Early rescue administration of surfactant and nasal continuous positive airway pressure in preterm infants <32 weeks gestation, Indian Pediatrics, 48, 601-5, 2011	Study design not of interest for review: Prospective cohort study

Study	Reason for Exclusion
Vento, G, Matassa, Pg, Ameglio, F, Capoluongo, E, Zecca, E, Tortorolo, L, Martelli, M, Romagnoli, C, Serum and ELF cytokines, pulmonary mechanics and late pulmonary outcome in premature infants: effect of HFOV in a randomized controlled trial, Pediatric Research, 52, 825, 2002	No outcomes of interest for review
Victor, S., Roberts, S. A., Mitchell, S., Aziz, H., Lavender, T., Extubate Trial, Group, Biphasic Positive Airway Pressure or Continuous Positive Airway Pressure: A Randomized Trial, Pediatrics, 138, 2016	Population not of interest for review: Post-extubation weaning
Wang, C., Chi, C., Wang, X., Guo, L., Wang, W., Zhao, N., Wang, Y., Zhang, Z., Li, E., Mechanical ventilation modes for respiratory distress syndrome in infants: A systematic review and network meta-analysis, Critical Care, 19 (1) (no pagination), 2015	Only 3 RCTs not included in other cochrane systematic reviews. 3 RCTs extracted from original papers
Wang, T. F., Dang, D., Liu, J. Z., Du, J. F., Wu, H., Bubble CPAP for preterm infants with respiratory distress: A meta-analysis, Hong Kong Journal of Paediatrics, 21, 86-92, 2016	No RCTs relevant for review
Wheeler, Kevin, Klingenberg, Claus, McCallion, Naomi, Morley, Colin J, Davis, Peter G, Volume-targeted versus pressure-limited ventilation in the neonate, Cochrane Database of Systematic Reviews, 2010	Superseded by Klingenberg 2017
Wilkinson, D., Andersen, C., O'Donnell, C. P., De Paoli, A. G., High flow nasal cannula for respiratory support in preterm infants, Cochrane Database of Systematic Reviews, CD006405, 2011	Superseeded by Wilkinson 2016
Wiswell, Te, Graziani, Lj, Kornhauser, Ms, Cullen, J, McKee, L, Spitzer, A, Early initiation of high-frequency JET ventilation in the management of respiratory distress syndrome is associated with a greater risk of adverse outcomes, American Journal of Perinatology, 63, 1996	HFJV not an intervention of interest for the review
Yadav, S., Thukral, A., Sankar, M. J., Sreenivas, V., Deorari, A. K., Paul, V. K., Agarwal, R., Bubble vs conventional continuous positive airway pressure for prevention of extubation failure in preterm very low birth weight infants: A pilot study, Indian Journal of Pediatrics, 79, 1163-1168, 2012	Population not of interest for review: Post-extubation weaning
Yagui,A.C., Vale,L.A., Haddad,L.B., Prado,C., Rossi,F.S., Deutsch,A.D., Rebello,C.M., Bubble CPAP versus CPAP with variable flow in newborns with respiratory distress: a randomized controlled trial, Jornal de Pediatria, 87, 499-504, 2011	Country not of interest for review: Brazil
Zaharie, G, Ion, Da, Schmidt, N, Popa, M, Kudor-Szabadi, L, Zaharie, T, Prophylactic	Country not of interest for review: Romania

Study	Reason for Exclusion
CPAP versus therapeutic CPAP in preterm newborns of 28-32 gestational weeks, Pneumologia (Bucharest, Romania), 57, 34-7, 2008	
Zaramella,P., Freato,F., Grazzina,N., Saraceni,E., Vianello,A., Chiandetti,L., Does helmet CPAP reduce cerebral blood flow and volume by comparison with Infant Flow driver CPAP in preterm neonates?, Intensive Care Medicine, 32, 1613-1619, 2006	Comparison only relevant for NMA and no outcomes of interest for NMA
Zhu, X. W., Zhao, J. N., Tang, S. F., Yan, J., Shi, Y., Noninvasive high-frequency oscillatory ventilation versus nasal continuous positive airway pressure in preterm infants with moderate-severe respiratory distress syndrome: A preliminary report, Pediatric pulmonology, 52, 1038-1042, 2017	Country of interest not of interest for review: China
Zhu, Xw, Zhao, Jn, Tang, Sf, Yan, J, Shi, Y, Noninvasive high-frequency oscillatory ventilation versus nasal continuous positive airway pressure in preterm infants with moderate-severe respiratory distress syndrome: a preliminary report, Pediatric PulmonologyPediatr Pulmonol, 52, 1038-1042, 2017	Country not of interest for review: China
Zivanovic, S., Peacock, J., Alcazar-Paris, M., Lo, J. W., Lunt, A., Marlow, N., Calvert, S., Greenough, A., United Kingdom Oscillation Study, Group, Late outcomes of a randomized trial of high-frequency oscillation in neonates, New England Journal of Medicine, 370, 1121-30, 2014	No outcomes of interest for review

Economic studies

Reference	Reason for exclusion
Fleeman N, Mahon J, Bates V, Dickson R, Dundar Y, Dwan K, Ellis L, Kotas E, Richardson M, Shah P, Shaw BN. The clinical effectiveness and cost-effectiveness of heated humidified high-flow nasal cannula compared with usual care for preterm infants: systematic review and economic evaluation. Health Technology Assessment, No. 20.30.	The analyses were stratified into 1) preterm babies who have been on prior ventilation, and 2) no prior ventilation. There was a lack of evidence for babies who had no prior ventilation and no economic analysis was undertaken. The committee concluded that the population is not relevant.

Excluded studies for question 3.7 What is the effectiveness of nitric oxide in preterm babies requiring invasive ventilation?

Clinical studies

Study	Reason for Exclusion
Inhaled nitric oxide in full-term and nearly full-term infants with hypoxic respiratory failure, New England journal of medicine, 336, 597-604, 1997	Babies were ≥ 34 weeks gestation and included full-term babies
Abman, S. H., Kinsella, J. P., Inhaled nitric oxide therapy of pulmonary hypertension and respiratory failure in premature and term neonates, Advances in PharmacologyAdv Pharmacol, 34, 457-74, 1995	Book chapter
Al Ethawi, Y., Inhaled nitric oxide in preterm infants undergoing mechanical ventilation, Journal of Clinical Neonatology, 1, 70-71, 2012	Abstract
Allen,M.C., Donohue,P., Gilmore,M., Cristofalo,E., Wilson,R.F., Weiner,J.Z., Robinson,K., Inhaled nitric oxide in preterm infants, Evidence Report/Technology Assessment, 1-315, 2010	Technology assessment
Askie, L. M., Ballard, R. A., Cutter, G., Dani, C., Elbourne, D., Field, D., Hascoet, J. M., Hibbs, A. M., Kinsella, J. P., Mercier, J. C., Rich, W., Schreiber, M. D., Srisuparp, P., Subhedar, N. V., Van Meurs, K. P., Voysey, M., Barrington, K., Ehrenkranz, R. A., Finer, N., Meta-Analysis of Preterm Patients on inhaled Nitric Oxide, Collaboration, Inhaled nitric oxide in preterm infants: a systematic review and individual patient data meta-analysis, BMC PediatricsBMC Pediatr, 10, 15, 2010	More recent Cochrane systematic review published; included studies checked for reference
Athena, Ip-H, et al.,, The Effect of Inhaled Nitric Oxide on Medical and Functional Outcomes of Premature Infants at Early School-Age, Pediatric academic society, http://www.abstracts2view.com/pas/, 2008	Abstract
Banks, Ba, Pallotto, E, Ballard, Ra, A randomized, double blind, placebo controlled crossover pilot trial of inhaled nitric oxide (iNO) in preterm infants with evolving chronic lung disease (CLD), Pediatric Research, 49, 284a, 2001	Abstract
Barrington,K.J., Finer,N.N., Inhaled nitric oxide for preterm infants: A systematic review, Pediatrics, 120, 1088-1099, 2007	More recent Cochrane systematic review published; included studies checked for reference
Chock, V. Y., Van Meurs, K. P., Hintz, S. R., Ehrenkranz, R. A., Lemons, J. A., Kendrick, D. E., Stevenson, D. K., Inhaled nitric oxide for preterm premature rupture of membranes, oligohydramnios, and pulmonary hypoplasia, American Journal of Perinatology, 26, 317-322, 2009	Original trial obtained (Van Meurs 2005), subgroup not relevant

Study	Reason for Exclusion
Clark, R. H., Huckaby, J. L., Kueser, T. J., Walker, M. W., Southgate, W. M., Perez, J. A., Roy, B. J., Keszler, M., Clinical Inhaled Nitric Oxide Research, Group, Low-dose nitric oxide therapy for persistent pulmonary hypertension: 1-year follow-up, Journal of Perinatology, 23, 300-3, 2003	Population not relevant - babies > 34 weeks; population included term infants
Desandes, R., Desandes, E., Droulle, P., Didier, F., Longrois, D., Hascoet, J. M., Inhaled nitric oxide improves oxygenation in very premature infants with low pulmonary blood flow, Acta PaediatricaActa Paediatr, 93, 66-9, 2004	Outcomes not relevant
Di Fiore, J. M., Hibbs, A. M., Zadell, A. E., Merrill, J. D., Eichenwald, E. C., Puri, A. R., Mayock, D. E., Courtney, S. E., Ballard, R. A., Martin, R. J., The effect of inhaled nitric oxide on pulmonary function in preterm infants, Journal of perinatology, 27, 766-771, 2007	Outcomes not relevant
Donohue, P. K., Gilmore, M. M., Cristofalo, E., Wilson, R. F., Weiner, J. Z., Lau, B. D., Robinson, K. A., Allen, M. C., Inhaled nitric oxide in preterm infants: A systematic review, Pediatrics, 127, e414-e422, 2011	More recent Cochrane systematic review published; included studies checked for reference
Ellington, M., Jr., O'Reilly, D., Allred, E. N., McCormick, M. C., Wessel, D. L., Kourembanas, S., Child health status, neurodevelopmental outcome, and parental satisfaction in a randomized, controlled trial of nitric oxide for persistent pulmonary hypertension of the newborn, Pediatrics, 107, 1351-6, 2001	Population not relevant - babies were not preterm; population includes term infants
Ellsworth, K. R., Ellsworth, M. A., Weaver, A. L., Mara, K. C., Clark, R. H., Carey, W. A., Association of Early Inhaled Nitric Oxide With the Survival of Preterm Neonates With Pulmonary Hypoplasia, JAMA PediatricsJama, Pediatr, e180761, 2018	Cohort study
Finer, N., Inhaled nitric oxide in neonates, Archives of Disease in Childhood: Fetal and Neonatal Edition, 77, F81-F84, 1997	Not randomised
Gin-Mestan, K, Lee, G, Fuller, J, Troyke, S, Hecox, Ke, Schreiber, Md, Neurodevelopmental outcome of premature infants treated with inhaled nitric oxide: longitudinal follow up of a prospective, randomized trial, Pediatric Research, 53, 38, 2003	Abstract
Gin-Mestan, Kk, Srisuparp, P, Carlson, Ad, Thomas, G, Lee, G, Marks, Jd, Schreiber, Md, Inhaled nitric oxide improves oxygenation in premature infants with respiratory distress syndrome: preliminary results of a prospective, randomized trial, Pediatric Research, 51, 348a, 2002	Abstract
Hamon, I, Schroeder, H, Buchweiller, Mc, Franck, P, Nicolas, Mb, Fresson, J, Dousset, B,	Abstract

Study	Reason for Exclusion
Nabet, P, Hascoet, Jm, Early effect of inhaled nitric oxide (iNO) on the oxidative balance in 23-32 weeks gestation infants: preliminary data from a randomized controlled trial, Pediatric Research, 49, 266a, 2001	
Handley, S. C., Steinhorn, R. H., Hopper, A. O., Govindaswami, B., Bhatt, D. R., Van Meurs, K. P., Ariagno, R. L., Gould, J. B., Lee, H. C., Inhaled nitric oxide use in preterm infants in California neonatal intensive care units, Journal of Perinatology, 36, 635-639, 2016	Cohort study
Hascoet, Jm, Fresson, J, Claris, O, Lombet, J, Liska, A, Cantagrel, S, al, Hosri J, Thiriez, G, Valdes, V, Cneude, F, Egreteau, L, Henrot, A, Buchweiller, Mc, Onody, P, Inhaled nitric oxide (iNO) in 23-31 weeks gestation (GA) infants: a European randomized controlled trial, preliminary data, Pediatric Research, 49, 282a, 2001	Abstract
Hibbs,A.M., Walsh,M.C., Martin,R.J., Truog,W.E., Lorch,S.A., Alessandrini,E., Cnaan,A., Palermo,L., Wadlinger,S.R., Coburn,C.E., Ballard,P.L., Ballard,R.A., One-year respiratory outcomes of preterm infants enrolled in the Nitric Oxide (to prevent) Chronic Lung Disease trial, Journal of Pediatrics, 153, 525-529, 2008	No relevant outcomes
Hoehn, T., Krause, M. F., Buhrer, C., Meta-analysis of inhaled nitric oxide in premature infants: An update, Klinische Padiatrie, 218, 57-61, 2006	Abstract
Howard, W Kilbride, Hugo, Escobar, Terrence, W Carver, Richard, J Sabath, Kelli, M Teson, Anne, M Holmes, Early Childhood Pulmonary Function and Exercise Outcomes in Previous Preterm Infants Who Received Neonatal Treatment With Inhaled Nitric Oxide (iNO) vs Placebo, Pediatric academic societies annual meeting; 2014 july 17 - 18; vienna, austria, 2014	Abstract
Huddy, C. L., Bennett, C. C., Hardy, P., Field, D., Elbourne, D., Grieve, R., Truesdale, A., Diallo, K., Innovo Trial Collaborating Group, The INNOVO multicentre randomised controlled trial: neonatal ventilation with inhaled nitric oxide versus ventilatory support without nitric oxide for severe respiratory failure in preterm infants: follow up at 4-5 years, Archives of Disease in Childhood Fetal & Neonatal EditionArch Dis Child Fetal Neonatal Ed, 93, F430-5, 2008	No relevant outcomes
Izhar, Fm, Rumilla, Km, Borg, Mj, Kim, Y-J, Hershenson, Mb, Schreiber, Md, Pulmonary safety of inhaled nitric oxide in premature newborn infants with respiratory distress syndrome, Pediatric Research, 47, 362a, 2000	Abstract

Study	Reason for Exclusion
Kinsella, Jp, Cutter, Gr, Walsh, Wf, Gerstmann, Dr, Bose, Cl, Hart, C, Sekar, Kc, Auten, Rl, Gerdes, Js, George, Tn, Southgate, Wm, Carriedo, H, Couser, Rj, Mammel, Mc, Hall, Dc, Pappagallo, M, Sardesai, S, Abman, Sh, Outcomes of Premature Infants Enrolled in the Early Inhaled Nitric Oxide for the Prevention of Chronic Lung Disease Trial, Pediatric academic societies annual meeting; 2009 may 2 5; baltimore MD, united states, 2009	Abstract
Kinsella,J.P., Truog,W.E., Walsh,W.F., Goldberg,R.N., Bancalari,E., Mayock,D.E., Redding,G.J., deLemos,R.A., Sardesai,S., McCurnin,D.C., Moreland,S.G., Cutter,G.R., Abman,S.H., Randomized, multicenter trial of inhaled nitric oxide and high-frequency oscillatory ventilation in severe, persistent pulmonary hypertension of the newborn, Journal of Pediatrics, 131, 55-62, 1997	Population not relevant - includes term infants
Kumar, V. H. S., Dadiz, R., Koumoundouros, J., Guilford, S., Lakshminrusimha, S., Response to pulmonary vasodilators in infants with congenital diaphragmatic hernia, Pediatric Surgery InternationalPediatr Surg Int, 28, 28, 2018	Cohort study; babies not preterm
Mercier, Jc, Dehan, M, Breart, G, Clement, S, O'Nody, P, Inhaled nitric oxide in neonatal respiratory failure. A randomized clinical trial, Pediatric Research, 43, 290A (Abstract), 1998	Conference abstract
Patrianakos-Hoobler, A. I., Marks, J. D., Msall, M. E., Huo, D., Schreiber, M. D., Safety and efficacy of inhaled nitric oxide treatment for premature infants with respiratory distress syndrome: Follow-up evaluation at early school age, Acta Paediatrica, International Journal of Paediatrics, 100, 524-528, 2011	No relevant outcomes
Rosenberg,A.A., Kennaugh,J.M., Moreland,S.G., Fashaw,L.M., Hale,K.A., Torielli,F.M., Abman,S.H., Kinsella,J.P., Longitudinal follow-up of a cohort of newborn infants treated with inhaled nitric oxide for persistent pulmonary hypertension, Journal of Pediatrics, 131, 70-75, 1997	Not randomised
Smyth, R. L., Inhaled nitric oxide treatment for preterm infants with hypoxic respiratory failure, Thorax, 55, S51-S55, 2000	Narrative review
Soll, R. F., Inhaled nitric oxide for respiratory failure in preterm infants, Neonatology, 102, 251-3, 2012	More recent Cochrane systematic review published; included studies checked for reference
Su,P.H., Chen,J.Y., Inhaled nitric oxide in the management of preterm infants with severe respiratory failure, Journal of Perinatology, 28, 112-116, 2008	Non OECD country - Taiwan (China)
Subhedar, N. V., Shaw, N. J., Neurodevelopmental outcome with inhaled nitric	Abstract

Study	Reason for Exclusion
oxide therapy, Journal of Pediatrics, 135, 266-7, 1999	
Subhedar, N. V., Shaw, N. J., Changes in oxygenation and pulmonary haemodynamics in preterm infants treated with inhaled nitric oxide, Archives of Disease in Childhood Fetal & Neonatal EditionArch Dis Child Fetal Neonatal Ed, 77, F191-7, 1997	No relevant outcomes
Tal, A, Greenberg, D, Av-Gay, Y, Golan-Tripto, I, Feinstein, Y, Ben-Shimol, S, Dagan, R, Goldbart, Ad, Nitric oxide inhalations in bronchiolitis: a pilot, randomized, double-blinded, controlled trial, Pediatric PulmonologyPediatr Pulmonol, 53, 95-102, 2018	Babies not preterm
Truffert, P., Llado-Paris, J., Mercier, J. C., Dehan, M., Breart, G., Early inhaled nitric oxide in moderately hypoxemic preterm and term newborns with RDS: The RDS subgroup analysis of the Franco-Belgian iNO Randomized Trial, European Journal of Pediatrics, 162, 646-647, 2003	Population not relevant - study assessed subgroup with RDS
Truog, W. E., Inhaled nitric oxide for the prevention of bronchopulmonary dysplasia, Expert Opinion on Pharmacotherapy, 8, 1505-13, 2007	Not a systematic review i.e. is a review of the literature
Walsh,, Neurodevelopmental Outcomes at 24 Months for Extremely Low Birth Weight Neonates in the NO CLD Trial of Inhaled Nitric Oxide (iNO) To Prevent Bronchopulmonary Dysplasia (BPD), Pediatric academic society, http://www.abstracts2view.com/pas/, 2007	Abstract
Watson, R. S., Clermont, G., Kinsella, J. P., Kong, L., Arendt, R. E., Cutter, G., Linde-Zwirble, W. T., Abman, S. H., Angus, D. C., Prolonged Outcomes After Nitric Oxide, Investigators, Clinical and economic effects of iNO in premature newborns with respiratory failure at 1 year, Pediatrics, 124, 1333-43, 2009	Outcomes not relevant - follow up at 12 months
Wei, Q-F, Pan, X-N, Li, Y, Feng, L, Yao, L-P, Liu, G-L, Meng, D-H, Xu, J, Guo, X-F, Liu, X-Z, Efficacy of inhaled nitric oxide in premature infants with hypoxic respiratory failure, Chinese Journal of Contemporary Pediatrics, 16, 805-809, 2014	Non OECD country - China
White,, No Effect of Inhaled Nitric Oxide on IVH Extension in Premature Infants with Moderate RDS, Pediatric academic society, http://www.abstracts2view.com/pas/, 2010	Abstract
Yang, Y., Feng, Y., Zhou, X. G., Pan, J. J., Zhou, X. Y., Inhaled nitric oxide in preterm infants: An updated meta-analysis, Journal of Research in Medical Sciences, 21, 41, 2016	More recent Cochrane systematic review; included studies checked for relevance
Yoder,B.A., Stoddard,R.A., Li,M., King,J., Dirnberger,D.R., Abbasi,S., Heated, humidified	No relevant comparisons

Study	Reason for Exclusion
high-flow nasal cannula versus nasal CPAP for respiratory support in neonates, Pediatrics, 131, e1482-e1490, 2013	

Economic studies

All economic studies were excluded at the initial title and abstract screening stage.

Appendix L- Research recommendations

Research recommendations for question 1.1 What respiratory support (excluding resuscitation) is the most effective for preterm babies before admission to the neonatal unit?

Does CPAP plus prophylactic surfactant, administered by a non-invasive technique in the delivery room, improve outcomes compared to CPAP alone in preterm babies?

Why this is important

There is some evidence that stabilising infants in the delivery room on CPAP alone leads to improved outcomes compared to intubation, surfactant administration and conventional ventilation. However it is also known that some babies may fail and require later intubation. It is difficult to predict which babies will need intubation and surfactant administration in the delivery room, although the likelihood increases in babies with a lower gestational age. Also, with the increasing experience of non-invasive surfactant administration there may be a group of babies that benefit from prophylactic surfactant administered by a non-invasive technique in the delivery room, not just when they fail non-invasive ventilation with CPAP.

Table 60: Research recommendation rationale

Research question	Does CPAP plus prophylactic surfactant, administered by a non-invasive technique in the delivery room, improve outcomes compared to CPAP alone, in preterm babies?
Importance to 'patients' or the population	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: Currently there is no evidence that CPAP plus prophylactic surfactant administered by non invasive technique in the delivery room improves outcomes compared to CPAP alone in preterm babies. Evidence from 1 Cochrane Systematic Review, 5 randomised controlled trials (RCTs) and 1 additional publication with long term neurodevelopmental outcomes that were identified in the NICE evidence review on the topic showed a trend towards decreasing BPD in the group receiving CPAP with prophylactic surfactant versus the group receiving CPAP alone. However, none of the studies identified any evidence of benefit on long term outcomes such as mortality or neurodevelopmental outcomes
Relevance to the NHS	Simple interventions at an early stage in baby's life would standardise clinical practice across neonatal units across NHS and might reduce length of stay, reduce 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	A number of small studies were found in the NICE evidence review but none are significantly powered to confidently demonstrate if use of CPAP plus surfactant is better than CPAP alone.
Equality	As there is equipoise in this area all infants should be automatically enrolled into this study in units taking part. Preterm infants have an equal right to safe and effective treatment to prevent BPD thus reducing future complications and improving their quality of life.

Table 61: Research recommendation modified PICO table

Criterion	Explanation
Population	Infants <30 weeks or <1.5Kg, not requiring invasive ventilation. Analysis by gestational age (or weight) cohorts.
Intervention	MIST/LISA or other non-invasive method of administering surfactant, including nebulised given in addition to CPAP
Comparator (without the risk factor)	• CPAP alone
Outcome	**Critical:** • BPD at 36 weeks PMA, • Mortality prior to discharge • Neurodevelopmental outcome at 2 years **Important:** • Combined survival without BPD or neurodisability • Need for intubation • Days on ventilator • Length of hospital stay • Cost analysis
Study design	Multicentre RCT comparing methods, with waivers to allow for the inclusion of babies where it has not been possible to obtain consent prior to delivery
Timeframe	2-5 years follow-up

Research recommendations for question 3.3 What is the most effective way of using surfactant in managing respiratory distress syndrome?

What is the best technique for delivering surfactant in a minimally invasive manner?

Why this is important

In preterm babies who develop respiratory distress syndrome (RDS) timely surfactant administration can be life saving. Originally surfactant was always administered by intubating and ventilating infants. There is some evidence that procedures to introduce surfactant in a less invasive manner reduce the long term morbidities such as BPD and also hospital stay. A number of minimally invasive techniques for surfactant administration have been developed and further research is required to determine the best method of administering surfactant to reduce long term morbidities.

Table 62: Research recommendation rationale

Research question	What is the best technique for delivering surfactant in a minimally invasive manner?
Importance to 'patients' or the population	BPD is an important cause of morbidity in preterm babies, prolonging hospital stay and having an impact on growth and neurodevelopment.
Relevance to NICE guidance	High Priority: There was evidence from 7 small randomised controlled trials (RCTs) that were identified in the NICE evidence review on the topic, but there is need for a larger multicentre research study to identify the optimal minimally invasive administration technique

Research question	What is the best technique for delivering surfactant in a minimally invasive manner?
Relevance to the NHS	Simple interventions at an early stage in a baby's life might substantially affect their length of hospital stay and also reduce long term respiratory admissions and later poor health. Clear guidance on a specific method would standardise practice in this area, and may lead to a reduction in NHS costs.
National priorities	There are no national networks to set research priorities in this area
Current evidence base	A number of small studies exist researching this question, but no randomised controlled trials with appropriate outcomes have been carried out.

Table 63: Research recommendation modified PICO table

Criterion	Explanation
Population	Babies <30 weeks or <1.5Kg
Intervention	Minimally invasive surfactant therapy (MIST), less invasive surfactant administration (LISA), laryngeal mask airway (LMA) or nebulised surfactant
Prognostic or risk factor	Baby with RDS and FiO2 >30-40%
Comparator (without the risk factor)	Compare each minimally invasive technique with other minimally invasive techniques
Outcome	**Critical:** • Bronchopulmonary dysplasia • Mortality • Neurodevelopment outcomes ≥18 months, • **Important:** • Combined survival without BPD or neurodisability • Need for reintubation • Days on ventilator • Length of hospital stay • Cost analysis.
Study design	Multicentre RCT comparing methods
Timeframe	5 years follow-up

What is the optimal dosing regimen of surfactant when delivered in a minimally invasive manner?

Why this is important

In preterm babies who develop respiratory distress syndrome timely surfactant administration can be life saving. In babies born at less than 30 weeks, around half will require surfactant administration and many will require further doses if the first dose is not sufficient. There are data from intubated babies suggesting a higher "rescue" dose of surfactant leads to better oxygenation, fewer repeat doses and longer half life of the active ingredient in the lungs. However no information of this type is available for surfactant when delivered via a minimally invasive technique. Robust data are needed on morbidities such as bronchpulmonary dysplasia (BPD), mortality, hospital stay and neurodevelopmental outcomes. As surfactant is more likely to leak out of the airway using a minimally invasive technique, the optimal dose needs to be determined

Table 64: Research recommendation rationale

Research question	What is the optimal dosing regimen of surfactant when delivered in a minimally invasive manner?
Importance to 'patients' or the population	BPD is an important cause of morbidity in preterm babies, prolonging hospital stay and impacting on growth and neurodevelopment.
Relevance to NICE guidance	High Priority: There was evidence from 7 small randomised controlled trials (RCTs) that were identified in the NICE evidence review on the topic, but there is need for a large, adequately powered, multicentre research study to identify the optimal dose of surfactant when administered with minimally invasive technique.
Relevance to the NHS	Simple interventions at an early stage in a baby's life might substantially affect their length of hospital stay and also reduce long term respiratory admissions and later health and development, and may lead to a reduction in NHS costs.
National priorities	There are no national networks to set research priorities in this area
Current evidence base	A number of small studies exist researching this question, but no randomised controlled trials with appropriate outcomes have been carried out.
Equality	N/A

Table 65: Research recommendation modified PICO table

Criterion	Explanation
Population	Babies <30 weeks or <1.5Kg
Intervention	200mg/kg Curosurf (possibly other doses) given via a minimally invasive technique (such as MIST or LISA)
Prognostic or risk factor	Baby with RDS and FiO2 >30-40%
Comparator	100mg/kg Curosurf
Outcome	**Critical:** • Bronchopulmonary dysplasia • Mortality • Neurodevelopment outcomes ≥18 months, **Important:** • Combined survival without BPD or neurodisability • Need for reintubation • Days on ventilator • Length of hospital stay • Cost analysis.
Study design	Multicentre RCT comparing doses
Timeframe	5 years follow-up

Research recommendations for question 3.1 What is the most effective way to administer oxygen during respiratory support?

What is the effectiveness of humidified and non-humidified supplemental low-flow oxygen in preterm babies?

Why this is important

Low flow oxygen is frequently used in neonatal units, as an integral part of respiratory support in preterm babies. The goal of oxygen therapy is to achieve adequate delivery of oxygen to the tissues without causing oxygen toxicity.

Oxygen can be delivered humidified or non-humidified and there is no evidence available on efficacy, potential risks, and the impact on lung function of these two different methods when used in preterm babies.

Table 66: Research recommendation rationale

Research question	What is the effectiveness of humidified and non-humidified supplemental low-flow oxygen in preterm babies?
Importance to 'patients' or the population	Oxygen is most commonly prescribed 'drug' in neonatal care. It is important to deliver oxygen to preterm babies who are not receiving invasive or non-invasive ventilation with the best system/method
Relevance to NICE guidance	In the NICE evidence review, no studies were identified that directly examined the safety or effectiveness of the low flow oxygen humidification. There is currently no national consensus on this practice.
Relevance to the NHS	Simple interventions at an early stage in a baby's life might substantially affect their length of hospital stay and also reduce long term respiratory admissions and later health and development, and may lead to a reduction in NHS costs. The results of the proposed research would standardise the clinical practice across neonatal units across NHS.
National priorities	There are variable practices across the country in both inpatients and at home/community.
Current evidence base	There is currently no robust evidence on the safety or effectiveness of the low flow oxygen humidification.
Equality	Preterm neonates have an equal right to safe and effective oxygen delivery.
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 babies affected are large and a well conducted multicentre study would be adequately powered and feasible.

Table 67: Research recommendation modified PICO table

Criterion	Explanation
Population	Preterm neonates requiring low flow oxygen less than 1 litre/min
Intervention	Humidified oxygen
Comparator (without the risk factor)	Non-humidified oxygen
Outcome	Nasal injury, blockage, bleeding Days in oxygen Bronchopulmonary dysplasia Length of hospital stay Respiratory function
Study design	Randomised controlled trial
Timeframe	2 years follow-up

What should be the target oxygen saturation range for preterm babies when using an automated oxygen titration system that creates a normal frequency saturation curve?

Why this is important

The use of an automated oxygen titration system which provides a normal frequency saturation curve, but without an appropriate oxygen saturation target range may lead to an increased proportion of babies falling below desirable levels of oxygen saturation, compared to manual adjustment where the curve is skewed to the right (higher end of the saturation range) by the nurses who will aim for the higher end of the saturation range.

Table 68: Research recommendation rationale

Research question	What should be the target oxygen saturation range for preterm babies when using an automated oxygen titration system that creates a normal frequency saturation curve?
Importance to 'patients' or the population	The use of automatic oxygen titration (with an appropriate target saturation range) may have survival benefits, and reduce the incidence of adverse events such as necrotising enterocolitis and retinopathy of prematurity.
Relevance to NICE guidance	There was no evidence in the NICE evidence review for the optimal oxygen saturation range to be used in conjunction with automated oxygen titration, so the committee were unable to make recommendations on automated oxygen titration.
Relevance to the NHS	Use of automated oxygen titration may reduce nursing workload, standardise clinical practice across neonatal units across NHS and might reduce mortality, length of stay, reduce long term respiratory admissions and improve later health, and so may reduce NHS costs
National priorities	To decrease morbidity and mortality related to prematurity.
Current evidence base	The use of automated oxygen titration has been shown to increase the time spent in the oxygen saturation range and reduce the number of manual adjustments.
Equality	Preterm babies have an equal right to safe and effective treatment to improve survival, prevent BPD, thus reducing future complications and improving their quality of life.

Table 69: Research recommendation modified PICO table

Criterion	Explanation
Population	Preterm babies receiving respiratory support with oxygen
Intervention	Automated oxygen titration set to target oxygen saturation ranges of: 91-95% 92-96% 93-97%
Comparator	Different target oxygen saturation ranges with each other
Outcome	Mortality prior to discharge Bronchopulmonary dysplasia Necrotising enterocolitis Retinopathy of prematurity
Study design	Multicentre randomised controlled trial, three arms

Criterion	Explanation
Timeframe	3 years follow-up

Research recommendations for question 3.2 What is the effectiveness and safety of the different assisted ventilation techniques in preterm babies?

What is the effectiveness of high pressure non-invasive positive pressure ventilation (NIPPV) compared with continuous positive airways pressure (CPAP) flow driver as the primary mode of ventilation?

Why this is important

Various non-invasive ventilation strategies are used to avoid severe respiratory distress syndrome and avoid ventilation or extubation failure, surfactant administration and also have been shown to prevent bronchopulmonary dysplasia (BPD) of preterm infants. However, the best mode of ventilation is uncertain. Non-invasive ventilation methods includes nasal continuous positive airway pressure (NCPAP), or various types of ventilation provided through soft nasal prongs or masks which are collectively called nasal intermittent positive pressure ventilation (NIPPV), and humidified oxygen delivered by high-flow nasal cannula (HF). NCPAP is a strategy for maintaining positive airway pressure throughout the respiratory cycle through the application of gas flow to an apparatus attached to the nose, and nasal intermittent positive pressure ventilation (NIPPV) provides intermittently higher levels of airway pressure, along with NCPAP through the same nasal device. The definition of NIPPV varies amongst the units and countries.

Table 70: Research recommendation rationale

Research question	What is the effectiveness of high pressure NIPPV compared to CPAP flow driver as the primary mode of ventilation?
Importance to 'patients' or the population	Non-invasive ventilation is increasingly used in preterm babies who require respiratory support.
Relevance to NICE guidance	In the NICE evidence review, there was no evidence that allowed a clear recommendation to be made regarding the use of NIPPV or CPAP. There is currently no consensus on the definition, guideline or use of NIPPV in the UK.
Relevance to the NHS	Bi-level CPAP and NIPPV have been used in various neonatal units across NHS.Bi-level CPAP is another variant of CPAP, or low-pressure NIPPV, that uses small pressure differences between inspiratory and expiratory phases. These are typically delivered through CPAP flow driver devices and generate low peak inspiratory pressures of about 9–11 cm water which can be synchronized using an abdominal pressure transducer. NIPPV is used with conventional ventilators to deliver peak inspiratory pressures similar to those on mechanical ventilation, with or without synchronization, but through nasal prongs.
National priorities	The results of proposed research would standardise the clinical practice across the UK. European 2016 guideline recommends that further work is needed to determine the best method of delivering NIPPV and the population most likely to benefit.
Current evidence base	Early NIPPV does appear to be superior to NCPAP alone for decreasing respiratory failure and the need for intubation and endotracheal tube

Research question	What is the effectiveness of high pressure NIPPV compared to CPAP flow driver as the primary mode of ventilation?
	ventilation among preterm infants with respiratory distress syndrome but has not consistently been shown to reduce rates of BPD. The evidence shows no difference in rates of BPD or death when comparing those who received NIPPV compared to bi-level CPAP. Additional studies are needed to confirm these results and to assess the safety of NIPPV compared with NCPAP alone in a larger patient population.
Equality	Preterm neonates have an equal right to safe and effective non-invasive ventilation.

Table 71: Research recommendation modified PICO table

Criterion	Explanation
Population	Preterm neonates requiring non-invasive ventilation
Intervention	NIPPV with conventional ventilators to deliver peak inspiratory pressures similar to those on mechanical ventilation
Comparator	CPAP delivered through CPAP flow driver devices
Outcome	**Critical:** • Respiratory failure needing intubation • Mortality • Bronchopulmonary dysplasia **Important:** • Air leaks • Days on respiratory support, • Days on oxygen therapy • Intraventricular haemorrhage • Neurodevelopmental outcomes at ≥18 months
Study design	Multicentre randomised controlled trial
Timeframe	2 years follow-up

Are there differences in long-term neurodevelopmental outcomes for preterm babies receiving volume-targeted ventilation (VTV) versus high frequency oscillatory ventilation (HFOV) as their primary means of ventilatory support?

Why this is important

There is evidence that volume targeted and high frequency oscillatory ventilation are the most effective modes of invasive ventilation in preterm babies, with demonstrated benefits for both mortality prior to discharge and BPD. However, there are no studies comparing these two modes of ventilation for neurodevelopmental outcomes, and a direct comparison may show a difference allowing a clear choice to be made

Table 72: Research recommendation rationale

Research question	Are there differences in long-term neurodevelopmental outcomes for preterm babies receiving volume-targeted ventilation versus high frequency oscillatory ventilation as their primary means of ventilatory support?
Importance to 'patients' or the population	Neurodevelopmental outcomes are critical as neurodevelopmental impairment can have life-long effects on a baby and their family.
Relevance to NICE guidance	There was no evidence in the NICE review that allowed better differentiation of the risks and benefits of volume targeted and high frequency oscillation ventilation, which would allow a specific recommendation to be made.
Relevance to the NHS	Potential to improve outcome for babies and reduce economic burden on NHS as a result of long term morbidity in this population
National priorities	To decrease morbidity and mortality related to prematurity.
Current evidence base	In the NICE evidence review. no evidence was identified for this outcome.
Equality	Preterm babies have an equal right to safe and effective treatment to improve neurodevelopmental outcome

Table 73: Resarch recommendation modified PICO table

Criterion	Explanation
Population	Preterm neonates requiring invasive respiratory support
Intervention	Volume targeted ventilation
Comparator	High frequency oscillatory ventilation
Outcome	Neurodevelopmental outcome at ≥ 18 months
Study design	Multicentre randomised controlled trial
Timeframe	2-5 years follow-up

Research recommendations for question 3.7 What is the effectiveness of nitric oxide in preterm babies requiring invasive ventilation?

No research recommendations were made for this review.

Appendix M – Economic evidence methodology checklists

Economic evidence methodology checklists for question 1.1 What respiratory support (excluding resuscitation) is the most effective for preterm babies before admission to the neonatal unit?

No economic evidence was identified for this review.

Economic evidence methodology checklists for question 3.3 What is the most effective way of using surfactant in managing respiratory distress syndrome?

No economic evidence was identified for this review.

Economic evidence methodology checklists for question 3.1 What is the most effective way to administer oxygen during respiratory support?

No economic evidence was identified for this review.

Economic evidence methodology checklists for question 3.2 What is the effectiveness and safety of the different assisted ventilation techniques in preterm babies?

CPAP versus Hi Flow

Study identification Huang L, Roberts CT, Manley BJ, Owen LS, Davis PG, Dalziel KM. Cost-Effectiveness Analysis of Nasal Continuous Positive Airway Pressure Versus Nasal High Flow Therapy as Primary Support for Infants Born Preterm. The Journal of Paediatrics, 196, 58-64, 2018		
Guidance topic: **Specialist neonatal respiratory care for babies born preterm** **What is the effectiveness and safety of the different assisted ventilation techniques?**		**Review question no: 3.2**
Checklist completed by: Eric Slade		
Section 1: Applicability (relevance to specific review questions and the NICE reference case as described in section 7.5)	**Yes/partly/no /unclear/NA**	**Comments**
1.1 Is the study population appropriate for the review question?	Yes	Infants ≥28 weeks gestation who required non-invasive ventilation
1.2 Are the interventions appropriate for the review question?	Yes	CPAP vs. Hi Flow with and withour CPAP rescue
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Partially	Australian study
1.4 Are the perspectives clearly stated and are they appropriate for the review question?	Yes	Treatment failure defined as the need of endotracheal intubation and invasive ventilation

1.5 Are all direct effects on individuals included and are all other effects included where they are material?	Partly	
1.6 Are all future costs and outcomes discounted appropriately?	NA	Time horizon: under 1 year
1.7 Is QALY used as an outcome and was it derived using NICE's preferred methods? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.4 above).	No	Treatment failure, difficulty in estimating QALYs in infants
1.8 Are costs and outcomes from other sectors fully and appropriately measured and valued?	NA	
1.9 Overall judgement: Partially applicable		
Other comments:		
Section 2: Study limitations (the level of methodological quality)	**Yes/partly/no /unclear/NA**	**Comments**
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	NA	Economic analysis alongside an RCT
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Partly	Time horizon: until death or first discharge from hospital (under 1 year)
2.3 Are all important and relevant outcomes included?	Yes	
2.4 Are the estimates of baseline outcomes from the best available source?	Partly	From a single RCT
2.5 Are the estimates of relative intervention effects from the best available source?	Partly	From a single RCT
2.6 Are all important and relevant costs included?	Yes	Direct healthcare costs
2.7 Are the estimates of resource use from the best available source?	Partly	From a single RCT
2.8 Are the unit costs of resources from the best available source?	No	Local sources
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	Statistical analysis, PSA
2.11 Is there any potential conflict of interest?	No	None
2.12 Overall assessment: Minor methodological limitations		
Other comments:		

CPAP versus NIPPV

Study identification Mowitz ME, Zupancic JA, Millar D, Kirpalani H, Gaulton JS, Roberts RS, Mao W, Dukhovny D. Prospective economic evaluation alongside the non-invasive ventilation trial. Journal of Perinatology, 37, 61-66, 2017	
Guidance topic: **Specialist neonatal respiratory care for babies born preterm**	**Review question no: 3.2**
Checklist completed by: Eric Slade	

Study identification Mowitz ME, Zupancic JA, Millar D, Kirpalani H, Gaulton JS, Roberts RS, Mao W, Dukhovny D. Prospective economic evaluation alongside the non-invasive ventilation trial. Journal of Perinatology, 37, 61-66, 2017		
Section 1: Applicability (relevance to specific review questions and the NICE reference case as described in section 7.5)	**Yes/partly/no /unclear/NA**	**Comments**
1.1 Is the study population appropriate for the review question?	Yes	Infants <30 weeks gestation and 1000g at birth who required non-invasive ventilation
1.2 Are the interventions appropriate for the review question?	Yes	CPAP vs. NIPPV
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Partially	US study
1.4 Are the perspectives clearly stated and are they appropriate for the review question?	Yes	Healthcare payer
1.5 Are all direct effects on individuals included and are all other effects included where they are material?	Yes	Mortality and BPD
1.6 Are all future costs and outcomes discounted appropriately?	NA	Time horizon: 44 weeks PMA
1.7 Is QALY used as an outcome and was it derived using NICE's preferred methods? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.4 above).	No	Survivors without BPD
1.8 Are costs and outcomes from other sectors fully and appropriately measured and valued?	NA	
1.9 Overall judgement: Partially applicable		
Other comments:		
Section 2: Study limitations (the level of methodological quality)	**Yes/partly/no /unclear/NA**	**Comments**
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	NA	Economic analysis alongside an RCT
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Partly	Time horizon: 44 weeks PMA
2.3 Are all important and relevant outcomes included?	Yes	Mortality, BPD
2.4 Are the estimates of baseline outcomes from the best available source?	Partly	From RCT
2.5 Are the estimates of relative intervention effects from the best available source?	Partly	From a single RCT
2.6 Are all important and relevant costs included?	Yes	Hospital costs, medication, procedures
2.7 Are the estimates of resource use from the best available source?	Partly	From a single RCT
2.8 Are the unit costs of resources from the best available source?	Unclear	
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	

Study identification Mowitz ME, Zupancic JA, Millar D, Kirpalani H, Gaulton JS, Roberts RS, Mao W, Dukhovny D. Prospective economic evaluation alongside the non-invasive ventilation trial. Journal of Perinatology, 37, 61-66, 2017		
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	Statistical analysis and deterministic sensitivity analysis
2.11 Is there any potential conflict of interest?	No	
2.12 Overall assessment: Minor methodological limitations		
Other comments:		

Economic evidence methodology checklists for question 3.7 What is the effectiveness of nitric oxide in preterm babies requiring invasive ventilation?

Inhaled nitric oxide versus no inhaled nitric oxide

Study identification Field D, Elbourne D, Truesdale A, Grieve R, Hardy P, Fenton AC, Subhedar N, Ahluwalia J, Halliday HL, Stocks J, Tomlin K. Neonatal ventilation with inhaled nitric oxide versus ventilatory support without inhaled nitric oxide for preterm infants with severe respiratory failure: the INNOVO multicentre randomised controlled trial (ISRCTN 17821339), Pediatrics, 115, 926-936, 2005 AND Huddy CL, Bennett CC, Hardy P, Field D, Elbourne D, Grieve R, Truesdale A, Diallo K. The INNOVO multicentre randomised controlled trial: neonatal ventilation with inhaled nitric oxide versus ventilatory support without nitric oxide for severe respiratory failure in preterm infants: follow up at 4–5 years, Archives of Disease in Childhood-Fetal and Neonatal Edition, 93, F430-435, 2008		
Guidance topic:		**Review question no:**
Checklist completed by: Eric Slade		
Section 1: Applicability (relevance to specific review questions and the NICE reference case as described in section 7.5)	**Yes/partly/no /unclear/NA**	**Comments**
1.1 Is the study population appropriate for the review question?	Yes	Infants of <34 weeks' gestation, <28 days old and with severe respiratory failure requiring respiratory support
1.2 Are the interventions appropriate for the review question?	Yes	iNO versus no iNO
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Yes	UK study
1.4 Are the perspectives clearly stated and are they appropriate for the review question?	Yes	NHS and PSS
1.5 Are all direct effects on individuals included and are all other effects included where they are material?	Yes	Mortality, BPD (dependency on oxygen) and neurodevelopmental outcomes
1.6 Are all future costs and outcomes discounted appropriately?	NA	Time horizon: 1 year

1.7 Is QALY used as an outcome and was it derived using NICE's preferred methods? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.4 above).	No	Mortality, BPD (dependency on oxygen) and neurodevelopmental outcomes
1.8 Are costs and outcomes from other sectors fully and appropriately measured and valued?	NA	
1.9 Overall judgement: Directly applicable		
Other comments:		
Section 2: Study limitations (the level of methodological quality)	**Yes/partly/no /unclear/NA**	**Comments**
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	NA	Economic analysis alongside an RCT
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	Time horizon: 1 year & 4-years
2.3 Are all important and relevant outcomes included?	Yes	Mortality, BPD and neurodevelopmental outcomes
2.4 Are the estimates of baseline outcomes from the best available source?	Partly	From RCT
2.5 Are the estimates of relative intervention effects from the best available source?	Partly	From a single RCT
2.6 Are all important and relevant costs included?	Yes	iNO, ventilator, supplemental oxygen, hospital stays, outpatient visits, GP practice and home visits, health visitor
2.7 Are the estimates of resource use from the best available source?	Partly	From a single RCT
2.8 Are the unit costs of resources from the best available source?	Yes	National sources
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	Can be calculated
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	Statistical analysis
2.11 Is there any potential conflict of interest?	Yes	One of the authors has been a paid speaker and has received support from British Oxygen and INO Therapeutics; another author received educational support from INO Therapeutics
2.12 Overall assessment: Minor limitations		
Other comments: At 1 year assessment outpatient and community costs were extrapolated from an initial sampling period over 4-weeks. However, this doesn't matter since these costs accounted only for a small proportion of total costs.		

In year 4 costs were estimated based on preceding 12 months.

Study identification **Watson RS, Clermont G, Kinsella JP, Kong L, Arendt RE, Cutter G, Linde-Zwirble WT, Abman SH, Angus DC. Clinical and economic effects of iNO in premature newborns with respiratory failure at 1 year, Pediatrics, 124, 1333-1343, 2009**		
Guidance topic:		**Review question no:**
Checklist completed by: Eric Slade		
Section 1: Applicability (relevance to specific review questions and the NICE reference case as described in section 7.5)	**Yes/partly/no /unclear/NA**	**Comments**
1.1 Is the study population appropriate for the review question?	No	Subjects were born at ≤34 weeks' gestation, weighed 500 to 1250 g, were 48 hours old and required invasive ventilation
1.2 Are the interventions appropriate for the review question?	Yes	iNO versus no iNO (placebo)
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Partly	US study
1.4 Are the perspectives clearly stated and are they appropriate for the review question?	Partly	Healthcare payer plus indirect costs
1.5 Are all direct effects on individuals included and are all other effects included where they are material?	Yes	QALYs
1.6 Are all future costs and outcomes discounted appropriately?	NA	Time horizon: 1 year
1.7 Is QALY used as an outcome and was it derived using NICE's preferred methods? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.4 above).	Partly	QALYs (assumptions and various published studies)
1.8 Are costs and outcomes from other sectors fully and appropriately measured and valued?		
1.9 Overall judgement: Partially applicable		
Other comments: • Utility weight of 0.2 during hospitalisation, the Quality of Well-being (QWB) scale, adult population with ARDS. • Utility weight for chronic neurological and /or pulmonary morbidity, older children or adults living with similar conditions with utility weights deriving using QWB and vignettes valued using TTO. • Utility weight for mild and severe hearing loss based on a published study looking at sequelae after bacterial meningitis in childhood. However, it is unclear how utility weights were derived from this study. • Utility weights for cerebral palsy, blindness or severe visual impairment derived from a sample of general population using HUI3 (≥16 years).		
Section 2: Study limitations (the level of methodological quality)	**Yes/partly/no /unclear/NA**	**Comments**
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	NA	Economic analysis alongside an RCT

2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	Time horizon: 1 year
2.3 Are all important and relevant outcomes included?	Yes	QALYs
2.4 Are the estimates of baseline outcomes from the best available source?	Partly	From RCT
2.5 Are the estimates of relative intervention effects from the best available source?	Partly	From a single RCT
2.6 Are all important and relevant costs included?	Yes	iNO acquisition costs, hospital admissions, medication usage, physician visits, A&E visits, readmissions and post-discharge costs
2.7 Are the estimates of resource use from the best available source?	Partly	From an RCT
2.8 Are the unit costs of resources from the best available source?	Partly	Local and national sources (billing information, cost reports, fee schedules)
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	Deterministic sensitivity analysis; PSA
2.11 Is there any potential conflict of interest?	Yes	The authors received consulting and/or lecture fees from Ikaria/iNO Therapeutics.
2.12 Overall assessment: Minor limitations		
Other comments:		

Study identification **Zupancic JA, Hibbs AM, Palermo L, Truog WE, Cnaan A, Black DM, Ballard PL, Wadlinger SR, Ballard RA. Economic evaluation of inhaled nitric oxide in preterm infants undergoing mechanical ventilation, Pediatrics, 124, 1325-1332, 2009**		
Guidance topic:		**Review question no:**
Checklist completed by: Eric Slade		
Section 1: Applicability (relevance to specific review questions and the NICE reference case as described in section 7.5)	**Yes/partly/no /unclear/NA**	**Comments**
1.1 Is the study population appropriate for the review question?	Yes	Infants with gestational age at birth of ≤32 weeks and required invasive ventilation
1.2 Are the interventions appropriate for the review question?	Yes	iNO versus no iNO (placebo)

1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Partly	US study
1.4 Are the perspectives clearly stated and are they appropriate for the review question?	Yes	Health care payer
1.5 Are all direct effects on individuals included and are all other effects included where they are material?	Partially	Survival, BPD
1.6 Are all future costs and outcomes discounted appropriately?	NA	Time horizon: under 1 year (until discharge)
1.7 Is QALY used as an outcome and was it derived using NICE's preferred methods? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.4 above).	No	The primary outcome measure was BPD free survival
1.8 Are costs and outcomes from other sectors fully and appropriately measured and valued?	NA	
1.9 Overall judgement: Partially applicable		
Other comments:		
Section 2: Study limitations (the level of methodological quality)	**Yes/partly/no /unclear/NA**	**Comments**
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	NA	Economic analysis alongside an RCT
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	Time horizon: up to 1 year
2.3 Are all important and relevant outcomes included?	Yes	Mortality, BPD
2.4 Are the estimates of baseline outcomes from the best available source?	Partly	From an RCT
2.5 Are the estimates of relative intervention effects from the best available source?	Partly	From a single RCT
2.6 Are all important and relevant costs included?	Yes	Direct healthcare costs
2.7 Are the estimates of resource use from the best available source?	Partly	From an RCT
2.8 Are the unit costs of resources from the best available source?	Partly	From various sources including a tertiary care NICU centre, national sources and other published sources
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	Statistical analysis; bootstrapping; sensitivity analysis
2.11 Is there any potential conflict of interest?	Yes	Manufacturer provided study gas and masked delivery systems for the trial. One author received reimbursement for participation in expert advisory panela and presentations.

		Another author received funding from the manufacturer to complete 24 month follow-up.
2.12 Overall assessment: Minor limitations		
Other comments:		

Appendix N – NMA analysis protocol

NMA analysis protocol for question 3.2 What is the effectiveness and safety of the different assisted ventilation techniques in preterm babies?

Non-invasive ventilation techniques

Item	Details
Review question	**What is the comparative effectiveness and safety of the different ventilation techniques in preterm babies needing respiratory support?**
Context	This NMA will aim to determine the optimal method of ventilation in preterm babies requiring non-invasive respiratory support and it will be used to inform the new national clinical guidance for specialist neonatal respiratory care for babies born preterm in England commissioned by the National Institute for Health and Care Excellence.
Searches	• We will search Medline, Medline In-Process, CCTR, CDSR, DARE, HTA, Embase up to May, 2018. • Standard animal/non-English language exclusion filter will be applied. • Only studies conducted post 1990 will be considered, as significant advances have occurred in antenatal and postnatal respiratory management since this time period and outcomes for preterm babies prior to 1990 are not the same as post 1990. • No supplementary search techniques will be used.
Types of study to be included	• Only randomised controlled trials (RCTs) with at least one relevant ventilation technique will be considered for inclusion. • RCTs with <15 participants per treatment arm will not be included. • We will include head-to head trials or trials versus standard ventilation technique (conventional invasive ventilation). • We will include double-blind and single-blind RCTs. • Since the anticipated duration of trials is less than 1 year we will include all trial durations and follow-up. • We will assume that any patient that meets all inclusion criteria is, in principle, equally likely to be randomised to any of the interventions in the synthesis comparator set.
Condition or domain being studied	This NMA will consider respiratory disorders, including respiratory distress syndrome and bronchopulmonary dysplasia (BPD).
Participants/ population	• We will include preterm babies (less than 37 weeks of gestation) who are on the respiratory support. • We will exclude babies with any congenital abnormalities except for patent ductus arteriosus; preterm babies who are ventilated solely due to a specific non-respiratory comorbidity, such as sepsis, NEC or neurological disorders; preterm babies on respiratory support for post-extubation weaning; and indirect populations (e.g. preterm babies requiring ventilation for non-respiratory reasons) will not be considered.
Intervention(s), exposure(s)	Non-invasive ventilation techniques will include: 1. CPAP 2. NIPPV 3. Hi Flow

Item	Details
	4. BiPAP/SiPAP • We will not consider in the NMA interventions that are not listed above, unless they act as the sole connectors of the interventions of interest (or their combinations) in the network. In this case, interventions not listed above will be included in the NMA but will not form part of the decision problem (decision of interest).
Comparator(s)/ control	All non-invasive ventilation techniques will be compared to each other.
Outcome(s)	• Mortality prior to discharge (safety and effectiveness). • Bronchopulmonary dysplasia (BPD) (defined as number of babies who are oxygen dependent at 36 weeks corrected for gestation or 28 days of age) (effectiveness).
Risk of bias (quality) assessment	• Risk of bias of all included trials will be assessed using the Cochrane risk of bias tool. • There is no plan to undertake the additional risk of bias analysis within a NMA. We do not expect there to be comparisons where one ventilation technique is systematically favoured over another.
Analysis of subgroups or subsets	Where data are available, networks will be examined separately stratified based on the following sub-groups of ventilated preterm babies: • Age at randomisation: <2 hours after birth; 2-6 hours; >6 hours • Gestational age: ≤26^{+6} weeks; 27-31^{+6} weeks; ≥32-36^{+6} weeks
Sifting and data extraction	• Dual sifting will be undertaken using STAR software. • Sifting and data extraction 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. • Excel software will be used for data extraction. • The data extracted will include: patients' characteristics including age at randomisation, gestational age; the number of preterm babies having the event of interest; the total number of preterm babies randomised; the time of event; intervention details. The study characteristics will also be extracted including country where the study was conducted, bias characteristics including (random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other potential bias). • Dual data extraction will not be undertaken. However, a random sample of extracted data will be checked by the second reviewer, with resolution of discrepancies in discussion with the senior reviewer if necessary.
Strategy for data synthesis	• Network meta-analysis will be conducted using WinBUGS codes (NICE Guidelines Technical Support Unit, University of Bristol, TSU). • The statistical analysis of mortality prior to discharge will be based on Poisson likelihoods with a log link function (discharge may be different for each trial); and the statistical analysis for the incidence of BPD on binomial likelihoods with a logit link function. • The exact model structure will be agreed with a TSU following the review of available clinical evidence

Item	Details
	• ORs (95% CI) will be used for reporting the results of the incidence of BPD and HRs (95% CI) for reporting the results of mortality. • Ranking of treatments will be provided (i.e. ranks, probability being best and probability of being in the top/bottom three). • Inconsistency will be checked for by comparing the standard network consistency model to an "inconsistency", or unrelated mean effects, model; and node splitting.
Organisational affiliation of the review	National Guideline Alliance
Review team members and their organisational affiliations	Audrey Tan – Systematic Reviewer, National Guideline Alliance Eric Slade – Health Economist, National Guideline Alliance Ifigeneia Mavranezouli – Senior Health Economist, National Guideline Alliance and UCL Kelly Williams – Systematic Reviewer, National Guideline Alliance Stephanie Arnold – Information Scientist, National Guideline Alliance
Funding sources/sponsors	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Conflicts of interest	None
Collaborators	None
Anticipated start and finish dates	08/2017 – 04/2019

Invasive ventilation techniques

Item	Details
Review question	**What is the comparative effectiveness and safety of the different ventilation techniques in preterm babies needing respiratory support?**
Context	This NMA will aim to determine the optimal method of ventilation in preterm babies requiring invasive respiratory support and it will be used to inform the new national clinical guidance for specialist neonatal respiratory care for babies born preterm in England commissioned by the National Institute for Health and Care Excellence.
Searches	• We will search Medline, Medline In-Process, CCTR, CDSR, DARE, HTA, Embase up to May, 2018. • Standard animal/non-English language exclusion filter will be applied. • Only studies conducted post 1990 will be considered, as 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. • No supplementary search techniques will be used.
Types of study to be included	• Only randomised controlled trials (RCTs) with at least one relevant ventilation technique will be considered for inclusion. • RCTs with <15 participants per treatment arm will not be included. • We will include head-to head trials or trials versus standard ventilation technique (conventional invasive ventilation). • We will include double-blind and single-blind RCTs.

Item	Details
	• Since the anticipated duration of trials is less than 1 year we will include all trial durations and follow-up. • We will assume that any patient that meets all inclusion criteria is, in principle, equally likely to be randomised to any of the interventions in the synthesis comparator set.
Condition or domain being studied	This NMA will consider respiratory disorders, including respiratory distress syndrome and bronchopulmonary dysplasia (BPD).
Participants/ population	• We will included preterm babies (less than 37 weeks of gestation) who are on the respiratory support. • We will exclude babies with any congenital abnormalities except for patent ductus arteriosus; preterm babies who are ventilated solely due to a specific non-respiratory comorbidity, such as sepsis, NEC and neurological disorders; preterm babies on respiratory support for post-extubation weaning; and indirect populations (e.g. preterm babies requiring ventilation for non-respiratory reasons) will not be considered.
Intervention(s), exposure(s)	Invasive ventilation techniques will include: 1.Volume targeted 2.Synchronised pressure limited 3.Synchronised intermittent mandatory 4.Non-synchronised pressure limited 5.High frequency • We will not consider in the NMA interventions that are not listed above, unless they act as the sole connectors of the interventions of interest (or their combinations) in the network. In this case, interventions not listed above will be included in the NMA but will not form part of the decision problem (decision of interest).
Comparator(s)/ control	All invasive ventilation techniques will be compared to each other. It is acknowledged that each technique comprises of various sub-sets of techniques. For example, volume targeted ventilation comprises of volume guaranteed ventilation (VGV), target tidal volume (TTV), pressure regulated volume control (PRVC) ventilation (PRVCV), etc. However, no differences in effectiveness are expected between the sub-sets of techniques. As a result, only interclass comparisons will be made.
Outcome(s)	• Mortality prior to discharge (safety and effectiveness). • Bronchopulmonary dysplasia (BPD) (defined as number of babies who are oxygen dependent at 36 weeks corrected for gestation or 28 days of age) (effectiveness).
Risk of bias (quality) assessment	• Risk of bias of all included trials will be assessed using Cochrane risk of bias tool. • There is no plan to undertake the additional risk of bias analysis within an NMA. We do not expect there to be comparisons where one ventilation technique is systematically favoured over another.
Analysis of subgroups or subsets	Where data are available, networks will be examined separately stratified based on the following sub-groups of ventilated preterm babies: • Age at randomisation: <2 hours after birth; 2-6 hours; >6 hours • Gestational age: ≤26^{+6} weeks; 27-31^{+6} weeks; ≥32-36^{+6} weeks
Sifting and data extraction	• Dual sifting will be undertaken using STAR software.

Item	Details
	• Sifting and data extraction 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. • Excel software will be used for data extraction. • The data extracted will include: patients' characteristics including age at randomisation, gestational age; the number of preterm babies having the event of interest; the total number of preterm babies randomised; the time of event; intervention details. The study characteristics will also be extracted including country where the study was conducted, bias characteristics including (random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other potential bias). • Dual data extraction will not be undertaken. However, a random sample of extracted data will be checked by the second reviewer, with resolution of discrepancies in discussion with the senior reviewer if necessary.
Strategy for data synthesis	• Network meta-analysis will be conducted using WinBUGS codes (NICE Guidelines Technical Support Unit, University of Bristol, TSU). • The statistical analysis of mortality prior to discharge will be based on Poisson likelihoods with a log link function (discharge may be different for each trial); and the statistical analysis for the incidence of BPD on binomial likelihoods with a logit link function. • The exact model structure will be agreed with a TSU following the review of available clinical evidence • ORs (95% CrI) will be used for reporting the results of the incidence of BPD and HRs (95% CrI) for reporting the results of mortality prior to discharge. • Ranking of treatments will be provided (i.e. ranks, probability being best and probability of being in the top/bottom three). • Inconsistency will be checked for by comparing the standard network consistency model to an "inconsistency", or unrelated mean effects, model; and node splitting.
Organisational affiliation of the review	National Guideline Alliance
Review team members and their organisational affiliations	Audrey Tan – Systematic Reviewer, National Guideline Alliance Eric Slade – Health Economist, National Guideline Alliance Ifigeneia Mavranezouli – Senior Health Economist, National Guideline Alliance and UCL Kelly Williams – Systematic Reviewer, National Guideline Alliance Stephanie Arnold – Information Scientist, National Guideline Alliance
Funding sources/sponsors	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Conflicts of interest	None
Collaborators	None
Anticipated start and finish dates	08/2017 – 04/2019

Appendix O – Network meta-analysis methods

Network meta-analysis methods for question 3.2 What is the effectiveness and safety of the different assisted ventilation techniques in preterm babies?

Introduction

The results of conventional pairwise meta-analyses of direct evidence alone do not help to fully inform which invasive and non-invasive ventilation technique is most effective in preterm babies requiring respiratory support.

Each pairwise comparison does not fully inform the choice between the different treatments and having a series of discrete pairwise comparisons can be incoherent and difficult to interpret.

In addition, direct comparisons of treatments of clinical interest are not fully available, for all comparisons.

To overcome these issues, a Bayesian network meta-analysis (NMA) was performed. Advantages of performing this type of analysis are as follows.

- It allows the synthesis of evidence on multiple treatments compared directly and indirectly without breaking randomisation. If treatment A has never been compared to treatment B in a head to head trial, but these two interventions have been compared to a common comparator, then an indirect treatment comparison can be derived using the relative effects of the two treatments versus the common comparator. Indirect estimates can be calculated whenever there is a path linking two treatments through a set of common comparators. All the randomised evidence is considered simultaneously within the same model.
- For every intervention in a connected network, a relative effect estimate (with its 95% credible intervals, CrIs) between any two interventions can be estimated. These estimates provide a useful clinical summary of the results and facilitate the formation of recommendations based on all relevant evidence, whilst appropriately accounting for uncertainty. Ranks of interventions may also be calculated.
- Estimates from the NMA can be used to directly parameterise treatment effectiveness in cost-effectiveness modelling of multiple treatments.

Conventional fixed effect meta-analysis assumes that the relative effect of one treatment compared to another is the same across an entire set of trials. In a random effects model, it is assumed that the relative effects are different in each trial but that they are from a single common distribution and that this distribution is common across all sets of trials.

NMA requires an additional assumption over conventional meta-analysis. The additional assumption is that intervention A has the same effect on people in trials of intervention A compared to intervention B as it does for people in trials of intervention A versus intervention C and so on. Thus, in an NMA, the assumption is that intervention A has the same effect across trials of A versus B, A versus C and so on.

The terms indirect treatment comparisons, mixed treatment comparisons and NMA are used interchangeably. We use the term NMA as the network consists of both indirect treatment comparisons (some trials have a common comparator and some do not) and mixed treatment comparisons (with at least one closed loop, combination of direct and indirect evidence).

Study selection and data collection

For full details see analysis protocol in appendix N.

Outcome measures

The guideline committee identified BPD at 36 weeks PMA and mortality prior to discharge as critical outcomes for assessing the effectiveness and safety of treatments. NMAs were performed on these outcomes for preterm babies requiring 1) non-invasive invasive ventilation and 2) invasive invasive ventilation.

Mortality prior to discharge

Data for mortality prior to discharge was reported as counts in the RCTs. The probability of mortality prior to discharge in each arm of a trial was estimated as the number of babies in the arm who died prior to discharge, divided by the total number of babies in this arm.

The time of discharge was unclear in the studies.

At the protocol drafting stage it was anticipated that time to event (death) may be potentially captured in the NMA model. However, this was not possible since time at risk was unclear from studies. Consequently, the results for mortality prior to discharge are presented as posterior median odd ratios (ORs).

BPD at 36 weeks PMA

Data for BPD at 36 weeks PMA was reported as counts in the RCTs. The probability of BPD in each arm of a trial was estimated as the number of babies in the arm who developed BPD at 36 weeks PMA, divided by the total number of babies in this arm.

In the RCTs BPD was reported either in all babies or survivors. Following the discussion with the committee the priority was given to BPD in all babies. However, if BPD in all babies was not reported BPD in survivors was used. It was noted that the difference between the number of observed events in all babies versus survivors is negligible and the impact on the results is likely to be insubstantial.

Results for BPD at 36 weeks PMA are presented as posterior median ORs.

Continuity correction

Combining data when zero events occur in some arms of a study, the log-OR becomes undefined (as does the variance), which causes problems in the analysis and precludes the estimation of relative effects.

Generally, standard TSU code runs without the need of continuity correction. However, due to the sparsity of data for the mortality prior to discharge outcome, non-invasive ventilation NMA, and also a relatively large number of arms with zero events a continuity corrections was required. Using a continuity correction for studies with zero counts allowed the log-OR to be estimated, and hence allowed synthesis via standard NMA methods. For the mortality prior to discharge outcome, non-invasive ventilation NMA a continuity correction of 0.5 was added to both the number of events and the number of non-events across all study arms, in studies in which one or more (but not all) arms had zero events.

Methodology

Model description

Both fixed and random effects Binomial models with logit link were run to synthesise data for mortality prior to discharge and BPD at 36 weeks PMA in preterm babies receiving treatment with 1) non-invasive invasive ventilation and 2) invasive invasive ventilation techniques.

The full description of standard fixed and random effects models using binomial likelihood with logit link can be found in NICE DSU Technical Support Document 2 (Dias 2011). Example of WinBUGS codes used to synthesise data can also be found at the end of NICE Guidelines Technical Support Unit, University of Bristol (TSU) report on the NMAs in appendix S.

For all the models except for preterm babies receiving treatment with invasive ventilation BPD outcome an uninformative prior on the between-study variance were used. The methods are reported in appendix S.

As per Technical Support Unit recommendation for preterm babies receiving treatment with invasive ventilation BPD outcome the informative prior on the between-study variance was used. The informative prior was selected from a list of predictive distributions for between-study heterogeneity that are typical of cause-specific mortality/major morbidity event/composite (mortality or morbidity) outcomes. The full description of the model used is in appendix S.

Analysis was undertaken following Bayesian statistics principles and conducted using Markov chain Monte Carlo simulation techniques implemented in WinBUGS 1.4.3. (Lunn 2000; Spiegelhalter 2001).

Each model was run until convergence was satisfactory and then the results were based on further sample of iterations on two chains.

The posterior mean of the residual deviance, which measures the magnitude of the differences between the observed data and the model predictions of the data, was used to assess and compare the goodness of fit of each model. Smaller values are preferred and in a well-fitting model the posterior mean residual deviance should be close to the number of data points in the network (each study arm contributes 1 data point) (Spiegelhalter 2002).

In addition to comparing how well the models fit the data using the posterior mean of the residual deviance, models were compared using the deviance information criterion (DIC). This is equal to the sum of the posterior mean of the residual deviance and the effective number of parameters and thus penalizes model fit with model complexity. Lower values are preferred and typically differences of 3-5 points are considered meaningful (Spiegelhalter 2002).

For each model fixed and random effects models were compared and the best fitting model was chosen based on the criteria described above.

An important assumption made in NMA concerns the consistency, that is, the agreement of the direct and indirect evidence informing the treatment contrasts and there should be no meaningful differences between these two sources of evidence. The consistency checks were undertaken by TSU and are summarised in appendix S.

References

Dias 2011

Dias S, Welton N, Sutton A, Ades A. NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials, 2011, last updated September 2016, available from http://scharr.dept.shef.ac.uk/nicedsu/technical-support-documents/evidence-synthesis-tsd-series/

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Lunn DJ, Thomas A, Best N, Spiegelhalter D. WinBUGS -- a Bayesian modelling framework: concepts, structure, and extensibility, Statistics and Computing, 10, 325-337, 2000

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Spiegelhalter D, Best N, Carlin B, van der Linde A. Bayesian measures of model complexity and fit. Journal of the Royal Statistical Society: Series B, 64, 583-616, 2002

Spiegelhalter 2004

Spiegelhalter DJ, Thomas A, Best NG, et al. WinBUGS User Manual: Version 5.1.4. Cambridge: MRC Biostatistics Unit, 2001

Appendix P – Summary of studies included in the network meta-analysis

Summary of studies included in the network meta-analysis for question 3.2 What is the effectiveness and safety of the different assisted ventilation techniques in preterm babies?

Non-invasive invasive ventilation

Table 74: Treatment arm-level details for included studies in the NMA of mortality prior to discharge

Study ID	CPAP	NIPPV	Hi Flow	BiPAP/SiPAP
Oncel 2016	6/100	4/100		
Ramanathan 2012	1/57	1/53		
Kirpalani 2013	45/505	37/504		
Lavizzari 2016	1.5/158.5*		0.5/158.5*	
Roberts 2016	1/286		1/278	
Wood 2013	2.5/60.5*			0.5/60.5*
Salvo 2015		0.5/62.5*		2.5/62.5*

BiPAP: Bilevel positive airway pressure; CPAP: Continuous positive airway pressure therapy; NIPPV: Nasal intermittent positive pressure ventilation; SiPAP: Synchronised positive airway pressure; NMA: Network meta-analysis

**Continuity corrected numbers (see Appendix O for the explanation)*

Table 75: Treatment arm-level details for included studies in the NMA of BPD at 36 weeks PMA

	CPAP	NIPPV	Hi Flow	BiPAP/SiPAP
Kugelman 2007	7/41	1/43		
Oncel 2016	10/100	6/100		
Ramanathan 2012	22/57	11/53		
Kirpalani 2013	139/505	157/504		
Bisceglia 2007	4/46	2/42		
Roberts 2016	17/286		17/278	
Shin 2017	0/44		1/43	
Yoder 2013	1/67		5/58	
Nair 2005	1/34		0/33	
Wood 2013	7/60			5/60
Kugelman 2014		2/38	1/38	
Salvo 2015		7/62		7/62
Lavizzari 2016	8/158		7/158	

BiPAP: Bilevel positive airway pressure; BPD: Bronchopulmonary dysplasia; CPAP: Continuous positive airway pressure therapy; NIPPV: Nasal intermittent positive pressure ventilation; NMA: network meta-analysis; SiPAP: Synchronised positive airway pressure

Invasive ventilation

Table 76: Treatment arm-level details for included studies in the NMA of mortality prior to discharge

	Non-synchronised pressure limited	High frequency	Synchronised intermittent mandatory	Synchronised pressure limited	Volume targeted
Gerstmann 1996	2/61	0/64			
Johnson 2002	105/397	100/400			
Ogawa 1993	1/46	0/46			
Rettwitz-volk 1998	4/50	5/46			
Thome 1999	15/144	14/140			
Van reempts 2003	20/153	25/147			
Bernstein 1996	10/160		11/167		
Baumer 2000	86/459			106/465	
Bereseford 2000	8/193			15/193	
Piotrowski 1997	8/30				4/27
Courtney 2002		33/244	40/254		
Craft 2003		3/22	3/24		
Durand 2001		5/24	4/24		
Moriette 2001		31/139	27/134		
Vento 2005		1/20	2/20		
Salvo 2012		5/44	5/44		
Lista 2008		1/19			1/21
Reyes 2006			5/54 and 6/53[a]		
D'Angio 2005			13/108		13/105
Guven 2013			5/30		3/42
Nafday 2005			1/18		2/16
Chowdhury 2013			2/20		2/20

[a] This study was classified as comparing the same mode of ventilation in both arms and were included to the estimation of between-study heterogeneity

	Non-synchronised pressure limited	High frequency	Synchronised intermittent mandatory	Synchronised pressure limited	Volume targeted
Piotrowski 2007			4/26		7/30
Dunman 2012				7/22	3/23
Sinha 1997				1/25	1/25
Lista 2004				6/23	5/30
Singh 2006				10/52	5/57
Unal 2017					2/21 and 4/21[c]
Ozdemir 2017					3/15 and 4/19 [c]

NMA: Network meta-analysis

Table 77: Treatment arm-level details for included studies in the NMA for BPD at 36 weeks PMA

	Non-synchronised pressure limited	High frequency	Synchronised pressure limited	Synchronised intermittent mandatory	Volume targeted
Gerstmann 1996	27/61	17/64			
Johnson 2002	163/397	165/400			
Thome 1999	30/144	32/140			
Van reempts 2003	19/153	24/147			
Baumer 2000	134/459		113/465		
Bereseford 2000	53/193		57/193		
Courtney 2002		70/244		93/254	
Craft 2003		13/22		13/24	
Durand 2001		5/24		14/24	
Moriette 2001		24/139		30/134	
Vento 2005		2/20		8/20	
Salvo 2012		1/44		3/44	
Lista 2008		2/19			2/21
Dunman 2012			7/22		3/23
Sinha 1997			6/25		1/25

	Non-synchronised pressure limited	High frequency	Synchronised pressure limited	Synchronised intermittent mandatory	Volume targeted
Lista 2004			4/23		3/30
Singh 2006			17/52		16/57
Reyes 2006				23/54 and 16/53[b]	
D'Angio 2005				32/108	27/105
Guven 2013				9/30	2/42
Nafday 2005				4/18	2/16
Unal 2017					6/21 and 7/21[d]
Ozdemir 2017					3/15 and 2/19 [d]

BPD: Bronchopulmonary dysplasia; NMA: Network meta-analysis

[b] This study was classified as comparing the same mode of ventilation in both arms and were included to the estimation of between-study heterogeneity

Appendix Q – Studies excluded from the network meta-analysis

Studies excluded from the network meta analysis for question 3.2 What is the effectiveness and safety of the different assisted ventilation techniques in preterm babies?

Non-invasive invasive ventilation

Study ID	Reason for exclusion	Excluded from	Reference
Bisceglia 2007	Zero counts in both arms	Mortality prior to discharge NMA	Bisceglia M, Belcastro A, Poerio V, Raimondi F, Mesuraca L, Crugliano C, Corapi UP. A comparison of nasal intermittent versus continuous positive pressure delivery for the treatment of moderate respiratory syndrome in preterm infants. Minerva pediatrica. 2007;59(2):91-5.
Nair 2005	Zero counts in both arms	Mortality prior to discharge NMA	Nair G, Karna P. Comparison of the effects of Vapotherm and nasal CPAP in respiratory distress in preterm infants. E-PAS. 2005;57:2054.
Yoder 2013	Zero counts in both arms	Mortality prior to discharge NMA	Yoder BA, Stoddard RA, Li M, King J, Dirnberger DR, Abbasi S. Heated, humidified high-flow nasal cannula versus nasal CPAP for respiratory support in neonates. Pediatrics. 2013;131(5):e1482-90.
Kugelman 2014	Zero counts in both arms	Mortality prior to discharge NMA	Klingenberg C, Pettersen M, Hansen EA, Gustavsen LJ, Dahl IA, Leknessund A, Kaaresen PI, Nordhov M. Patient comfort during treatment with heated humidified high flow nasal cannulae versus nasal continuous positive airway pressure: a randomised cross-over trial. Archives of Disease in Childhood-Fetal and Neonatal Edition. 2014;99(2):F134-7.

Invasive invasive ventilation

Study ID	Reason for exclusion	Excluded from	Reference
Kezler 1997	Cross over RCT, with large number of babies crossing over in one arm but not the other; HFJV not an intervention of interest	Mortality prior to discharge and BPD at 36 weeks PMA NMAs	Keszler M, Modanlou HD, Brudno DS, Clark FI, Cohen RS, Ryan RM, Kaneta MK, Davis JM. Multicenter controlled clinical trial of high-frequency jet ventilation in preterm infants with uncomplicated respiratory distress syndrome. Pediatrics. 1997;100(4):593-9.

Study ID	Reason for exclusion	Excluded from	Reference
Wiswell 1996	Cross over RCT plus HFJV not an intervention of interest	Mortality prior to discharge and BPD at 36 weeks PMA NMAs	Wiswell TE, Graziani LJ, Kornhauser MS, Cullen J, Merton DA, McKee L, Spitzer AR. High-frequency jet ventilation in the early management of respiratory distress syndrome is associated with a greater risk for adverse outcomes. Pediatrics. 1996 Dec 1;98(6):1035-43.
Donn 1994	Zero counts in both arms	Mortality prior to discharge NMA	Donn SM, Nicks JJ, Becker MA. Flow-synchronized ventilation of preterm infants with respiratory distress syndrome. Journal of perinatology: official journal of the California Perinatal Association. 1994;14(2):90-4.
Rettwitz-volk 1998	Zero counts in both arms	BPD at 36 weeks PMA NMA	Rettwitz-Volk W, Veldman A, Roth B, Vierzig A, Kachel W, Varnholt V, Schlösser R, von Loewenich V. A prospective, randomised, multicenter trial of high-frequency oscillatory ventilation compared with conventional ventilation in preterm infants with respiratory distress syndrome receiving surfactant. The Journal of pediatrics. 1998;132(2):249-54.

Appendix R – Supplementary results

Supplementary results for question 3.2 What is the effectiveness and safety of the different assisted ventilation techniques in preterm babies?

Model fit characteristics

Non-invasive invasive ventilation

Table 78: Model fit characteristics for mortality prior to discharge

Model	Between-study standard deviation (95% CrI)	Residual deviance[a]	DIC
Fixed effect - consistency	N/A	13.49	60.863
Random effects - consistency	0.744 (95% CrI: 0.03, 3.72)	13.61	62.635
Fixed effect - inconsistency	---	12.53	60.515

CrI: credible interval; DIC: deviance information criterion; N/A: not applicable;
(a) Compare 14 data points

Table 79: Model fit characteristics for BPD at 36 weeks PMA

Model	Between-study standard deviation (95% CrI)	Residual deviance[a]	DIC
Fixed effect - consistency	N/A	36.76	138.045
Random effects - consistency	0.59 (95% CrI: 0.13, 1.64)	27.68	133.533
Random effects - inconsistency	0.74 (95% CrI: 0.20, 2.23)	27.53	135.129

CrI: credible interval; DIC: deviance information criterion; N/A: not applicable; BPD: Bronchopulmonary dysplasia
(a) Compare 26 points

Invasive invasive ventilation

Table 80: Model fit characteristics for mortality prior to discharge

Model	Between-study standard deviation (95% CrI)	Residual deviance[a]	DIC
Fixed effect - consistency	N/A	47.32	278.596
Random effects - consistency	0.11 (95% CrI: 0.00, 0.38)	47.58	280.690
Fixed effect - inconsistency	N/A	50.03	285.190

CrI: credible interval; DIC: deviance information criterion; N/A: not applicable
(a) Compare 58 data points

Table 81: Model fit characteristics for BPD at 36 weeks PMA

Model	Between-study standard deviation (95% CrI)	Residual deviance[a]	DIC
Fixed effect – consistency	N/A	57.26	269.185
Random effects (vague prior on between-study standard deviation) – consistency	0.33 (95% CrI: 0.03, 0.78)	48.11	269.185
Random effects (informative prior on between-study variance) - consistency	0.17 (95% CrI: 0.02, 0.53)	51.71	267.772
Random effects (informative prior on between-study variance) - inconsistency	0.16 (95% CrI: 0.02, 0.55)	52.42	269.969

CrI: Credible interval; DIC: deviance information criterion; N/A: Not applicable; BPD: Bronchopulmonary dysplasia

(a) Compare 46 data points

Appendix S – Inconsistency checks

Inconsistency checks for question 3.2 What is the effectiveness and safety of the different assisted ventilation techniques in preterm babies?

Prepared by: Caitlin Daly and Sofia Dias (NICE Technical Support Unit, University of Bristol)

Non-invasive ventilation

Introduction

The purpose of this analysis was to assess the consistency assumption in the network meta-analysis (NMA) model used to estimate the comparative effectiveness of non-invasive ventilation techniques in specialist neonatal respiratory care (SNRC) for babies born preterm. The outcomes included in this analysis were 1) mortality prior to discharge and 2) bronchopulmonary dysplasia (BPD) at 36 weeks postmenstrual age (PMA).

Methods

Inconsistency checks

An important assumption made in NMA concerns the consistency, that is, the agreement of the direct and indirect evidence informing the treatment contrasts (1, 2). There should be no meaningful differences between these two sources of evidence.

To conduct consistency checks, an appropriate base-case model (fixed or random effects) must be determined beforehand. We assessed and compared the fit of a fixed effect model and a random effects model with a vague prior distribution on the between-study standard deviation (Uniform(0,5)). To determine if there is evidence of inconsistency, the selected consistency model (fixed or random effects) was compared to an “inconsistency”, or unrelated mean effects, model (1, 2). The latter is equivalent to having separate, unrelated, meta-analyses for every pairwise contrast, with a common variance parameter assumed in the case of random effects models. Note that the consistency assumption can only be assessed when there are closed loops of direct evidence on 3 treatments that are informed by at least 3 independent sources of evidence (3).

The posterior mean of the residual deviance, which measures the magnitude of the differences between the observed data and the model predictions of the data, was used to assess and compare the goodness of fit of each model (4). Smaller values are preferred and in a well-fitting model the posterior mean residual deviance should be close to the number of data points in the network (each study arm contributes 1 data point on average) (4).

In addition to assessing how well the models fit the data using the posterior mean of the residual deviance, models were compared using the deviance information criterion (DIC). This is equal to the sum of the posterior mean deviance and the effective number of parameters and thus penalizes model fit with model complexity (4). Lower values are preferred and differences of 3 points were considered meaningful (4).

The posterior median between-study standard deviation, which measures the heterogeneity of treatment effects estimated by trials within contrasts, was also used to compare models. If the inconsistency model has smaller heterogeneity compared to the consistency model, then this indicates potential inconsistency in the data.

We performed further checks for evidence of inconsistency either through Bucher’s method or node-splitting (1-3, 5, 6). Bucher’s method compares the direct and indirect estimates for a contrast in a loop (e.g., A-B-C) where the direct estimate of contrast B vs. C is compared to

its corresponding indirect estimate, which is informed from the direct estimates of the other contrasts in the loop (A vs. B and A vs. C) (2, 5). This method was used to assess consistency in the network, where there was a single loop and the network contains sparse evidence with zero events, limiting the stability of the results of more sophisticated methods such as the node-splitting method. The BPD network, on the other hand, contained multiple loops and the node-splitting method was used to further assess the consistency assumption in this network. The node-splitting method permits the direct and indirect evidence contributing to an estimate of a relative effect to be split and compared (2, 6).

Results

Outcome: Mortality prior to discharge

Inconsistency checks were performed using the fixed effect model, as there were no meaningful differences between the fixed and random effects models in terms of the posterior mean residual deviance and DIC (Table 82). The posterior mean residual deviance, 14.63, is close to the number of expected data points, suggesting a good fit of the fixed effect model which is not improved when fitting a random effects model.

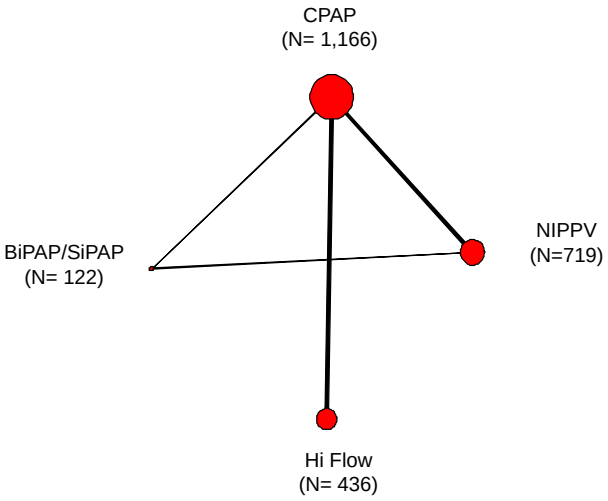
Table 82: Model fit statistics.

Model	Between Study Heterogeneity - Standard Deviation (95% CrI[a])	Residual deviance[b]	DIC[c]
Fixed effect - consistency	N/A	13.49	60.863
Random effects - consistency	0.744 (95% CrI: 0.03, 3.72)	13.61	62.635
Fixed effect - inconsistency	---	12.53	60.515

[a] Credible Interval (CrI)
[b] Posterior mean residual deviance compared to 16 total data points
[c] Deviance information criteria (DIC) – lower values preferred

Since there was a closed loop of direct evidence within the network that was informed by at least 3 distinct sets of trials, inconsistency checks were possible for this outcome (Figure 58). Convergence was satisfactory for the fixed effect model assuming inconsistency after 40,000 iterations and the consistency and inconsistency models were compared using results based on samples from a further 80,000 iterations on two chains. WinBUGS code for the inconsistency model is provided in appendix 1.

Figure 58: Network diagram of comparisons for which direct evidence on mortality prior to discharge was available



There are no meaningful differences between the fit of the fixed effect consistency model and inconsistency model (Table 82).

However, there is some evidence of potential inconsistency in this network, as the inconsistency model better predicted data points in the Wood 2013 and Salvo 2015 studies (Figure 59). Wood 2013 is the only study comparing CPAP and BiPAP/SiPAP, while Salvo 2015 is the only study comparing NiPPV and BiPAP/SiPAP and both these studies are part of the only loop in the network.

We used the Bucher approach to compare the direct and indirect evidence contributing to these comparisons (Table 83). The Bayesian p-value for Bucher's test of consistency is 0.052, close to the commonly referred 0.05 significance level, reflecting a 5.2% probability of no conflict between the direct and indirect estimates.

Figure 59: Deviance contributions for the fixed effect consistency and inconsistency models.

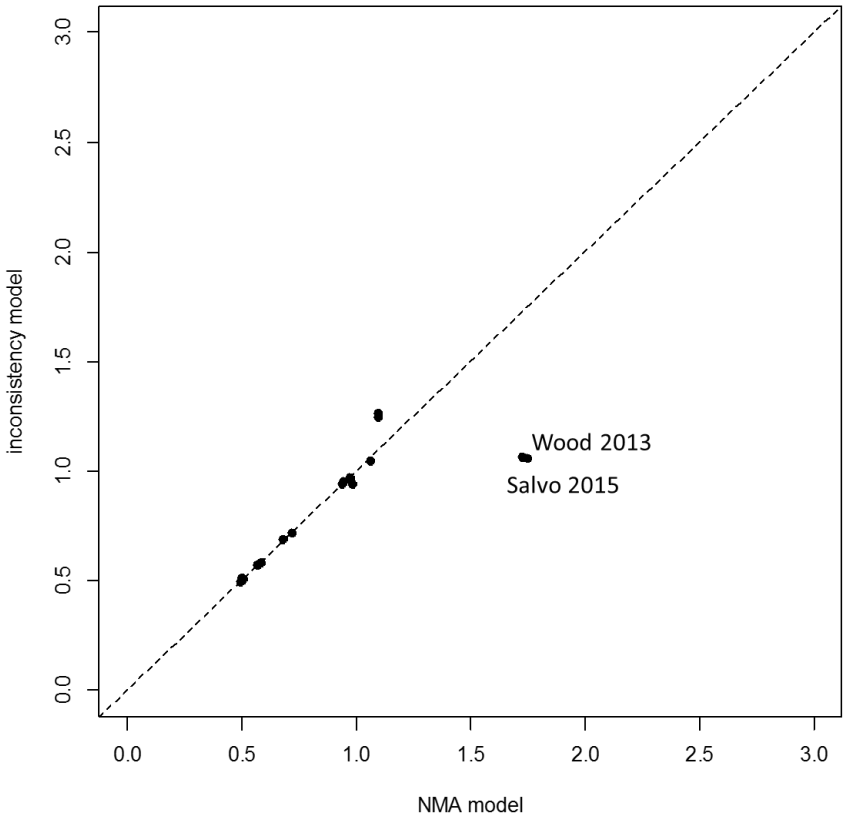


Table 83: Comparison of direct and indirect estimates of the log odds ratios and 95% CrIs obtained using Bucher's method.

	NIPPV vs. CPAP	BiPAP/SiPAP vs. CPAP	BiPAP/SiPAP vs. NIPPV
Direct estimate	-0.23 (-0.66, 0.19)	-2.29 (-8.46, 0.68)	2.27 (-0.70, 8.59)
Indirect estimate	-4.94 (-13.28, -0.22)	2.05 (-0.97, 8.35)	-2.07 (-8.25, 0.95)
NMA estimate[a]	-0.27 (-0.70, 0.15)	-0.15 (-1.93, 1.63)	0.13 (-1.65, 1.92)
p-value	0.052		

[a] Network meta-analysis (NMA) estimates obtained from fixed effect model, assuming consistency

[b] values of <0.05 indicate the presence of inconsistency

Outcome: Bronchopulmonary Dysplasia (BPD)

Since there were closed loops of direct evidence within the network that were informed by at least 3 distinct sets of trials, checks for inconsistency were possible for this outcome (Figure 60). Inconsistency checks were performed using the random effects model, as lower DIC suggested the random effects model should be preferred (Table 84). The posterior mean residual deviance, 27.68, is close to the number of expected data points, suggesting a good fit of the random effects model which is greatly improved when compared to the fixed effect model.

Figure 60: Network diagram of comparisons for which direct evidence on BPD was available.

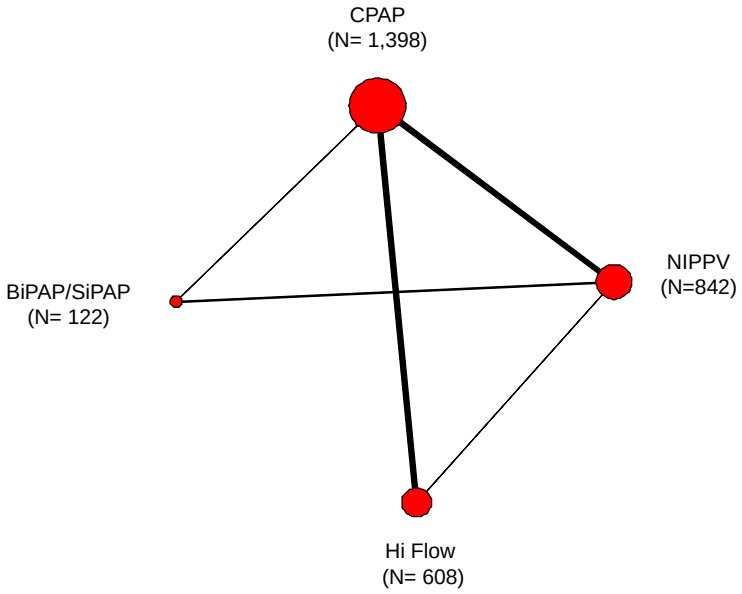


Table 84: Model fit statistics.

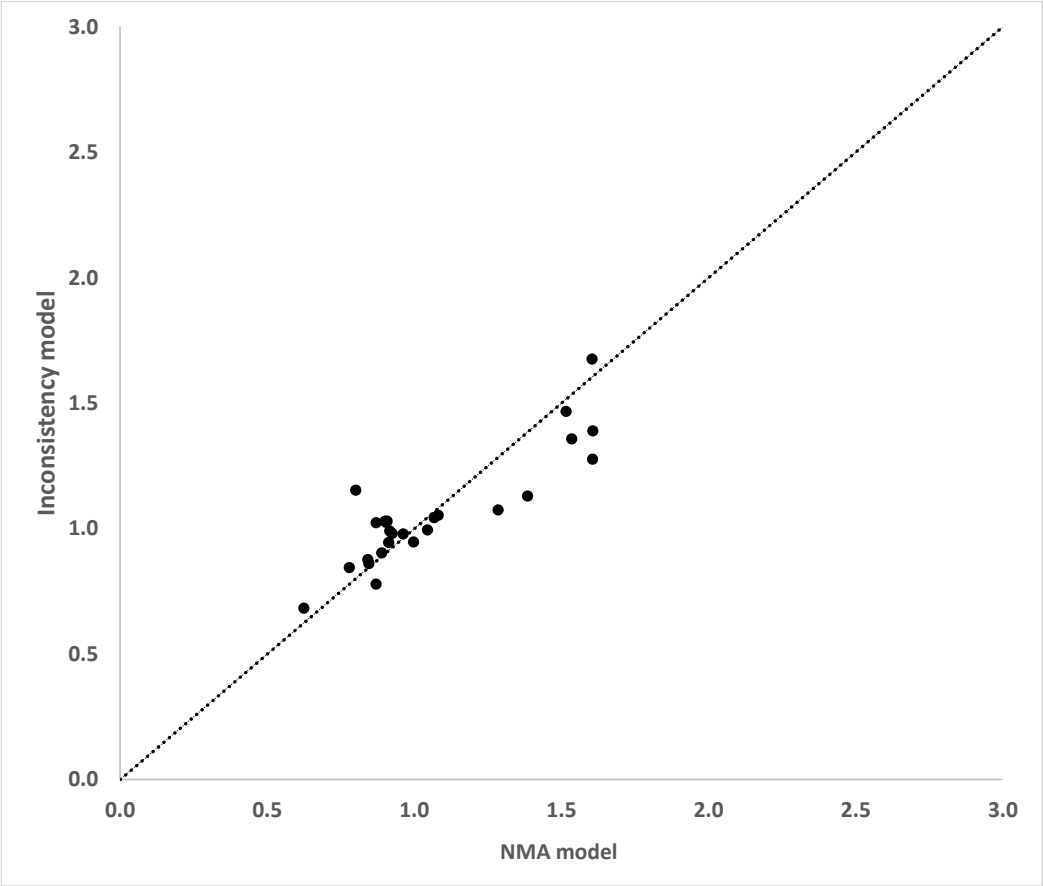
Model	Between Study Heterogeneity - Standard Deviation (95% CrI[a])	Residual deviance[b]	DIC[c]
Fixed effect – consistency	---	36.76	138.045
Random effects – consistency	0.59 (0.12, 1.64)	27.68	133.533
Random effects - inconsistency	0.74 (0.20, 2.23)	27.53	135.129

[a] Credible Interval (CrI)
[b] Posterior mean residual deviance compared to 26 total data points
[c] Deviance information criteria (DIC) – lower values preferred

Convergence was satisfactory for the random effects model assuming inconsistency after 40,000 iterations and the consistency and inconsistency models were compared using results based on samples from a further 80,000 iterations on two chains. WinBUGS code for the inconsistency model is provided in appendix 2.

No evidence of inconsistency was found through comparison of the consistency and inconsistency random effects models, as there were no meaningful differences between posterior mean residual deviance and DIC (Table 84). The area below the line of equality in Figure 61 highlights where the inconsistency model better predicted data points and the improvements were not meaningful.

Figure 61: Deviance contributions for the random effects consistency and inconsistency models.



Further checks for inconsistency using the node-splitting method (random effects model) did not find any evidence of inconsistency between the direct and indirect estimates (Table 85, Figure 62). In addition to the relative treatment effects estimated through NMA, we present direct and indirect estimates in Table 86. The direct and indirect estimates are reported based on results given by the node-splitting models. All NMA estimates are reported based on the results from the random effects model that assumes consistency (7, 8).

Table 85: Summary of node-splitting results.

Node split model	Heterogeneity (SD)		Residual deviance[a]	p-value[b]
	median	95% CrI		
NIPPV vs. CPAP	0.68	(0.18; 1.89)	27.13	0.45
Hi Flow vs. CPAP	0.63	(0.17; 1.74)	27.20	0.26
BiPAP/SiPAP vs. CPAP	0.68	(0.17; 2.03)	27.70	0.97
Hi Flow vs. NIPPV	0.61	(0.17; 1.68)	27.24	0.26
BiPAP/SiPAP vs. NIPPV	0.67	(0.16; 1.97)	27.81	0.97
NMA (no nodes split)	0.57	(0.14; 1.60)	27.59	---

[a]Posterior mean residual deviance compared to 26 total data points
[b]p-values < 0.05 is indicative of evidence of inconsistency between the direct and indirect estimates

Figure 62: Direct, indirect and network estimates of relative treatment effects based on node-splitting results. Treatments codes: 1 – CPAP, 2 – NIPPV, 3 – Hi Flow, 4 – BiPAP/SiPAP.

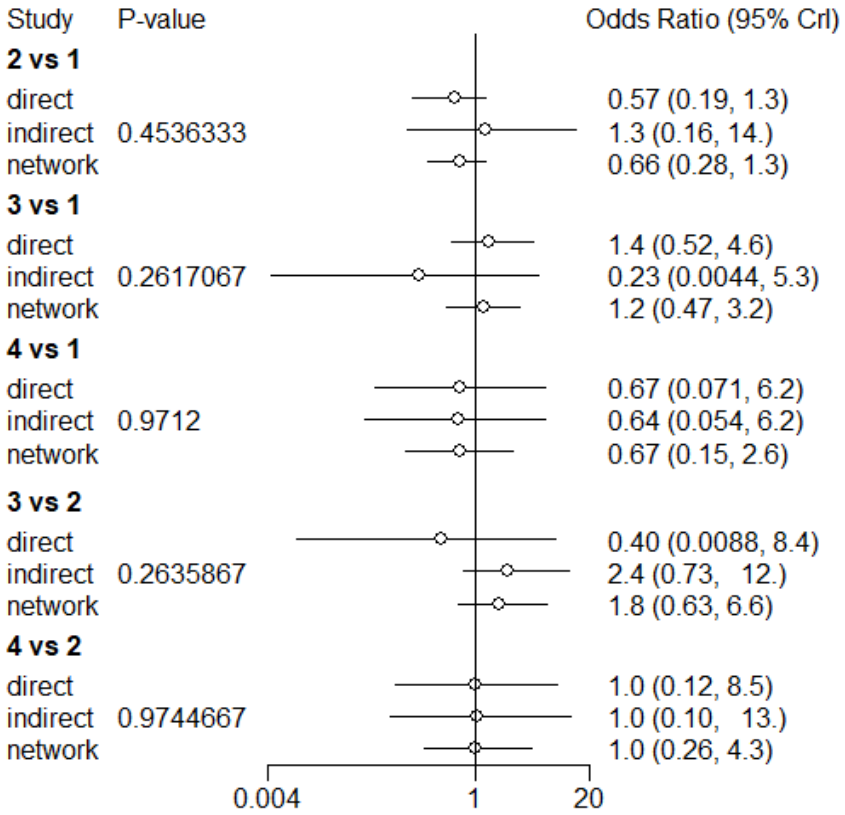


Table 86: Direct, indirect and NMA estimates of all relative treatment effects.

		Direct[a]			Indirect[b]			NMA[c]		
Treatment 1	Treatment 2	median log(OR)	2.5%	97.5%	median log(OR)	2.5%	97.5%	median log(OR)	2.5%	97.5%
CPAP	NIPPV	-0.55	-1.68	0.25	0.26	-1.83	2.64	-0.42	-1.31	0.27
CPAP	Hi Flow	0.35	-0.65	1.53	-1.48	-5.42	1.66	0.13	-0.84	1.11
CPAP	BiPAP/SiPAP	-0.40	-2.65	1.82	-0.45	-2.92	1.83	-0.42	-1.90	0.96
NIPPV	Hi Flow	-0.93	-4.73	2.13	0.87	-0.31	2.47	0.55	-0.53	1.85
NIPPV	BiPAP/SiPAP	0.00	-2.14	2.15	0.05	-2.27	2.53	0.01	-1.39	1.47
Hi Flow	BiPAP/SiPAP	---	---	---	-0.24	-0.24	0.48	-0.24	-0.24	0.48

[a]Direct estimates presented when available.
[b]Indirect estimates obtained from node-splitting models. For NIPPV vs. BiPAP/SiPAP, there was no direct evidence, hence estimates obtained from random effects model, assuming consistency.
[c]Network meta-analysis (NMA) estimates obtained from random effects model, assuming consistency.

Conclusion

The inconsistency checks did not identify any evidence of inconsistency in the direct and indirect evidence included in the network meta-analyses for the BPD outcome. While there was some evidence to suggest violation of the consistency assumption for the mortality prior to discharge outcome, the NMA model fit the data well.

Invasive ventilation

Introduction

The purpose of this analysis was to assess the consistency assumption in the network meta-analysis (NMA) model used to estimate the comparative effectiveness of specialist neonatal respiratory care (SNRC) interventions for babies born preterm. The outcomes included in this analysis were 1) mortality prior to discharge and 2) Bronchopulmonary Dysplasia (BPD) at 36 weeks PMA.

Methods

Inconsistency checks

An important assumption made in NMA concerns the consistency of the direct and indirect evidence informing the treatment contrasts (1, 2). There should be no meaningful differences between these two sources of evidence.

To conduct the inconsistency checks, an appropriate base-case model (fixed or random effects) must be determined beforehand. We assessed and compared the fit of a fixed effect model and a random effects model with a vague prior on the between-study standard deviation (Uniform(0,5)). To determine if there is evidence of inconsistency, the selected consistency model (fixed or random effects) was compared to an “inconsistency”, or unrelated mean effects, model (1, 2). The latter is equivalent to having separate, unrelated, meta-analyses for every pairwise contrast, with a common variance parameter assumed in the case of random effects models. Note that the consistency assumption can only be assessed when there are closed loops of direct evidence on 3 treatments that are informed by at least 3 independent sources of evidence (3).

The posterior mean of the residual deviance, which measures the magnitude of the differences between the observed data and the model predictions of the data, was used to assess and compare the goodness of fit of each model (4). Smaller values are preferred and in a well-fitting model the posterior mean residual deviance should be close to the number of data points in the network (each study arm contributes 1 data point) (4).

In addition to comparing how well the models fit the data using the posterior mean of the residual deviance, models were compared using the deviance information criterion (DIC). This is equal to the sum of the posterior mean of the residual deviance and the effective number of parameters and thus penalizes model fit with model complexity (4). Lower values are preferred and differences of 5 points were considered meaningful (4).

The posterior median between-study standard deviation, which measures the heterogeneity of treatment effects estimated by trials within contrasts, was also used to compare models. If the inconsistency model has smaller heterogeneity compared to the consistency model, then this indicates potential inconsistency in the data.

We performed further checks for evidence of inconsistency through node-splitting (2, 3, 6, 8). This method permits the direct and indirect evidence contributing to an estimate of a relative effect to be split and compared.

Results

Outcome: Mortality prior to discharge

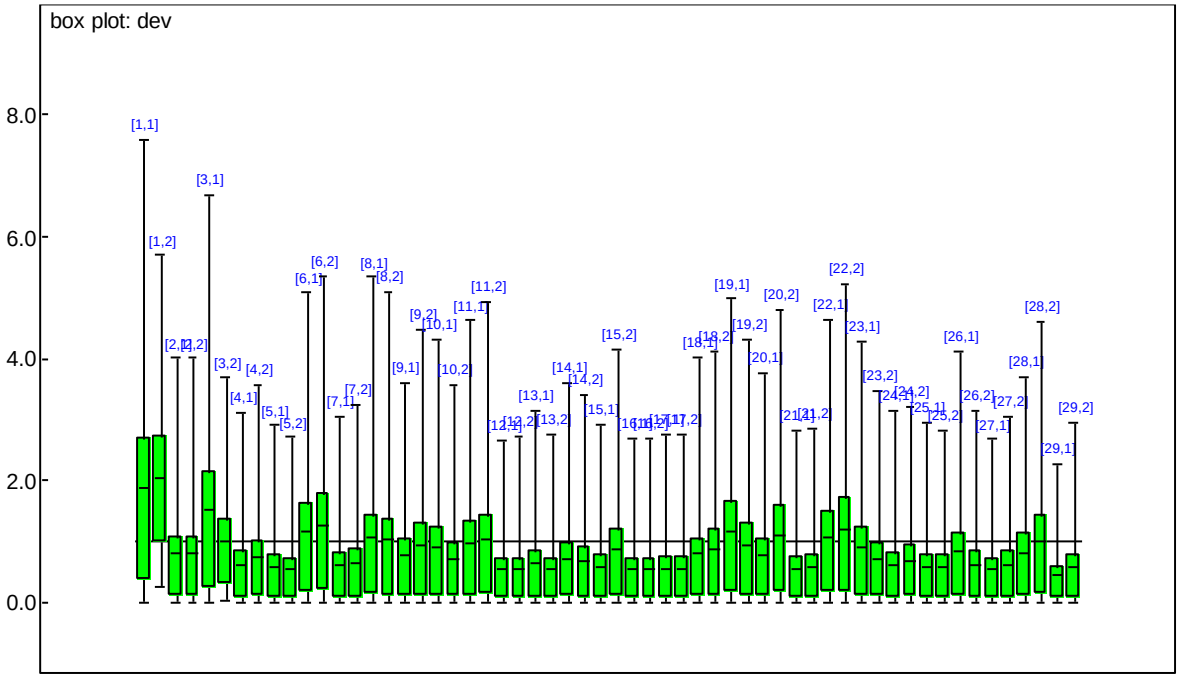
Inconsistency checks were performed using the fixed effect model, as there were no meaningful differences between the fixed and random effects models in terms of the posterior mean residual deviance and DIC (Table 87). Note, however, that the posterior mean residual deviance is substantially lower than the number of data points (n=58), suggesting an issue of overfitting in the model. Figure 63 summarizes the posterior deviance values for each study arm and there are many arms with a posterior median deviance of less than 1. There is no clear reason for this.

Table 87: Model fit statistics.

Model	Between Study Heterogeneity - Standard Deviation (95% CrI[a])	Residual deviance[b]	DIC[c]
Fixed effect - consistency	---	47.32	278.596
Random effects - consistency	0.11 (0.00, 0.38)	47.58	280.690
Fixed effect - inconsistency	---	50.03	285.190

[a] Credible Interval (CrI)
[b] Posterior mean residual deviance compared to 58 total data points
[c] Deviance information criteria (DIC) – lower values preferred

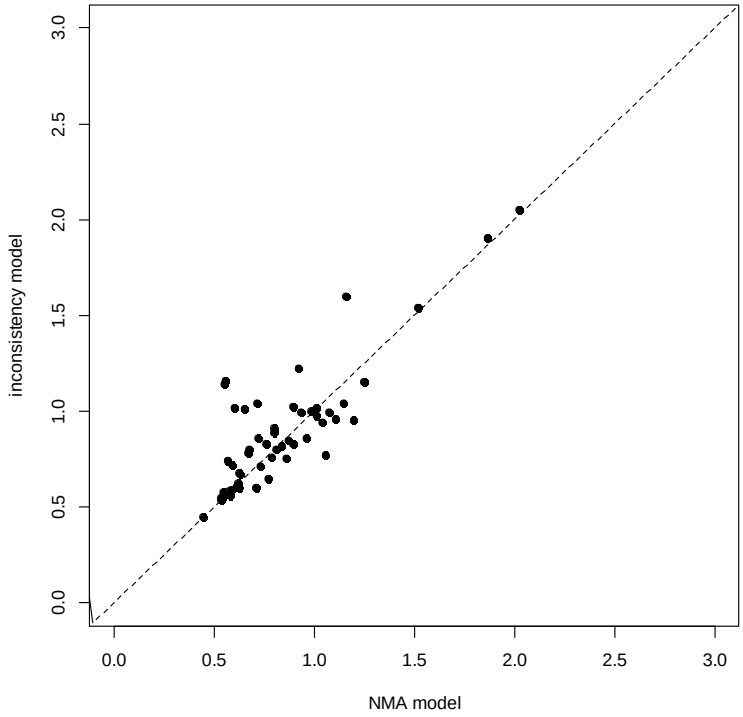
Figure 63: Box plots of the posterior deviance values for each study arm. Arms are labelled as [i,j], where i indicates the study index and j indicates the study arm within study i.



Since there were closed loops of direct evidence within the network that were informed by at least 3 distinct sets of trials, inconsistency checks were possible for this outcome. Convergence was satisfactory for the fixed effect model assuming inconsistency after 20,000 iterations and the consistency and inconsistency models were compared using results based on samples from a further 40,000 iterations on two chains. WinBUGS code for the inconsistency model is provided Appendix 3.

No evidence of inconsistency was found through comparison of the consistency and inconsistency fixed effect models, as lower posterior mean residual deviance and DIC suggested that the consistency model provided a better fit (Table 87). The area below the line of equality in Figure 64 highlights where the inconsistency model better predicted data points and the improvements were minimal.

Figure 64: Deviance contributions for the fixed effect consistency and inconsistency models.



Further checks for inconsistency using the node-splitting method (fixed effect model) did not find any evidence of inconsistency between the direct and indirect estimates (Table 88, Figure 65). In addition to the relative treatment effects estimated through NMA, we present direct (when available) and indirect estimates in Table 89. Where direct evidence is available on treatment comparisons, the direct and indirect estimates are reported based on results given by the node-splitting models. Otherwise, the indirect estimates are taken from the NMA model. All NMA estimates are reported based on the results from the fixed effect model that assumes consistency (7, 8).

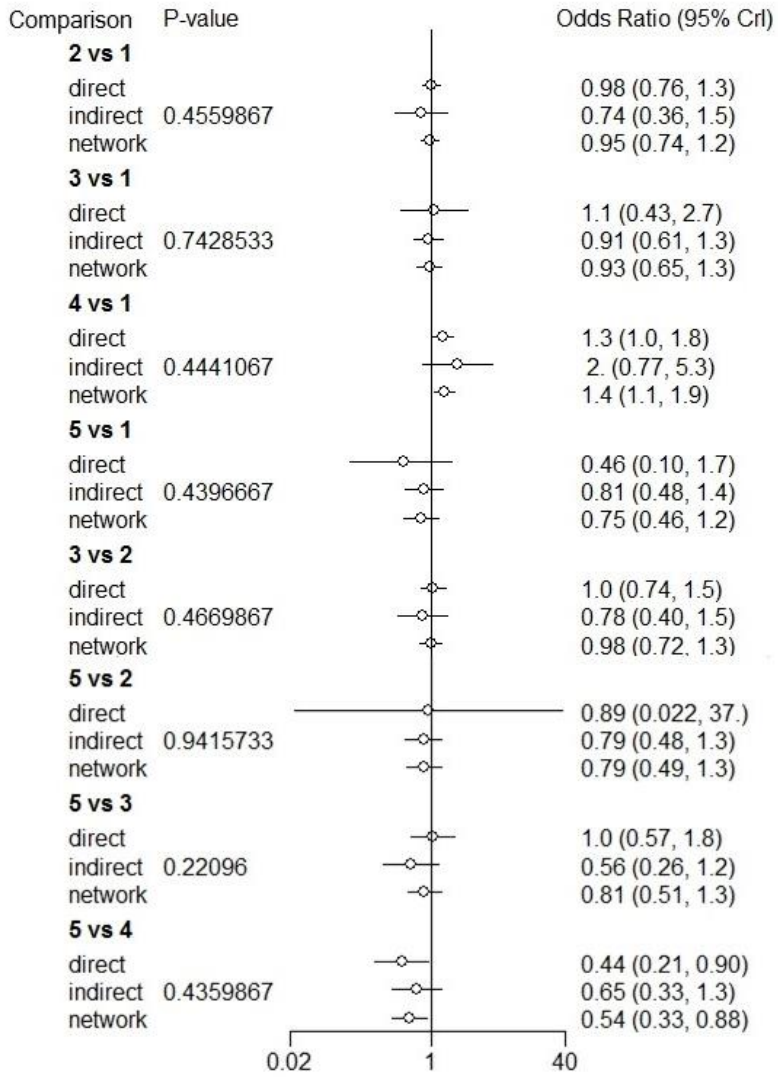
Table 88: Summary of node-splitting results.

Node split model	DIC	p-value[a]
High frequency ventilation vs. Non-synchronised pressure limited ventilation	75.47	0.46
Synchronised intermittent mandatory ventilation vs. Non-synchronised pressure limited ventilation	76.01	0.74
Synchronised pressure limited ventilation vs. Non-synchronised pressure limited ventilation	75.56	0.44
Volume targeted ventilation vs. Non-synchronised pressure limited ventilation	75.56	0.44
Synchronised intermittent mandatory ventilation vs. High frequency ventilation	75.59	0.47

Node split model	DIC	p-value[a]
Volume targeted ventilation vs. High frequency ventilation	76.6	0.94
Volume targeted ventilation vs. Synchronised intermittent mandatory ventilation	74.7	0.22
Volume targeted ventilation vs. Synchronised pressure limited ventilation	75.59	0.44
NMA (no nodes split)	73.99	---

[a]p-values < 0.05 is indicative of evidence of inconsistency between the direct and indirect estimates

Figure 65: Direct, indirect and network estimates of relative treatment effects based on node-splitting results.



Treatments codes: 1 – Non-synchronised pressure limited ventilation, 2 – High frequency ventilation, 3 – Synchronised intermittent mandatory ventilation, 4 – Synchronised pressure limited ventilation, 5 – Volume targeted ventilation.

Table 89: Direct, indirect and NMA estimates of all relative treatment effects.

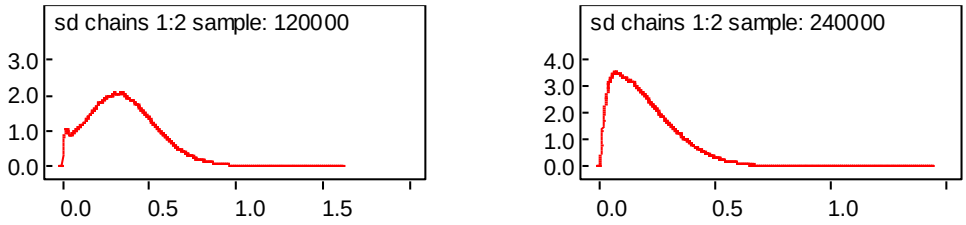
		Direct[a]			Indirect[b]			NMA[c]		
Treatment 1	**Treatment 2**	**median log(OR)**	**2.5%**	**97.5%**	**median log(OR)**	**2.5%**	**97.5%**	**median log(OR)**	**2.5%**	**97.5%**
Non-synchronised pressure limited ventilation	High frequency ventilation	-0.02	-0.28	0.24	-0.31	-1.03	0.41	-0.05	-0.30	0.19
Non-synchronised pressure limited ventilation	Synchronised intermittent mandatory ventilation	0.06	-0.85	0.98	-0.10	-0.49	0.29	-0.08	-0.42	0.28
Non-synchronised pressure limited ventilation	Synchronised pressure limited ventilation	0.30	0.00	0.60	0.69	-0.27	1.66	0.33	0.05	0.62
Non-synchronised pressure limited ventilation	Volume targeted ventilation	-0.78	-2.27	0.54	-0.21	-0.73	0.30	-0.28	-0.77	0.20
High frequency ventilation	Synchronised intermittent mandatory ventilation	0.04	-0.31	0.38	-0.25	-0.93	0.44	-0.02	-0.32	0.28
High frequency ventilation	Synchronised pressure limited ventilation	-	-	-	0.39	0.02	0.76	0.39	0.02	0.76
High frequency ventilation	Volume targeted ventilation	-0.11	-3.81	3.62	-0.23	-0.73	0.26	-0.23	-0.72	0.26
Synchronised intermittent mandatory ventilation	Synchronised pressure limited ventilation				0.41	-0.02	0.84	0.41	-0.02	0.84
Synchronised intermittent mandatory ventilation	Volume targeted ventilation	0.02	-0.57	0.61	-0.59	-1.36	0.18	-0.21	-0.67	0.26
Synchronised pressure limited ventilation	Volume targeted ventilation	-0.83	-1.58	-0.11	-0.44	-1.11	0.25	-0.62	-1.11	-0.12

[a]Direct estimates presented when available.
[b]Indirect estimates obtained from node-splitting models when direct evidence is available, otherwise equal to NMA estimates.
[c]Network meta-analysis (NMA) estimates obtained from fixed effect model, assuming consistency.

Outcome: Bronchopulmonary Dysplasia (BPD) at 36 weeks PMA

Upon determining the appropriate base-case model (random effects), a spike in the posterior distribution of the between-study standard deviation of the random effects model was observed, suggesting there was little evidence contributing to the between-study heterogeneity (Figure 66). As a result, we used a random effects model with an informative prior on the between-study variance in the comparison of potential base-case models. The informative prior on the between-study variance was selected from a list of predictive distributions for between-study heterogeneity that are typical of cause-specific mortality/major morbidity event/composite (mortality or morbidity) outcomes (9). Predictive distributions are available for a variety of intervention comparison types (e.g., non-pharmalogical vs. placebo/control, non-pharmalogical vs. pharmalogical, non-pharmalogical vs. non-pharmalogical). To be conservative, we selected the predictive distribution for non-pharmalogical vs. placebo/control comparisons (log-normal(-3.93, 1.91^2)), as it had the largest variance among the distributions for various comparison types. WinBUGS code for the random effects model with an informative prior on the between-study variance is provided in Appendix 4.

Figure 66: Posterior between-study standard deviation of the random effects model with a vague prior on the between-study standard deviation (left) and informative prior on the between-study variance (right) for BPD outcome.



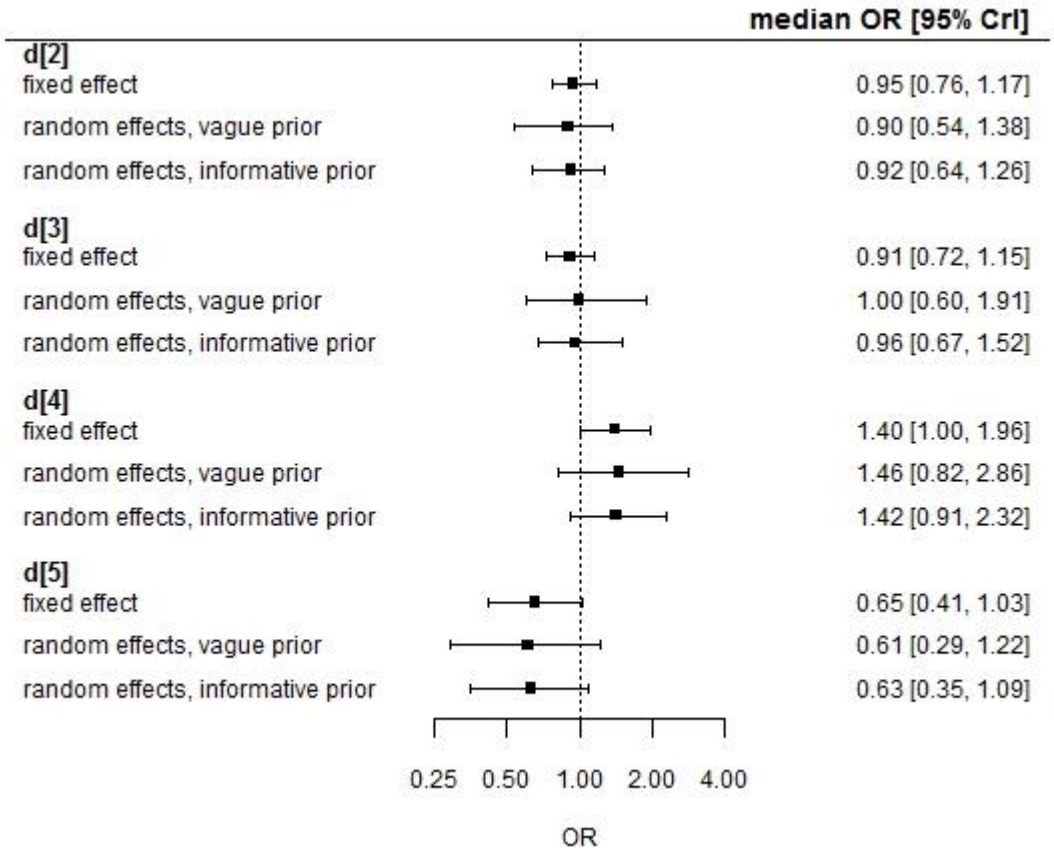
Based on the posterior mean residual deviance, none of the models provide a good fit (Table 90). Aside from the increased uncertainty expected in random effects models, compared to fixed effect models, there are no substantial differences within the treatment effects estimated by the three models (Figure 67). Lower posterior mean residual deviance and DIC suggested both random effects models provided a better fit than the fixed effect model. Since the between-study heterogeneity was smaller in the random effects model with the informative prior on the between-study variance, inconsistency checks were performed with this model. Note that the model does not seem to fit the data well for Gerstmann 1996, Durand 2001, Vento 2005, Sinha 1997, D'Angio 2005, Guven 2013 (Figure 68).

Table 90: Model fit statistics.

Model	Between Study Heterogeneity - Standard Deviation (95% CrI[a])	Residual deviance[b]	DIC[c]
Fixed effect	---	57.26	269.185
Random effects (vague prior on between-study standard deviation)	0.33 (0.03, 0.78)	48.11	267.491
Random effects (informative prior on between-study variance)	0.17 (0.02, 0.53)	51.71	267.772

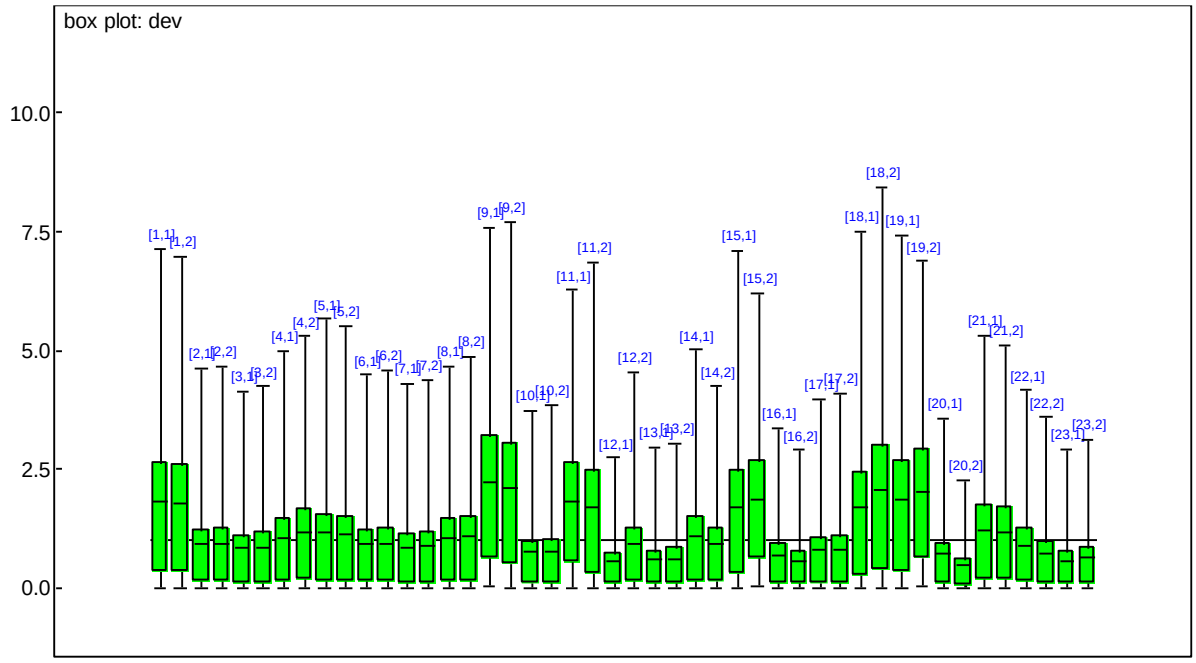
[a] Credible Interval (CrI)
[b] Posterior mean residual deviance compared to 46 total data points
[c] Deviance information criteria (DIC) – lower values preferred

Figure 67: Estimated treatment effects relative to non-synchronised pressure limited ventilation.



Treatments codes: 2 – High frequency ventilation, 3 – Synchronised pressure limited ventilation, 4 – Synchronised intermittent mandatory ventilation, 5 – Volume targeted ventilation.

Figure 68: Box plots of the posterior deviance values for each study arm. Arms are labelled as [i,j], where i indicates the study index and j indicates the study arm within study i.



Convergence was satisfactory for the random effects model assuming inconsistency after 60,000 iterations and the consistency and inconsistency models were compared using results based on samples from a further 120,000 iterations on two chains. WinBUGS code for the inconsistency model is provided in the Appendix 5.

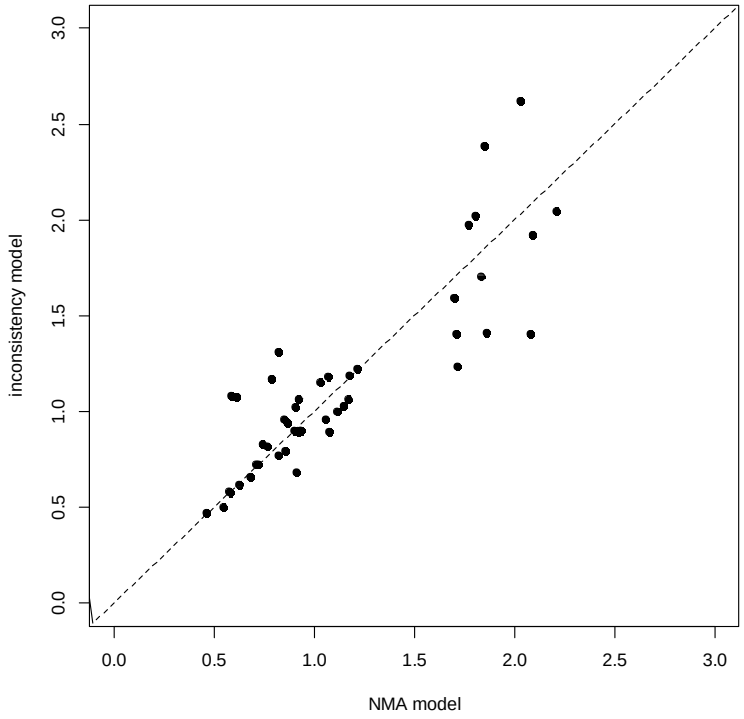
No evidence of inconsistency was found through comparison of the consistency and inconsistency random effects models, as there were no meaningful differences between posterior mean residual deviance and DIC (Table 91). The area below the line of equality in Figure 69 highlights where the inconsistency model better predicted data points and the improvements were not meaningful.

Table 91: Model fit statistics of random effects models with informative prior on between-study variance

Model	Between Study Heterogeneity - Standard Deviation (95% CrI[a])	Residual deviance[b]	DIC[c]
Consistency model	0.17 (0.02, 0.53)	51.71	267.772
Inconsistency model	0.16 (0.02, 0.55)	52.42	269.969

[a] Credible Interval (CrI)
[b] Posterior mean residual deviance compared to 46 total data points
[c] Deviance information criteria (DIC) – lower values preferred

Figure 69: Deviance contributions for the random effects consistency and inconsistency models.



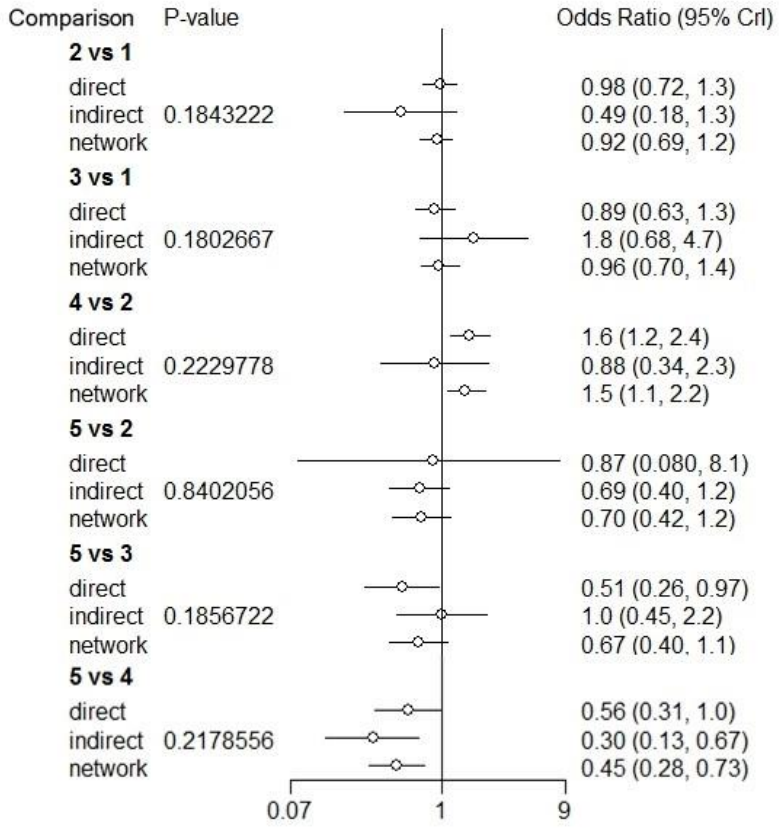
Further checks for inconsistency using the node-splitting method (random effects model) did not find any evidence of inconsistency between the direct and indirect estimates (Table 92 Figure 70). In addition to the relative treatment effects estimated through NMA, we present direct (when available) and indirect estimates in Table 93. Where direct evidence is available on treatment comparisons, the direct and indirect estimates are reported based on results given by the node-splitting models. Otherwise, the indirect estimates are taken from the NMA model. All NMA estimates are reported based on the results from the random effects model that assumes consistency (7, 8).

Table 92: Summary of node-splitting results

Node split model	Heterogeneity (SD)		DIC	p-value[a]
	median	95% CrI		
High frequency ventilation vs. Non-synchronised pressure limited ventilation	0.15	(0.07, 0.3)	74.41	0.18
Synchronised pressure limited ventilation vs. Non-synchronised pressure limited ventilation	0.15	(0.07, 0.29)	74.26	0.18
Synchronised intermittent mandatory ventilation vs. High frequency ventilation	0.15	(0.07, 0.29)	74.76	0.22
Volume targeted ventilation vs. High frequency ventilation	0.15	(0.07, 0.31)	76.08	0.84
Volume targeted ventilation vs. Synchronised pressure limited ventilation	0.15	(0.07, 0.3)	74.38	0.19
Volume targeted ventilation vs. Synchronised intermittent mandatory ventilation	0.15	(0.07, 0.29)	74.68	0.22
NMA (no nodes split)	0.15	(0.07, 0.3)	74.09	---

[a]p-values < 0.05 is indicative of evidence of inconsistency between the direct and indirect estimates

Figure 70: Direct, indirect and network estimates of relative treatment effects based on node-splitting results.



Treatments codes: 1 – Non-synchronised pressure limited ventilation, 2 – High frequency ventilation, 3 – Synchronised pressure limited ventilation, 4 – Synchronised intermittent mandatory ventilation, 5 – Volume targeted ventilation.

Table 93: Direct, indirect and NMA estimates of all relative treatment effects.

Treatment 1	Treatment 2	Direct[a]			Indirect[b]			NMA[c]		
		median log(OR)	2.5%	97.5%	median log(OR)	2.5%	97.5%	median log(OR)	2.5%	97.5%
Non-synchronised pressure limited ventilation	High frequency ventilation	-0.02	-0.33	0.27	-0.72	-1.70	0.27	-0.08	-0.45	0.23
Non-synchronised pressure limited ventilation	Synchronised pressure limited ventilation	-0.12	-0.46	0.23	0.58	-0.39	1.54	-0.04	-0.40	0.42
Non-synchronised pressure limited ventilation	Synchronised intermittent mandatory ventilation				0.35	-0.09	0.84	0.35	-0.09	0.84
Non-synchronised pressure limited ventilation	Volume targeted ventilation				-0.46	-1.04	0.08	-0.46	-1.04	0.08
High frequency ventilation	Synchronised pressure limited ventilation				0.04	-0.39	0.62	0.04	-0.39	0.62
High frequency ventilation	Synchronised intermittent mandatory ventilation	0.50	0.15	0.87	-0.13	-1.07	0.83	0.44	0.10	0.86
High frequency ventilation	Volume targeted ventilation	-0.14	-2.53	2.09	-0.38	-0.91	0.14	-0.37	-0.93	0.18
Synchronised pressure limited ventilation	Synchronised intermittent mandatory ventilation				0.39	-0.17	0.91	0.39	-0.17	0.91
Synchronised pressure limited ventilation	Volume targeted ventilation	-0.68	-1.35	-0.03	0.01	-0.79	0.80	-0.43	-1.03	0.09
Synchronised intermittent mandatory ventilation	Volume targeted ventilation	-0.58	-1.18	0.00	-1.21	-2.04	-0.39	-0.81	-1.38	-0.31

[a]Direct estimates presented when available.
[b]Indirect estimates obtained from node-splitting models when direct evidence is available, otherwise equal to NMA estimates.
[c]Network meta-analysis (NMA) estimates obtained from random effects model, assuming consistency.

Conclusion

The inconsistency checks did not identify any evidence of inconsistency in the direct and indirect evidence included in the network meta-analyses for both outcomes. However, we note the lack of good fit for the models of both outcomes and this should be considered when interpreting the results.

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Appendices

Appendix 1. WinBUGS code for inconsistency model - Mortality prior to discharge (non-invasive ventilation)

Appendix 2. NIV WinBUGS code for inconsistency model used in this report - BPD at 36 weeks PMA (non-invasive ventilation)

Appendix 3. WinBUGS code for inconsistency model used in this report - Mortality prior to discharge (invasive ventilation)

Appendix 4. WinBUGS code for random effects model with an informative prior on the between-study variance – BPD at 36 weeks PMA (invasive ventilation)

Appendix 5. WinBUGS code for inconsistency model used in this report - BPD at 36 weeks PMA (invasive ventilation)

Appendix 1. WinBUGS code for inconsistency model - Mortality prior to discharge (non-invasive ventilation)

```
# Binomial likelihood, logit link, MTC

# Fixed effect model

model{                                                  # *** PROGRAM STARTS

for(i in 1:ns){                                         # LOOP THROUGH STUDIES

  mu[i] ~ dnorm(0,.0001)                                # vague priors for all trial baselines

  for (k in 1:na[i]) {                                        # LOOP THROUGH ARMS

    r[i,k] ~ dbin(p[i,k],n[i,k])                              # binomial likelihood

    logit(p[i,k]) <- mu[i] + d[t[i,1],t[i,k]]                 # model for linear predictor

    rhat[i,k] <- p[i,k] * n[i,k]                              # expected value of the numerators

    dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))       #Deviance contribution

        + (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))

  }

  resdev[i] <- sum(dev[i,1:na[i]])    # summed residual deviance contribution for this trial

}

totresdev <- sum(resdev[])            # Total Residual Deviance


# pairwise ORs and LORs for all possible pair-wise comparisons

for (c in 1:(nt-1)){

       d[c,c] <- 0

       for (k in (c+1):nt){

            d[c,k] ~ dnorm(0,.0001)          # priors for all mean trt effects

           # or[c,k] <- exp(d[c,k])          # all pairwise ORs

       }

}


# Bucher Inconsistency assessment for loop (1,2,4)

# Indirect estimates

dInd.24 <- d[1,4]-d[1,2]

dInd.12 <- d[1,4]-d[2,4]

dInd.14 <- d[1,2]+d[2,4]

# differences between direct and indirect
```

```
diff.24 <- dInd.24-d[2,4]

diff.12 <- dInd.12-d[1,2]

diff.14 <- dInd.14-d[1,4]

# p-values

p.24 <- step(diff.24)

p.12 <- step(diff.12)

p.14 <- step(diff.14)


}                                                  # *** PROGRAM ENDS
```

Appendix 2. NIV WinBUGS code for inconsistency model used in this report - BPD at 36 weeks PMA (non-invasive ventilation)

```
# Binomial likelihood, logit link

# Random effect model, multi-arm trials

model{                                                  # *** PROGRAM STARTS

for(i in 1:ns){                                         # LOOP THROUGH STUDIES

  delta[i,1] <- 0                                        # treatment effect is zero for control
arm

  mu[i] ~ dnorm(0,.0001)                                # vague priors for all trial baselines

  for (k in 1:na[i]) {                                          # LOOP THROUGH ARMS

    r[i,k] ~ dbin(p[i,k],n[i,k])                                # binomial likelihood

    logit(p[i,k]) <- mu[i] + delta[i,k]                         # model for linear predictor

     rhat[i,k] <- p[i,k] * n[i,k]                                 # expected value of the
numerators

     dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))             #Deviance contribution

         + (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))

  }

  resdev[i] <- sum(dev[i,1:na[i]])                            # summed residual deviance
contribution for this trial

  for (k in 2:na[i]) {                                   # LOOP THROUGH ARMS

     delta[i,k] ~ dnorm(d[t[i,1],t[i,k]],tau)            # trial-specific LOR distributions

   }

}

totresdev <- sum(resdev[])                              #Total Residual Deviance

sd ~ dunif(0,5)

tau <- pow(sd,-2)


for (c in 1:(nt-1)){

       d[c,c] <- 0

       for (k in (c+1):nt){
```

```
            d[c,k] ~ dnorm(0,.0001)                          # priors for all mean trt effects
           # or[c,k] <- exp(d[c,k])                          # all pairwise ORs
       }
}

}                                                            # *** PROGRAM ENDS
```

Appendix 3. WinBUGS code for inconsistency model used in this report - Mortality prior to discharge (invasive ventilation)

```
# Binomial likelihood, logit link, MTC
# Fixed effect model
model{                          # *** PROGRAM STARTS
for(i in 1:ns){                 # LOOP THROUGH STUDIES
       mu[i] ~ dnorm(0,.0001)         # vague priors for all trial baselines
       for (k in 1:na[i]) {           # LOOP THROUGH ARMS
              r[i,k] ~ dbin(p[i,k],n[i,k])                   # binomial likelihood
              logit(p[i,k]) <- mu[i] + d[t[i,1],t[i,k]]      # model for linear predictor
              rhat[i,k] <- p[i,k] * n[i,k]                   # expected value of the numerators
              dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
       # Deviance contribution
              + (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
       }
       resdev[i] <- sum(dev[i,1:na[i]]) # summed residual deviance contribution for this trial
}
totresdev <- sum(resdev[])            # Total Residual Deviance

for (c in 1:nt){
       d[c,c] <- 0
       }
for (c in 1:(nt-1)){
       for (k in (c+1):nt){
            d[c,k] ~ dnorm(0,.0001)   # priors for all mean trt effects
            or[c,k] <- exp(d[c,k])    # all pairwise ORs
       }
}

}                                     # *** PROGRAM ENDS
```

Appendix 4. WinBUGS code for random effects model with an informative prior on the between-study variance – BPD at 36 weeks PMA (invasive ventilation)

```
# Binomial likelihood, logit link
# Random effect model, multi-arm trials
model{                              # *** PROGRAM STARTS
for(i in 1:ns){                     # LOOP THROUGH STUDIES
  w[i,1] <- 0                       # adjustment for multi-arm trials is zero for control arm
  delta[i,1] <- 0                   # treatment effect is zero for control arm
  mu[i] ~ dnorm(0,.0001)            # vague priors for all trial baselines
  for (k in 1:na[i]) {              # LOOP THROUGH ARMS
    r[i,k] ~ dbin(p[i,k],n[i,k])    # binomial likelihood
    logit(p[i,k]) <- mu[i] + delta[i,k]           # model for linear predictor
     rhat[i,k] <- p[i,k] * n[i,k]                 # expected value of the numerators
     dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))      #Deviance contribution
         + (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
  }
  resdev[i] <- sum(dev[i,1:na[i]])     # summed residual deviance contribution for this trial
  for (k in 2:na[i]) {                              # LOOP THROUGH ARMS
     delta[i,k] ~ dnorm(md[i,k],taud[i,k])          # trial-specific LOR distributions
     # mean of LOR distributions (with multi-arm correction)
     md[i,k] <- d[t[i,k]] - d[t[i,1]] + sw[i,k]
# precision of LOR distributions (with multi-arm correction)
     taud[i,k] <- tau *2*(k-1)/k
     w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])     # adjustment for multi-arm RCTs
     sw[i,k] <- sum(w[i,1:k-1])/(k-1)              # cumulative adjustment for multi-arm trials
   }
}
totresdev <- sum(resdev[])                  # Total Residual Deviance
d[1]<- 0                                    # treatment effect is zero for reference treatment
for (k in 2:nt)  { d[k] ~ dnorm(0,.0001)}   # vague priors for treatment effects
#informative prior on between-study variance based on Turner 2015
#outcome: cause-specific mortality/major morbidity event/composite (mortality or morbidity)
#intervention type: non-pharma vs. placebo/control
#LN(-3.93, 1.91^2)
tausq.prec<-pow(1.91,-2)                     #precision of informative distribution
tausq~dlnorm(-3.93,tausq.prec)               #informative prior on between-trial variance
sd<-pow(tausq,0.5)                           #between-trial SD
tau<-pow(tausq,-1)                           #between-trial precision
```

```
# pairwise ORs and LORs for all possible pair-wise comparisons
for (c in 1:(nt-1)) {  for (k in (c+1):nt) {
       or[c,k] <- exp(d[k] - d[c])
       lor[c,k] <- (d[k]-d[c])
      }
}

# ranking
for (k in 1:nt) {
        # rk[k] <- nt+1-rank(d[],k) # assumes events are "good"
        rk[k] <- rank(d[],k) # assumes events are "bad"
}

# Absolute effects
A ~ dnorm(meanA,precA)        #  both based on baseline model for treatment A
for (k in 1:nt) { logit(T[k]) <- A + d[k] }
}                                                    # *** PROGRAM ENDS
```

Appendix 5. WinBUGS code for inconsistency model used in this report - BPD at 36 weeks PMA (invasive ventilation)

```
# Binomial likelihood, logit link
# Random effect model, multi-arm trials
model{                              # *** PROGRAM STARTS
for(i in 1:ns){                     # LOOP THROUGH STUDIES
  w[i,1] <- 0                       # adjustment for multi-arm trials is zero for control arm
  delta[i,1] <- 0                   # treatment effect is zero for control arm
  mu[i] ~ dnorm(0,.0001)            # vague priors for all trial baselines
  for (k in 1:na[i]) {              # LOOP THROUGH ARMS
    r[i,k] ~ dbin(p[i,k],n[i,k])             # binomial likelihood
    logit(p[i,k]) <- mu[i] + delta[i,k]      # model for linear predictor
     rhat[i,k] <- p[i,k] * n[i,k]            # expected value of the numerators
     dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))             #Deviance contribution
         + (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
  }
  resdev[i] <- sum(dev[i,1:na[i]])            # summed residual deviance contribution for this
trial
  for (k in 2:na[i]) {                        # LOOP THROUGH ARMS
     delta[i,k] ~ dnorm(d[t[i,1],t[i,k]],tau)    # trial-specific LOR distributions
   }
```

```
}
totresdev <- sum(resdev[])                    # Total Residual Deviance

#informative prior on between-study variance based on Turner 2014
#outcome: cause-specific mortality/major morbidity event/composite (mortality or morbidity)
#intervention type: non-pharma vs. placebo/control
#LN(-3.93, 1.91^2)
tausq.prec <- pow(1.91,-2)            #precision of informative distribution
tausq ~ dlnorm(-3.93,tausq.prec)      #informative prior on between-trial variance
sd <- pow(tausq,0.5)                  #between-trial SD
tau <- pow(tausq,-1)                  #between-trial precision

for (c in 1:nt){
       d[c,c] <- 0
       }
for (c in 1:(nt-1)){
       for (k in (c+1):nt){
            d[c,k] ~ dnorm(0,.0001)          # priors for all mean trt effects
            or[c,k] <- exp(d[c,k])           # all pairwise ORs
       }
}



}                                             # *** PROGRAM ENDS
```

Appendix T – Threshold analysis

Threshold analysis for question 3.2 What is the effectiveness and safety of the different assisted ventilation techniques in preterm babies?

Prepared by: David Phillippo, Caitlin Daly, Sofia Dias (NICE Technical Support Unit, University of Bristol)

Introduction and methods

If studies included in a network meta-analysis (NMA) are assessed to have flaws in their conduct or reporting, the reliability of results from the NMA can be in doubt. Therefore, analysts and decision makers need to assess the robustness of any conclusions based on the NMA to potential biases in the included evidence.

Suppose that we ask, “how much would the evidence have to change before the recommendation changes?” This is the motivation behind threshold analysis, which is a standard form of sensitivity analysis used in health economics. In its basic form we can simply re-run the NMA repeatedly, iteratively changing the data until a new recommendation is reached (1).

A more sophisticated approach that does not require multiple re-runs of the NMA derives algebraic threshold solutions by working backwards mathematically from a set of NMA estimates (in this case, their Bayesian posterior distribution) (2). This is computationally much faster and offers additional flexibility: for example, we can consider potential bias adjustments to individual study estimates or to a set of estimates on a treatment comparison, or we can produce thresholds for treatment ranks other than the best. Furthermore, by starting from the NMA estimates we can work with analyses of any size or complexity. The R package nmathresh has been developed to perform threshold analysis quickly and easily and is available from https://cran.r-project.org/package=nmathresh. The result is a set of bias-adjustment thresholds which describe how much each data point could change (or be adjusted for bias) before the recommendation changes and what the revised recommendation would be. If the evidence is expected to be biased by an amount within these thresholds, then there would not be any change to the treatment recommendation.

Threshold analysis may be carried out at two levels: (i) at a study level, assessing the influence of individual study estimates on the recommendation and (ii) at a contrast level, where the influence of the combined evidence on each treatment contrast is considered.

The results of the threshold analysis should lead to further scrutiny of the evidence to which the recommendation is sensitive and may placate any concerns raised about potential biases to which the treatment recommendation is not sensitive.

The remainder of this appendix contains the results of the threshold analyses for invasive ventilation techniques and the code used to conduct the threshold analysis using the nmathresh R package. The code for the BPD outcome only is presented here, but analysis for the mortality prior to discharge outcome proceeds in an identical fashion with the different input data.

References:

1. Caldwell DM, Ades AE, Dias S, Watkins S, Li T, Taske N, et al. A threshold analysis assessed the credibility of conclusions from network meta-analysis. Journal of Clinical Epidemiology. 2016;7(15):68-7.

2. Phillippo DM, Welton NJ, Dias S, Didelez V, Ades AE. Sensitivity of treatment recommendations to bias in network meta-analysis. Journal of the Royal Statistical Society: Series A (Statistics in Society). 2017.

Appendices

Appendix 1: Threshold plots for BPD at 36 weeks PMA

The following results are for the BPD outcome, where the base-case best and worst ranked treatments were volume targeted and synchronised intermittent mandatory respectively. The treatment codes are 1 = non-synchronised pressure limited; 2 = high frequency; 3 = synchronised pressure limited; 4 = synchronised intermittent mandatory; 5 = volume targeted.

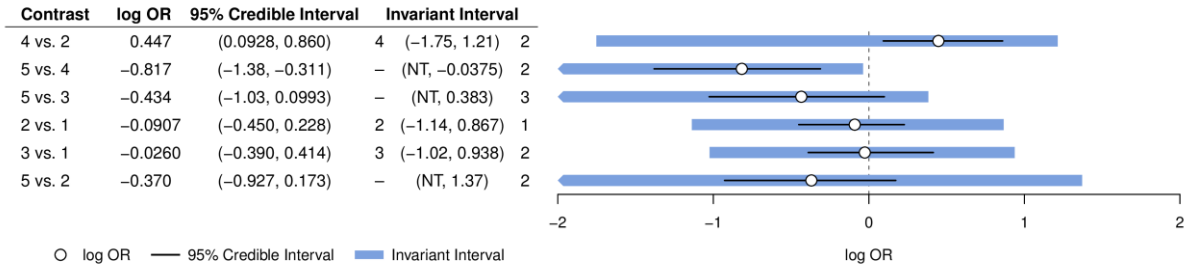

Figure 71: Contrast level threshold analysis for the BPD outcome, for the best ranked treatment. Large changes in the odds ratios of BPD would be required for the best ranked treatment to change; the smallest threshold is for more than a factor of 2 change in the odds ratio.

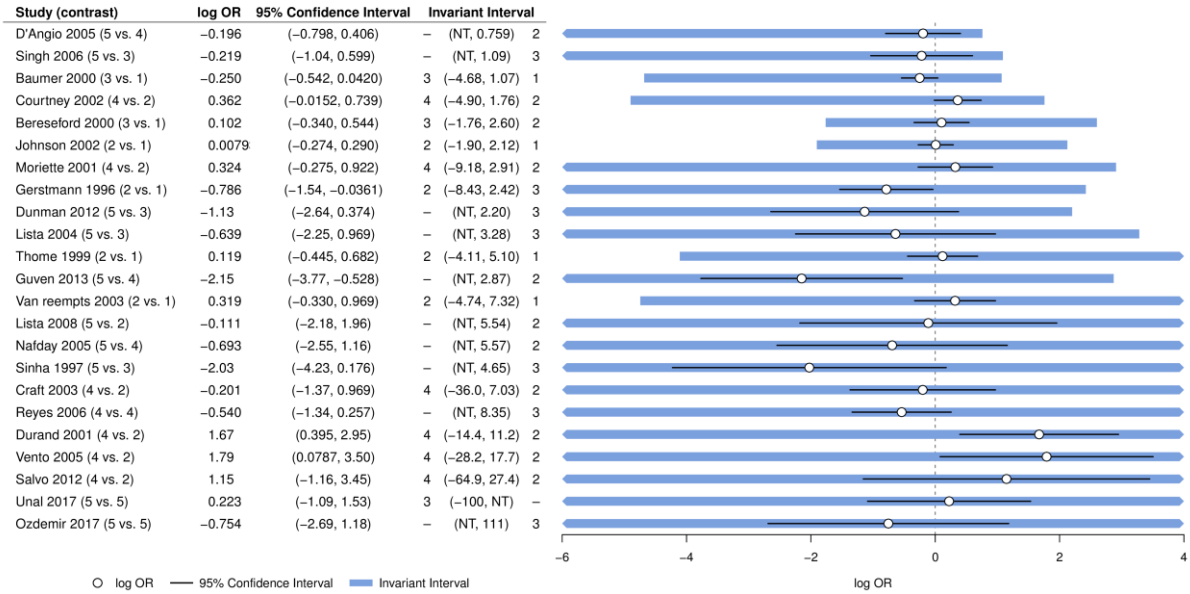

Figure 72: Study level threshold analysis for the BPD outcome, for the best ranked treatment. Large changes in the odds ratios of BPD would be required for the best ranked treatment to change. The smallest threshold is that of the D'Angio 2005 study and corresponds to a change in the odds ratio between

treatment 5 and 4 of more than a factor of 2.5 before the best ranked treatment would change (to treatment 2).

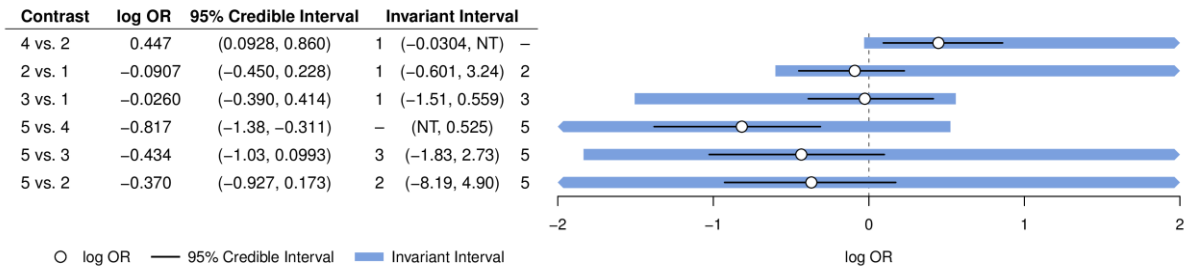

Figure 73: Contrast level threshold analysis for the BPD outcome, for the worst ranked treatment. Moderately large changes in the odds ratios of BPD would be required for the worst ranked treatment to change, with the smallest being a reduction of -0.48 in the log odds ratio of the 4 vs. 2 contrast.

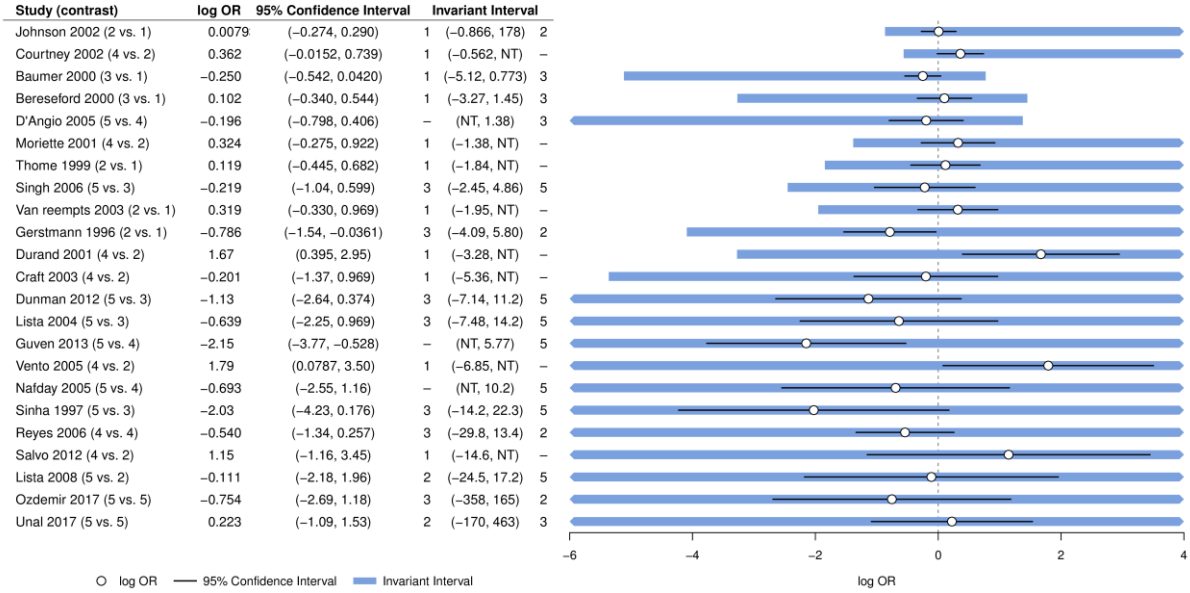

Figure 74: Study level threshold analysis for the BPD outcome, for the worst ranked treatment. Moderately large changes in the odds ratios of BPD would be required for the worst ranked treatment to change, with the smallest being a reduction in the log odds ratio of the Johnson 2002 study of -0.87.

Appendix 2: Threshold plots for mortality prior to discharge

The following results are for the mortality prior to discharge outcome, where the base-case best and worst ranked treatments were volume targeted and synchronised pressure limited respectively. The treatment codes are 1 = non-synchronised pressure limited; 2 = high frequency; 3 = synchronised pressure limited; 4 = synchronised intermittent mandatory; 5 = volume targeted.

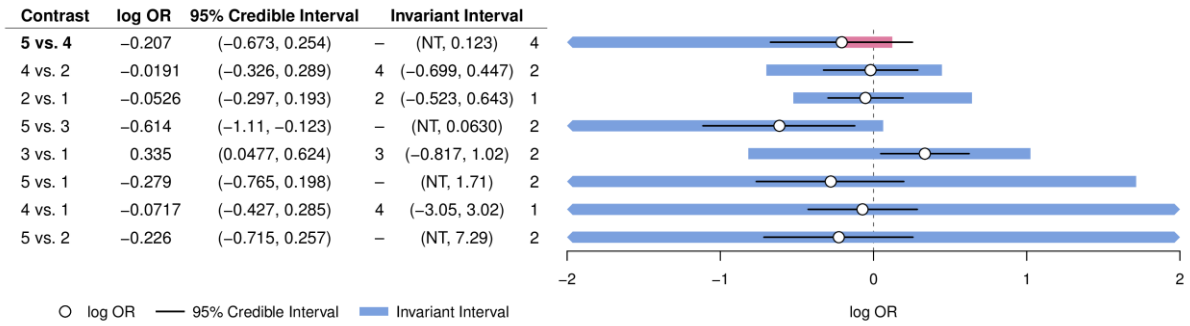

Figure 75: Contrast level threshold analysis for the mortality prior to discharge outcome, for the best ranked treatment. The upper end of the credible interval for the 5 vs. 4 contrast crosses the threshold, so the best ranked treatment is sensitive to the level of uncertainty in the data.

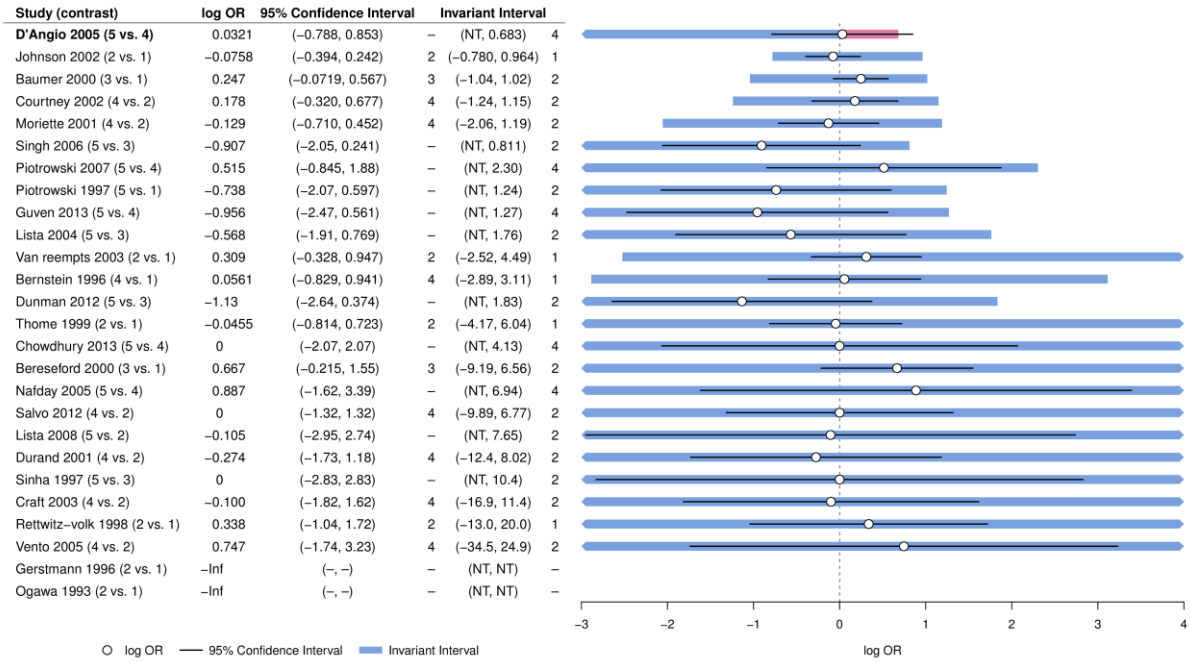

Figure 76: Study level threshold analysis for the mortality prior to discharge outcome, for the best ranked treatment. The upper end of the credible interval for the

D'Angio 2005 study crosses the threshold, so the best ranked treatment is sensitive to the level of uncertainty in the data.

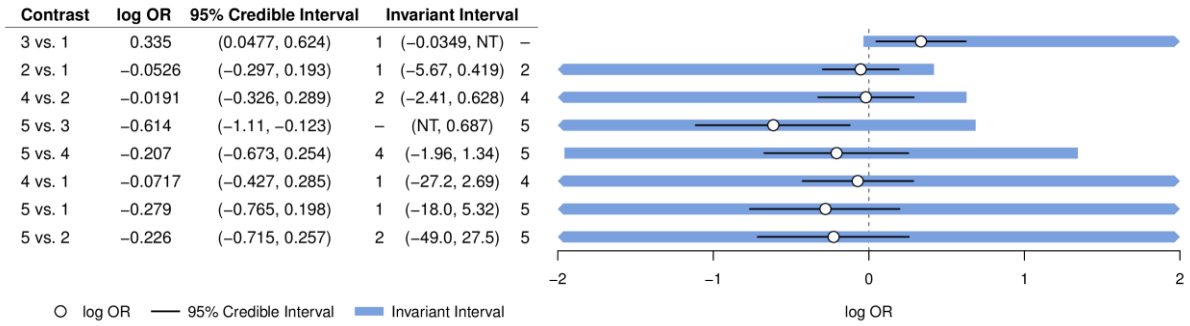

Figure 77: Contrast level threshold analysis for the mortality prior to discharge outcome, for the worst ranked treatment. The smallest threshold corresponds to a reduction in the log odds ratio of 3 vs. 1 of -0.37.

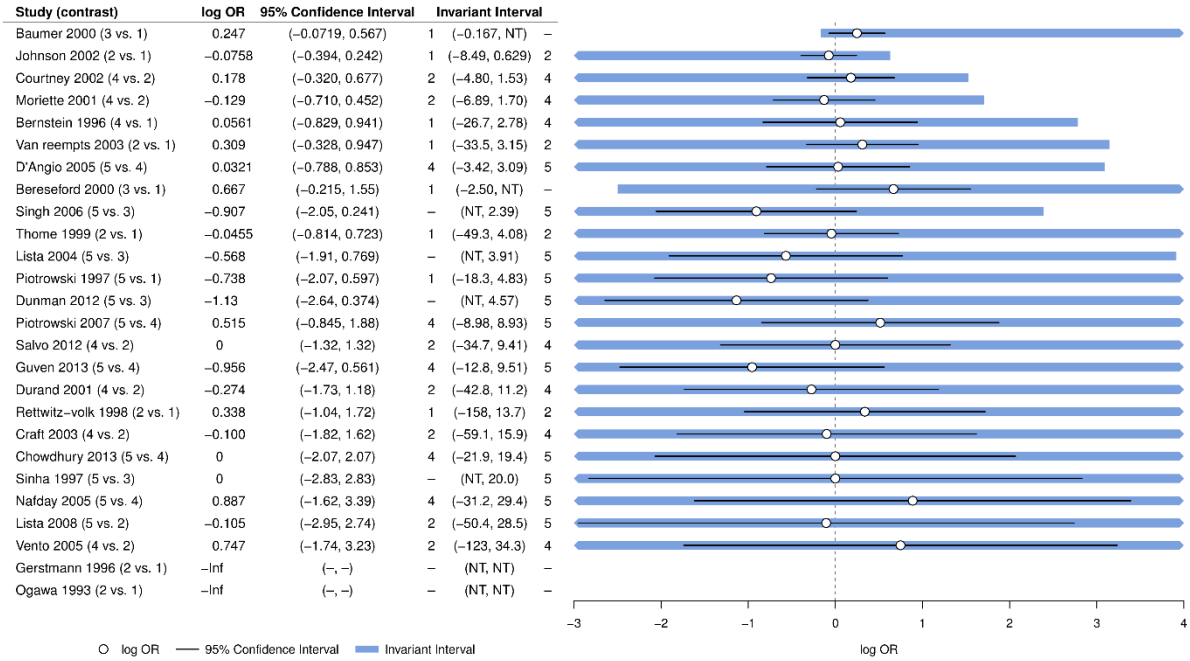

Figure 78: Study level threshold analysis for the mortality prior to discharge outcome, for the worst ranked treatment. Moderately large changes in the odds ratios of mortality would be required for the worst ranked treatment to change, with the smallest being a reduction in the log odds ratio of the Baumer 2002 study of -0.41.

Appendix 3: R code for BPD at 36 weeks PMA – study level analysis

Prior to running this code, the NMA output from WinBUGS is read in to R using the *coda* package and risk of bias information is extracted for presentation alongside the threshold

forest plot. The key function calls are *nma_thresh*, which performs the threshold analysis and *thresh_forest*, which produces the threshold plots.

```
############################################################
# Ventilation - BPD study level threshold analysis
############################################################

library(nmathresh)  # For performing threshold analysis
library(coda)       # For reading in the CODA from WinBUGS
library(tidyverse)  # For data manipulation and graphics

# Read in the posterior information from the CODA
source("./Ventilation - read BPD coda.R")

# Read in the study information
study_dat <- read_tsv("../WinBUGS/BPD_study_data.txt")

# Read in Risk of Bias table
source("./Ventilation - read RoB.R")

# NOTE: We only have two arm trials.
# Calculate log odds ratios and standard errors to input to nma_thresh.
# Also calculate CIs and construct nice labels for plotting later.

study_dat <- study_dat %>%
  mutate(logOR = log(r.2 * (n.1 - r.1) / ((n.2 - r.2) * r.1)),
         V = 1/r.1 + 1/r.2 + 1/(n.1 - r.1) + 1/(n.2 - r.2),
         CI_lo = logOR + qnorm(0.025)*sqrt(V),
         CI_hi = logOR + qnorm(0.975)*sqrt(V),
         # Tidy up study names for labelling (remove anything after the year)
         study = str_extract(study, ".+[0-9]{4}"),
         label = str_c(study, " (", t.2, " vs. ", t.1, ")")) %>%
  # Join with risk of bias
  left_join(rob %>% mutate_at(vars(ends_with("_bias")),
                              funs(str_sub(., end = 1))))

# Since we only have two arm studies, the likelihood covariance matrix is simply diagonal.
lik_cov <- diag(study_dat$V)

# Calculate thresholds
# Note that we can leave delta.design as the default (identity matrix) since we are
considering thresholds on the logORs (not on each arm count).
thresh <- nma_thresh(mean.dk = d.mean,    # Posterior means
                     lhood = lik_cov,     # Likelihood covariance matrix
                     post = ddelta.cov,   # Posterior covariance matrix
                     nmatype = "random",  # Specify RE NMA
                     opt.max = FALSE)     # Best treatment minimises log OR

# Display thresholds on forest plot
pdf("Ventilation - BPD study level.pdf", width = 15, height = 8)
thresh_forest(thresh,
              y = logOR, CI.lo = CI_lo, CI.hi = CI_hi, label = label, data = study_dat,
              orderby = map2_dbl(thresh$thresholds$lo, thresh$thresholds$hi,
                                 ~min(abs(.x), abs(.y))),
              refline = 0, label.title = "Study (contrast)",
              y.title = "log OR", xlab = "log OR",
              II.colw = "#7BA0DE", II.cols = "#DE7BA0", CI.lwd = 1.5,
              calcdim = FALSE)
dev.off()

# With RoB table
pdf("Ventilation - BPD study level with RoB.pdf", width = 15, height = 8)
thresh_forest(thresh,
              y = logOR, CI.lo = CI_lo, CI.hi = CI_hi, label = label, data = study_dat,
              orderby = map2_dbl(thresh$thresholds$lo, thresh$thresholds$hi,
                                 ~min(abs(.x), abs(.y))),
```

```
              refline = 0, label.title = "Study (contrast)",
              y.title = "log OR", xlab = "log OR",
              II.colw = "#7BA0DE", II.cols = "#DE7BA0", CI.lwd = 1.5,
              add.columns = study_dat %>% select(ends_with("_bias")),
              add.columns.hjust = 0,
              add.columns.title = c("Sel", "Perf", "Det", "Att", "Rep", "Oth"),
              calcdim = FALSE)
dev.off()

# Also calculate thresholds for worst treatment
thresh_worst <- nma_thresh(mean.dk = d.mean,   # Posterior means
                           lhood = lik_cov,    # Likelihood covariance matrix
                           post = ddelta.cov,  # Posterior covariance matrix
                           nmatype = "random", # Specify RE NMA
                           trt.rank = length(d.mean) + 1, # Thresholds for worst ranked
                           opt.max = FALSE)    # Best treatment minimises log OR

pdf("Ventilation - BPD study level (worst ranked).pdf", width = 15, height = 8)
thresh_forest(thresh_worst,
              y = logOR, CI.lo = CI_lo, CI.hi = CI_hi, label = label, data = study_dat,
              orderby = map2_dbl(thresh_worst$thresholds$lo, thresh_worst$thresholds$hi,
                                 ~min(abs(.x), abs(.y))),
              refline = 0, label.title = "Study (contrast)",
              y.title = "log OR", xlab = "log OR",
              II.colw = "#7BA0DE", II.cols = "#DE7BA0", CI.lwd = 1.5,
              calcdim = FALSE)
dev.off()

pdf("Ventilation - BPD study level (worst ranked) with RoB.pdf", width = 15, height = 8)
thresh_forest(thresh_worst,
              y = logOR, CI.lo = CI_lo, CI.hi = CI_hi, label = label, data = study_dat,
              orderby = map2_dbl(thresh_worst$thresholds$lo, thresh_worst$thresholds$hi,
                                 ~min(abs(.x), abs(.y))),
              refline = 0, label.title = "Study (contrast)",
              y.title = "log OR", xlab = "log OR",
              II.colw = "#7BA0DE", II.cols = "#DE7BA0", CI.lwd = 1.5,
              add.columns = study_dat %>% select(ends_with("_bias")),
              add.columns.hjust = 0,
              add.columns.title = c("Sel", "Perf", "Det", "Att", "Rep", "Oth"),
              calcdim = FALSE)
dev.off()
```

Appendix 4: R code for BPD at 36 weeks PMA – contrast level analysis

Prior to running this code, the NMA output from WinBUGS is read in to R using the *coda* package. The key function calls are *recon_vcov*, which estimates the contrast likelihood covariance matrix, *nma_thresh*, which performs the threshold analysis and *thresh_forest*, which produces the threshold plots.

```
############################################################
# Ventilation - BPD contrast level threshold analysis
############################################################

library(nmathresh)  # For performing threshold analysis
library(coda)       # For reading in the CODA from WinBUGS
library(tidyverse)  # For data manipulation and graphics

# Read in the posterior information from the CODA
source("./Ventilation - read BPD coda.R")

# Read in the study information
study_dat <- read_tsv("../WinBUGS/BPD_study_data.txt")

# Number of treatments
K <- length(unique(c(study_dat$t.1, study_dat$t.2)))
```

```
# Construct the contrast design matrix
# NOTE: We only have two arm studies
contrs <- select(study_dat, t.1, t.2) %>% unique() %>%
  # Remove contrasts of treatments against themselves
  filter(t.1 != t.2)

X <- matrix(0, nrow = nrow(contrs), ncol = K - 1)
X[cbind(1:nrow(contrs), contrs$t.1 - 1)] <- -1
X[cbind(1:nrow(contrs), contrs$t.2 - 1)] <- 1

# Reconstruct the contrast level likelihood covariance matrix
lik_cov <- recon_vcov(d.cov,  # Posterior covariance matrix
                      prior.prec = 0.0001,  # Prior precision
                      X = X)  # Contrast design matrix


# Calculate contrast level thresholds
thresh <- nma_thresh(mean.dk = d.mean,  # Posterior means
                     lhood = lik_cov,   # Likelihood covariance matrix
                     post = d.cov,      # Posterior covariance matrix
                     X = X,             # Contrast design matrix
                     nmatype = "fixed", # FE NMA, as contrast level
                     opt.max = FALSE)   # Best treatment minimises log OR

# Create data frame of contrast details for plot
contr_dat <- data_frame(logOR = dd.mean,
                        CI_lo = dd.summary$quantiles[,"2.5%"],
                        CI_hi = dd.summary$quantiles[,"97.5%"],
                        label = str_c(contrs$t.2, " vs. ", contrs$t.1))

# Display thresholds on forest plot
pdf("Ventilation - BPD contrast level.pdf", width = 12, height = 3)
thresh_forest(thresh,
              y = logOR, CI.lo = CI_lo, CI.hi = CI_hi, label = label, data = contr_dat,
              orderby = map2_dbl(thresh$thresholds$lo, thresh$thresholds$hi,
                                 ~min(abs(.x), abs(.y))),
              refline = 0, label.title = "Contrast", y.title = "log OR", xlab = "log OR",
              CI.title = "95% Credible Interval", xlim = c(-2, 2),
              II.colw = "#7BA0DE", II.cols = "#DE7BA0", CI.lwd = 1.5,
              calcdim = FALSE)
dev.off()

# Also calculate thresholds for worst ranked
thresh_worst <- nma_thresh(mean.dk = d.mean,  # Posterior means
                           lhood = lik_cov,   # Likelihood covariance matrix
                           post = d.cov,      # Posterior covariance matrix
                           X = X,             # Contrast design matrix
                           nmatype = "fixed", # FE NMA, as contrast level
                           trt.rank = K,      # Thresholds for worst ranked
                           opt.max = FALSE)   # Best treatment minimises log OR

pdf("Ventilation - BPD contrast level (worst ranked).pdf", width = 12, height = 3)
thresh_forest(thresh_worst,
              y = logOR, CI.lo = CI_lo, CI.hi = CI_hi, label = label, data = contr_dat,
              orderby = map2_dbl(thresh_worst$thresholds$lo, thresh_worst$thresholds$hi,
                                 ~min(abs(.x), abs(.y))),
              refline = 0, label.title = "Contrast", y.title = "log OR", xlab = "log OR",
              CI.title = "95% Credible Interval", xlim = c(-2, 2),
              II.colw = "#7BA0DE", II.cols = "#DE7BA0", CI.lwd = 1.5,
              calcdim = FALSE)
dev.off()
```