National Institute for Health and Care Excellence

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Specialist neonatal respiratory care for babies born preterm

[D] Evidence reviews for monitoring

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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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Monitoring

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

- Review question 4.1 What oxygen levels are optimal in the management of preterm babies?
- Review question 4.2 What is the best method for measuring oxygen levels in diagnosing hyperoxia or hypoxia in preterm babies?
- Review question 4.3 What carbon dioxide levels are optimal in the management of preterm babies?
- Review question 4.4 What blood pressure monitoring strategies are associated with improved outcomes in preterm babies requiring respiratory support?

Review question 4.1 What oxygen levels are optimal in the management of preterm babies?

Introduction

Oxygen levels in preterm babies are monitored with the aim of ensuring both adequate tissue oxygenation and to minimise the risk of oxygen toxicity and oxidative stress, and oxygen delivery is adjusted to achieve a certain target oxygen level.

Liberal (higher oxygen level targeting) and restrictive (lower oxygen level targeting) in preterm babies are both thought to be associated with increased morbidity and mortality, and there is variation in practice regarding the optimal target oxygen range which will minimise these competing risks.

This review will look at the evidence for the effectiveness of higher versus lower oxygen saturation target ranges in preterm babies, including the incidence of mortality, retinopathy of prematurity, bronchopulmonary dysplasia (BPD), necrotising enterocolitis, and neurodevelopmental impairment, to determine the optimal target oxygen range.

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 **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	Different oxygen saturation levels in preterm babies requiring respiratory support: - Higher target range for oxygen saturation levels - Lower target range for oxygen saturation levels
Comparison	Higher vs lower target range for oxygen saturation levels
Outcome	**Critical outcomes:** • Severe retinopathy of prematurity (defined as stage 3 or 4 retinopathy of prematurity, or retinopathy of prematurity requiring surgery or use of bevacizumab) • Mortality prior to discharge • Neurodevelopmental outcomes at ≥18 months: ○ Cerebral palsy (reported as presence or absence of condition, **not** severity of condition) ○ Neurodevelopmental delay (reported as dichotomous outcomes, **not** continuous outcomes such as mean change in score)

	- 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:** • Bronchopulmonary dysplasia (oxygen dependency at 36 weeks corrected gestation or 28 days of age) • Necrotising enterocolitis • Patent ductus arteriosus requiring medical or surgical treatment

CP: cerebral palsy; MDI: mental development index; PDI: psychomotor developmental index; SD: standard deviation

For full details see review protocol in appendix A.

Clinical evidence

Included studies

For preterm babies monitored for optimal oxygen saturation levels 8 studies were included. There was 1 meta-analysis (Askie 2018 with 6 publications that were included in this review (BOOST II Australia 2016; BOOST II UK 2016; BOOST NZ 2014; COT 2013; SUPPORT 2010; Vaucher 2012 [a subcomponent of *SUPPORT 2010*]). 1 additional RCT was also identified (Askie 2003).

One meta-analysis (Askie 2018), that included 6 publications (BOOST II Australia 2016; BOOST II UK 2016; BOOST NZ 2014; COT 2013; SUPPORT 2010; Vaucher 2012 [*SUPPORT 2010*]) compared higher oxygen target saturation levels versus lower oxygen target saturation levels in preterm babies aged <28 weeks gestation who were randomised at birth or soon after.

One RCT compared higher oxygen target saturation levels versus lower oxygen target saturation levels in preterm babies dependent on oxygen at 30 weeks PMA (post menstrual age) who were randomised at 32 weeks PMA (Askie 2003).

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
NEOPROM collaboration meta-analysis				
Askie 2018	n=4965 Preterm babies with a gestational age of <28 weeks enrolled within 24 hours of birth	91-95% versus 85-89% oxygen target range Follow up at 18-24 months	Treated ROP Mortality prior to discharge Neurodevelopmental outcomes: • Cerebral palsy with GMFCS ≥2 • Bayleys III language or cognitive <70 • Bayleys III language or cognitive <85 • Deafness requiring hearing aids or worse • Severe visual impairment BPD at 36 weeks PMA Severe necrotising enterocolitis PDA requiring medical or surgical intervention	
RCTs included in the NEOPROM collaboration meta-analysis (Askie 2018)				
BOOST II Australia Australia	n=1135 Preterm babies with a gestational age <28 weeks and born within the last 24 hours	91-95% versus 85-89% oxygen target range Follow up at 2 years	Severe ROP (defined as treated ROP) Mortality prior to discharge Neurodevelopmental outcomes: • Cerebral palsy with inability to walk at 2 years of age • Cognitive or language score of <85 on BSID-III	

Study and setting	Population	Intervention/ comparison	Outcomes	Comments
			• Cognitive or language score of <70 on BSID-III • Deafness requiring (or too severe to benefit from) hearing aids • Severe visual loss BPD at 36 weeks PMA Necrotising enterocolitis requiring surgery or leading to death PDA requiring medical or surgical intervention	
BOOST II UK UK	n=973 Preterm babies with a gestational age <28 weeks and born within the last 24 hours	91-95% versus 85-89% oxygen target range Follow up at 2 years	Severe ROP (defined as treated ROP) Mortality prior to discharge Neurodevelopmental outcomes: • Cerebral palsy with inability to walk at 2 years of age • Cognitive or language score of <85 on BSID-III • Cognitive or language score of <70 on BSID-III • Deafness requiring (or too severe to benefit from) hearing aids • Severe visual loss BPD at 36 weeks PMA Necrotising enterocolitis requiring surgery or leading to death PDA requiring medical or surgical intervention	

Study and setting	Population	Intervention/ comparison	Outcomes	Comments
BOOST NZ New Zealand	n=340 Preterm babies with a gestational age <28 weeks and born within the last 24 hours	91-95% versus 85-89% oxygen target range Follow up at 2 years	Severe ROP (defined as ≥ stage 3 or retinal surgery) Mortality prior to discharge Neurodevelopmental outcomes: • Cerebral palsy with inability to walk at 2 years of age • Cognitive or language score of <85 on BSID-III • Cognitive or language score of <70 on BSID-III • Deafness requiring (or too severe to benefit from) hearing aids • Severe visual loss BPD at 36 weeks PMA Necrotising enterocolitis requiring surgery or leading to death PDA requiring medical or surgical intervention	
COT 2013 International	n=1201 Preterm babies with a gestational age 23^{+0} to 26^{+7} and born within the last 24 hours	91-95% versus 85-89% oxygen target range Follow up at 2 years	Severe ROP (defined as unilateral or bilateral disease of stages 4 or 5; received cryotherapy or laser in at least 1 eye or if they received retinal injection with bevacizumab or another anti-vascular endothelial growth factor) Mortality prior to discharge Neurodevelopmental outcomes:	

Study and setting	Population	Intervention/ comparison	Outcomes	Comments
			• Cerebral palsy with inability to walk at 2 years of age • Cognitive or language score of <85 on BSID-III • Cognitive or language score of <70 on BSID-III • Deafness requiring (or too severe to benefit from) hearing aids • Severe visual loss BPD at 36 weeks PMA Necrotising enterocolitis defined as diagnosed during surgery or by a finding of pneumatosis intestinalis, hepatobiliary gas or free intraperitoneal air on x-ray PDA requiring medical or surgical intervention	
SUPPORT 2010 USA	n=1316 Preterm babies with a gestational age 23^{+0} to 26^{+7}	91-95% versus 85-89% oxygen target range	Severe ROP (defined by trialists) Mortality prior to discharge BPD at 36 weeks PMA Necrotising enterocolitis defined as modified Bell's stage ≥2 on a scale ranging from 1-3 PDA requiring medical or surgical intervention	
Vaucher 2012 USA	n= 990 18-22 months corrected age	91-95% versus 85-89% oxygen target range	Neurodevelopmental outcomes: • Moderate or severe cerebral palsy	

Study and setting	Population	Intervention/ comparison	Outcomes	Comments
	Surviving from Finer 2010 RCT	Follow up at 18-22 months	• Cognitive or language score of <85 on BSID-III • Cognitive or language score of <70 on BSID-III • Hearing impairment • Bilateral blindness	
RCTs not included in the NEOPROM collaboration meta-analysis (Askie 2018)				
Askie 2003 Australia	n=333 Preterm babies <30 weeks and remained dependent on supplemental oxygen at 32 weeks	95-98% versus 91-94% oxygen target range Follow up at 12 months	Severe ROP (grading according to the international classification of ROP) Mortality prior to discharge BPD at 36 weeks PMA	

BPD: bronchopulmonary dysplasia; BSID: Bayley scales of infant development; GMFCS: gross motor function classification system; NEOPROM: Neonatal Oxygenation Prospective Meta-Analysis; PDA: patent ductus arteriosus; PMA: postmenstrual age; ROP: retinopathy of prematurity;

See appendix D for full evidence tables.

Quality assessment of clinical studies included in the evidence review

See appendix F for full GRADE tables.

Economic evidence

No economic evidence on the cost effectiveness of oxygen levels in the management of preterm babies 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. Higher oxygen target saturation levels versus lower oxygen target saturation levels

Critical outcomes

Severe retinopathy of prematurity (ROP)

Preterm babies enrolled at birth or soon after

All pulse oximeters

- Low quality evidence from 5 RCTs (n=4,885) indicated there may a clinically significant increase in severe ROP among preterm babies with a gestational age of <28 weeks who had 91-95% oxygen target saturation levels compared to 85-89% oxygen target saturation levels, but there is uncertainty around the estimate.

Original algorithm – Massimo pulse oximeter

- Low quality evidence from 5 RCTs (n=3,139) showed no clinically significant increase in severe ROP among preterm babies with a gestational age of <28 weeks who had 91-95% oxygen target saturation levels compared to 85-89% oxygen target saturation levels.

Revised algorithm – Massimo pulse oximeter or other pulse oximeter device

- Moderate quality evidence from 3 RCTs (n=1,746) showed a clinically significant increase in severe ROP among preterm babies with a gestational age of <28 weeks who had 91-95% oxygen target saturation levels compared to 85-89% oxygen target saturation levels.

Preterm babies enrolled at 32 weeks postmenstrual age (PMA) dependent on supplemental oxygen

Stage 3 or 4 ROP

- Low quality evidence from 1 RCT (n=358) showed no clinically significant difference in stage 3 or 4 ROP among preterm babies with a gestational age of <30 weeks who had 95-98% oxygen target saturation levels compared to 91-94% oxygen target saturation levels.

Preterm babies who received ablative retinal surgery

- Moderate quality evidence from 1 RCT (n=358) showed no clinically significant difference in stage 3 or 4 ROP among preterm babies with a gestational age of <30 weeks who had 95-98% oxygen target saturation levels compared to 91-94% oxygen target saturation levels.

Mortality prior to discharge

Preterm babies enrolled at birth or soon after

All pulse oximeters

- Moderate quality evidence from 5 RCTs (n=4,885) showed a clinically significant reduction in mortality prior to discharge among preterm babies with a gestational age of <28 weeks who had 91-95% oxygen target saturation levels compared to 85-89% oxygen target saturation levels.

Original algorithm – Massimo pulse oximeter

- High quality evidence from 5 RCTs (n=3,139) showed no clinically significant reduction in mortality prior to discharge among preterm babies with a gestational age of <28 weeks who had 91-95% oxygen target saturation levels compared to 85-89% oxygen target saturation levels.

Revised algorithm – Massimo pulse oximeter or other pulse oximeter device

- Moderate quality evidence from 3 RCTs (n=1,746) showed a clinically significant reduction in mortality prior to discharge among preterm babies with a gestational

age of <28 weeks who had 91-95% oxygen target saturation levels compared to 85-89% oxygen target saturation levels.

Preterm babies enrolled at 32 weeks PMA dependent on supplemental oxygen

- Low quality evidence from 1 RCT (n=358) showed no clinically significant reduction in mortality prior to discharge among preterm babies with a gestational age of <30 weeks who had 95-98% oxygen target saturation levels compared to 91-94% oxygen target saturation levels.

Neurodevelopmental outcomes at ≥ 18 months: cerebral palsy defined as a gross motor function classification system (GMFCS) score ≥2

Preterm babies enrolled at birth or soon after

All pulse oximeters

- Low quality evidence from 5 RCTs (n=3,810) showed no clinically significant difference in cerebral palsy at 18 months of age or older among preterm babies with a gestational age of <28 weeks who had 91-95% oxygen target saturation levels compared to 85-89% oxygen target saturation levels

Original algorithm – Massimo pulse oximeter

- Low quality evidence from 5 RCTs (n=2,457) showed no clinically significant difference in cerebral palsy at 18 months of age or older among preterm babies with a gestational age of <28 weeks who 91-95% oxygen target saturation levels compared to 85-89% oxygen target saturation levels

Revised algorithm – Massimo pulse oximeter or other pulse oximeter device

- Low quality evidence from 3 RCTs (n=1,353) showed no clinically significant difference in cerebral palsy at 18 months of age or older among preterm babies with a gestational age of <28 weeks who had 91-95% oxygen target saturation levels compared to 85-89% oxygen target saturation levels

Neurodevelopmental outcomes at ≥ 18 months: severe cognitive impairment defined as Bayleys III language or cognitive score <70

Preterm babies enrolled at birth or soon after

All pulse oximeters

- Moderate quality evidence from 5 RCTs (n=3,393) showed no clinically significant difference in severe cognitive impairment at 18 months of age or older among preterm babies with a gestational age of <28 weeks who had 91-95% oxygen target saturation levels compared to 85-89% oxygen target saturation levels

Original algorithm – Massimo pulse oximeter

- Low quality evidence from 5 RCTs (n=2,257) showed no clinically significant difference in severe cognitive impairment at 18 months of age or older among preterm babies with a gestational age of <28 weeks who had 91-95% oxygen target saturation levels compared to 85-89% oxygen target saturation levels

Revised algorithm – Massimo pulse oximeter or other pulse oximeter device

- Very low quality evidence from 3 RCTs (n=1,136) showed no clinically significant difference in severe cognitive impairment at 18 months of age or older among preterm babies with a gestational age of <28 weeks who had 91-95% oxygen target saturation levels compared to 85-89% oxygen target saturation levels

Neurodevelopmental outcomes at ≥ 18 months: moderate cognitive impairment defined as Bayleys III language or cognitive score <85

Preterm babies enrolled at birth or soon after

All pulse oximeters

- Moderate quality evidence from 5 RCTs (n=3,429) showed no clinically significant difference in moderate cognitive impairment at 18 months of age or older among preterm babies with a gestational age of <28 weeks who had 91-95% oxygen target saturation levels compared to 85-89% oxygen target saturation levels

Original algorithm – Massimo pulse oximeter

- Moderate quality evidence from 5 RCTs (n=2,269) showed no clinically significant difference in moderate cognitive impairment at 18 months of age or older among preterm babies with a gestational age of <28 weeks who had 91-95% oxygen target saturation levels compared to 85-89% oxygen target saturation levels

Revised algorithm – Massimo pulse oximeter or other pulse oximeter device

- Low quality evidence from 3 RCTs (n=1,160) showed no clinically significant difference in moderate cognitive impairment at 18 months of age or older among preterm babies with a gestational age of <28 weeks who had 91-95% oxygen target saturation levels compared to 85-89% oxygen target saturation levels

Neurodevelopmental outcomes at ≥ 18 months: severe hearing impairment

Preterm babies enrolled at birth or soon after

All pulse oximeters

- Low quality evidence from 5 RCTs (n=3,798) showed no clinically significant difference in severe hearing impairment at 18 months of age or older among preterm babies with a gestational age of <28 weeks who had 91-95% oxygen target saturation levels compared to 85-89% oxygen target saturation levels.

Original algorithm – Massimo pulse oximeter

- Moderate quality evidence from 5 RCTs (n=2,446) showed no clinically significant difference in severe hearing impairment at 18 months of age or older among preterm babies with a gestational age of <28 weeks who had 91-95% oxygen target saturation levels compared to 85-89% oxygen target saturation levels

Revised algorithm – Massimo pulse oximeter or other pulse oximeter device

- Moderate quality evidence from 3 RCTs (n=1,352) showed no clinically significant difference in severe hearing impairment at 18 months of age or older among preterm babies with a gestational age of <28 weeks who had 91-95% oxygen target saturation levels compared to 85-89% oxygen target saturation levels.

Neurodevelopmental outcomes at ≥ 18 months: severe visual impairment

Preterm babies enrolled at birth or soon after

All pulse oximeters

- Low quality evidence from 5 RCTs (n=3,811) showed no clinically significant difference in severe visual impairment at 18 months of age or older among preterm babies with a gestational age of <28 weeks who had 91-95% oxygen target saturation levels compared to 85-89% oxygen target saturation levels.

Original algorithm – Massimo pulse oximeter

- Low quality evidence from 5 RCTs (n=2,455) showed no clinically significant difference in severe visual impairment at 18 months of age or older among preterm babies with a gestational age of <28 weeks who had 91-95% oxygen target saturation levels compared to 85-89% oxygen target saturation levels

Revised algorithm – Massimo pulse oximeter or other pulse oximeter device

- Low quality evidence from 3 RCTs (n=1,356) showed no clinically significant difference in severe visual impairment at 18 months of age or older among preterm babies with a gestational age of <28 weeks who had 91-95% oxygen target saturation levels compared to 85-89% oxygen target saturation levels

Important outcomes

Bronchopulmonary dysplasia (BPD) at 36 weeks PMA

Preterm babies enrolled at birth or soon after

All pulse oximeters

- Low quality evidence from 5 RCTs (n=4,885) showed a clinically significant increase in BPD at 36 weeks PMA among preterm babies with a gestational age of <28 weeks who had 91-95% oxygen target saturation levels compared to 85-89% oxygen target saturation levels

Original algorithm – Massimo pulse oximeter

- Low quality evidence from 5 RCTs (n=3,139) showed no clinically significant increase in BPD at 36 weeks PMA among preterm babies with a gestational age of <28 weeks who had 91-95% oxygen target saturation levels compared to 85-89% oxygen target saturation levels

Revised algorithm – Massimo pulse oximeter or other pulse oximeter device

- Moderate quality evidence from 3 RCTs (n=1,746) showed a clinically significant increase in BPD at 36 weeks PMA among preterm babies with a gestational age of <28 weeks who had 91-95% oxygen target saturation levels compared to 85-89% oxygen target saturation levels

Preterm babies enrolled at 32 weeks PMA dependent on supplemental oxygen

- Moderate quality evidence from 1 RCT (n=358) showed a clinically significant increase in BPD at 36 weeks PMA among preterm babies with a gestational age of <30 weeks who had 95-98% oxygen target saturation levels compared to 91-94% oxygen target saturation levels

Necrotising enterocolitis defined as requiring surgery or leading to death

Preterm babies enrolled at birth or soon after

All pulse oximeters

- Moderate quality evidence from 5 RCTs (n=4,885) showed a clinically significant decrease in necrotising enterocolitis among preterm babies with a gestational age of <28 weeks who had 91-95% oxygen target saturation levels compared to 85-89% oxygen target saturation levels.

Original algorithm – Massimo pulse oximeter

- Moderate quality evidence from 5 RCTs (n=3,139) showed a clinically significant decrease in necrotising enterocolitis among preterm babies with a gestational age of <28 weeks who had 91-95% oxygen target saturation levels compared to 85-89% oxygen target saturation levels

Revised algorithm – Massimo pulse oximeter or other pulse oximeter device

- Moderate quality evidence from 3 RCTs (n=1,746) showed that there may be clinically significant decrease in necrotising enterocolitis among preterm babies with a gestational age of <28 weeks who had 91-95% oxygen target saturation levels compared to 85-89% oxygen target saturation levels

Patent ductus arteriosus (PDA) requiring medical or surgical intervention

Preterm babies enrolled at birth or soon after

All pulse oximeters

- High quality evidence from 5 RCTs (n=4,885) showed no clinically significant difference in PDA requiring medical or surgical intervention among preterm babies with a gestational age of <28 weeks who had 91-95% oxygen target saturation levels compared to 85-89% oxygen target saturation levels

Original algorithm – Massimo pulse oximeter

- High quality evidence from 5 RCTs (n=3,139) showed no clinically significant difference in PDA requiring medical or surgical intervention among preterm babies with a gestational age of <28 weeks who had 91-95% oxygen target saturation levels compared to 85-89% oxygen target saturation levels

Revised algorithm – Massimo pulse oximeter or other pulse oximeter device

- High quality evidence from 3 RCTs (n=1,746) showed no clinically significant difference in PDA requiring medical or surgical intervention among preterm babies with a gestational age of <28 weeks who had 91-95% oxygen target saturation levels compared to 85-89% oxygen target saturation levels

See appendix F for forest plots.

Economic evidence statements

- No economic evidence on the cost effectiveness of oxygen levels in the management of preterm babies was available.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee agreed that mortality, neurodevelopmental outcomes and retinopathy of prematurity (ROP) were the critical outcomes for this review, since the choice of target oxygen levels must achieve a balance: a high enough target range is required to prevent death and disability, but it must not be so high that it leads to ROP, a condition that is known to arise in premature babies exposed to high oxygen saturations.

Bronchopulmonary dysplasia (BPD), necrotising enterocolitis (NEC) and a patent ductus arteriosus (PDA) were considered important outcomes as inadequate oxygen levels can predispose to the development of NEC, BPD and lead to a PDA failing to close.

The quality of the evidence

The evidence was assessed using the GRADE methodology. The quality of evidence in this review ranged from very low to high quality. The evidence on a higher target range of oxygen compared to a lower target range of oxygen was of moderate to high quality for mortality prior to discharge, BPD at 36 weeks PMA, PDA, and NEC, whereas the evidence for neurodevelopmental outcomes and severe ROP was mostly of moderate to low or very low quality.

Most of the outcomes were based on large studies, and for more than half of outcomes the quality was rated moderate to high. These factors added to the committee's confidence and the strength of recommendations that were made.

The evidence was most often downgraded because of the uncertainty around the risk point estimate, which was primarily because of the low event rate. Furthermore neurodevelopmental outcomes were further downgraded because of a high rate of attrition, which is very common in long-term follow up studies.

The evidence included papers which reported oxygen saturations measured using Masimo pulse oximeters which used an old algorithm (called 'original Masimo') and also data from other pulse oximeter brands or those using the updated Masimo pulse oximeters in which the algorithm had been corrected (called 'revised Masimo'). The committee were aware that the error in the original Masimo algorithm led to a reduction in saturation values reported between 87 and 90%, and values above 87% were elevated by up to 2%. The committee therefore chose to focus on evidence which used alternative pulse oximeters or ones using the revised Masimo algorithm. In clinical practice it is well established that the problems caused by this old algorithm had meant that it was difficult to target the lower oxygen saturation range accurately and this had led to confusion over mortality results.

For severe ROP and BPD, the quality of the evidence was further downgraded because of heterogeneity. Stratified analysis showed homogeneous results in studies using the revised Masimo algorithm but heterogeneity remained in studies using the original Masimo algorithm. Subgroup analysis to explore gestational age as a source of heterogeneity was not possible. The various methods of diagnosis and follow up of severe ROP and BPD in different countries may also have contributed to heterogeneity.

Benefits and harms

There was evidence for reduced mortality prior to discharge with higher target oxygen levels, but no difference in any neurodevelopmental outcomes.

The evidence showed that rates of severe ROP were higher with higher target oxygen ranges, as the committee had expected, but this did not translate into differences in severe visual impairment, where there was no significant difference seen between the higher and lower ranges. The committee discussed the fact that this may be due to better management of ROP, and updated guidelines from the Royal College of Ophthalmologists (or equivalent guidelines inother countries where

the study was conducted|) which included better screening and treatment recommendations.

There were increased rates of BPD at 36 weeks PMA with the higher target oxygen range for an analysis of all monitors and algorithms. Rates of NEC were decreased with the higher oxygen target ranges for all monitors, and the original and revised Masimo separate or combined. Finally, there was no difference in the rates of PDA between the higher and lower target ranges.

Balancing the results for mortality prior to discharge and ROP the committee agreed that it was more beneficial to babies to use the higher target oxygen level to reduce mortality prior to discharge, as ROP could be treated successfully.

The committee were aware that their recommendations were based on evidence in babies who were less than 28 weeks, but agreed that it would be reasonable to extrapolate the results to all preterm babies as it was unlikely the results would change with age, and there was therefore no need to put an age limit in the recommendation.

Cost effectiveness and resource use

There was no evidence on the cost effectiveness of oxygen levels in the management of preterm babies. The committee explained that the recommendations in this area will have negligible impact on the costs and resource use given that majority of units already use 91 to 95% as their target saturation level for preterm babies. Also, the committee noted that babies are already are on oxygen and being closely monitored and using the recommended target saturation level, or changing to this level if it is different to what is currently being used, will not result in additional intervention costs. The committee further explained that higher target oxygen is associated with lower mortality prior to discharge. However, there is an increased risk of ROP. Overall, the committee were of a view that ROP is easy and inexpensive to manage and improving mortality prior to discharge will result in substantial quality-adjusted life year gains and as such the recommendations in this area are likely to represent a cost effective use of NHS resources.

Other factors the committee took into account

One of the studies (Askie 2003) had recruited babies much later than the other studies included in the review: preterm babies who were dependent on oxygen at 32 weeks post-menstrual age, compared to the other studies which randomized preterm babies less than 28 weeks soon after birth. This study also used higher oxygen target levels, using a higher target range of 95 to 98% compared to a lower target range of 91 to 94%. This was in contrast to the higher ranges of 91 to 95% and lower ranges of 85 to 89% used in the other studies. The committee therefore discussed the results of this study separately, noting that there was no difference in the rates of ROP and mortality between the two target ranges, but that the population was much older and the oxygen target ranges differed, and so this study did not fit with the rest of the evidence they had reviewed. They did however, agree that it would be beneficial to find out if this very high oxygen target range could be used to reduce mortality prior to discharge in preterm babies (28 to 32 weeks, or <30 weeks) without increasing complications, and they therefore made a research recommendation.

The committee were aware from their clinical experience that when babies reached 36 weeks PMA they were no longer at risk of ROP and so it is acceptable common

practice that many units liberalise oxygen from that point (with upper levels of 98-99% saturation being permissible).

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Review question 4.2 What is the best method for measuring oxygen levels in diagnosing hyperoxia or hypoxia in preterm babies?

Introduction

Preterm babies frequently require oxygen therapy in order to maintain oxygen levels which are considered to be in the normal range. The goal of treatment is to maintain normoxia because there is evidence to show that both too much oxygen (hyperoxia) and too little oxygen (hypoxia) carry risks, and ideally babies should be monitored continually with an accurate non-invasive method.

The gold standard method of measuring oxygen levels in preterm babies is through blood gas sampling from an arterial specimen. However, this technique has risks associated with the need for indwelling arterial lines, and removal of multiple blood samples, and it is not generally possible to maintain this method over long periods of time. The alternative methods of non-invasive oxygen monitoring include transcutaneous measurement, and measuring oxygen saturation using pulse oximetry.

Transcutaneous monitors use a small probe which contains an oxygen sensing electrode attached to the skin. The skin has to be "arterialised" by warming in order to ensure that the oxygen tension between the superficial skin and that of the tissue supplied by the capillaries below comes into equilibrium, allowing sampling of the gas which lies just above the skin surface. This method produces a result which is expressed (like a blood gas) in terms of the partial pressure of oxygen (PaO_2). This method requires more user knowledge to calibrate and set up, and the probes require frequent re-siting to avoid marking the fragile skin of the preterm baby.

Pulse oximeters use a combination of two wavelengths of light which are passed through tissue (e.g. the finger, earlobe, or infant foot) and then detected as they emerge. The absorption of the electromagnetic energy by the interrogated tissue varies according to the percentage of oxygen which is bound to haemoglobin. The value of peripheral capillary oxygen saturation (SpO_2) is calculated from the ratio of the absorption at the two wavelengths. The absorption also varies with the cardiac rhythm, and this is used to extract only the portion which is "pulsatile". Pulse oximetry is a safe technique but there is a degree of uncertainty over its accuracy, particularly in the higher range of oxygen saturations.

The aim of this review is to determine which method of measuring oxygen levels is the most accurate at detecting hyperoxia and hypoxia and to evaluate the risks and benefits associated with each method, in order to determine which is the most appropriate for use in various clinical situations.

Summary of the protocol

See Table 3 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 requiring respiratory support:

	Exclusions: • Studies with an indirect population will not be considered
Index test	• Pulse oximetry oxygen saturation (SpO_2) • Transcutaneous oxygen measurement ($tcPO_2$)
Reference test	• Arterial oxygen saturation (PaO_2)
Outcome	**Critical outcomes:** • Sensitivity • Specificity • Area under the receiver operating curve (AUROC) • Positive likelihood ratio (LR+) • Negative likelihood ratio (LR-) **Important outcomes:** • Adverse events • Infection • Burns • Ischaemic limbs • Emboli/thrombi • Blood loss due to excess sampling

AUROC: Area Under the receiver operating curve; LR-: negative likelihood ratio; LR+: positive likelihood ratio; SpO2: Pulse oximetry oxygen saturation; $TcPO_2$: transcutaneous oxygen measurement

Clinical evidence

Included studies

One cohort study was included in this review (Duc 1979), which compared transcutaneous oxygen measurement ($tcPO_2$) to arterial oxygen saturation (PaO_2).

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

The study identified for this diagnostic question was a prospective cohort study. Diagnostic statistics were obtained by taking collecting data from its two cohorts at multiple time points. More details can be found in the clinical evidence table (appendix D),

Table 4 provides a brief summary of the included study.

Table 4: Summary of included studies

Study and setting	Population	Index test	Reference standard	Outcomes	Comments
Duc 1979 Prospective cohort study	n=26 (66 series of measureme-nts and 335 blood samples) Artificially ventilated with hyaline membrane disease Gestational age range: 29-38 weeks PMA	Transcutaneous PO_2 – sampled hourly for 4 hours	Arterial PO_2 from umbilical catheter – sampled hourly for 4 hours	True positive, true negative, false positive, false negative for hyperoxia, normoxia, and hypoxia	No mean gestational age of babies in the study

PMA: post-menstrual age; PO_2: partial pressure of oxygen

See appendix D for clinical evidence tables.

Quality assessment of clinical studies included in the evidence review

The evidence for this review question is presented in Table 5 and Table 6.

<u>$TcPO_2$ for the identification of hyperoxia and hypoxia</u>

Table 5: Summary of clinical evidence profile for $tcPO_2$ in the identification of hyperoxia (defined as PaO_2 > 100 mm Hg)

Index test	Sensitivity (95%CI)	Specificity (95% CI)	LR +	LR-	N	Quality of the evidence (GRADE)	Comments/study
$TcPO_2$	79% (63 to 90%)	97% (94-99%)	26 (13-50)	0.22 (0.12 - 0.39)	26 (335 blood samples)	Low[1,2]	Population 29-38 weeks PMA with no mean for gestational age

CI: confidence interval; LR-: negative likelihood ratio; LR+: positive likelihood ratio; PMA: post-menstrual age; $TcPO_2$: transcutaneous oxygen measurement
[1] Population of infants with hyaline membrane disease includes infants up to 38 weeks PMA
[2] Lower 95% CI crosses 75% boundary for sensitivity

Table 6: Summary of clinical evidence profile for $tcPO_2$ in the identification of hypoxia (defined as PaO_2 <50 mm Hg)

Index test	Sensitivity (95%CI)	Specificity (95% CI)	LR +	LR-	N	Quality of the evidence (GRADE)	Comments/study
$TcPO_2$	84% (64 to 95%)	96% (93-98%)	23 (12-42)	0.17 (0.07-0.71)	26 (335 blood samples)	Very low[1,2]	Population 29-38 weeks with no mean for gestational age

CI: confidence interval; LR-: negative likelihood ratio; LR+: positive likelihood ratio; PMA: post-menstrual age; $TcPO_2$: transcutaneous oxygen measurement
[1] Population of infants with hyaline membrane disease includes infants up to 38 weeks PMA
[2] 95% CI crosses 75% and 90% boundary for sensitivity

See appendix F for full modified GRADE for Diangostic Test Accuracy tables.

Economic evidence

No economic evidence on the cost effectiveness of methods for measuring oxygen levels in diagnosing hyperoxia or hypoxia in preterm babies was identified by the literature searches of the economic literature undertaken for this review.

Economic model

This topic was prioritised for de novo economic modelling. The committee explained that some methods of measuring oxygen levels have more favourable diagnostic accuracy and have very different costs (that is, transcutaneous method is very expensive). However, the clinical evidence was insufficient to inform de-novo economic modelling in this area.

Clinical evidence statements

Pulse oximetry oxygen saturation

- No studies reported on the diagnostic accuracy of pulse oxygen saturation

$TcPO_2$

Hyperoxia

- One retrospective cohort study (n=26; 365 measurements; low quality) reported that the sensitivity and specificity of $tcPO_2$ for hyperoxia defined as PaO_2 >100 mm Hg was 79% (63-90%) and 97% (94-99%), respectively. The positive likelihood ratio and negative likelihood ratio reported for hyperoxia defined as PaO_2 >100 mm Hg was 26 (13-50) and 0.22 (0.12-0.39), respectively.

Hypoxia

- One retrospective cohort study (n=26; 365 measurements; very low quality) reported that the sensitivity and specificity of $tcPO_2$ for hypoxia defined as PaO_2 <50 mm Hg was 84% (64-95%) and 96% (93-98%), respectively. The positive likelihood ratio and negative likelihood ratio reported for hypoxia defined as PaO_2 <50 mm Hg was 23 (12-42) and 0.17 (0.07-0.71), respectively.

See appendix F for Forest plots

Economic evidence statements

- No economic evidence on the cost effectiveness of methods for measuring oxygen levels in diagnosing hyperoxia or hypoxia in preterm babies was available.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee agreed that the correct identification of hyperoxia and hypoxia is important as both can lead to life changing long-term conditions such as neurodevelopmental impairment. Although, the committee considered both false positives and false negatives to be important as both can have detrimental effects on the preterm baby, the committee prioritised sensitivity as the most critical outcome, as the implications of missing a case of hyperoxia or hypoxia could have a significant and life-changing effect on a preterm baby. In contrast, incorrectly identifying hyperoxia or hypoxia may lead to unnecessary additional management but the implications are unlikely to be as severe.

The committee agreed that adverse effects were important when considering the most appropriate monitoring tool, as even if a monitoring tool was very accurate at diagnosing hyperoxia or hypoxia it may not be the most appropriate tool for the preterm baby – for example transcutaneous monitoring may not be suitable for extremely preterm babies because of the risk of skin damage at the sensor site. However, adverse effects of interest were not reported in the studies.

The quality of the evidence

The evidence on diagnostic accuracy was assessed using an adapted GRADE approach for diagnostic studies. The quality of the evidence in this review ranged from very low to low. The quality of evidence was most often downgraded because of methodological limitations affecting the risk of bias and the uncertainty around the sensitivity result for hyperoxia and hypoxia.

Methodological limitations were attributed to the fact that the population of babies in the study included in the review may not have been a purely preterm population as the study included babies up to 38 weeks post-menstrual age. The committee agreed to include the study given that all babies had respiratory distress syndrome and gestational age calculations in the late 1970s (when the study was conducted) were not as accurate as they currently are. Additionally, the committee highlighted that the cut-off for the diagnosis of hyperoxia in the included study was 100mmHg, but in current practice levels of 80mmHg are used, in line with evidence showing an increased risk of retinopathy of prematurity above this threshold.

Benefits and harms

The evidence on the best method for measuring oxygen levels in diagnosing hyperoxia or hypoxia in preterm babies was very limited. Although there has been significant research comparing the different methods of oxygen monitoring, the studies did not meet our inclusion criteria for the review. The main reason for excluding studies was that the populations in the diagnostic accuracy studies were not 100% preterm babies, most often studies were a mixture of preterm with term babies or children, and in some cases adults. The committee were clear that only studies with 100% preterm babies

should be included in this review as preterm and term babies may respond differently, for example due to differences in skin composition. Another reason studies failed to meet our inclusion criteria were the outcomes measured: many studies reported their results as correlation plots rather than sensitivity or specificity, or provided insufficient data to be able to tabulate a 2 x 2 table and calculate the data for the required critical outcomes. A review on the diagnostic accuracy of $tcPO_2$ and SpO_2 compared to SaO_2 (Poets 1994) provided a table with sensitivity and specificity for studies that included all preterm babies, however the reliability of these results could not be assured as the data was not reported in the original papers and their methods reported that their sensitivity and specificity results were calculated from the correlation plots.

There were no studies assessing the diagnostic accuracy of pulse oximetry (SpO_2) compared to the standard arterial blood gas monitoring (PaO_2) that met the review's inclusion criteria. A recent study from Iran (Niknafs 2015) compared SpO_2 to PaO_2 in preterm babies and reported sensitivity, specificity, and likelihood ratios for hyperoxia and hypoxia. However no confidence intervals were provided in the paper and there was insufficient data to construct a 2 x 2 table. Thus, the committee agreed that the paper should be excluded as it would be difficult to draw conclusions. The committee did not feel this was a priority to recommend for further research. Rather, based on clinical consensus and clinical practice in the UK, the committee agreed that pulse oximetry should remain the first line modality for continuous monitoring of oxygen saturation levels in preterm babies due to its widespread acceptability, ease of use, relatively low cost and non-invasive nature.

The evidence assessing the diagnostic accuracy of transcutaneous oxygen saturation ($tcPO_2$) compared to the gold standard or arterial oxygen saturation (PaO_2) was of very low quality and very old. The committee agreed that $tcPO_2$ techniques have changed substantially over the years and that it was difficult to draw conclusions from a study in the late 1970s. In light of the limited evidence, the committee could not make any strong recommendations for the use of $tcPO_2$ for measuring oxygen levels in preterm babies. The committee discussed the fact that there is variation in practice in $tcPO_2$ use in the UK, as it can be awkward to use, expensive, and although the incidence of skin damage has reduced with advances in technology the technique still can cause red rings on the skin that may alarm staff and parents/carers. The committee agreed that $tcPO_2$ continuous monitoring was useful in unstable preterm babies. Transcutaneous monitoring allows healthcare professionals to examine trends, and is particularly useful when frequent adjustment of oxygen levels is required, for example in pulmonary hypertension of the newborn. In view of this, the committee agreed that $tcPO_2$ should be considered in preterm babies on invasive ventilation who are clinically unstable and require continuous monitoring to guide management.

The committee discussed that although the gold standard of arterial blood gas monitoring accurately identifies hyperoxia and hypoxia, this is not a continuous monitoring tool and cannot be used as the sole method for oxygen monitoring. Intermittent arterial oxygen measurement is routinely used alongside a continuous monitoring tool in current clinical practice, which the committee endorse as safe practice, but chose not to make a specific recommendation about this. The committee appreciated that not all preterm babies can have an arterial line sited, and even when successful cannulation is achieved the life of the catheters does not generally match the duration of oxygen therapy. There is a need for a continuous, accurate, non-invasive method of monitoring oxygen levels over long periods of time.

In view of the sparsity of evidence, the committee agreed that further research needs to be conducted as a mater of priority looking at the diagnostic accuracy of $tcPO_2$ and

SpO_2 against the gold standard PaO_2 in diagnosing hyperoxia and hypoxia in a pure preterm baby population.

Cost effectiveness and resource use

There was no evidence on the cost effectiveness of methods for measuring oxygen levels in diagnosing hyperoxia or hypoxia in preterm babies. The committee discussed the lack of clinical and economic evidence in this area. It was noted that transcutaneous method is very expensive when compared with pulse oximetry and arterial blood gas monitoring. Given the lack of clinical evidence and significantly lower intervention costs the committee were of a view that pulse oximetry should continue to be used as the primary method of monitoring when preterm babies require oxygen therapy. The committee also noted that arterial oxygen sampling has similar intervention costs to pulse oximetry and it remains the gold standard but arterial oxygen is not always technically possible and it can't provide a continuous measurement.

The committee explained that transcutaneous monitoring could be justified, irrespective of the cost, in babies who are unstable and who require invasive respiratory support requiring frequent adjustments. This is because, transcutaneous monitoring is the only form of accurate monitoring available that is continuous. By contrast infrequent one-off readings from arterial blood gases would be little help for babies whose condition is unstable and so the use of transcutaneous monitoring was deemed to be essential in ensuring a positive outcome.

Overall, given that transcutaneous monitoring lacked any clear additional benefits and had a higher cost when compared with other methods, the committee supported the use of pulse oximetry as the primary mode of continuous monitoring when preterm babies require oxygen therapy. The committee further explained that most centres are using pulse oximetry and as such the recommendations in this area are unlikely to result in a significant resource impact.

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Review question 4.3 What carbon dioxide levels are optimal in the management of preterm babies?

Introduction

Carbon dioxide is cleared by healthy lung tissue, and can build up when there is respiratory failure. Cerebral blood flow is affected by carbon dioxide levels, and alterations in cerebral blood flow predispose a preterm baby's vulnerable brain to peri/intraventricular haemorrhage (P/IVH) and/or periventricular leukomalacia (PVL).

Monitoring of carbon dioxide levels is crucial during artificial ventilation, but evidence of lung injury induced by volutrauma has led to efforts to reduce this damage, with "permissive hypercapnia" (allowing elevated carbon dioxide levels in the blood) becoming a common lung protective strategy in ventilated preterm babies. However, the safety and the optimal range of carbon dioxide values for permissive hypercapnia are not clear.

This review aims to identify the optimal levels of carbon dioxide in the management of preterm babies in order to improve outcomes.

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, necrotising enterocolitis, neurological disorders
Intervention	Higher target range for partial pressure of carbon dioxide
Comparison	Lower target range for partial pressure of carbon dioxide
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: o Cerebral Palsy (CP) (reported as presence or absence of condition, **not** severity of condition) o Neurodevelopmental delay (reported as dichotomous outcomes, **not** continuous outcomes such as mean change in score) - Severe (score of >2 SD below normal on validated assessment scales, **or** on 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 the 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:** • Periventricular leukomalacia • Severe intraventricular haemorrhage • Days on invasive ventilation • Pneumothorax

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

Clinical evidence

Included studies

Four randomised controlled trials (RCTs) were included in this review (Carlo 2002; Mariani 1999; Thome 2006; Thome 2015). One additional publication with neurodevelopmental outcomes of one of the RCTs was identified, maintaining the original randomisation but reporting the longer term outcomes (Thome 2017 [Thome 2015])

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

Excluded studies

Studies not included in this review, with reasons for their 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.

Table 8: Summary of included studies

Study and setting	Population	Intervention/ comparison	Outcomes	Comments
Carlo 2002 RCT USA	n=220 Preterm babies weighing 501-1000g who were intubated, receiving invasive	Higher target: partial pressure of carbon dioxide target >52 mmHg Lower target: partial pressure	Mortality prior to discharge BPD at 36 weeks PMA Cerebral Palsy defined as	Follow-up time: Primary outcomes were followed up at 36 weeks PMA. Neurodevelopmental outcomes

Study and setting	Population	Intervention/ comparison	Outcomes	Comments
	ventilation before 12 hours of age, and had an indwelling vascular catheter. Preterm babies weighing 751-1000g were also required to have a FiO_2 ≥0.3 and have had at least 1 dose of surfactant.	of carbon dioxide target <48 mmHg	moderate or severe at 18-22 months of age Severe cognitive impairment defined as a MDI <70 or PDI <70 on the Bayley's II scale of infant development Deafness requiring amplification Bilateral blindness Periventricular leukomalacia Severe IVH (grade III or IV) Days on invasive ventilation Pneumothorax	were followed up at 18-22 months.
Mariani 1999 RCT USA	n=49 Preterm babies weighing 601-1250g with surfactant-treated RDS on assisted ventilation before 24 hours of age	Higher target: arterial partial pressure of carbon dioxide 45-55 mmHg Lower target: arterial partial pressure of carbon dioxide 35-45 mmHg	Mortality prior to discharge BPD at 28 days PMA Periventricular leukomalacia Severe IVH (grade III or IV) Days on invasive ventilation Air leak	Follow-up time: days 5 through 7 after birth and then 28 ±7 or when clinically indicated
Thome 2006 RCT USA	n=66 Preterm babies with a gestational age $23\text{-}28^{+6}$ and	Higher target: arterial partial pressure of carbon dioxide of 55-65 mmHg (7.3-8.7 kPa) for	Mortality prior to discharge BPD at 36 weeks PMA	Follow-up time: up to seven days of life

Study and setting	Population	Intervention/ comparison	Outcomes	Comments
	requiring invasive ventilation within 6 hours of birth	the first 7 days after birth Lower target: arterial partial pressure of carbon dioxide 35-45 mmHg (4.7-6.0 kPa) for the first 7 days after birth	Cerebral Palsy at 18-22 months of age Severe cognitive impairment defined as a MDI <70 or PDI <70 on the Bayley's II scale of infant development Hearing impairment defined as use of hearing aids Vision impairment defined as use of corrective or contact lenses, blind with some functional vision, or no useful vision Severe IVH (grade III or IV) Pneumothorax	
Thome 2015 RCT Germany	n=362 Preterm babies with a gestational age 23-28^{+6} and requiring invasive ventilation within 24 hours of birth	Higher target: arterial or capillary partial pressure of carbon dioxide of 55-65 mmHg from days 1-3 of life; 60-70 mmHg from days 4-6 of life; and 65-75 mmHg from days 7-14 of life Lower target: arterial or capillary partial pressure of carbon dioxide of 40-50 mmHg from days 1-3 of life; 45-55 mmHg	Mortality prior to discharge BPD at 36 weeks PMA Periventricular leukomalacia Severe IVH (grade III or IV) Pneumothorax	Arterial or capillary partial pressure of carbon dioxide level Follow-up time: Up to 23–28 weeks plus 6 days

Study and setting	Population	Intervention/ comparison	Outcomes	Comments
		from days 4-6 of life; and 50-60 mmHg from days 7-14 of life		
Thome 2017 RCT Germany	n=311 18-22 months corrected age Surviving from Thome 2015	See Thome 2015	Cerebral Palsy defined as a GMFCS score of ≥1 Severe cognitive impairment defined as a MDI <70 or PDI <70 on the Bayley's II scale of infant development Deafness undefined Blindness undefined	Follow-up time: 18-22 months

BPD: bronchopulmonary dysplasia; FiO2: fraction of inspired oxygen; GMFCS: gross motor function classification system; IVH: intraventricular haemorrhage; MDI: mental development index; PDI: psychomotor developmental index; RCT: randomised controlled trial; RDS: respiratory distress syndrome

See appendix D for clinical evidence tables.

Quality assessment of clinical studies included in the evidence review

See appendix F for full GRADE tables.

Economic evidence

No economic evidence on the cost effectiveness of carbon dioxide levels 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. Higher target range for partial pressure of carbon dioxide versus lower target range for partial pressure of carbon dioxide

Critical outcomes

Mortality prior to discharge

- Moderate quality evidence from 4 RCTs (n=693) showed no clinically significant difference in mortality prior to discharge among preterm babies who had a higher target range for partial pressure of carbon dioxide compared to a lower target range for partial pressure of carbon dioxide.

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

- Moderate quality evidence from 3 RCTs (n=644) showed no clinically significant difference in BPD at 36 weeks PMA among preterm babies who had a higher target range for partial pressure of carbon dioxide compared to a lower target range for partial pressure of carbon dioxide.

BPD at 28 days PMA

- Low quality evidence from 1 RCT (n=49) showed no clinically significant difference in BPD at 28 days PMA among preterm babies who had a higher target range for partial pressure of carbon dioxide compared to a lower target range for partial pressure of carbon dioxide.

Neurodevelopmental outcomes at ≥18 months: cerebral palsy

- Low quality evidence from 3 RCTs (n=452) showed no clinically significant difference in cerebral palsy at 18 months of age or older among preterm babies who had a higher target range for partial pressure of carbon dioxide compared to a lower target range for partial pressure of carbon dioxide.

Neurodevelopmental outcomes at ≥18 months: severe cognitive impairment

Mental development index score <70

- Low quality evidence from 3 RCTs (n=433) showed no clinically significant difference in mental development index scores of <70 using the Bayley's scale of infant and toddler development (BSID-II) at 18 months of age or older among preterm babies who had a higher target range for partial pressure of carbon dioxide compared to a lower target range for partial pressure of carbon dioxide.

Psychomotor developmental index score <70

- Low quality evidence from 3 RCTs (n=410) showed no clinically significant difference in psychomotor development index scores of <70 using the Bayley's scale of infant and toddler development (BSID-II) at 18 months of age or older among preterm babies who had a higher target range for partial pressure of carbon dioxide compared to a lower target range for partial pressure of carbon dioxide.

Neurodevelopmental outcomes at ≥18 months: moderate cognitive impairment

Mental development index score <85

- Low quality evidence from 1 RCT (n=249) showed no clinically significant difference in mental development index scores of <85 using the Bayley's scale of infant and toddler development (BSID-II) at 18 months of age or older among preterm babies with a gestational age of 23-28^{+6} weeks who had a higher target range for partial pressure of carbon dioxide compared to a lower target range for partial pressure of carbon dioxide.

Psychomotor developmental index score <85

- Low quality evidence from 1 RCT (n=226) showed no clinically significant difference in psychomotor development index scores of <85 using the Bayley's scale of infant and toddler development (BSID-II) at 18 months of age or older among preterm babies with a gestational age of 23-28^{+6} weeks who had a higher target range for partial pressure of carbon dioxide compared to a lower target range for partial pressure of carbon dioxide.

Neurodevelopmental outcomes at ≥18 months: severe hearing impairment

- Very low quality evidence from 3 RCTs (n=446) showed no clinically significant difference in severe hearing impairment at 18 months of age or older among preterm babies who had a higher target range for partial pressure of carbon dioxide compared to a lower target range for partial pressure of carbon dioxide.

Neurodevelopmental outcomes at ≥18 months: severe visual impairment

- Very low quality evidence from 3 RCTs (n=447) showed no clinically significant difference in severe visual impairment at 18 months of age or older among preterm babies who had a higher target range for partial pressure of carbon dioxide compared to a lower target range for partial pressure of carbon dioxide.

Important outcomes

PVL

- Low quality evidence from 3 RCTs (n=628) showed no clinically significant difference in PVL among preterm babies who had a higher target range for partial pressure of carbon dioxide compared to a lower target range for partial pressure of carbon dioxide.

Severe IVH (grade III or IV)

- Low quality evidence from 4 RCTs (n=693) showed no clinically significant difference in severe IVH (grade III or IV) among preterm babies who had a higher target range for partial pressure of carbon dioxide compared to a lower target range for partial pressure of carbon dioxide.

Days on invasive ventilation

- High quality evidence from 1 RCTs (n=220) showed no clinically significant difference in the number of days on invasive ventilation among preterm babies who had a higher target range for partial pressure of carbon dioxide compared to a lower target range for partial pressure of carbon dioxide.

- Moderate quality evidence from 1 RCT (n=49) showed no clinically significant difference in the number of days on invasive ventilation among preterm babies who

had a higher target range for partial pressure of carbon dioxide compared to a lower target range for partial pressure of carbon dioxide.

Pneumothorax

- Moderate quality evidence from 4 RCTs (n=522) showed no clinically significant difference in pneumothorax among preterm babies who had a higher target range for partial pressure of carbon dioxide compared to a lower target range for partial pressure of carbon dioxide.

See appendix E for Forest plots.

Economic evidence statements

- No economic evidence on the cost effectiveness of carbon dioxide levels 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 reducing the rates of mortality and BPD were of utmost importance for preterm babies on respiratory support, and therefore these were considered the critical outcomes for decision making. However, the committee also agreed that neurodevelopmental outcomes were critically important as these could have a life-long impact on the affected individual and their parents or carers.

The most significant risks of hypercapnia and hypocapnia in preterm babies are IVH and PVL, respectively, thus the committee prioritised these outcomes as important. 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 respiratory support, 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 was assessed using the GRADE methodology. The quality of evidence in this review ranged from very low to moderate quality. The evidence on a higher target range of carbon dioxide compared to a lower target range of carbon dioxide was of moderate quality for mortality prior to discharge, BPD at 36 weeks PMA, and pneumothorax, whereas the evidence for neurodevelopmental outcomes and the other important outcomes was of low or very low quality.

The quality of evidence was most often downgraded because of the uncertainty around the risk point estimate, which was primarily because of the low event rate. Furthermore, neurodevelopmental outcomes were further downgraded because of a high rate of attrition, which is very common in long-term follow up studies.

Most of the studies included were not blinded due to the nature of the interventions, but the committee agreed that as most of the outcomes were objective, and that subjective outcomes had strict pre-defined criteria for assessment, the likely impact on the risk of bias was low.

Benefits and harms

In preterm babies on invasive ventilation, the committee decided that carbon dioxide levels should be tolerated in the range of 4.5-8.5 kPa on days 1-3 of age, then 4.5-10 kPa thereafter.

The evidence showed that there were no differences in the any of the outcomes between higher and lower target ranges for the partial pressure of carbon dioxide in preterm babies on invasive ventilation. The committee recognised that the higher target ranges specified in the studies were in line with the definition of permissive hypercapnia and that higher carbon dioxide levels within this range had no detrimental effects on clinical outcomes and long-term neurodevelopmental outcomes. In view of this, the committee agreed that when monitoring carbon dioxide levels in preterm babies on invasive ventilation that a higher target range was tolerated, thus negating the need for an excessively stringent target range. The committee highlighted that a very tight target range was very difficult to maintain and involved constant manipulation of the ventilators by healthcare professionals.

The committee recognised that the studies included in the review all had different lower and higher carbon dioxide target ranges. In view of this, combined with their experience, the committee agreed that the lowest range shown in several studies to have no detrimental effect (4.5 kPa) should be the one adopted as the lower level in their recommended range.

The higher levels were set in three stages: (8.5 kPa from Day 1-3; 9.3 kPa from Day 4-6; 10 kPa from Day 7-14) and the committee agreed that for babies from 1-3 days the upper limit should be set at 8.5 kPa to avoid the dangerous hypercapnia. From 4 days onwards they adopted the upper limit of 10 kPa also identified from Thome 2015 and 2017. This was based on their clinical experience that the difference in upper limits tolerated between day 3 and 7 would be negligible and would have minimal detrimental effects on a preterm baby on invasive ventilation, and that a 2-stage range was easier to implement in practice than a 3-stage range.

Although not all included studies reported the gestational age in their inclusion criteria the committee agreed that, based on gestational weight and the fact that the babies were all on invasive ventilation, it was reasonable to assume that the preterm babies were <29 weeks. The committee agreed that the carbon dioxide target range in the recommendation could be used for all preterm babies as the evidence was in the most vulnerable group of preterm babies and the committee did not envisage any significant need for a different target range for the more mature preterm babies on invasive ventilation.

The committee highlighted that although the scope of this question was to focus on the optimal target range for carbon dioxide, that carbon dioxide level monitoring was not generally used in isolation but rather used alongside pH when making clinical decisions. The committee were also aware from their clinical experience that a low carbon dioxide level was dangerous, and therefore, although no evidence had been reviewed covering this, they agreed that it was important to include in the recommendations the action that should be taken.

All the evidence for the optimal target range for the partial pressure of carbon dioxide was in preterm babies on invasive ventilation and the committee recognised that there was an absence of evidence in preterm babies on non-invasive ventilation. Given that preterm babies on non-invasive ventilation are a significant proportion of the preterm baby population and that the optimal target range of carbon dioxide may be different,

and may guide healthcare professionals when to commence invasive ventilation, the committee therefore made it a priority to recommend that further research was needed in this area.

Cost effectiveness and resource use

There was no evidence on the cost effectiveness of carbon dioxide levels in preterm babies requiring respiratory support. The committee explained that carbon dioxide level monitoring is an integral part of care provided to preterm babies that require respiratory support and providing the recommended target range would not have resource implications. Carbon dioxide monitoring is deemed essential in ensuring the success of treatment. The recommendations do not involve a change in practice and therefore no additional resource impact.

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Review question 4.4 What blood pressure monitoring strategies are associated with improved outcomes in preterm babies requiring respiratory support?

Introduction

Preterm babies are regularly monitored to ensure adequate systemic perfusion (oxygen supply to tissues). In combination with clinical observations, biochemical parameters, urine output and clinical examination, blood pressure (BP) can be used as a surrogate marker for systemic perfusion.

Depending on the clinical condition of the baby, blood pressure may be continuously monitored via an indwelling arterial catheter placed in either an umbilical or peripheral artery, and in more stable babies it may be measured non-invasively using the oscillometric (cuff-reading) technique. The optimal target range for BP in babies of different gestational ages and weights is not precisely known, but observational studies have defined a “normal” range present in babies who have an uncomplicated course.

Identifying babies with reduced tissue oxygen supply who would benefit from intervention is clinically difficult, as it is not known what specific BP range is associated with adequate perfusion and better long term outcomes.

This review aims to compare outcomes with the use of invasive monitoring versus oscillometric measurements, and between different target blood pressure ranges in preterm babies on invasive respiratory support, to identify if a specific approach to both blood pressure monitoring and blood pressure management is associated with better outcomes.

Summary of the protocol

See Table 9 for a summary of the population, intervention, comparison and outcome (PICO) characteristics of this review.

Table 9: 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	a) Different methods for measuring blood pressure: <u>Invasive blood pressure monitoring:</u> • Umbilical arterial catheter • Peripheral arterial catheter <u>Non-invasive blood pressure monitoring:</u> • Oscillometric

	b) Different blood pressure targets
Comparison	a) Different monitoring methods comparisons: • Monitoring versus no monitoring • Invasive versus non-invasive monitoring • Comparison of frequency of differing intermittent non-invasive regimens b) Different blood pressure target levels: • Mean BP ≥30 mmHg versus gestational age in mmHg, in the first 72 hours after birth • Mean BP ≥9th centile for gestational age versus ≥30 mmHg, in first 72 hours after birth • Mean BP ≥9th centile for gestational age versus gestational age in mmHg, in the first 72 hours after birth
Outcome	**Critical outcomes:** • Mortality prior to discharge • Neurodevelopmental outcomes at ≥18 months: ○ Cerebral palsy (CP) (reported as presence or absence of condition, **not** severity of condition) ○ Neurodevelopmental delay (reported as dichotomous outcomes, **not** continuous outcomes such as mean change in score) - Severe (score of >2 SD below normal on validated assessment scales, **or** on Bayleys assessment scale of mental developmental index (MDI) or psychomotor developmental index (PDI) <70 or complete inability to assign score due to CP or severe cognitive delay) - Moderate (Score of 1-2 SD below normal on validated assessment scales, **or** on Bayleys assessment scale of MDI or PDI 70-84) ○ Neurosensory impairment (reported as presence or absence of condition, **not** severity of condition) - Severe hearing impairment (for example, deaf) - Severe visual impairment (for example, blind) • Severe intraventricular haemorrhage (grade 3 or 4) **Important outcomes:** • Periventricular leukomalacia • Necrotising enterocolitis • Renal impairment • Vascular complications associated with invasive monitoring

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

Clinical evidence

Included studies

No clinical evidence was identified for this review

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

No clinical evidence was identified for this review (and so there are no evidence tables in appendix D). No meta-analysis was undertaken for this review (and so there are no forest plots in appendix E).

Quality assessment of clinical studies included in the evidence review

No clinical evidence was identified for this review (and so no quality assessment was undertaken and there are no GRADE tables in appendix F).

Economic evidence

No economic evidence on the cost effectiveness of methods for measuring blood pressure or different blood pressure target levels in preterm babies requiring respiratory care 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

- No clinical evidence was identified for this review (and so there are no clinical evidence statements).

Economic evidence statements

- No economic evidence on the cost effectiveness of methods for measuring blood pressure or different blood pressure target levels in preterm babies requiring respiratory care was available.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

Monitoring of blood pressure in preterm babies is carried out to ensure adequate blood pressure is maintained, to ensure that babies do not become hypotensive or hypertensive, and as a surrogate marker to ensure adequate tissue perfusion. Maintenance of adequate perfusion, in turn, serves as a marker for adequate oxygen delivery to the brain and other organs. Hypertension can increase the risk of bleeds into the brain, while hypotension and inadequate perfusion can also lead to brain damage and impaired neurological development. The critical outcomes for this review were therefore mortality prior to discharge, neurodevelopmental outcomes, and severe intraventricular haemorrhage.

Reduced blood supply to the kidneys and intestine can lead to kidney impairment and necrotising enterocolitis respectively, and periventricular leukomalacia may also be more likely. Thus these were chosen as important outcomes. The committee were also aware that invasive blood pressure monitoring can lead to vascular complications and so this was also selected as an important outcome.

The quality of the evidence

There was no evidence available for this review so the committee made recommendations based on their knowledge and experience.

Benefits and harms

The committee discussed the fact that there is currently no evidence to define what is normal blood pressure in preterm babies, what is abnormal, and how it should be measured. Many units may use the arbitrary guide that a preterm baby's mean arterial blood pressure should equal the gestational age in mmHg (so for example a baby born 30 weeks should have a blood pressure of 30mmHg, at 32 weeks 32 mmHg), while other units may use a standard arbitrary target of ≥30mmHg for babies of all gestations. The committee also discussed the fact that while there was no evidence for the benefits of monitoring blood pressure there were potential risks with invasive monitoring such as thrombosis, infection or vascular damage. The committee agreed that blood pressure was often used as a surrogate marker for adequate tissue perfusion, but that lactate may be a better indicator of perfusion status. Also, some treatments for low blood pressure may achieve better blood pressure values by reducing tissue perfusion, which might ultimately decrease intact survival. The committee agreed that if inadequate perfusion was present, it should be treated to improve perfusion, not just to bring blood pressure up to an arbitrary level. Finally, the committee discussed the fact that fluctuating blood pressure could lead to more serious clinical consequences than a stable blood pressure, including an increased risk of IVH. This fluctuating blood pressure may result from inappropriate treatment of a blood pressure, which led to swings, and it may therefore be preferable not to treat on the basis of blood pressure values alone.

The committee agreed that their recommendation should reflect the fact that there is no evidence to support any particular method of monitoring blood pressure, or target level, and based on their clinical experience they recommended that inadequate perfusion should be treated with the aim of increasing perfusion, and not to attain a

certain blood pressure target. They also prioritised further research into the optimal method and frequency of measuring blood pressure, and the optimal target blood pressure range for preterm babies.

Cost effectiveness and resource use

There was no evidence on the cost effectiveness of different methods for measuring blood pressure or different blood pressure target levels in preterm babies requiring respiratory care. The committee questioned the value of blood pressure monitoring in preterm babies requiring respiratory care and explained that blood pressure monitoring may potentially result in unnecessary further invasive tests, unnecessary treatment and there is also a potential for increased adverse events. The committee explained that targeting babies with poor perfusion only may lead to the reduction in the use of unnecessary blood pressure monitoring and result in the cost savings to the NHS.

Other factors the committee took into account

The committee were aware of an ongoing study that may help define blood pressure target in babies, but also made research recommendations to address the optimal blood pressure target and method of monitoring.

References

No clinical evidence was identified for this review so there are no references.

Appendices

Appendix A – Review protocols

Review protocol for question 4.1 What oxygen levels are optimal in the management of preterm babies?

Field (based on PRISMA-P	Content
Review question in SCOPE	What is the best method for monitoring blood oxygen levels?
Review question in guideline	What oxygen levels are optimal in the management of preterm babies?
Type of review question	Intervention
Objective of the review	To determine the optimal oxygen saturation levels in the management of preterm babies
Eligibility criteria – population/disease/condition/issue/domain	Preterm babies Exclusions: Preterm babies with any 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)	Different oxygen saturation levels in preterm babies requiring respiratory support: Higher target range for oxygen saturation levels Lower target range for oxygen saturation levels
Eligibility criteria – comparator(s)/control or reference (gold) standard	Higher vs lower target range for oxygen saturation levels

Field (based on PRISMA-P	Content
Outcomes and prioritisation	Critical outcomes: Severe retinopathy of prematurity (defined as stage 3 or 4 Retinopathy of Prematurity, or Retinopathy of Prematurity requiring surgery or use of bevacizumab) Mortality prior to discharge Neurodevelopmental outcomes at >18 months: Cerebral palsy (reported as presence or absence of condition, not severity of condition) Neurodevelopmental delay (reported as dichotomous outcomes, not continuous outcomes such as mean change in score) 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) Severe hearing impairment (e.g. deaf) Severe visual impairment (e.g. blind) Important outcomes: Bronchopulmonary dysplasia (oxygen dependency at 36 weeks PMA or 28 days of age) Necrotising enterocolitis Patent ductus arteriosus requiring medical or surgical treatment
Eligibility criteria – study design	Systematic reviews of RCTs RCTs If insufficient RCTs: prospective cohort studies If insufficient prospective cohort studies: retrospective cohort studies

Field (based on PRISMA-P	Content
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: Pulse oximeter used Masimo SET Radical pulse oximeter using old algorithm Masimo SET Radical pulse oximeter using updated algorithm plus all other pulse oximeter devices Gestational age: <26+6 weeks 27-31+6 weeks 32-36+6 weeks
Selection process – duplicate screening/selection/analysis	Sifting, data extraction, appraisal of methodological quality and GRADE assessment will be performed by the systematic reviewer. Resolution of any disputes will be with the senior systematic reviewer and the Topic Advisor. Quality control will be performed by the senior systematic reviewer. Dual sifting and data extraction will not be undertaken for this question.
Data management (software)	Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). 'GRADEpro' will be used to assess the quality of evidence for each outcome. NGA STAR software will be used for study sifting, data extraction, recording quality assessment using checklists and generating bibliographies/citations.
Information sources – databases and dates	Sources to be searched: Medline, Medline In-Process, CCTR, CDSR, DARE, HTA, Embase Limits (e.g. date, study design): Apply standard animal/non-English language exclusion

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 ante-natal and post-natal respiratory management since this time period and outcomes for preterm babies prior to 1990 are not the same as post 1990.
Identify if an update	Not an update
Author contacts	Developer: NGA
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual
Search strategy	For details please see appendix B
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix D (clinical evidence tables) or H (economic evidence tables).
Data items – define all variables to be collected	For details please see evidence tables in appendix D (clinical evidence tables) or H (economic evidence tables).
Methods for assessing bias at outcome/study level	Standard study checklists were used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis (where suitable)	For details please see section 6.4 of Developing NICE guidelines: the manual
Methods for analysis – combining studies and exploring (in)consistency	Appraisal of methodological quality: The methodological quality of each study will be assessed using an appropriate checklist:

Field (based on PRISMA-P	Content
	• AMSTAR for systematic reviews • Cochrane risk of bias tool for RCTs • Cochrane risk of bias tool for non-randomised studies The quality of the evidence for an outcome (i.e. across studies) will be assessed using GRADE. Synthesis of data: Pairwise meta-analysis will be conducted where appropriate When meta-analysing continuous data, final and change scores will be pooled and if any studies reports both, the method used in the majority of studies will be analysed. Minimally important differences: Default values will be used of: 0.8 and 1.25 for dichotomous outcomes; 0.5 times SD for continuous outcomes, unless more appropriate values are identified by the guideline committee or in the literature. Mortality – 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

Field (based on PRISMA-P	Content
	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 4.2 What is the best method for measuring oxygen levels in diagnosing hyperoxia or hypoxia in preterm babies?

Field (based on PRISMA-P	Content
Review question in SCOPE	What is the best method for monitoring blood oxygen levels?
Review question in guideline	What is the best method for measuring oxygen levels in diagnosing hyperoxia or hypoxia in preterm babies?
Type of review question	Diagnostic
Objective of the review	To determine the optimal method for diagnosing hyperoxia or hypoxia in preterm babies.
Eligibility criteria – population/disease/condition/issue/domain	Preterm babies requiring respiratory support Exclusions: Studies with indirect populations will not be considered
Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	Index test: severity assessment tools/clinical markers Pulse oximetry oxygen saturation (SpO2) Transcutaneous oxygen measurement (tcPO2)
Eligibility criteria – comparator(s)/control or reference (gold) standard	Reference standards:

Field (based on PRISMA-P	Content
	Arterial oxygen saturation (PaO2)
Outcomes and prioritisation	Critical outcomes: Sensitivity Specificity Area Under the Receiver Operating Curve (AUROC) Positive likelihood ratio (LR+) Negative likelihood ratio (LR-) Important outcomes: Adverse events Infection Burns Ischaemic limbs Emboli/thrombi Blood loss due to excess sampling
Eligibility criteria – study design	Studies in which the index test and the reference standard would be compared in the same individuals and 2x2 tables will be constructed: Cross-sectional studies Prospective cohort studies where cross-sectional data were reported therefore 2 x 2 tables could be tabulated Exclude: case-control studies
Other inclusion exclusion criteria	Inclusion: English language Developed countries with a neonatal care system similar to the UK (e.g. OECD countries) No date limit was applied as the GC confirmed that the technology has not changed significantly over time and older studies might still be useful
Proposed sensitivity/sub-group analysis, or meta-regression	Stratified analyses based on the following sub-groups of pre-term babies: Gestational age:

Field (based on PRISMA-P	Content
	a) 0-7 days b) >7 days For Massimo pulse oximeters, correction of algorithm: Pre-correction of algorithm Post-correction of algorithm Position of probe: Pre-ductal (RH) Post-ductal (everywhere else)
Selection process – duplicate screening/selection/analysis	Sifting, data extraction, appraisal of methodological quality (NICE checklists QUADAS-2) and an adapted version of the GRADE assessment will be performed by the systematic reviewer. Resolution of any disputes will be with the senior systematic review and the Topic Advisor. Quality control will be performed by the senior systematic reviewer. Dual sifting and data extraction will not be undertaken for this question.
Data management (software)	Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). 'GRADEpro' will be used to assess the quality of evidence for each outcome. NGA STAR software will be used for study sifting, data extraction, recording quality assessment using checklists and generating bibliographies/citations.
Information sources – databases and dates	Sources to be searched: Medline, Medline In-Process, CCTR, CDSR, DARE, HTA, Embase Limits (e.g. date, study design): Apply standard animal/non-English language exclusion Limit to RCTs and systematic reviews in first instance but download all results No study date limiits
Identify if an update	Not an update

Field (based on PRISMA-P	Content
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 Appraisal of methodological quality: The methodological quality of each study will be assessed using an appropriate checklist: • AMSTAR for systematic reviews • QUADAS-2 for diagnostic studies The quality of the evidence for an outcome (i.e. across studies) will be assessed using GRADE. 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 using STATA The cut-offs for diagnostic accuracy measures: Sensitivity and specificity:

Field (based on PRISMA-P	Content
	High >90% Moderate 75-90% Low <75% Positive likelihood ratio: Very useful test >10 Moderately useful test 5-10 Not a useful test <5 Negative likelihood ratio: Very useful test <0.1 Moderately useful test 0.1 to 0.2 Not a useful test >0.2
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

Field (based on PRISMA-P	Content
	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 protocols for question 4.3 What carbon dioxide levels are optimal in the management of preterm babies?

Field (based on PRISMA-P	Content
Review question in SCOPE	What is the best method for monitoring blood carbon dioxide levels?
Review question in guideline	What carbon dioxide levels are optimal in the management of preterm babies requiring respiratory support?
Type of review question	Intervention
Objective of the review	To determine the optimal carbon dioxide levels in the management of preterm babies requiring respiratory support
Eligibility criteria – population/disease/condition/issue/domain	Preterm babies who require respiratory support Exclusions: Preterm babies with any 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.

Field (based on PRISMA-P	Content
	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)	Different carbon dioxide levels in preterm babies requiring respiratory support: Higher target range for partial pressure of carbon dioxide Lower target range for partial pressure of carbon dioxide
Eligibility criteria – comparator(s)/control or reference (gold) standard	Higher vs lower target range for partial pressure of carbon dioxide
Outcomes and prioritisation	Critical outcomes: Mortality at discharge Bronchopulmonary Dysplasia (Oxygen dependency at 36 weeks PMA or 28 days of age) Neurodevelopmental outcomes at >18 months: Cerebral Palsy (reported as presence or absence of condition, not severity of condition) Neurodevelopmental delay (reported as dichotomous outcomes, not continuous outcomes such as mean change in score) Severe (Score of >2 SD below normal on validated assessment scales, or on 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: Periventricular leucomalacia

Field (based on PRISMA-P	Content
	Severe intraventricular haemorrhage (grade 3 or 4) Days on invasive ventilaion Pneumothorax
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: Gestational age: <26+6 weeks 27-31+6 weeks 32-36+6 weeks Post-natal age: >72 hrs < 72 hrs
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 reviewer and the Topic Advisor. Quality control will be performed by the senior systematic reviewer. Dual sifting and data extraction will not be undertaken for this question.

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 of the full guideline
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 When meta-analysing continuous data, final and change scores will be pooled and if any studies reports both, the method used in the majority of studies will be analysed. Minimally important differences: Default values will be used of: 0.8 and 1.25 for dichotomous outcomes; 0.5 times SD for continuous outcomes, unless more appropriate values are identified by the guideline committee or in the literature. Mortality – any change (statistically significant)
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual. If sufficient relevant RCT evidence is available, publication bias will be explored using RevMan software to examine funnel plots.

Field (based on PRISMA-P	Content
	Trial registries will be examined to identify missing evidence: Clinical trials.gov, NIHR Clinical Trials Gateway
Assessment of confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual
Rationale/context – Current management	For details please see the introduction to the evidence review in the full guideline.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by The National Guideline Alliance and chaired by Dr Janet Rennie in line with section 3 of Developing NICE guidelines: the manual. Staff from The National Guideline Alliance undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see the methods chapter of the full guideline.
Sources of funding/support	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Name of sponsor	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Roles of sponsor	NICE 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 4.4 What blood pressure monitoring strategies are associated with improved outcomes in preterm babies requiring respiratory support?

Field (based on PRISMA-P	Content
Review question in SCOPE	What is the best method for monitoring blood pressure?
Review question in guideline	What blood pressure monitoring strategies are associated with improved outcomes in preterm babies requiring respiratory support?

Field (based on PRISMA-P	Content
Type of review question	Intervention
Objective of the review	a. To determine the optimal method of measuring blood pressure in the management of preterm babies requiring respiratory support b. To determine the optimal target blood pressure levels in the management of preterm babies requiring respiratory support
Eligibility criteria – population/disease/condition/issue/domain	Preterm babies who require respiratory support Exclusions: Preterm babies with any congenital abnormalities, excluding patent ductus arteriosus Preterm babies who are ventilated solely due to a specific non-respiratory comorbidity, such as sepsis, NEC, neurological disorders RCTs with <15 participants in each arm will not routinely be included. Consideration will be given to their inclusion if the evidence from larger RCTs is judged not to be sufficient – in quality or quantity. Studies where >2/3 of preterm babies receive respiratory support will be included in the review
Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	a. Different methods for measuring blood pressure: <u>Invasive blood pressure monitoring:</u> - Umbilical arterial catheter - Peripheral arterial catheter <u>Non-invasive blood pressure monitoring:</u> - Oscillometric b. Different blood pressure target levels
Eligibility criteria – comparator(s)/control or reference (gold) standard	a. Different monitoring methods comparisons: • Monitoring versus no monitoring

Field (based on PRISMA-P	Content
	• Invasive versus non-invasive monitoring • Comparison of frequency of differing intermittent non-invasive regimens b. Different blood pressure target levels: • Mean BP ≥30mmHg versus gestational age in mmHg, in the first 72 hours after birth • Mean BP ≥9th centile for gestational age versus ≥30mmHg, in first 72 hours after birth • Mean BP ≥9th centile for gestational age versus gestational age in mmHg, in first 72 hours after birth These blood pressure target levels were chosen on the basis of current clinical practice as accepted levels for preterm babies, and based on the committee's expertise.
Outcomes and prioritisation	Critical outcomes: Mortality prior to discharge 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) ○ 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)

Field (based on PRISMA-P	Content
	○ Severe hearing impairment (e.g deaf) ○ Severe visual impairment (e.g blind) Severe intraventricular haemorrhage (grade 3 or 4) Important outcomes Periventricular leukomalacia Necrotising enterocolitis Renal impairment Vascular complications associated with invasive monitoring
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: Type of Invasive Monitoring - umbilical arterial monitoring - peripheral arterial monitoring Gestational age: <26+6 weeks 27-31+6 weeks 32-36+6 weeks
Selection process – duplicate screening/selection/analysis	Sifting, data extraction, appraisal of methodological quality and GRADE assessment will be performed by the systematic reviewer. Resolution of any

Field (based on PRISMA-P	Content
	disputes will be with the senior systematic reviewer and the Topic Advisor. Quality control will be performed by the senior systematic reviewer. Dual sifting and data extraction will not be undertaken for this question.
Data management (software)	Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). 'GRADEpro' will be used to assess the quality of evidence for each outcome. NGA STAR software will be used for study sifting, data extraction, recording quality assessment using checklists and generating bibliographies/citations.
Information sources – databases and dates	Sources to be searched: Medline, Medline In-Process, CCTR, CDSR, DARE, HTA, Embase Limits (e.g. date, study design): Apply standard animal/non-English language exclusion Limit to RCTs and systematic reviews in first instance but download all results Dates: from 1990 Studies conducted post 1990 will be considered for this review question, as the GC felt that significant advances have occurred in ante-natal and post-natal respiratory management since this time period and outcomes for preterm babies prior to 1990 are not the same as post 1990.
Identify if an update	Not an update
Author contacts	Developer: NGA
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual
Search strategy	For details please see appendix B.
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix D (clinical evidence tables) or H (economic evidence tables).
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 When meta-analysing continuous data, final and change scores will be pooled and if any studies reports both, the method used in the majority of studies will be analysed. Minimally important differences: Default values will be used of: 0.8 and 1.25 for dichotomous outcomes; 0.5 times SD for continuous outcomes, unless more appropriate values are identified by the guideline committee or in the literature. Mortality – 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.

Field (based on PRISMA-P	Content
	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

Appendix B – Literature search strategies

Literature search strategies for question 4.1 What oxygen levels are optimal in the management of preterm babies?

Systematic reviews and RCTs

Date of initial search: 06/12/2017

Database(s): Embase 1980 to 2017 Week 49, 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: 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*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	*oxygen/ae, ad, an, cr, do, to
25	oxygen blood level/
26	oxygen therapy/ad, ae, do
27	oxygen desaturation/
28	exp oximetry/
29	hypoxia/ or newborn hypoxia/
30	hyperoxia/
31	(or/24-30) use emez
32	*Oxygen/ad, ae, an, bl, to
33	Oxygen Inhalation Therapy/ad, ae, bl, to
34	exp Oximetry/
35	Hypoxia/
36	Hyperoxia/
37	(or/32-36) use ppez
38	31 or 37
39	((oxygen or o2 or sp02) adj2 (level* or saturat* or titrat* or overdos* or toxic* or balanc* or target* or high* or low*)).tw.
40	(hypoxi* or hyperoxi*).tw.
41	or/38-40
42	23 and 41

#	Searches
43	limit 42 to english language
44	limit 43 to yr="1990 -Current"
45	Letter/ use ppez
46	letter.pt. or letter/ use emez
47	note.pt.
48	editorial.pt.
49	Editorial/ use ppez
50	News/ use ppez
51	exp Historical Article/ use ppez
52	Anecdotes as Topic/ use ppez
53	Comment/ use ppez
54	Case Report/ use ppez
55	case report/ or case study/ use emez
56	(letter or comment*).ti.
57	or/45-56
58	randomized controlled trial/ use ppez
59	randomized controlled trial/ use emez
60	random*.ti,ab.
61	or/58-60
62	57 not 61
63	animals/ not humans/ use ppez
64	animal/ not human/ use emez
65	nonhuman/ use emez
66	exp Animals, Laboratory/ use ppez
67	exp Animal Experimentation/ use ppez
68	exp Animal Experiment/ use emez
69	exp Experimental Animal/ use emez
70	exp Models, Animal/ use ppez
71	animal model/ use emez
72	exp Rodentia/ use ppez
73	exp Rodent/ use emez
74	(rat or rats or mouse or mice).ti.
75	or/62-74
76	44 not 75
77	Meta-Analysis/
78	Meta-Analysis as Topic/
79	systematic review/
80	meta-analysis/
81	(meta analy* or metanaly* or metaanaly*).ti,ab.
82	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
83	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
84	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
85	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
86	(search* adj4 literature).ab.
87	(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.
88	cochrane.jw.
89	((pool* or combined) adj2 (data or trials or studies or results)).ab.
90	(or/77-78,81,83-88) use ppez
91	[or/186-189,191-196 use emez]
92	or/90-91
93	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.
94	93 use ppez
95	(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.
96	95 use ppez
97	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.
98	97 use emez
99	94 or 96
100	98 or 99
101	92 or 100
102	76 and 101
103	remove duplicates from 102

Observational studies

Date of initial search: 06/12/2017

Database(s): Embase 1980 to 2017 Week 49, 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	or/1-17
19	*oxygen/
20	oxygen blood level/
21	oxygen therapy/ad, ae, do
22	oxygen desaturation/
23	exp oximetry/
24	hypoxia/ or newborn hypoxia/
25	hyperoxia/
26	or/19-25 use emez
27	*Oxygen/
28	Oxygen Inhalation Therapy/ad, ae, bl
29	exp Oximetry/
30	Hypoxia/
31	Hyperoxia/
32	or/27-31 use ppez
33	26 or 32
34	((oxygen or o2 or spo2) adj2 (level* or saturat* or titrat* or overdos* or toxic* or balanc* or target* or high* or low*)).tw.
35	(hypoxi* or hyperoxi*).tw.
36	or/33-35
37	18 and 36
38	limit 37 to english language
39	limit 38 to yr="1990 -Current"
40	Letter/ use ppez
41	letter.pt. or letter/ use emez
42	note.pt.
43	editorial.pt.
44	Editorial/ use ppez
45	News/ use ppez
46	exp Historical Article/ use ppez
47	Anecdotes as Topic/ use ppez
48	Comment/ use ppez
49	Case Report/ use ppez
50	case report/ or case study/ use emez
51	(letter or comment*).ti.

#	Searches
52	or/40-51
53	randomized controlled trial/ use ppez
54	randomized controlled trial/ use emez
55	random*.ti,ab.
56	or/53-55
57	52 not 56
58	animals/ not humans/ use ppez
59	animal/ not human/ use emez
60	nonhuman/ use emez
61	exp Animals, Laboratory/ use ppez
62	exp Animal Experimentation/ use ppez
63	exp Animal Experiment/ use emez
64	exp Experimental Animal/ use emez
65	exp Models, Animal/ use ppez
66	animal model/ use emez
67	exp Rodentia/ use ppez
68	exp Rodent/ use emez
69	(rat or rats or mouse or mice).ti.
70	or/57-69
71	39 not 70
72	Epidemiologic Studies/
73	Case Control Studies/
74	Retrospective Studies/
75	Cohort Studies/
76	Longitudinal Studies/
77	Follow-Up Studies/
78	Prospective Studies/
79	Cross-Sectional Studies/
80	or/72-79 use ppez
81	clinical study/
82	case control study/
83	family study/
84	longitudinal study/
85	retrospective study/
86	prospective study/
87	cohort analysis/
88	or/81-87 use emez
89	((retrospective$ or cohort$ or longitudinal or follow?up or prospective or cross section$) adj3 (stud$ or research or analys$)).ti.
90	80 or 88 or 89
91	71 and 90
92	remove duplicates from 91

Health economics

Date of initial search: 06/12/2017

Database(s): Embase 1980 to 2017 Week 49, 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.

#	Searches
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	or/1-17
19	*oxygen/
20	oxygen blood level/
21	oxygen therapy/ad, ae, do
22	oxygen desaturation/
23	exp oximetry/
24	hypoxia/ or newborn hypoxia/
25	hyperoxia/
26	or/19-25 use emez
27	*Oxygen/
28	Oxygen Inhalation Therapy/ad, ae, bl
29	exp Oximetry/
30	Hypoxia/
31	Hyperoxia/
32	or/27-31 use ppez
33	26 or 32
34	((oxygen or o2 or spo2) adj2 (level* or saturat* or titrat* or overdos* or toxic* or balanc* or target* or high* or low*)).tw.
35	(hypoxi* or hyperoxi*).tw.
36	or/33-35
37	18 and 36
38	limit 37 to english language
39	limit 38 to yr="1990 -Current"
40	Letter/ use ppez
41	letter.pt. or letter/ use emez
42	note.pt.
43	editorial.pt.
44	Editorial/ use ppez
45	News/ use ppez
46	exp Historical Article/ use ppez
47	Anecdotes as Topic/ use ppez
48	Comment/ use ppez
49	Case Report/ use ppez
50	case report/ or case study/ use emez
51	(letter or comment*).ti.
52	or/40-51
53	randomized controlled trial/ use ppez
54	randomized controlled trial/ use emez
55	random*.ti,ab.
56	or/53-55
57	52 not 56
58	animals/ not humans/ use ppez
59	animal/ not human/ use emez
60	nonhuman/ use emez
61	exp Animals, Laboratory/ use ppez
62	exp Animal Experimentation/ use ppez
63	exp Animal Experiment/ use emez
64	exp Experimental Animal/ use emez
65	exp Models, Animal/ use ppez
66	animal model/ use emez
67	exp Rodentia/ use ppez
68	exp Rodent/ use emez
69	(rat or rats or mouse or mice).ti.
70	or/57-69
71	39 not 70
72	Economics/
73	Value of life/
74	exp "Costs and Cost Analysis"/
75	exp Economics, Hospital/

#	Searches
76	exp Economics, Medical/
77	Economics, Nursing/
78	Economics, Pharmaceutical/
79	exp "Fees and Charges"/
80	exp Budgets/
81	or/72-80 use ppez
82	health economics/
83	exp economic evaluation/
84	exp health care cost/
85	exp fee/
86	budget/
87	funding/
88	or/82-87 use emez
89	budget*.ti,ab.
90	cost*.ti.
91	(economic* or pharmaco?economic*).ti.
92	(price* or pricing*).ti,ab.
93	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
94	(financ* or fee or fees).ti,ab.
95	(value adj2 (money or monetary)).ti,ab.
96	or/89-94
97	81 or 88 or 96
98	71 and 97
99	remove duplicates from 98

Systematic reviews, RCTs, health economics

Date of initial search: 06/12/2017

Database: The Cochrane Library, issue 12 of 12, December 2017

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
#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] this term only
#12	MeSH descriptor: [Oxygen Inhalation Therapy] this term only
#13	MeSH descriptor: [Oximetry] explode all trees
#14	MeSH descriptor: [Hypoxia] this term only
#15	MeSH descriptor: [Hyperoxia] this term only
#16	((oxygen or o2 or spo2) N2 (level* or saturat* or titrat* or overdos* or toxic* or balanc* or target* or high* or low*))
#17	{or #11-#16}
#18	#10 and #17 Publication Year from 1990 to 2017

Literature search strategies for question 4.2 What is the best method for measuring oxygen levels in diagnosing hyperoxia or hypoxia in preterm babies?

Date of initial search: 17/01/2018

Database(s): Embase Classic+Embase 1947 to 2018 January 16, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Date of updated search: 12/06/2018

Database(s): Embase Classic & Embase 1947 to 2018 June 11, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

#	Searches
1	exp Infant, Newborn/ use ppez
2	newborn/ use emczd
3	prematurity/ use emczd
4	(infan* or neonat* or neo-nat*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 emczd
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 emczd
11	exp Intensive Care, Neonatal/ use ppez
12	newborn intensive care/ use emczd
13	exp Intensive Care Units, Neonatal/ use ppez
14	neonatal intensive care unit/ use emczd
15	Neonatal Nursing/ use ppez
16	exp newborn nursing/ use emczd
17	newborn care/ use emczd
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	hypoxia/ use emczd
25	newborn hypoxia/ use emczd
26	hyperoxia/ use emczd
27	Hypoxia/ use ppez
28	hyperoxia/ use ppez
29	(hypox* or anox* or hyperox*).tw.
30	((oxygen* or o2) adj3 (deficien* or asphyx* or low or lower or depriv* or insufficien*)).tw.
31	((oxygen* or o2) adj3 (excess* or high* or increas* or "too much" or optim* or concentrat*)).tw.
32	or/24-31
33	oxygen/ use emczd
34	physiologic monitoring/
35	diagnosis/
36	diagnostic accuracy/
37	dose response/
38	blood analysis/
39	(or/34-38) use emczd
40	33 and 39
41	hypoxia/di or newborn hypoxia/di
42	hyperoxia/di
43	oxygen blood level/
44	oxyhemoglobin/an
45	oxygen desaturation/
46	arterial oxygen saturation/
47	oxygen saturation/
48	exp oximetry/
49	oxygen analyzer/
50	oximeter/
51	pulse oximeter/
52	cutaneous oxygen monitor/
53	(or/41-52) use emczd
54	40 or 53
55	Oxygen/ use ppez
56	Monitoring, Physiologic/
57	Diagnosis/
58	"Diagnostic Techniques and Procedures"/
59	Dose-Response Relationship, Drug/
60	(or/56-59) use ppez

#	Searches
61	55 and 60
62	Hypoxia/di
63	Hyperoxia/di
64	exp Oximetry/
65	Oxyhemoglobins/an
66	Oxygen/an
67	(or/62-66) use ppez
68	61 or 67
69	((oxygen* or o2 or spo2 or tcpo2 or pao2 or blood gas) adj3 (level* or measur* or monitor* or test* or oximetr* or caprometr* or determin* or analy* or titrat*)).tw.
70	((hypox* or hyperox*) adj3 (diagnos* or level* or measur* or monitor* or determin* or test* or detect*)).tw.
71	(oximeter* or oxymeter*).tw.
72	or/54,68-71
73	23 and 32 and 72
74	limit 73 to english language
75	Letter/ use ppez
76	letter.pt. or letter/ use emczd
77	note.pt.
78	editorial.pt.
79	Editorial/ use ppez
80	News/ use ppez
81	exp Historical Article/ use ppez
82	Anecdotes as Topic/ use ppez
83	Comment/ use ppez
84	Case Report/ use ppez
85	case report/ or case study/ use emczd
86	(letter or comment*).ti.
87	or/75-86
88	randomized controlled trial/ use ppez
89	randomized controlled trial/ use emczd
90	random*.ti,ab.
91	or/88-90
92	87 not 91
93	animals/ not humans/ use ppez
94	animal/ not human/ use emczd
95	nonhuman/ use emczd
96	exp Animals, Laboratory/ use ppez
97	exp Animal Experimentation/ use ppez
98	exp Animal Experiment/ use emczd
99	exp Experimental Animal/ use emczd
100	exp Models, Animal/ use ppez
101	animal model/ use emczd
102	exp Rodentia/ use ppez
103	exp Rodent/ use emczd
104	(rat or rats or mouse or mice).ti.
105	or/92-104
106	74 not 105
107	remove duplicates from 106

Health economics

Date of initial search: 18/01/2018

Database(s): Embase Classic+Embase 1947 to 2018 January 16, 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: 13/06/2018

Database(s): Embase Classic & Embase 1947 to 2018 June 11, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

#	Searches
1	exp Infant, Newborn/ use ppez
2	newborn/ use emczd

#	Searches
3	prematurity/ use emczd
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 emczd
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 emczd
11	exp Intensive Care, Neonatal/ use ppez
12	newborn intensive care/ use emczd
13	exp Intensive Care Units, Neonatal/ use ppez
14	neonatal intensive care unit/ use emczd
15	Neonatal Nursing/ use ppez
16	exp newborn nursing/ use emczd
17	newborn care/ use emczd
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	hypoxia/ use emczd
25	newborn hypoxia/ use emczd
26	hyperoxia/ use emczd
27	Hypoxia/ use ppez
28	hyperoxia/ use ppez
29	(hypox* or anox* or hyperox*).tw.
30	((oxygen* or o2) adj3 (deficien* or asphyx* or low or lower or depriv* or insufficien*)).tw.
31	((oxygen* or o2) adj3 (excess* or high* or increas* or "too much" or optim* or concentrat*)).tw.
32	or/24-31
33	oxygen/ use emczd
34	physiologic monitoring/
35	diagnosis/
36	diagnostic accuracy/
37	dose response/
38	blood analysis/
39	or/34-38 use emczd
40	33 and 39
41	hypoxia/di or newborn hypoxia/di
42	hyperoxia/di
43	oxygen blood level/
44	oxyhemoglobin/an
45	oxygen desaturation/
46	arterial oxygen saturation/
47	oxygen saturation/
48	exp oximetry/
49	oxygen analyzer/
50	oximeter/
51	pulse oximeter/
52	cutaneous oxygen monitor/
53	or/41-52 use emczd
54	40 or 53
55	Oxygen/ use ppez
56	Monitoring, Physiologic/
57	Diagnosis/
58	"Diagnostic Techniques and Procedures"/
59	Dose-Response Relationship, Drug/
60	or/56-59 use ppez
61	55 and 60
62	Hypoxia/di
63	Hyperoxia/di
64	exp Oximetry/
65	Oxyhemoglobins/an
66	Oxygen/an
67	or/62-66 use ppez
68	61 or 67

#	Searches
69	((oxygen* or o2 or spo2 or tcpo2 or pao2 or blood gas) adj3 (level* or measur* or monitor* or test* or oximetr* or caprometr* or determin* or analy* or titrat*)).tw.
70	((hypox* or hyperox*) adj3 (diagnos* or level* or measur* or monitor* or determin* or test* or detect*)).tw.
71	(oximeter* or oxymeter*).tw.
72	or/54,68-71
73	23 and 32 and 72
74	limit 73 to english language
75	Letter/ use ppez
76	letter.pt. or letter/ use emczd
77	note.pt.
78	editorial.pt.
79	Editorial/ use ppez
80	News/ use ppez
81	exp Historical Article/ use ppez
82	Anecdotes as Topic/ use ppez
83	Comment/ use ppez
84	Case Report/ use ppez
85	case report/ or case study/ use emczd
86	(letter or comment*).ti.
87	or/75-86
88	randomized controlled trial/ use ppez
89	randomized controlled trial/ use emczd
90	random*.ti,ab.
91	or/88-90
92	87 not 91
93	animals/ not humans/ use ppez
94	animal/ not human/ use emczd
95	nonhuman/ use emczd
96	exp Animals, Laboratory/ use ppez
97	exp Animal Experimentation/ use ppez
98	exp Animal Experiment/ use emczd
99	exp Experimental Animal/ use emczd
100	exp Models, Animal/ use ppez
101	animal model/ use emczd
102	exp Rodentia/ use ppez
103	exp Rodent/ use emczd
104	(rat or rats or mouse or mice).ti.
105	or/92-104
106	74 not 105
107	remove duplicates from 106
108	Economics/
109	Value of life/
110	exp "Costs and Cost Analysis"/
111	exp Economics, Hospital/
112	exp Economics, Medical/
113	Economics, Nursing/
114	Economics, Pharmaceutical/
115	exp "Fees and Charges"/
116	exp Budgets/
117	or/108-116 use ppez
118	health economics/
119	exp economic evaluation/
120	exp health care cost/
121	exp fee/
122	budget/
123	funding/
124	or/118-123 use emczd
125	budget*.ti,ab.
126	cost*.ti.
127	(economic* or pharmaco?economic*).ti.
128	(price* or pricing*).ti,ab.
129	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
130	(financ* or fee or fees).ti,ab.
131	(value adj2 (money or monetary)).ti,ab.
132	or/125-130
133	117 or 124 or 132
134	107 and 133

Cochrane Library

Date of initial search: 17/01/2018

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

Date of updated search: 13/06/2018

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

ID	Search
#1	MeSH descriptor: [Infant, Newborn] explode all trees
#2	(infan* or neonat* or neo-nat* or newborn* or baby or babies)
#3	(preterm or pre-term or prematur* or pre-matur* or pre?mie* or premie*1)
#4	(low near birth near weigh*)
#5	MeSH descriptor: [Intensive Care, Neonatal] this term only
#6	MeSH descriptor: [Intensive Care Units, Neonatal] this term only
#7	(special and care and baby and unit*)
#8	((newborn or neonatal or neo-natal) near (ICU*1 or unit*))
#9	(SCBU or NICU)
#10	{or #1-#9}
#11	MeSH descriptor: [Hypoxia] this term only
#12	MeSH descriptor: [Hyperoxia] this term only
#13	(hypox* or anox* or hyperox*)
#14	((oxygen* or o2) near/3 (deficien* or asphyx* or low or lower or depriv* or insufficien*))
#15	((oxygen* or o2) near/3 (excess* or high* or increas* or "too much" or optim* or concentrat*))
#16	{or #11-#15}
#17	#10 and #16
#18	MeSH descriptor: [Oxygen] this term only
#19	MeSH descriptor: [Monitoring, Physiologic] this term only
#20	MeSH descriptor: [Diagnosis] this term only
#21	MeSH descriptor: [Diagnostic Techniques and Procedures] this term only
#22	MeSH descriptor: [Dose-Response Relationship, Drug] this term only
#23	{or #19-#22}
#24	#18 and #23
#25	MeSH descriptor: [Hypoxia] this term only and with qualifier(s): [Diagnosis - DI]
#26	MeSH descriptor: [Hyperoxia] this term only and with qualifier(s): [Diagnosis - DI]
#27	MeSH descriptor: [Oximetry] explode all trees
#28	MeSH descriptor: [Oxygen] this term only and with qualifier(s): [Analysis - AN]
#29	{or #24-#28}
#30	((oxygen* or o2 or spo2 or tcpo2 or pao2 or blood gas) near/3 (level* or measur* or monitor* or test* or oximetr* or caprometr* or determin* or analy* or titrat*))
#31	((hypox* or hyperox*) near/3 (diagnos* or level* or measur* or monitor* or determin* or test*))
#32	(oximeter* or oxymeter*)
#33	#29 or #30
#34	#17 and #33

Literature search strategies for question 4.3 What carbon dioxide levels are optimal in the management of preterm babies?

Systematic reviews and RCTs

Date of initial search: 20/12/2017

Database(s): Embase 1980 to 2017 Week 51, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Date of updated search: 12/06/2018

Database(s): Embase Classic & Embase 1947 to 2018 June 11, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

#	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	carbon dioxide/
25	carbon dioxide blood level/
26	exp capnometry/
27	hypercapnia/
28	hypocapnia/
29	or/24-28 use emez
30	Carbon Dioxide/
31	Blood Gas Monitoring, Transcutaneous/
32	Capnography/
33	Hypercapnia/
34	Hypocapnia/
35	or/30-34 use ppez
36	29 or 35
37	((carbon and dioxide) or (carbon dioxide or co2)).tw.
38	(capnomet* or capnogra*).tw.
39	(hypercapn* or hypocapn*).tw.
40	or/36-39
41	23 and 40
42	limit 41 to english language
43	limit 42 to yr="1990 -Current"
44	Letter/ use ppez
45	letter.pt. or letter/ use emez
46	note.pt.
47	editorial.pt.
48	Editorial/ use ppez
49	News/ use ppez
50	exp Historical Article/ use ppez
51	Anecdotes as Topic/ use ppez
52	Comment/ use ppez
53	Case Report/ use ppez
54	case report/ or case study/ use emez
55	(letter or comment*).ti.
56	or/44-55
57	randomized controlled trial/ use ppez
58	randomized controlled trial/ use emez
59	random*.ti,ab.
60	or/57-59
61	56 not 60
62	animals/ not humans/ use ppez
63	animal/ not human/ use emez
64	nonhuman/ use emez
65	exp Animals, Laboratory/ use ppez
66	exp Animal Experimentation/ use ppez

#	Searches
67	exp Animal Experiment/ use emez
68	exp Experimental Animal/ use emez
69	exp Models, Animal/ use ppez
70	animal model/ use emez
71	exp Rodentia/ use ppez
72	exp Rodent/ use emez
73	(rat or rats or mouse or mice).ti.
74	or/61-73
75	43 not 74
76	remove duplicates from 75
77	Meta-Analysis/
78	Meta-Analysis as Topic/
79	systematic review/
80	meta-analysis/
81	(meta analy* or metanaly* or metaanaly*).ti,ab.
82	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
83	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
84	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
85	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
86	(search* adj4 literature).ab.
87	(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.
88	cochrane.jw.
89	((pool* or combined) adj2 (data or trials or studies or results)).ab.
90	or/77-78,81,83-88 use ppez
91	or/79-82,84-89 use emez
92	or/90-91
93	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.
94	93 use ppez
95	(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.
96	95 use ppez
97	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.
98	97 use emez
99	94 or 96
100	98 or 99
101	92 or 100
102	76 and 101

Observational studies

Date of initial search: 20/12/2017

Database(s): Embase 1980 to 2017 Week 51, 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: 13/06/2018

Database(s): Embase Classic & Embase 1947 to 2018 June 12, 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

#	Searches
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	carbon dioxide/
25	carbon dioxide blood level/
26	exp capnometry/
27	hypercapnia/
28	hypocapnia/
29	or/24-28 use emez
30	Carbon Dioxide/
31	Blood Gas Monitoring, Transcutaneous/
32	Capnography/
33	Hypercapnia/
34	Hypocapnia/
35	or/30-34 use ppez
36	29 or 35
37	((carbon and dioxide) or (carbon dioxide or co2)).tw.
38	(capnomet* or capnogra*).tw.
39	(hypercapn* or hypocapn*).tw.
40	or/36-39
41	23 and 40
42	limit 41 to english language
43	limit 42 to yr="1990 -Current"
44	Letter/ use ppez
45	letter.pt. or letter/ use emez
46	note.pt.
47	editorial.pt.
48	Editorial/ use ppez
49	News/ use ppez
50	exp Historical Article/ use ppez
51	Anecdotes as Topic/ use ppez
52	Comment/ use ppez
53	Case Report/ use ppez
54	case report/ or case study/ use emez
55	(letter or comment*).ti.
56	or/44-55
57	randomized controlled trial/ use ppez
58	randomized controlled trial/ use emez
59	random*.ti,ab.
60	or/57-59
61	56 not 60
62	animals/ not humans/ use ppez
63	animal/ not human/ use emez
64	nonhuman/ use emez
65	exp Animals, Laboratory/ use ppez
66	exp Animal Experimentation/ use ppez
67	exp Animal Experiment/ use emez
68	exp Experimental Animal/ use emez
69	exp Models, Animal/ use ppez
70	animal model/ use emez
71	exp Rodentia/ use ppez
72	exp Rodent/ use emez
73	(rat or rats or mouse or mice).ti.
74	or/61-73
75	43 not 74

#	Searches
76	remove duplicates from 75
77	Epidemiologic Studies/
78	Case Control Studies/
79	Retrospective Studies/
80	Cohort Studies/
81	Longitudinal Studies/
82	Follow-Up Studies/
83	Prospective Studies/
84	Cross-Sectional Studies/
85	or/77-84 use ppez
86	clinical study/
87	case control study/
88	family study/
89	longitudinal study/
90	retrospective study/
91	prospective study/
92	cohort analysis/
93	or/86-92 use emez
94	((retrospective$ or cohort$ or longitudinal or follow?up or prospective or cross section$) adj3 (stud$ or research or analys$)).ti.
95	85 or 93 or 94
96	76 and 95

Health economics

Date of initial search: 20/12/2017

Database(s): Embase 1980 to 2017 Week 51, 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: 13/06/2018

Database(s): Embase Classic & Embase 1947 to 2018 June 12, 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	carbon dioxide/
25	carbon dioxide blood level/
26	exp capnometry/
27	hypercapnia/

#	Searches
28	hypocapnia/
29	or/24-28 use emez
30	Carbon Dioxide/
31	Blood Gas Monitoring, Transcutaneous/
32	Capnography/
33	Hypercapnia/
34	Hypocapnia/
35	or/30-34 use ppez
36	29 or 35
37	((carbon and dioxide) or (carbon dioxide or co2)).tw.
38	(capnomet* or capnogra*).tw.
39	(hypercapn* or hypocapn*).tw.
40	or/36-39
41	23 and 40
42	limit 41 to english language
43	limit 42 to yr="1990 -Current"
44	Letter/ use ppez
45	letter.pt. or letter/ use emez
46	note.pt.
47	editorial.pt.
48	Editorial/ use ppez
49	News/ use ppez
50	exp Historical Article/ use ppez
51	Anecdotes as Topic/ use ppez
52	Comment/ use ppez
53	Case Report/ use ppez
54	case report/ or case study/ use emez
55	(letter or comment*).ti.
56	or/44-55
57	randomized controlled trial/ use ppez
58	randomized controlled trial/ use emez
59	random*.ti,ab.
60	or/57-59
61	56 not 60
62	animals/ not humans/ use ppez
63	animal/ not human/ use emez
64	nonhuman/ use emez
65	exp Animals, Laboratory/ use ppez
66	exp Animal Experimentation/ use ppez
67	exp Animal Experiment/ use emez
68	exp Experimental Animal/ use emez
69	exp Models, Animal/ use ppez
70	animal model/ use emez
71	exp Rodentia/ use ppez
72	exp Rodent/ use emez
73	(rat or rats or mouse or mice).ti.
74	or/61-73
75	43 not 74
76	remove duplicates from 75
77	Economics/
78	Value of life/
79	exp "Costs and Cost Analysis"/
80	exp Economics, Hospital/
81	exp Economics, Medical/
82	Economics, Nursing/
83	Economics, Pharmaceutical/
84	exp "Fees and Charges"/
85	exp Budgets/
86	or/77-85 use ppez
87	health economics/
88	exp economic evaluation/
89	exp health care cost/
90	exp fee/
91	budget/
92	funding/
93	or/87-92 use emez
94	budget*.ti,ab.

#	Searches
95	cost*.ti.
96	(economic* or pharmaco?economic*).ti.
97	(price* or pricing*).ti,ab.
98	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
99	(financ* or fee or fees).ti,ab.
100	(value adj2 (money or monetary)).ti,ab.
101	or/94-99
102	86 or 93 or 101
103	76 and 102

Systematic reviews, RCTs, health economics

Date of initial search: 20/12/2017

Database: The Cochrane Library, issue 12 of 12, December 2017

Date of updated search: 13/06/2018

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
#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: [Carbon Dioxide] this term only
#12	MeSH descriptor: [Blood Gas Monitoring, Transcutaneous] this term only
#13	MeSH descriptor: [Capnography] this term only
#14	MeSH descriptor: [Hypercapnia] this term only
#15	MeSH descriptor: [Hypocapnia] this term only
#16	(carbon dioxide or co2 or hypercapn* or hypocapn*)
#17	{or #11-#16}
#18	#10 and #17 Publication Year from 1990 to 2017

Literature search strategies for question 4.4 What blood pressure monitoring strategies are associated with improved outcomes in preterm babies requiring respiratory support?

Date of initial search: 20/03/2018

Database(s): Embase 1980 to 2017 Week 51, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Date of updated search: 12/06/2018

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

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

#	Searches
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	*blood pressure measurement/
20	*blood pressure monitoring/
21	exp blood pressure meter/
22	exp blood pressure monitor/
23	exp blood pressure/ and monitoring/
24	umbilical artery catheter/ or umbilical artery catheterization/
25	peripheral arterial tonometry/
26	*artery catheterization/
27	*oscillometry/
28	(or/19-27) use emez
29	*Blood Pressure Determination/
30	exp Sphygmomanometers/
31	(Monitoring, Physiologic/ or Physical Examination/) and Blood Pressure/
32	(exp Catheters/ or Catheterization/) and Umbilical Arteries/
33	*Catheterization, Peripheral/
34	*Oscillometry/
35	(or/29-34) use ppez
36	((blood pressure or bp) adj3 (assess* or determin* or examin* or measur* or monitor*)).tw.
37	((umbilic* or peripheral) adj2 (artery or arteries or arterial) adj2 (access or cannula* or catheter* or line or lines or tonometr*)).tw.
38	(oscillomet* or oscillogra* or sphygmomanomet*).tw.
39	or/36-38
40	28 or 35 or 39
41	18 and 40
42	limit 41 to english language
43	limit 42 to yr="1990 -Current"
44	Letter/ use ppez
45	letter.pt. or letter/ use emez
46	note.pt.
47	editorial.pt.
48	Editorial/ use ppez
49	News/ use ppez
50	exp Historical Article/ use ppez
51	Anecdotes as Topic/ use ppez
52	Comment/ use ppez
53	Case Report/ use ppez
54	case report/ or case study/ use emez
55	(letter or comment*).ti.
56	or/44-55
57	randomized controlled trial/ use ppez
58	randomized controlled trial/ use emez
59	random*.ti,ab.
60	or/57-59
61	56 not 60
62	animals/ not humans/ use ppez
63	animal/ not human/ use emez
64	nonhuman/ use emez
65	exp Animals, Laboratory/ use ppez
66	exp Animal Experimentation/ use ppez
67	exp Animal Experiment/ use emez
68	exp Experimental Animal/ use emez
69	exp Models, Animal/ use ppez
70	animal model/ use emez
71	exp Rodentia/ use ppez
72	exp Rodent/ use emez
73	(rat or rats or mouse or mice).ti.

#	Searches
74	or/61-73
75	43 not 74
76	remove duplicates from 75

Health economics

Date of initial search: 20/03/2018

Database(s): Embase 1980 to 2018 Week 12, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Date of updated search: 12/06/2018

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

#	Searches
1	exp Infant, Newborn/ use ppez
2	newborn/ use emez
3	prematurity/ use emez
4	(infan* or neonat* or newborn* or baby or babies).ti,ab,jw,nw.
5	(preterm or pre-term or prematur* or pre-matur* or pre?mie* or premie*1).tw.
6	exp low birth weight/ use emez
7	(low adj3 birth adj3 weigh*).tw.
8	(LBW or VLBW).tw.
9	exp Intensive Care, Neonatal/ use ppez
10	newborn intensive care/ use emez
11	exp Intensive Care Units, Neonatal/ use ppez
12	neonatal intensive care unit/ use emez
13	(special and care and baby and unit*).tw.
14	((newborn or neonatal) adj ICU*1).tw.
15	(SCBU or NICU).tw.
16	exp Respiratory Distress Syndrome, Newborn/ use ppez
17	neonatal respiratory distress syndrome/ use emez
18	or/1-17
19	*blood pressure measurement/
20	*blood pressure monitoring/
21	exp blood pressure meter/
22	exp blood pressure monitor/
23	exp blood pressure/ and monitoring/
24	umbilical artery catheter/ or umbilical artery catheterization/
25	peripheral arterial tonometry/
26	*artery catheterization/
27	*oscillometry/
28	(or/19-27) use emez
29	*Blood Pressure Determination/
30	exp Sphygmomanometers/
31	(Monitoring, Physiologic/ or Physical Examination/) and Blood Pressure/
32	(Catheters/ or Catheterization/) and Umbilical Arteries/
33	*Catheterization, Peripheral/
34	*Oscillometry/
35	(or/29-34) use ppez
36	((blood pressure or bp) adj3 (assess* or determin* or examin* or measur* or monitor*)).tw.
37	((umbilic* or peripheral) adj2 (artery or arteries or arterial) adj2 (access or cannula* or catheter* or line or lines or tonometr*)).tw.
38	(oscillomet* or oscillogra* or sphygmomanomet*).tw.
39	or/36-38
40	28 or 35 or 39
41	18 and 40
42	limit 41 to english language
43	limit 42 to yr="1990 -Current"
44	Economics/
45	Value of life/
46	exp "Costs and Cost Analysis"/

#	Searches
47	exp Economics, Hospital/
48	exp Economics, Medical/
49	Economics, Nursing/
50	Economics, Pharmaceutical/
51	exp "Fees and Charges"/
52	exp Budgets/
53	(or/44-52) use ppez
54	health economics/
55	exp economic evaluation/
56	exp health care cost/
57	exp fee/
58	budget/
59	funding/
60	(or/54-59) use emez
61	budget*.ti,ab.
62	cost*.ti.
63	(economic* or pharmaco?economic*).ti.
64	(price* or pricing*).ti,ab.
65	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
66	(financ* or fee or fees).ti,ab.
67	(value adj2 (money or monetary)).ti,ab.
68	or/61-66
69	53 or 60 or 68
70	43 and 69
71	remove duplicates from 70

Date of initial search: 20/03/2018

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

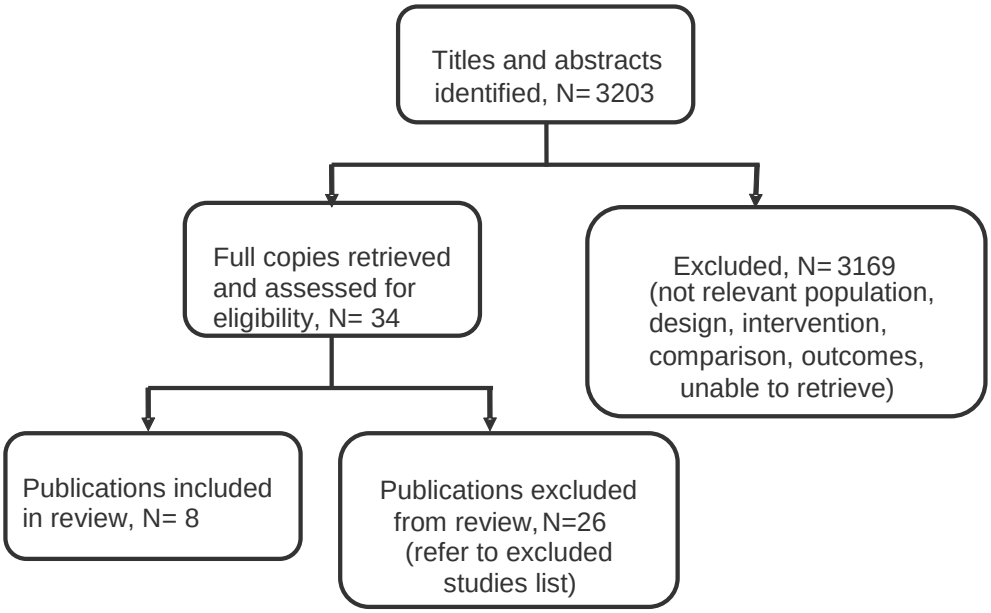
Date of updated search: 13/06/2018

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

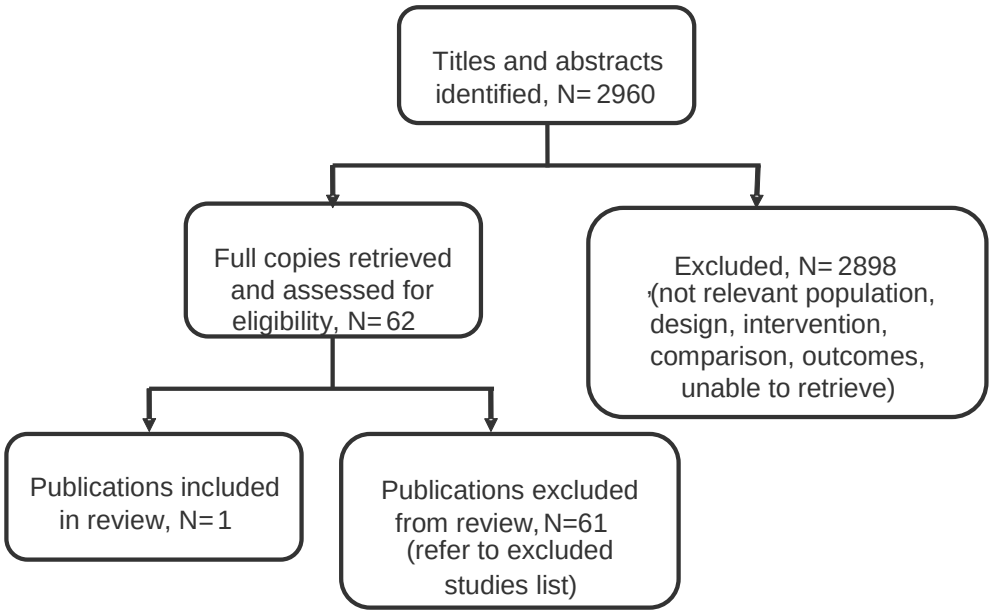
ID	Search
#1	MeSH descriptor: [Infant, Newborn] explode all trees
#2	(infan* or neonat* or neo-nat* or newborn* or baby or babies)
#3	(preterm or pre-term or prematur* or pre-matur* or pre?mie* or premie*1)
#4	(low near birth near weigh*)
#5	MeSH descriptor: [Intensive Care, Neonatal] this term only
#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: [Blood Pressure Determination] this term only
#12	MeSH descriptor: [Sphygmomanometers] explode all trees
#13	MeSH descriptor: [Catheterization, Peripheral] this term only
#14	MeSH descriptor: [Oscillometry] this term only
#15	{or #11-#14}
#16	MeSH descriptor: [Monitoring, Physiologic] this term only
#17	MeSH descriptor: [Physical Examination] this term only
#18	{or #16-#17}
#19	MeSH descriptor: [Blood Pressure] this term only
#20	#18 and #19
#21	MeSH descriptor: [Catheters] explode all trees
#22	MeSH descriptor: [Catheterization] this term only
#23	{or #21-#22}
#24	MeSH descriptor: [Umbilical Arteries] this term only
#25	#23 and #24
#26	#15 or #20 or #25
#27	((blood pressure or bp) N3 (assess* or determin* or examin* or measur* or monitor*))
#28	((umbilic* or peripheral) N3 (artery or arteries or arterial) N3 (access or cannula* or catheter* or line or lines or tonometr*))
#29	(oscillomet* or oscillogra* or sphygmomanomet*)
#30	{or #27-#29}
#31	#26 or #30

Appendix C – Clinical evidence study selection

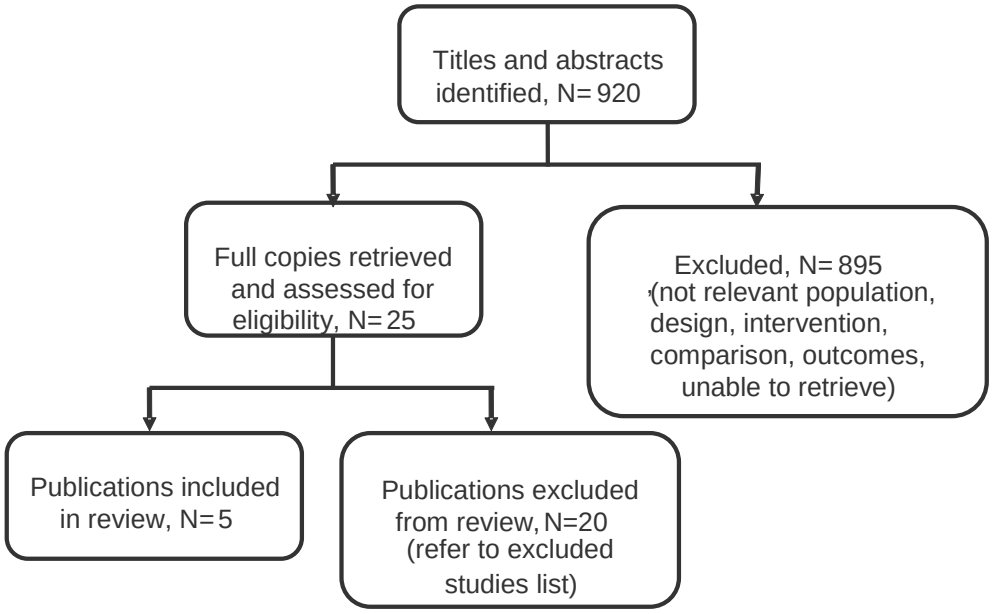
Clinical evidence study selection for question 4.1 What oxygen levels are optimal in the management of preterm babies?



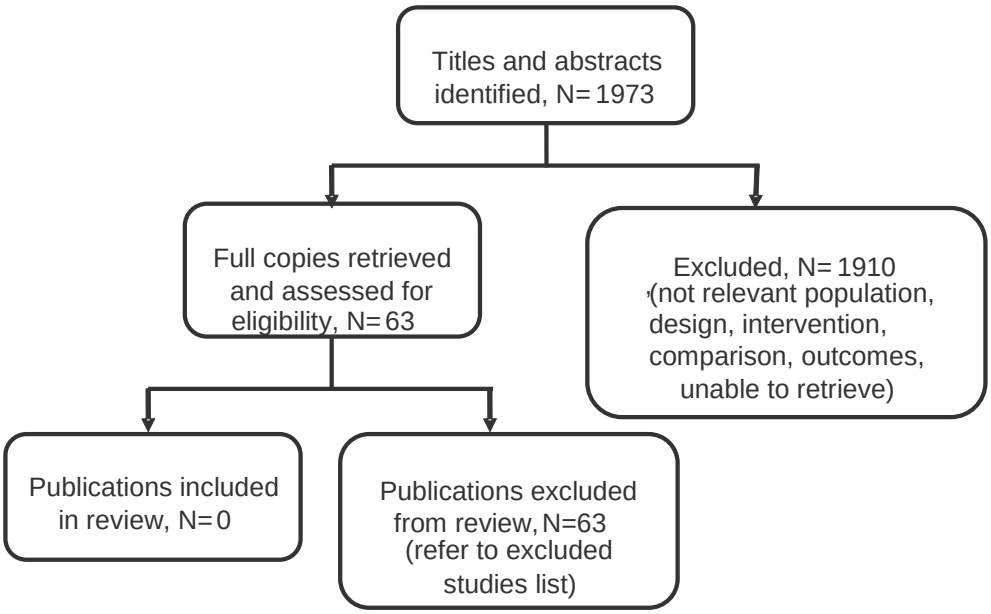
Clinical evidence study selection for question 4.2 What is the best method for measuring oxygen levels in diagnosing hyperoxia or hypoxia in preterm babies?



Clinical evidence study selection for question 4.3 What carbon dioxide levels are optimal in the management of preterm babies?



Clinical evidence study selection for question 4.4 What blood pressure monitoring strategies are associated with improved outcomes in preterm babies requiring respiratory support?



Appendix D – Clinical evidence tables

Clinical evidence tables for question 4.1 What oxygen levels are optimal in the management of preterm babies?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Askie, L. M., Henderson-Smart, D. J., Irwig, L., Simpson, J. M., Oxygen-saturation targets and outcomes in extremely preterm infants, New England Journal of MedicineN Engl J Med, 349, 959-67, 2003 **Ref Id** 751952 **Country/ies where the study was carried out** Australia **Study type** Randomised controlled trial **Aim of the study**	**Sample size** n= 333 babies randomised, and an additional 25 eligible multiples were assigned to the same group as their sibling (n=178 standard saturation group; n=180 high-saturation group) **Characteristics** Gestation age , weeks in mean (SD in parentheses): standard saturation group: 26.6 (1.7); high saturation group: 26.5 (1.6) Birth weight in grams (SD in parentheses): standard saturation group: 918 (229);	**Interventions** Target oxygen saturation range of either 91 to 94 percent (standard-saturation group) or 95 to 98 percent (high-saturation group), as measured with a pulse oximeter (model N-3000, Nellcor) whose algorithm assesses functional oxygen saturation.	**Details** Methods: Randomised, multicentre (Australia), trial Primary outcomes: The primary outcomes assessed at a corrected age of one year (the chronologic age plus the number of weeks of prematurity) included growth, in terms of the mean weight, the mean length, the mean head circumference, and the proportion of infants with a weight below the 10th percentile, and the presence of a major developmental abnormality, defined as blindness, cerebral palsy, or a score on the revised Griffiths Mental Developmental Scales that was more than 2 SD below the mean (general	**Results** **Outcome: Severe Retinopathy of Prematurity (randomised population)** Askie 2003: higher oxygen target: 22/180; lower oxygen target 28/178 (stage 3 or 4 ROP)/ higher oxygen target: 11/180; lower oxygen target: 20/178 (ablative retinal surgery) **Outcome: Death before discharge** Askie 2003: higher oxygen target: 9/180; lower oxygen target 5/178 **Outcome: Bronchopulmonary Dysplasia at 36 weeks PMA (randomised population)** Askie 2003: higher oxygen target: 116/180; lower oxygen target 82/178	**Limitations** Random sequence generation: Low risk (Randomization was stratified with the use of a dynamic balancing method to ensure a balance of treatment-group assignments within each stratum defined according to hospital, singleton or multiple birth, and gestational age (22 to 27 weeks or 28 to 29 weeks)) Allocation concealment: Low risk (Central telephone randomization ensured concealment of the treatment-group assignments.) Blinding of participants and personnel: Low risk (Blinding was maintained by oximeter design)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
To determine whether maintaining the oxygen saturation at a level higher than the standard range in extremely preterm infants with a long-term dependence on supplemental oxygen improves growth and neurodevelopmental outcomes. Secondary aims were to determine whether the higher oxygen-saturation levels had other beneficial or adverse physical or psychosocial effects on infants or parents. **Study dates** September 1996 - September 2000 **Source of funding** Supported by the National Health and Medical Research Council of Australia (grants 960876 and 991030 to Drs.	high saturation group: 916 (231) Male sex %: standard saturation group: 52; high saturation group: 54 Surfactant treatment %: standard saturation group: 78; high saturation group: 76 Antenatal steroids %: standard saturation group: 83; high saturation group: 83 **Inclusion criteria** Infants born at less than 30 weeks of gestational age (determined on the basis of the first day of the mother's last menstrual period, prenatal ultrasonography, or both or, if these data were not available, postnatal clinical assessment) who		quotient,<77). Blindness was defined as a visual acuity in both eyes of less than 6/60. Cerebral palsy was diagnosed if the child had nonprogressive motor impairment characterized by abnormal muscle tone and a decreased range or decreased control of movements, accompanied by neurologic signs. Secondary outcomes: The secondary outcomes included the effect of the treatment-group assignment on the duration of oxygen therapy, the duration of assisted ventilation and of the hospital stay, and the frequency of homebased oxygen therapy. Parental stress and parent–infant interaction were assessed by means of validated scales (the Edinburgh Postnatal Depression Scale, the Infant Temperament Questionnaire, the Toddler Temperament Scale, the		Blinding of outcome assessors: Low risk (Parents and assessors were unaware of allocation) Incomplete outcome data (attrition bias): Low risk (all infants followed up for the outcomes of interest for this review) Selective reporting: low risk (All outcomes pre-specified in the registration record were reported) **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Henderson-Smart, Irwig, and Simpson and Public Health Postgraduate Research Scholarship 997549 to Dr. Askie); the Financial Markets Foundation for Children, Australia (funding to Drs. Henderson-Smart, Irwig, and Simpson); and the Centre for Perinatal Health Services Research, University of Sydney, Sydney, Australia.	remained dependent on supplemental oxygen (delivered by any method and at any level) at 32 weeks of postmenstrual age were eligible for enrolment. Dependence on supplemental oxygen at 32 weeks of postmenstrual age, rather than 36 weeks, was used as a criterion for inclusion because it was current clinical practice to choose between the standard target range for oxygen saturation and a higher target range at this point in the infant's life **Exclusion criteria** Criteria for exclusion before		Parenting Stress Index, Short Form, and the Impact-on-Family Scale. Retinopathy of prematurity was assessed by routine ophthalmic examinations at two-week intervals from enrolment until the resolution of retinopathy, with grading according to the International Classification of Retinopathy of Prematurity. Reports by the parents on the use of health services and rehospitalizations during the first year of life were obtained through quarterly telephone contact by the research nurses, and rehospitalizations were confirmed through a review of the medical records. Causes of death were classified according to the codes of the International Classification of Diseases, Ninth Revision, and confirmed on the basis of the hospital discharge summary, a		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	randomization included major congenital abnormalities, major surgery or a severe intracranial disorder diagnosed before 32 weeks of postmenstrual age, and a multiple birth in which three or more infants were eligible.		post-mortem examination report, a coroner's report, or a death certificate.		
Full citation Boost-Ii Australia, United Kingdom Collaborative, Groups, Tarnow-Mordi, W., Stenson, B., Kirby, A., Juszczak, E., Donoghoe, M., Deshpande, S., Morley, C., King, A., Doyle, L. W., Fleck, B. W., Davis, P. G., Halliday, H. L., Hague, W., Cairns, P., Darlow, B. A., Fielder, A. R., Gebski, V., Marlow, N., Simmer, K., Tin, W., Ghadge, A., Williams, C., Keech, A., Wardle, S. P.,	**Sample size** Please see Askie et al 2018 NEOPROM Collaboration Meta-analysis **Characteristics** **Inclusion criteria** **Exclusion criteria**	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Kecskes, Z., Kluckow, M., Gole, G., Evans, N., Malcolm, G., Luig, M., Wright, I., Stack, J., Tan, K., Pritchard, M., Gray, P. H., Morris, S., Headley, B., Dargaville, P., Simes, R. J., Brocklehurst, P., Outcomes of Two Trials of Oxygen-Saturation Targets in Preterm Infants, New England Journal of Medicine, 374, 749-60, 2016 **Ref Id** 473181 **Country/ies where the study was carried out** **Study type** **Aim of the study** **Study dates** **Source of funding**					

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Carlo, Wa, Finer, Nn, Walsh, Mc, Rich, W, Gantz, Mg, Laptook, Ar, Yoder, Ba, Faix, Rg, Das, A, Poole, Wk, Schibler, K, Newman, Ns, Ambalavanan, N, Frantz, Id, Piazza, Aj, Sánchez, Pj, Morris, Bh, Laroia, N, Phelps, Dl, Poindexter, Bb, Cotten, Cm, Meurs, Kp, Duara, S, Narendran, V, Sood, Bg, O'Shea, Tm, Bell, Ef, Ehrenkranz, Ra, Watterberg, Kl, Higgins, Rd, Target ranges of oxygen saturation in extremely preterm infants, New England journal of medicine, 362, 1959-1969, 2010 **Ref Id** 666065 **Country/ies where the study was carried out**	**Sample size** Please see Askie et al 2018 NEOPROM Collaboration Meta-analysis **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 Darlow, B. A., Marschner, S. L., Donoghoe, M., Battin, M. R., Broadbent, R. S., Elder, M. J., Hewson, M. P., Meyer, M. P., Ghadge, A., Graham, P., McNeill, N. J., Kuschel, C. A., Tarnow-Mordi, W. O., Benefits Of Oxygen Saturation Targeting-New Zealand Collaborative, Group, Randomized controlled trial of oxygen saturation targets in very preterm infants: two year	**Sample size** Please see Askie et al 2018 NEOPROM Collaboration Meta-analysis **Characteristics** **Inclusion criteria** **Exclusion criteria**	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
outcomes, Journal of Pediatrics, 165, 30-35.e2, 2014 **Ref Id** 752182 **Country/ies where the study was carried out** **Study type** **Aim of the study** **Study dates** **Source of funding**					
Full citation Boost Ii United Kingdom Collaborative Group, Boost Ii Australia Collaborative Group, Boost Ii New Zealand Collaborative Group, Stenson, B. J.,	**Sample size** Please see Askie et al 2018 NEOPROM Collaboration Meta-analysis	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Tarnow-Mordi, W. O., Darlow, B. A., Simes, J., Juszczak, E., Askie, L., Battin, M., Bowler, U., Broadbent, R., Cairns, P., Davis, P. G., Deshpande, S., Donoghoe, M., Doyle, L., Fleck, B. W., Ghadge, A., Hague, W., Halliday, H. L., Hewson, M., King, A., Kirby, A., Marlow, N., Meyer, M., Morley, C., Simmer, K., Tin, W., Wardle, S. P., Brocklehurst, P., Oxygen saturation and outcomes in preterm infants, New England Journal of MedicineN Engl J Med, 368, 2094-104, 2013 **Ref Id** 752407 **Country/ies where the study was carried out** **Study type** **Aim of the study**	**Characteristics** **Inclusion criteria** **Exclusion criteria**				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates **Source of funding**					
Full citation Schmidt, B., Whyte, R. K., Asztalos, E. V., Moddemann, D., Poets, C., Rabi, Y., Solimano, A., Roberts, R. S., Canadian Oxygen Trial, Group, Effects of targeting higher vs lower arterial oxygen saturations on death or disability in extremely preterm infants: a randomized clinical trial, JAMA, 309, 2111-20, 2013 **Ref Id** 665555 **Country/ies where the study was carried out**	**Sample size** Please see Askie et al 2018 NEOPROM Collaboration Meta-analysis **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 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, P. W., Goldstein, R. F., Acarregui, M. J., Adams-Chapman, I., Pappas, A., Hintz, S. R., Poindexter, B., Dusick, A. M.,	**Sample size** Please see Askie et al 2018 NEOPROM Collaboration Meta-analysis **Characteristics** **Inclusion criteria** **Exclusion criteria**	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
McGowan, E. C., Ehrenkranz, R. A., Bodnar, A., Bauer, C. R., Fuller, J., O'Shea, T. M., Myers, G. J., Higgins, R. D., Support Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network, Neurodevelopmental outcomes in the early CPAP and pulse oximetry trial, New England Journal of Medicine, 367, 2495-504, 2012 **Ref Id** 412035 **Country/ies where the study was carried out** **Study type** **Aim of the study** **Study dates**					

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding					
Full citation Askie, L. M., Darlow, B. A., Finer, N., et al.,, Association between oxygen saturation targeting and death or disability in extremely preterm infants in the neonatal oxygenation prospective meta-analysis collaboration, JAMAJama, 319, 2190-2201, 2018 **Ref Id** 883963 **Country/ies where the study was carried out** International **Study type** Meta-analysis of individual participant data from 5 RCTs	**Sample size** **SUPPORT 2010*** n=1316 randomised (n=654 lower oxygen target; n=662 higher oxygen target) **COT 2013*** n= 1201 randomised (n=602 lower oxygen target; n=599 higher oxygen target) **BOOST NZ 2014*** n= 340 randomised (n=170 lower oxygen target; n=170 higher oxygen target) **BOOST II Australia 2016*** n= 1135 randomised (n=568 lower oxygen target; n=567 higher oxygen target) **BOOST II UK 2016*** n= 973 randomised (n= 486 lower oxygen target; n=487 higher oxygen target)	**Interventions** **SUPPORT 2010** Infants were monitored with target ranges of oxygen saturation of 85% to 89% or 91% to 95% using oximeters with concealed saturation offsets of +3% in actual range 85% to 92% (low target) and -3% in range 88% to 95% (high target), with true readings displayed 84% and below and 96% and above. Caregivers were asked to adjust the concentration of oxygen to maintain displayed saturations between 88% and 92% when the infant was receiving supplemental	**Details** **SUPPORT 2010** Methods: Randomised, multicentre (USA) trial with a 2-by-2 factorial design Co-primary outcomes: survival at discharge from hospital without severe ROP (threshold ROP and/or the need for surgical intervention/ use of bevacizumab) assessed until diagnosis or resolution; and death or survival with neurodevelopmental impairment at 18 to 22 months corrected age Neurodevelopmental impairment was defined as having any of the following: * BSID-III cognitive or language score < 70 * GMFCS level 2 or higher * Moderate to severe cerebral palsy * Hearing impairment	**Results** **Outcome: Severe Retinopathy of Prematurity (randomised population)** **Original algorithm** SUPPORT 2010: higher oxygen target: 93/662; lower oxygen target: 36/654 BOOST NZ 2014: higher oxygen target: 13/170; lower oxygen target: 14/170 BOOST II Australia 2016: higher oxygen target: 26/346; lower oxygen target: 27/346 BOOST II UK 2016: higher oxygen target: 28/114; lower oxygen target: 19/113 COT 2013: higher oxygen target: 28/278; lower oxygen target: 33/286 **Revised algorithm** BOOST II Australia 2016: higher oxygen target: 21/221; lower oxygen target: 9/222 BOOST II UK 2016: higher oxygen target: 59/369; lower oxygen target: 49/371	**Limitations** As the NEOPROM collaboration was a meta-analysis of 5 RCT, rather than a systematic review, the individual RCTs in the meta-analysis were assessed **Quality of studies included in the NEOPROM collaboration meta-analysis:** Risk of bias assessed using Cochrane risk of bias tool **SUPPORT 2010** Random sequence generation: Low risk (Permuted-block randomisation was used, with stratification according to study centre and gestational age (24 weeks 0 days to 25 weeks 6 days or 26weeks 0 days to 27weeks 6 days). Multiple births were

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study To compare the effects of different target ranges for oxygen saturation as measured by pulse oximetry on death or major morbidity **Study dates** Not applicable **Source of funding** The data analysis was supported by grant RO3HD 079867 from the Eunice Kennedy Shriver National Institute of Child Health, National Institutes of Health, Department of Health and Human Services, Support for staff of the National Health and Medical Research Council (NHMRC)	***Extracted from original paper by NGA technical team** **Characteristics SUPPORT 2010*** Gestational age, weeks in mean (SD in parentheses): lower oxygen target = 26 (1); higher oxygen target= 26 (1) Birth weight, grams in mean (SD in parentheses): lower oxygen target = 836 (193); higher oxygen target= 825 (193) Male %: lower oxygen level= 52.1; higher oxygen level= 56 Apgar score <3 at 5 min %: lower oxygen target= 5.2 ; higher oxygen target= 3.6 Surfactant treatment %: lower oxygen	oxygen. Alarms were suggested to be set so that an alarm would sound at displayed saturation values of 85% and 95%, but they could be changed for individual patients. Infants were also randomly assigned to continuous positive airway pressure or intubation and surfactant. Intervention was initiated within 2 hours of birth and continued until 36 weeks of postmenstrual age or until the infant was breathing ambient air, whichever occurred first. Infants who were returned to supplemental oxygen were reassigned to the	* Bilateral visual impairment Secondary outcomes: severe retinopathy of prematurity, death before discharge, death by 36 weeks postmenstrual age, BPD defined by use of supplemental oxygen at 36 weeks, BPD physiological definition at 36 weeks, intraventricular haemorrhage grade 3 or 4, periventricular leukomalacia, necrotising enterocolitis stage ≥ 2, pneumothorax, postnatal corticosteroids for BPD, death by 7 days, death by 14 days, late-onset sepsis, patent ductus arteriosus requiring medical treatment, patent ductus arteriosus requiring surgical treatment, any air leaks in first 14 days **COT 2013** Methods: Randomised, multicentre (Canada, USA, Argentina, Finland, Germany, and Israel) trial	COT 2013: higher oxygen target: 30/279; lower oxygen target: 26/284 **Outcome: Mortality prior to discharge** **Original algorithm** SUPPORT 2010: higher oxygen target: 93/662; lower oxygen target: 36/654 BOOST NZ 2014: higher oxygen target: 24/170; lower oxygen target: 21/170 BOOST II Australia 2016: higher oxygen target: 56/346; lower oxygen target: 57/346 BOOST II UK 2016: higher oxygen target: 29/114; lower oxygen target: 20/113 COT 2013: higher oxygen target: 48/278; lower oxygen target: 28/286 **Revised algorithm** BOOST II Australia 2016: higher oxygen target: 67/221; lower oxygen target: 95/222 BOOST II UK 2016: higher oxygen target: 27/369; lower oxygen target: 42/371 COT 2013: higher oxygen target: 37/279; lower oxygen target: 45/284	randomised to the same group) Allocation concealment: Low risk (Sealed, sequentially numbered with central tracking opaque envelopes. Oximeter allocation was identifiable (via colour-coded dots) to designated research staff but not to clinical staff. Bedside adjustment of supplemental oxygen was performed only by clinical staff) Blinding of participants and personnel: Low risk (Blinding was maintained by oximeter design) Blinding of outcome assessors: Low risk (Parents and assessors were unaware of allocation) Incomplete outcome data (attrition bias): Low risk (Of the 1316 infants enrolled, 1234 (93.8%) had adequate data for the analysis of the composite primary outcome at 18 to

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	target= 81.3; higher oxygen target= 84.5 Maternal corticosteroid treatment %: lower oxygen target= 96.8; higher oxygen target= 95.6 **COT 2013*** Gestational age, weeks in mean (SD in parentheses): lower oxygen target = 25.6 (1.2) ; higher oxygen target= 25.6 (1.2) Birth weight, grams in mean (SD in parentheses): lower oxygen target = 829 (188); higher oxygen target= 845 (197) Male %: lower oxygen level= 44.7; higher oxygen level= 44.4 Apgar score, median (range in parentheses): lower oxygen target= 7 (6-	study oximeter. All infants in this trial were managed with oximeters using the original calibration software. **COT 2013** Infants were monitored with target ranges of oxygen saturation of 85% to 89% or 91% to 95% using oximeters with concealed saturation offsets of +3% in actual range 85% to 92% (low target) and -3% in range 88% to 95% (high target), with true readings displayed 84% and below and 96% and above. Caregivers were asked to adjust the concentration of oxygen to maintain displayed saturations between 88% and 92% when the infant was receiving	Primary outcome: death or survival with major disability at 18 to 21 months corrected age. Major disability was defined as having any of the following: * Cognitive score < 85 or language score < 85 on BSID-III * Severe visual loss * Cerebral palsy with GMFCS level 2 or higher * Deafness requiring hearing aids Secondary outcomes: retinopathy of prematurity (severe retinopathy of prematurity defined as unilateral or bilateral disease of stages 4 or 5; received cryotherapy or laser therapy in at least 1 eye or if they received retinal injection with bevacizumab or another anti-vascular endothelial growth factor agent), brain injury, patent ductus arteriosus, necrotising enterocolitis, bronchopulmonary	**Outcome: Cerebral Palsy at 18 months of age or older (defined as GMFS level 2 or higher)** **Original algorithm** Vaucher 2012: higher oxygen target: 20/551; lower oxygen target: 20/479 BOOST NZ 2014: higher oxygen target: 7/141; lower oxygen target: 5/144 BOOST II Australia 2016: higher oxygen target: 15/283; lower oxygen target: 11/277 BOOST II UK 2016: higher oxygen target: 7/83; lower oxygen target: 10/88 COT 2013: higher oxygen target: 13/219; lower oxygen target: 17/232 **Revised algorithm** BOOST II Australia 2016: higher oxygen target: 10/173; lower oxygen target: 5/169 BOOST II UK 2016: higher oxygen target: 17/287; lower oxygen target: 25/265 COT 2013: higher oxygen target: 14/232; lower oxygen target: 12/227	22 months corrected age 35 infants were of unknown status (21 low target group, 14 high target group) and 47 had incomplete or no follow-up (21 low target group, 26 high target group). If Bayley scores were missing, children were excluded from the primary outcome analysis No participants were excluded after randomisation. All outcome analyses followed the principle of intention-to-treat. The follow- up rate and the mean corrected age at neurodevelopmental assessment were similar for all treatment groups (in the 2-by-2 factorial design) Selective reporting: low risk (The predetermined sample size of 1310 infants was achieved. The original study protocol specified a composite primary outcome of death before 36 weeks of post-menstrual age or severe

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	8) ; higher oxygen target= 7 (6-8) Surfactant treatment %: lower oxygen target= 89.5; higher oxygen target= 84.8 Maternal corticosteroid treatment %: lower oxygen target= 88.4; higher oxygen target= 89.8 **BOOST NZ 2014*** Gestational age, weeks in mean (SD in parentheses): lower oxygen target = 26.1 (123); higher oxygen target= 26.1 (1.19) Birth weight, grams in mean (SD in parentheses): lower oxygen target = 873 (202); higher oxygen target= 884 (186) Male %: lower oxygen level= 52.9; higher oxygen level= 52.9	supplemental oxygen. Alarms were set so that an alarm would sound at displayed saturation values of 86% and 94%. Intervention was initiated within 24 hours of birth and continued until 36 weeks of postmenstrual age irrespective of supplemental oxygen therapy, and until 40 weeks in infants receiving oxygen therapy at 35 weeks. The oximeters used in this trial were modified with a revised calibration software in early 2009. 47%of infants in this trial were managed with oximeters using the original calibration software, 47% with oximeters using the	dysplasia, duration of use of positive airway pressure and supplemental oxygen, hospital re-admissions for respiratory disease, chronic use of respiratory medications, and mean composite cognitive, language and motor scores **BOOST NZ 2014** Methods: Randomised, multicentre (New Zealand) trial. Primary outcome: death or survival with major disability at 24 months corrected age. Major disability was defined as having any of the following: * Cognitive score < 85 or language score < 85 on BSID-III, or MDI < 70 on the BSIDII assessment * Severe visual loss * Cerebral palsy defined as GMFCS level 2 or higher * Deafness requiring hearing aids In 33 infants where Bayley	**Outcome: Severe cognitive impairment at 18 months of age or older (Bayleys III score <70 cognitive or language scale)** **Original algorithm** Vaucher 2012: higher oxygen target: 95/505; lower oxygen target: 72/472 BOOST NZ 2014: higher oxygen target: 4/114; lower oxygen target: 7/116 BOOST II Australia 2016: higher oxygen target: 21/263; lower oxygen target: 24/252 BOOST II UK 2016: higher oxygen target: 8/58; lower oxygen target: 8/54 COT 2013: higher oxygen target: 30/211; lower oxygen target: 29/221 **Revised algorithm** BOOST II Australia 2016: higher oxygen target: 18/163; lower oxygen target: 14/153 BOOST II UK 2016: higher oxygen target: 21/201; lower oxygen target: 26/191 COT 2013: higher oxygen target: 28/213; lower oxygen target: 29/214	ROP, but this was changed to death before discharge or severer before any data analyses were performed. All other outcomes pre-specified in the registration record were reported, including assessment of the need for oxygen at 36 weeks postmenstrual age and safety outcomes) Other bias: low risk (The baseline characteristics of the 2 treatment groups were similar) **COT 2013** Random sequence generation: Low risk (A computer-generated randomisation scheme at a remote co-ordinating centre assigned the infants to treatment groups in a 1:1 ratio. Randomisation was stratified by study centre and balanced within randomly sized blocks of 2 or 4 patients. Siblings

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Apgar score, median (range in parentheses): lower oxygen target= 8 (6-9) ; higher oxygen target= 8 (7-9) Maternal corticosteroid treatment %: lower oxygen target= 88.2; higher oxygen target= 89.4 **BOOST-II Australia 2016*** Gestational age, weeks in mean (SD in parentheses): lower oxygen target = 26 (1.16); higher oxygen target= 26 (1.18) Birth weight, grams in mean (SD in parentheses): lower oxygen target = 817 (177); higher oxygen target= 833 (190) Male %: lower oxygen level= 51.6; higher oxygen level= 52.1	revised calibration software, and 6% were exposed to both. **BOOST NZ 2014** Infants were monitored with target ranges of oxygen saturation of 85% to 89% or 91% to 95% using oximeters with concealed saturation offsets of +3% in actual range 85% to 92% (low target) and -3% in range 88% to 95% (high target), with true readings displayed 84% and below and 96% and above. Caregivers were asked to adjust the concentration of oxygen to maintain displayed saturations between 88% and 92% when the infant was receiving supplemental oxygen. Alarm limits	scores were unavailable and there were no other events defining major disability, an alternative definition of disability (use of < 10 words) was used Secondary outcomes: severe ROP (≥ stage 3, or retinal surgery), oxygen dependency or respiratory support at 36 weeks' gestational age, days of continuous positive airway pressure, days of endotracheal intubation, days of oxygenation in both hospital and days at home, a patent ductus arteriosus diagnosed by echocardiography and requiring treatment, necrotising enterocolitis requiring surgery or a cause of death, weight at 2 **BOOST-II Australia 2016** Methods: Randomised, multicentre (Australia) trial. Primary outcome: death or survival with major disability at 24 months corrected age. Major disability was	**Outcome: Moderate cognitive impairment at 18 months of age or older (Bayleys III score <85 cognitive or language scale)** **Original algorithm** Vaucher 2012: higher oxygen target: 252/505; lower oxygen target: 221/472 BOOST NZ 2014: higher oxygen target: 37/114; lower oxygen target: 34/116 BOOST II Australia 2016: higher oxygen target: 69/263; lower oxygen target: 73/252 BOOST II UK 2016: higher oxygen target: 18/58; lower oxygen target: 24/54 COT 2013: higher oxygen target: 88/214; lower oxygen target: 83/221 **Revised algorithm** BOOST II Australia 2016: higher oxygen target: 46/163; lower oxygen target: 51/153 BOOST II UK 2016: higher oxygen target: 60/201; lower oxygen target: 55/191 COT 2013: higher oxygen target: 85/227; lower oxygen target: 93/224	within multiple births were randomised individually) Allocation concealment: Low risk (Study oximeters were labelled with sequential participant numbers according to the randomisation scheme. The allocation remained unknown to the members of the clinical and research teams and all staff at the co-ordinating centre) Blinding of participants and personnel: Low risk (Blinding was maintained by oximeter design. There is evidence that the algorithm used for blinding caused a difference in nursing behaviour with high versus low oximeters, which reduced separation and which could have resulted in detection or co-intervention bias) Blinding of outcome assessors: Low risk (Parents and assessors were unaware of allocation)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Maternal corticosteroid treatment %: lower oxygen target= 88.2; higher oxygen target= 91.5 **BOOST-II UK 2016*** Gestational age, weeks in mean (SD in parentheses): lower oxygen target = 26 (1.30); higher oxygen target= 26 (1.31) Birth weight, grams in mean (SD in parentheses): lower oxygen target = 818 (182); higher oxygen target= 824 (188) Male %: lower oxygen level= 53.1; higher oxygen level= 53.2 Maternal corticosteroid treatment %: lower oxygen target= 91.8; higher oxygen target= 90.1	were recommended (but not mandated) to be set so that an alarm would sound at displayed saturation values of 87% and 93%. Intervention was initiated within 24 hours of birth, continued for at least two weeks and was discontinued when infants no longer required oxygen (pre-specified definition) or otherwise at 36 weeks. All infants in this trial were managed with oximeters using the original calibration software **BOOST-II Australia 2016** Infants were monitored with target ranges of oxygen saturation of 85% to 89% or 91% to 95% using	defined as having any of the following: * Cognitive score < 85 or language score < 85 on BSID-III * Severe visual loss * Cerebral palsy with inability to walk at 2 years corrected age * Deafness requiring hearing aids In 85 infants where Bayley scores were unavailable and there were no other events defining major disability, an alternative definition of disability (use of < 10 words, delayed development < 12 months, other severe impairment) was used Secondary outcomes: death at discharge, death at 36 weeks' postmenstrual age, treated retinopathy of prematurity, necrotising enterocolitis requiring surgery or leading to death, severe intraventricular haemorrhage (≥ grade 3), other brain injury, patent	**Outcome: Severe hearing impairment at 18 months of age or older** **Original algorithm** Vaucher 2012: higher oxygen target: 6/511; lower oxygen target: 7/479 BOOST NZ 2014: higher oxygen target: 1/139; lower oxygen target: 2/142 BOOST II Australia 2016: higher oxygen target: 3/276; lower oxygen target: 8/278 BOOST II UK 2016: higher oxygen target: 7/82; lower oxygen target: 7/88 COT 2013: higher oxygen target: 7/220; lower oxygen target: 12/231 **Revised algorithm** BOOST II Australia 2016: higher oxygen target: 6/175; lower oxygen target: 3/167 BOOST II UK 2016: higher oxygen target: 25/287; lower oxygen target: 15/264 COT 2013: higher oxygen target: 4/232; lower oxygen target: 6/227	Incomplete outcome data (attrition bias): Low risk (Of the 1201 infants enrolled, 1147 (95.5%) had adequate data for the analysis of the composite primary outcome at 18 to 21 months corrected age 39 infants were of unknown status (17 low target group, 22 high target group) and 15 had incomplete or no follow-up (7 low target group, 8 high target group). If Bayley scores were missing, children were excluded from the primary outcome analysis. No participants were excluded after randomisation. All outcome analyses followed the principle of intention-to-treat. The follow-up rate and the mean corrected age at neurodevelopmental assessment were similar for both treatment groups) Selective reporting: low risk (The predetermined sample size of 1201

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Extracted from original paper by NGA technical team** **Inclusion criteria** **SUPPORT 2010 Infants who were born between 24 weeks 0 days of gestation and 27 weeks 6 days of gestation for whom a decision had been made to provide full resuscitation were eligible for enrolment at birth **COT 2013*** Infants with gestational ages of 23 weeks 0 days through 27 weeks 6 days were eligible for enrolment during the first 24 hours after birth **BOOST NZ 2014*** Eligible infants were <28 weeks' gestation, <24 hours	oximeters with concealed saturation offsets of +3% in actual range 85% to 92% (low target) and -3% in range 88% to 95% (high target), with true readings displayed 84% and below and 96% and above. Caregivers were asked to adjust the concentration of oxygen to maintain displayed saturations between 88% and 92% when the infant was receiving supplemental oxygen. Alarm limits were recommended to be set so that an alarm would sound at displayed saturation values of 86% and 94%. Intervention was initiated within 24 hours of birth and discontinued when infants no longer	ductus arteriosus (requiring medical or surgical treatment), oxygen dependency at 36 weeks' postmenstrual age, bronchopulmonary dysplasia (physiological definition) **BOOST-II UK 2016** Methods: Randomised, multicentre (UK) trial. Primary outcome: death or survival with major disability at 24 months corrected age. Major disability was defined as having any of the following: * Cognitive score < 85 or language score < 85 on BSID-III * Severe visual loss * Cerebral palsy with inability to walk at 2 years corrected age * Deafness requiring (or too severe to benefit from) hearing aids In 176 infants where Bayley scores were unavailable and there were no other events defining	**Outcome: Severe visual impairment at 18 months of age or older** **Original algorithm** Vaucher 2012: higher oxygen target: 6/511; lower oxygen target: 7/479 BOOST NZ 2014: higher oxygen target: 1/140; lower oxygen target: 0/143 BOOST II Australia 2016: higher oxygen target: 0/284; lower oxygen target: 2/281 BOOST II UK 2016: higher oxygen target: 1/80; lower oxygen target: 4/87 COT 2013: higher oxygen target: 1/219; lower oxygen target: 3/231 **Revised algorithm** BOOST II Australia 2016: higher oxygen target: 2/175; lower oxygen target: 1/171 BOOST II UK 2016: higher oxygen target: 10/289; lower oxygen target: 8/262 COT 2013: higher oxygen target: 2/232; lower oxygen target: 2/227 **Outcome: Bronchopulmonary**	infants was achieved. All outcomes pre-specified in the registration record were reported) Other bias: low risk (There were imbalances in surfactant administration and in oxygen therapy before randomisation. Otherwise the baseline characteristics were similar in both groups) **BOOST NZ 2014** Random sequence generation: Low risk (Computer-generated randomisation lists were prepared by an independent statistician. Stratification was by NICU, sex, gestation < 26 or ≥ 26 weeks, and inborn or outborn. Siblings within multiple births were randomised individually) Allocation concealment: Low risk (Central telephone randomisation by independent statistician)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	of age, and either born in or transferred into a trial NICU. **BOOST-II Australia 2016*** Infants were eligibleif they had been born within the past 24 hours and before 28 weeks' gestation **BOOST-II UK 2016*** Infants were eligible if they had been born within the past 24 hours and before 28 weeks' gestation ***Extracted from original paper by NGA technical team** **Exclusion criteria** **SUPPORT 2010*** Infants born in other hospitals and those known to have major congenital anomalies were excluded. **COT 2013***	required oxygen (pre-specified definition) or otherwise at 36 weeks. Infants who were returned to supplemental oxygen were reassigned to the study oximeter. The oximeters used in this trial were modified with a revised calibration algorithm in early 2009. 62% of infants in this trial were managed with oximeters with the original calibration algorithm and 38% with oximeters using the revised calibration algorithm **BOOST-II UK 2016** Infants were monitored with target ranges of oxygen saturation of 85% to 89% or 91% to 95% using oximeters with	major disability, an alternative definition of disability (incomplete BSID-III score, Denver Developmental Screening Test, Griffiths Mental Development Scales, Schedule of Growing Skills, WPPS-III, PARCA-R, paediatric assessment, GP assessment, parental report review of all data) was used Secondary outcomes: death at discharge, death at 36 weeks' postmenstrual age, treated retinopathy of prematurity, necrotising enterocolitis requiring surgery or leading to death, severe intraventricular haemorrhage (≥ grade 3), other brain injury, patent ductus arteriosus (requiring medical or surgical treatment), oxygen dependency at 36 weeks' postmenstrual age, bronchopulmonary dysplasia (physiological definition).	**Dysplasia at 36 weeks PMA (randomised population, preterm babies on positive airway pressure with endotracheal tube, positive airways pressure without endotracheal tube, and supplemental oxygen without positive airway pressure at 36 weeks PMA)** **Original algorithm** SUPPORT 2010: higher oxygen target: 274/662; lower oxygen target: 208/654 BOOST NZ 2014: higher oxygen target: 87/170; lower oxygen target: 64/170 BOOST II Australia 2016: higher oxygen target: 145/346; lower oxygen target: 126/346 BOOST II UK 2016: higher oxygen target: 54/114; lower oxygen target: 58/113 COT 2013: higher oxygen target: 198/278; lower oxygen target: 214/286 **Revised algorithm** BOOST II Australia 2016: higher oxygen target: 107/221; lower oxygen target: 85/222	Blinding of participants and personnel: Low risk (Blinding was maintained by oximeter design) Blinding of outcome assessors: Low risk (Parents and assessors were unaware of allocation) Incomplete outcome data (attrition bias): Low risk (Of the 340 infants enrolled, 335 (98.5%) had adequate data for the analysis of the composite primary outcome at 24 months corrected age. No infants were of unknown status and 5 had incomplete or no follow-up (3 low target group, 2 high target group).Where Bayley scores were missing in a child without cerebral palsy, blindness, or deafness, "major disability" was defined as < 10 words by parent report at the paediatric assessment (n = 33 children). If none of these data were available, the

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Not reported **BOOST NZ 2014*** Exclusion criteria were a congenital anomaly affecting oxygenation or long-term development, imminent death, or the inability to follow up at 2 years (principally non–English-speaking parents or known to be moving overseas). **BOOST-II Australia 2016*** Infants were excluded if they were considered to be unlikely to survive, had a major congenital abnormality, or would not be available for follow-up. **BOOST-II UK 2016*** Infants were excluded if they were considered to be unlikely to	concealed saturation offsets of +3% in actual range 85% to 92% (low target) and -3% in range 88% to 95% (high target), with true readings displayed 84% and below and 96% and above (see Figure 4). Caregivers were asked to adjust the concentration of oxygen to maintain displayed saturations between 88% and 92% when the infant was receiving supplemental oxygen. Upper alarm limits were recommended to be set so that an alarm would sound at a displayed saturation value of 94%. No lower alarm limit was specified. Intervention was initiated within 24 hours of birth and		BOOST II UK 2016: higher oxygen target: 181/369; lower oxygen target: 146/371 COT 2013: higher oxygen target: 219/279; lower oxygen target: 194/284 **Outcome: Severe necrotising enterocolitis requiring surgery or leading to death (randomised population)** **Original algorithm** SUPPORT 2010: higher oxygen target: 37/662; lower oxygen target: 51/654 BOOST NZ 2014: higher oxygen target: 12/170; lower oxygen target: 15/170 BOOST II Australia 2016: higher oxygen target: 16/346; lower oxygen target: 23/346 BOOST II UK 2016: higher oxygen target: 11/114; lower oxygen target: 17/113 COT 2013: higher oxygen target: 15/278; lower oxygen target: 22/286 **Revised algorithm** BOOST II Australia 2016: higher oxygen target: 177/221; lower oxygen target: 18/222	primary endpoint was considered missing No participants were excluded after randomisation. All outcome analyses followed the principle of intention-to-treat. The follow- up rate and the mean corrected age at neurodevelopmental assessment were similar for both treatment groups) Selective reporting: low risk (The predetermined sample size of 320 infants was exceeded, with a final sample size of 340 being achieved. All outcomes prespecified in the registration record were reported) Other bias: low risk (The baseline characteristics of the 2 treatment groups were similar) **BOOST-II Australia 2016** Random sequence generation: Low risk (A computer-generated minimisation procedure

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	survive, had a major congenital abnormality, or would not be available for follow-up. ***Extracted from original paper by NGA technical team**	discontinued when infants no longer required oxygen (pre-specified definition) or otherwise at 36 weeks. Infants who were returned to supplemental oxygen were reassigned to the study oximeter. The oximeters used in this trial were modified with a revised calibration in early 2009. 23% of infants in this trial were managed with oximeters using the original calibration software, and 77% with oximeters using the revised calibration software		BOOST II UK 2016: higher oxygen target: 41/369; lower oxygen target: 54/371 COT 2013: higher oxygen target: 15/279; lower oxygen target: 24/284 **Outcome: Patent ductus arteriosus requiring medical or surgical treatment (randomised population)** **Original algorithm** SUPPORT 2010: higher oxygen target: 242/662; lower oxygen target: 234/654 BOOST NZ 2014: higher oxygen target: 90/170; lower oxygen target: 104/170 BOOST II Australia 2016: higher oxygen target: 166/346; lower oxygen target: 165/346 BOOST II UK 2016: higher oxygen target: 47/114; lower oxygen target: 46/113 COT 2013: higher oxygen target: 148/278; lower oxygen target: 149/286 **Revised algorithm** BOOST II Australia 2016: higher oxygen target: 111/221; lower oxygen target: 1114/222	was used to balance study group assignment according to sex, gestational age, and centre. Siblings within multiple birthswere randomised individually) Allocation concealment: Low risk (Central randomisation by computer) Blinding of participants and personnel: Low risk (Blinding was maintained by oximeter design) Blinding of outcome assessors: Low risk (Parents and assessors were unaware of allocation) Incomplete outcome data (attrition bias): Low risk (Of the 1135 infants enrolled, 1094 (96.4%) had adequate data for the analysis of the composite primary outcome at 24 months corrected age 12 infants were of unknown status (7 low target group, 5 high target group) and 29 had incomplete or no

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				BOOST II UK 2016: higher oxygen target: 139/369; lower oxygen target: 152/371 COT 2013: higher oxygen target: 158/279; lower oxygen target: 158/284	follow-up (12 low target group, 17 high target group). When Bayley III scores were missing, alternative measures of disability were used, including Bayley II scales, paediatric health status assessment, or a Short Health Status Questionnaire collected via phone call to parents or a GP visit (n = 85 children). If none of these data were available, the primary endpoint was considered missing No participants were excluded after randomisation. All outcome analyses followed the principle of intention-to-treat. The follow-up rate and the mean corrected age at neurodevelopmental assessment were similar for both treatment groups) Selective reporting: low risk (All outcomes pre-specified in the

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					registration record were reported) Other bias: unclear risk (Investigator concerns resulting from the significantly increased mortality risk with the lower SpO2 target range in the SUPPORT Trial publication led to an unscheduled safety analysis when 1135 of the planned 1200 infants (95%) had been recruited. A decision was made to terminate recruitment in both the BOOST-II UK and BOOST-II Australia trials based on a pre-specified rule. There was an 8.5% excess in 36-week mortality in the low target group monitored with an oximeter incorporating the revised calibration software (data pooled from both studies, P < 0.001 with a significant treatment by software subgroup interaction, P = 0.006).The early stopping of the trial

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					(with 81% of the final planned sample size at that point) raises the question of whether this overestimates treatment effect) **BOOST-II UK 2016** Random sequence generation: Low risk (A computer-generated minimisation procedure was used to balance study group assignment according to sex, gestational age, and centre. Siblings within multiple births were randomised individually) Allocation concealment: Low risk (Central randomisation by computer) Blinding of participants and personnel: Low risk (Blinding was maintained by oximeter design) Blinding of outcome assessors: Low risk (Parents and assessors were unaware of allocation)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					Incomplete outcome data (attrition bias): Low risk (Of the 973 infants enrolled, 941 (96.7%) had adequate data for the analysis of the composite primary outcome at 24 months corrected age 6 infants were of unknown status (2 low target group, 4 high target group) and 26 had incomplete or no follow-up (11 low target group, 15 high target group). When Bayley III scores were missing, alternative measures of disability were used, including Bayley II scales, paediatric health status assessment, or a Short Health Status Questionnaire collected via phone call to parents or a GP visit (n = 176 children). If none of these data were available, the primary endpoint was considered missing. No participants were excluded after randomisation. All

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					outcome analyses followed the principle of intention-to-treat. The follow-up rate and the mean corrected age at neurodevelopmental assessment were similar for both treatment groups) Selective reporting: low risk (All outcomes pre-specified in the registration record were reported) Other bias: unclear risk (Investigator concerns resulting from the significantly increased mortality risk with the lower SpO2 target range in the SUPPORT Trial publication led to an unscheduled safety analysis when 973 of the planned 1200 infants (81%) had been recruited. A decision was made to terminate recruitment in both the BOOST-II UK and BOOST-II Australia trials based on a pre-specified rule. There was an 8.5%

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					excess in 36-week mortality in the low target group monitored with an oximeter incorporating the revised calibration software (data pooled from both studies, P < 0.001 with a significant treatment by software subgroup **Other information**

Clinical evidence tables for question 4.2 What is the best method for measuring oxygen levels in diagnosing hyperoxia or hypoxia in preterm babies?

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Full citation Duc, G., Frei, H., Klar, H., Tuchschmid, P., Reliability of continuous transcutaneous PO<inf>2</inf>	**Sample size** n=26 (66 series of measurements and 335 blood samples) **Characteristics**	**Tests** Index test: Transcutaneous PO2 (tcPO2) Reference standard: arterial PO2 (from umbilical catheter)	**Methods** <u>tcPO2</u> Measurements were performed according to hte method described by Hutch et al by means of commercially available electrodes and analysers (Hellige	**Results** **Hypoxaemia** <u>tcPO2 vs arterial PO2</u> | | Confirmed hypoxaemia | No hypoxaemia | Total |	**Limitations** **QUADAS-2** a quality assessment tool for diagnostic accuracy studies: <u>Patient Selection</u> A. Risk of Bias Was a consecutive or random sample of

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>(Hellige) in respiratory distress syndrome of the newborn, Birth Defects: Original Article Series, 15, 305-313, 1979

Ref Id

802388

Country/ies where the study was carried out

Not reported

Study type

Prospective cohort study

Aim of the study
To define the probability of error in measurements of tcPO2 by systematic monitoring over 4 hours with hourly PaO2 sampling</td>
<td>Gestational age range in weeks: 29-38
Birthweight range in grams: 1,500-3,210
Inspired oxygen concentration 40-100%
Servicontrolled temperature of 35.5-36.5 degrees celcius

Inclusion Criteria
Artificially ventilated with hyaline membrane disease

Exclusion Criteria
Babies with circulatory disturbances (low blood pressure or</td>
<td></td>
<td>and Drager). The electrode was calibrated with air at room temperature. The PO2 was calculated after correction of water vapor perital pressure at the same temperature. The zero point was set using the solution recommended by one of the manufacturing companies (Hellige). The present core temperature of the electrode was 44 degrees celcius.
The cutaneous electrode was placed over the lower thorax or the back, areas unlikely to be perfused by preductal blood. After application of the electrode, 10 minutes or more were allowed for equilibration before sampling in order to obtain complete local hyperemia.</td>
<td>
<table>
<tr><td>Hypoxaemia in index test</td><td>21</td><td>10</td><td>31</td></tr>
<tr><td>No hypoxaemia in index test</td><td>4</td><td>300</td><td>304</td></tr>
<tr><td>Total</td><td>25</td><td>310</td><td>335</td></tr>
</table>
Sensitivity 84% (95% CI 64-95%)*
Specificity 96% (95% CI 93-98%)*
Positive likelihood ratio 23 (12-42)*
Negative likelihood ratio 0.17 (0.07-0.41)*
*Calculated by the NGA technical team

Hyperoxaemia
<u>tcPO2 vs arterial PO</u>
<table>
<tr><td></td><td>Confirmed hyperoxaemia</td><td>No hyperoxaemia</td><td>Total</td></tr>
<tr><td>Hyperoxaemia in index test</td><td>33</td><td>9</td><td>42</td></tr>
<tr><td>No hyperoxaemia in index test</td><td>9</td><td>284</td><td>293</td></tr>
<tr><td>Total</td><td>42</td><td>293</td><td>335</td></tr>
</table>
</td>
<td>patients enrolled? Yes.
Was a case-control design avoided? Yes.
Did the study avoid inappropriate exclusions? Yes.
Could the selection of patients have introduced bias? Low risk.
B. Concerns regarding applicability:
Not all participants had a gestational age of 37 weeks PMA or less
Are there concerns that the included patients and setting do not match the review question? High concern.
<u>Index Test</u>
A. Risk of Bias
Were the index test results interpreted without knowledge of the results of the</td>
</tr>
</table>

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Study dates Not reported **Source of funding** Not reported	poor peripheral circulation)		Arterial PO2 The arterial umbilical catheter was placed with the tip between 2nd and 4th lumbar vertebrae. PaO2 determinations were performed using AVL gas check. The study lasted four hours. PaO2 was sampled hourly and compared with tcPO2 registered at the same time. PaO2 samples were also taken when tcPO2 was observed to be above 100 mm Hg or below 50 mm Hg. An attempt was made to keep tcPO2 between 50 and 100 mm Hg. Most of the babies had been previouisly monitored for several hours when the study started.	Sensitivity 79% (95% CI 63-90%)* Specificity 97% (95% CI 94-99%)* Positive likelihood ratio 26 (13-50)* Negative likelihood ratio 0.22 (0.12-0.39)* *Calculated by the NGA technical team	reference standard? No. If a threshold was used, was it pre-specified? Yes. (hypoxaemia PaO2 <50 mm Hg; normoxaemia PaO2 50-100 mm Hg; hyperoxaemia PaO2 >100 mm Hg) Could the conduct or interpretation of the index test have introduced bias? Low risk. B. Concerns regarding applicability: The paper does not report who interpreted the index test or the level of experience of the person(s). Are there concerns that the index test, its conduct, or interpretation differ from the review question? Low risk

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Reference Standard A. Risk of Bias Is the reference standards likely to correctly classify the target condition? Yes. Were the reference standard results interpreted without knowledge of the results of the index tests? No. Could the reference standard, its conduct, or its interpretation have introduced bias? Low risk. B. Concerns regarding applicability Are there concerns that the target condition as defined by the reference standard does not match the question? Low concern. Flow and Timing A. Risk of Bias

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Was there an appropriate interval between index test and reference standard? Yes, tcPO2 and PaO2 sampled at same time. Did all patients receive the same reference standard? Yes. Were all patients included in the analysis? Yes Could the patient flow have introduced bias? Low risk.

Clinical evidence tables for question 4.3 What carbon dioxide levels are optimal in the management of preterm babies?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Carlo,W.A., Stark,A.R., Wright,L.L., Tyson,J.E., Papile,L.A., Shankaran,S., Donovan,E.F., Oh,W., Bauer,C.R., Saha,S.,	**Sample size** n= 220 randomised (n= 109 minimal ventilation ; n=111 routine ventilation)	**Interventions** Infants treated with both ventilatory strategies were treated with	**Details** Methods: Randomised, multicentre trial with a 2-by-2 factorial design Primary outcomes: The combined primary outcome	**Results** Outcome: mortality prior to discharge minimal ventilation: 23/109 ; routine ventilation: 22/111	**Limitations** Random sequence generation: Low risk (Infants were stratified by center and birth weight (501-750 g; 751-1000 g)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Poole,W.K., Stoll,B., Minimal ventilation to prevent bronchopulmonary dysplasia in extremely-low-birth-weight infants, Journal of Pediatrics, 141, 370-374, 2002 **Ref Id** 208654 **Country/ies where the study was carried out** USA **Study type** Randomised controlled trial **Aim of the study** To determine whether minimal ventilation decreases death or bronchopulmonary dysplasia **Study dates** February 1998 - September 1998	**Characteristics** Birth weight in grams (SD in parentheses): minimal ventilation= 742 (130); routine ventilation= 728 (135) Gestational age in weeks (SD in parentheses): minimal ventilation= 25 (2); routine ventilation= 25 (2) Race %: black: minimal ventilation= 46; routine ventilation= 48 white: minimal ventilation= 39; routine ventilation= 43 other: minimal ventilation= 48; routine ventilation= 56 Males sex %: minimal ventilation= 46; routine ventilation= 48 Antenatal steroids %: minimal ventilation= 74; routine ventilation= 75 Surfactant %: minimal ventilation= 98; routine ventilation= 96	pressure limited ventilation. Minimal ventilation group: partial pressure of carbon dioxide target >52 mmHg Routine ventilation group: partial pressure of carbin dioxide target <48 mmHg	measure was death by 36 weeks PMA or moderate to severe BPD (defined as supplemental oxygen administrationfor at least 12 hours on the day that the infant reached 36 PMA) Secondary outcomes: Death by 36 weeks, invasive ventilator in survivors at 36 weeks, pulmoary interstitial emphysema, pneumothorax, open-label steroids, reintubation, IVH III or IV, periventricular leucomalacia, necrolising enterocolitis, duration of oxygen supplementation, duration of ventilation, length of hospitalisation. Neurodevelopmental outcomes: Infants were evaluated at 18 to 22 months, with age corrected by masked, certified examiners as part of the Network Follow-up Study. Neurodevelopmental impairment was defined as any of the following: Bayley II mental developmental	Outcome: Bronchopulmonary dysplasia at 36 weeks PMA minimal ventilation: 40/109 ; routine ventilation: 46/111 Outcome: Cerebral Palsy minimal ventilation: 11/98 ; routine ventilation: 20/101 Outcome: Severe cognitive impairment MDI <70 minimal ventilation: 47/75 ; routine ventilation: 43/80 PDI <70 minimal ventilation: 32/75 ; routine ventilation: 33/80 Outcome: Bilateral blindness minimal ventilation: 1/75 ; routine ventilation: 0/80 Outcome: Deafness	and randomly assigned to one of four groups according to a combination of ventilator strategy (minimal or routine ventilation) and study medication. Treatment wasassigned by using a random, permuted block algorithm) Allocation concealment: Low risk (Ventilator strategy assignments used a central computerized telephone system and were initiated before 12 hours after birth) Blinding of participants and personnel: Unclear (no details as whether participants and personnel were blinded) Blinding of outcome assessors: Low risk (Assessors for neurodevelopmental outcomes were blinded, no details of blinding for primary and secondary outcomes)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding Not reported	**Inclusion criteria** Infants weighing 501 g to 1000 g who we re intubated, receiving invasive ventilation before 12 hours of age, and had an indwelling vascular catheter were eligible for the study. Infants weighing 751 g to 1000 g also were required to receive fractional concentration of oxygen in inspired gas (FiO2) ≥0.3 and at least one dose of surfactant before eligibility. **Exclusion criteria** Infants were ineligible if they met any of the following exclusion criteria: major congenital anomaly, congenital nonbacterial infection, permanent neuromuscular condition affecting respiration, findings indicating a very low		index <70, psychomotor developmental index <70, moderate to severe cerebral palsy, bilateral blindness, or deafness requiring amplification. Extubation criteria required all of the following: a ventilator rate <15 per minute, FiO2 <0.50, and arterial pH>7.25. Reintubation criteria were pH<7.20, apnea/hypoventilation, atelectasis, or as clinically indicated.	minimal ventilation: 6/75 ; routine ventilation: 5/80 Outcome: periventricular leucomalacia minimal ventilation: 10/109 ; routine ventilation: 10/111 Outcome: severe IVH (grade III or IV) minimal ventilation: 20/109 ; routine ventilation: 26/111 (defined as intracranial haemorrhage) Outcome: total days on invasive ventilation in mean (SD in parentheses) minimal ventilation: 26 (22) ; routine ventilation: 30 (25) Outcome: pneumothorax minimal ventilation: 8/109 ; routine ventilation: 4/111	Incomplete outcome data (attrition bias): High risk (10% loss to follow up without explanation) Selective reporting: low risk (All outcomes specified in the methods were reported) **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	likelihood of recovery (pH <6.8 or bradycardia with hypoxemia for >2 hours), or previous postnatal corticosteroid treatment.				
Full citation Mariani,G., Cifuentes,J., Carlo,W.A., Randomized trial of permissive hypercapnia in preterm infants, Pediatrics, 104, 1082-1088, 1999 **Ref Id** 193105 **Country/ies where the study was carried out** USA **Study type** Randomised controlled trial **Aim of the study** To evaluate whether a strategy of permissi ve hypercapnia,	**Sample size** n= 49 randomised (n=25 normocapnia; n=24 permissive hypercapnia) **Characteristics** Birth weight in grams (SD in parentheses): hypercapnia= 853 (156); normocapnia= 856 (173) Gestational age in weeks (SD in parentheses): hypercapnia= 26 (1); normocapnia= 26 (2) Entry age in hours (range in parentheses): hypercapnia= 8.5 (5.5-14); normocapia= 9 (5-12) Antenatal steroids %: hypercapnia= 71; normocapnia= 52	**Interventions** Permissive hypercapnia group: ventilatory management was directed to maintain arterial Paco2 between 45 and 55 mm Hg and pH ≥7.20. Normocapnia group: ventilatory management was directed to maintain arterial Paco2 between 35 and 45 mm Hg and pH ≥7.25. These goals were used for the first 96 hours after randomization. After that time, the	**Details** Methods: randomised controlled trial Outcomes: The total duration of assisted ventilation was calculated fromthe sum of all periods of assisted ventilation until final extubation.Time on continuous positive airway pressure was not counted as assisted ventilation. The total duration of oxygen supplementation was calculated from the sum of all periods of any technique of oxygen supplementation, including after transfer or discharge. BPD was defined as oxygen requirement and abnormal chestradiograph on day 28 of postnatal age, with oxygen requirement for	**Results** Outcome: Mortality prior to discharge permissive hypercapnia: 3/24 ; normocapnia: 3/25 Outcome: BPD at 28 days PMA permissive hypercapnia: 9/24 ; normocapnia: 14/25 Outcome: Days on invasive ventilation median (range in parentheses) permissive hypercapnia: 2.5 (1.5-11.5) ; normocapnia: 9.5 (2.0-22.5) p value= 0.17	**Limitations** Random sequence generation: Low risk (The patients were assigned to either a permissive hypercapnia or a normocapnia group using a permuted block randomization procedure consisting of a random sequence of blocks of 4, 6, 8, and 10.) Allocation concealment: Low risk (The group assignments were recorded and sealed within sequentially numbered opaque envelopes. The odds of assignment to one of the two groups were not known to the investigators.)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
initiated during the first 24 hours after birth in neonates weighing 601 to 1250 g at birth, decreasesthe number of days of assisted ventilation **Study dates** November 1, 1995 - December 9, 1996. **Source of funding** Grant M01-RR00032 from the National Institutes of Health.	Apgar score at 1 min median: hypercapnia= 3; normocapnia= 3 Apgar score at 5 min median: hypercapnia= 7; normocapnia= 6 Pre-randomisation FiO2 median (range in parentheses): hypercapnia= 0.35 (0.27-0.48); normocapnia= 0.5 (0.25-0.66) **Inclusion criteria** Infants were eligible for the study if all the following criteria were met: 1) birth weight of 601 to 1250 g; 2) surfactant-treated RDS on assisted ventilation; 3) postnatal age ,24 hours; and 4) written parental informed consent. **Exclusion criteria**	changes in the ventilator settings were directed at the pH criteria, allowing high levels of Paco2 also in the normocapnia group. The goal for Pao2 level was between 50 and 80 mm Hg in both groups	at least 21 of the first 28 days. Air leaks included pneumothorax and/or pulmonary interstitial emphysema. The severity of intraventricular hemorrhage was graded according to the criteriaof Papile et al.16 A hemorrhage was considered to have progressed if: 1) a new intraventricular hemorrhage developed from an initial negative head ultrasound; 2) there was a progression in any grade of intraventricular hemorrhage; or 3) a second intraventricular hemorrhage was noted in the hemisphere opposite from the existing hemorrhage. A diagnosis of periventricular leukomalacia was made if the cranial ultrasound showed postnatal development of multiple cystic echolucencies in the cerebral white matter. Proven sepsis was defined as a positive blood culture result for bacteria or fungus treated by the clinicians at	Outcome: periventricular leucomalacia permissive hypercapnia: 2/24 ; normocapnia: 2/25 Outcome: severe IVH (grade III or IV) permissive hypercapnia: 7/24 ; normocapnia: 5/25 Outcome: air leak permissive hypercapnia: 2/24 ; normocapnia: 4/25 , Outcome: Mortality prior to discharge permissive hypercapnia: 3/24 ; normocapnia: 3/25 Outcome: BPD at 28 days PMA permissive hypercapnia: 9/24 ; normocapnia: 14/25 Outcome: Days on invasive ventilation median (range in parentheses)	Blinding of participants and personnel: Low risk (Because this study could not have been masked, to decrease the influence of any potential bias on duration of assisted ventilation, we defined and followed strict extubation and reintubation criteria and used precise indications for those therapies that have been reported to influence extubation success, such as aminophylline and dexamethasone) Blinding of outcome assessors: Low risk (unblinded however most outcomes were objective and the subjective outcomes had strict criteria to reduce subjectivity and bias) Incomplete outcome data (attrition bias): Low risk (all babies followed-up) Selective reporting: low risk (All outcomes

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Infants were excluded for any of the following reasons: 1) 5-minute Apgar score <3; 2) small for gestational age; 3) congenital anomalies or suspected congenital infection; 4) multiple pregnancy of triplets or more; and 5) infant not expected to need prolonged ventilatory assistance as judged by the attending neonatologist.		any time during hospitalization. The presence of patent ductus arteriosus was confirmed by echocardiography. Modified Bell's criteria were used for necrotizing enterocolitis staging. Objective criteria were used for extubation to minimize bias. Infants were extubated from assisted ventilation if all the following criteria were met: peak inspiratory pressure ≤19 cm H2O, ventilator rate ≤10 per minute, Fio2 ≤0.4, and arterial pH ≥7.25. An aminophylline loading dose was given before extubation. Continuous positive airway pressure was used as clinically indicated. Reintubation was performed for a pH <7.20, respiratory failure, or severe apneic episodes needing assisted ventilation according to the attending physician. The defined extubation criteria were followed for every	permissive hypercapnia: 2.5 (1.5-11.5) ; normocapnia: 9.5 (2.0-22.5) p value= 0.17 Outcome: periventricular leucomalacia permissive hypercapnia: 2/24 ; normocapnia: 2/25 Outcome: severe IVH (grade III or IV) permissive hypercapnia: 7/24 ; normocapnia: 5/25 Outcome: air leak permissive hypercapnia: 2/24 ; normocapnia: 4/25 , Outcome: Mortality prior to discharge permissive hypercapnia: 3/24 ; normocapnia: 3/25 Outcome: BPD at 28 days PMA	specified in the methods were reported) , Random sequence generation: Low risk (The patients were assigned to either a permissive hypercapnia or a normocapnia group using a permuted block randomization procedure consisting of a random sequence of blocks of 4, 6, 8, and 10.) Allocation concealment: Low risk (The group assignments were recorded and sealed within sequentially numbered opaque envelopes. The odds of assignment to one of the two groups were not known to the investigators.) Blinding of participants and personnel: Low risk (Because this study could not have been masked, to decrease the influence of any potential bias on duration of assisted

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			period on assisted ventilation, except when patients required more than one reintubation for apnea. In these patients, a new extubation was attempted 5 to 7 days after the previous failure. Patients were weaned from oxygen supplementation when they were able to maintain oxygen saturation ≥90% while breathing air. Methods: randomised controlled trial Outcomes: The total duration of assisted ventilation was calculated fromthe sum of all periods of assisted ventilation until final extubation.Time on continuous positive airway pressure was not counted as assisted ventilation. The total duration of oxygen supplementation was calculated from the sum of all periods of any technique of oxygen supplementation, including after transfer or	permissive hypercapnia: 9/24 ; normocapnia: 14/25 Outcome: Days on invasive ventilation median (range in parentheses) permissive hypercapnia: 2.5 (1.5-11.5) ; normocapnia: 9.5 (2.0-22.5) p value= 0.17 Outcome: periventricular leucomalacia permissive hypercapnia: 2/24 ; normocapnia: 2/25 Outcome: severe IVH (grade III or IV) permissive hypercapnia: 7/24 ; normocapnia: 5/25 Outcome: air leak permissive hypercapnia: 2/24 ; normocapnia: 4/25	ventilation, we defined and followed strict extubation and reintubation criteria and used precise indications for those therapies that have been reported to influence extubation success, such as aminophylline and dexamethasone) Blinding of outcome assessors: Low risk (unblinded however most outcomes were objective and the subjective outcomes had strict criteria to reduce subjectivity and bias) Incomplete outcome data (attrition bias): Low risk (all babies followed-up) Selective reporting: low risk (All outcomes specified in the methods were reported) , Random sequence generation: Low risk (The patients were assigned to either a permissive hypercapnia or a

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			discharge. BPD was defined as oxygen requirement and abnormal chestradiograph on day 28 of postnatal age, with oxygen requirement for at least 21 of the first 28 days. Air leaks included pneumothorax and/or pulmonary interstitial emphysema. The severity of intraventricular hemorrhage was graded according to the criteriaof Papile et al.16 A hemorrhage was considered to have progressed if: 1) a new intraventricular hemorrhage developed from an initial negative head ultrasound; 2) there was a progression in any grade of intraventricular hemorrhage; or 3) a second intraventricular hemorrhage was noted in the hemisphere opposite from the existing hemorrhage. A diagnosis of periventricular leukomalacia was made if the cranial ultrasound showed postnatal development of multiple cystic echolucencies in the		normocapnia group using a permuted block randomization procedure consisting of a random sequence of blocks of 4, 6, 8, and 10.) Allocation concealment: Low risk (The group assignments were recorded and sealed within sequentially numbered opaque envelopes. The odds of assignment to one of the two groups were not known to the investigators.) Blinding of participants and personnel: Low risk (Because this study could not have been masked, to decrease the influence of any potential bias on duration of assisted ventilation, we defined and followed strict extubation and reintubation criteria and used precise indications for those therapies that have been reported to influence extubation success, such

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			cerebral white matter. Proven sepsis was defined as a positive blood culture result for bacteria or fungus treated by the clinicians at any time during hospitalization. The presence of patent ductus arteriosus was confirmed by echocardiography. Modified Bell's criteria were used for necrotizing enterocolitis staging. Objective criteria were used for extubation to minimize bias. Infants were extubated from assisted ventilation if all the following criteria were met: peak inspiratory pressure ≤19 cm H2O, ventilator rate ≤10 per minute, Fio2 ≤0.4, and arterial pH ≥7.25. An aminophylline loading dose was given before extubation. Continuous positive airway pressure was used as clinically indicated. Reintubation was performed for a pH <7.20, respiratory failure, or severe apneic		as aminophylline and dexamethasone) Blinding of outcome assessors: Low risk (unblinded however most outcomes were objective and the subjective outcomes had strict criteria to reduce subjectivity and bias) Incomplete outcome data (attrition bias): Low risk (all babies followed-up) Selective reporting: low risk (All outcomes specified in the methods were reported) , Random sequence generation: Low risk (The patients were assigned to either a permissive hypercapnia or a normocapnia group using a permuted block randomization procedure consisting of a random sequence of blocks of 4, 6, 8, and 10.) Allocation concealment: Low risk (The group

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			episodes needing assisted ventilation according to the attending physician. The defined extubation criteria were followed for every period on assisted ventilation, except when patients required more than one reintubation for apnea. In these patients, a new extubation was attempted 5 to 7 days after the previous failure. Patients were weaned from oxygen supplementation when they were able to maintain oxygen saturation ≥90% while breathing air.		assignments were recorded and sealed within sequentially numbered opaque envelopes. The odds of assignment to one of the two groups were not known to the investigators.) Blinding of participants and personnel: Low risk (Because this study could not have been masked, to decrease the influence of any potential bias on duration of assisted ventilation, we defined and followed strict extubation and reintubation criteria and used precise indications for those therapies that have been reported to influence extubation success, such as aminophylline and dexamethasone) Blinding of outcome assessors: Low risk (unblinded however most outcomes were objective and the subjective outcomes had strict criteria

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					to reduce subjectivity and bias) Incomplete outcome data (attrition bias): Low risk (all babies followed-up) Selective reporting: low risk (All outcomes specified in the methods were reported) **Other information**
Full citation Thome, Uh, Carroll, W, Wu, Tj, Johnson, Rb, Roane, C, Young, D, Carlo, Wa, Outcome of extremely preterm infants randomized at birth to different PaCO2 targets during the first seven days of life, Biology of the Neonate, 90, 218-225, 2006 **Ref Id** 668231	**Sample size** n= 66 randomised (n=33 minimal ventilation; n=32 standard ventilation) n=32 for neurodevelopmental follow-up (n=14 minimal ventilation [attrition: n=12 died before 36 weeks PMA; n=5 died after 36 weeks PMA; n=2 lost to follow-up]; n=18 standard ventilation [attrition: n=6 died before 36 weeks PMA; n=3 died after 36	**Interventions** Invasive ventilation was provided by InfantStar 500 ventilators. High frequency ventilation was not used. Minimal ventilation: Arterial PaCO2 of 55-65 mmHg (7.3-8.7 kPa) for the first 7 days after birth Standard ventilation: Arterial PaCO2 of 35-45	**Details** Methods: randomised controlled trial Outcomes: The total duration of assisted ventilation was calculated fromthe sum of all periods of assisted ventilation until final extubation.Time on continuous positive airway pressure was not counted as assisted ventilation. The total duration of oxygen supplementation was calculated from the sum of all periods of any technique	**Results** Outcome: Mortality prior to discharge minimal ventilation: 12/33 ; normal ventilation: 6/32 Outcome: BPD at 36 weeks PMA minimal ventilation: 9/33 ; normal ventilation: 13/32 Outcome: Cerebral Palsy at 18 months of age or older	**Limitations** Random sequence generation: Low risk (The patients were assigned to either a permissive hypercapnia or a normocapnia group using a permuted block randomization procedure consisting of a random sequence of blocks of 4, 6, 8, and 10.) Allocation concealment: Low risk (The group assignments were recorded and sealed within

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out USA **Study type** Randomised controlled trial **Aim of the study** To test the hypothesis that a strategy of minimal ventilation would lead to a reduced combined incidence of BPD (defined as requirement for supplemental oxygen, continuous positive airway pressure or invasive ventilation at a postmenstrual age of 36 weeks PMA) or death prior to 36 weeks PMA in comparison to standard ventilation **Study dates** August 2000-November 2001 **Source of funding**	weeks PMA; n=5 lost to follow-up]) **Characteristics** Gestational age in weeks (range in parentheses): minimal ventilation= 24.7 (23-28.9); standard ventilation= 24.7 (23-28.3) Birth wegith in grams (range in parentheses): minimal ventilation= 660 (353-944); standard ventilation= 621 (432-1,204) Male: minimal ventilation= 52%; standard ventilation= 47% Black race: minimal ventilation= 61%; standard ventilation= 53% Prenatal steroids (any): minimal ventilation= 85%; standard ventilation= 75% 5-min Apgar score (range in parentheses): minimal ventilation= 6 (5-7); standard ventilation= 6 (4-7)	mmHg (4.7-6.0 kPa) for the first 7 days after birth	of oxygen supplementation, including after transfer or discharge. BPD was defined as oxygen requirement and abnormal chestradiograph on day 28 of postnatal age, with oxygen requirement for at least 21 of the first 28 days. Air leaks included pneumothorax and/or pulmonary interstitial emphysema. The severity of intraventricular hemorrhage was graded according to the criteria of Papile et al. A hemorrhage was considered to have progressed if: 1) a new intraventricular hemorrhage developed from an initial negative head ultrasound; 2) there was a progression in any grade of intraventricular hemorrhage; or 3) a second intraventricular hemorrhage was noted in the hemisphere opposite from the existing hemorrhage. A diagnosis of periventricular leukomalacia was made if the cranial ultrasound showed postnatal	minimal ventilation: 4/14 ; normal ventilation: 4/18 Outcome; Severe cognitive impairement at 18 months of age or older MDI <70 minimal ventilation: 7/12 ; normal ventilation: 7/17 PDI <70 minimal ventilation: 4/12 ; normal ventilation: 4/17 Outcome: Hearing impairment at 18 months of age or older minimal ventilation: 2/14 ; normal ventilation: 2/18 Outcome: Visual impairment at 18 months of age or older minimal ventilation: 3/14 ; normal ventilation: 5/18	sequentially numbered opaque envelopes. The odds of assignment to one of the two groups were not known to the investigators.) Blinding of participants and personnel: Low risk (Because this study could not have been masked, to decrease the influence of any potential bias on duration of assisted ventilation, we defined and followed strict extubation and reintubation criteria and used precise indications for those therapies that have been reported to influence extubation success, such as aminophylline and dexamethasone) Blinding of outcome assessors: Low risk (unblinded however most outcomes were objective and the subjective outcomes had strict criteria to reduce subjectivity and bias)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Not reported	Surfactant replacement: minimal ventilation= 91%; standard ventilation= 94% **Inclusion criteria** Inborn preterm infants, with a gestational age between 23 and 28 completed weeks, and requiring invasive ventilation within 6 h of birth were eligible. **Exclusion criteria** Patients with major congenital malformations, including congenital heart disease (except patent ductus arteriosus), pulmonary or gastrointestinal malformations, renal dysplasias, chromosomal anomalies and hydrops fetalis, as well as patients with air leaks before randomization were excluded		development of multiple cystic echolucencies in the cerebral white matter. Proven sepsis was defined as a positive blood culture result for bacteria or fungus treated by the clinicians at any time during hospitalization. The presence of patent ductus arteriosus was confirmed by echocardiography. Modified Bell's criteria were used for necrotizing enterocolitis staging. Objective criteria were used for extubation to minimize bias. Infants were extubated from assisted ventilation if all the following criteria were met: peak inspiratory pressure $\leq$19 cm H2O, ventilator rate $\leq$10 per minute, Fio2 $\leq$0.4, and arterial pH $\geq$7.25. An aminophylline loading dose was given before extubation. Continuous positive airway pressure was used as clinically indicated. Reintubation was performed	Outcome: severe IVH (grade III or IV) minimal ventilation: 8/33 ; normal ventilation: 9/32 Outcome: Pneumothorax minimal ventilation: 3/33 ; normal ventilation: 5/32	Incomplete outcome data (attrition bias): Low risk (all babies followed-up) Selective reporting: low risk (All outcomes specified in the methods were reported) **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			for a pH <7.20, respiratory failure, or severe apneic episodes needing assisted ventilation according to the attending physician. The defined extubation criteria were followed for every period on assisted ventilation, except when patients required more than one reintubation for apnea. In these patients, a new extubation was attempted 5 to 7 days after the previous failure. Patients were weaned from oxygen supplementation when they were able to maintain oxygen saturation ≥90% while breathing air.		
Full citation Thome, U. H., Genzel-Boroviczeny, O., Bohnhorst, B., Schmid, M., Fuchs, H., Rohde, O., Avenarius, S., Topf, H. G., Zimmermann, A., Faas, D., Timme, K., Kleinlein, B., Buxmann, H., Schenk, W.,	**Sample size** n= 359 randomised (n= 179 high target level; n=180 control level) n= 311 survivors at 2 years of age (n=152 high target level; n=159 control level)	**Interventions** See Thome 2015	**Details** Methods: See Thome 2015 Outcomes: All surviving infants were invited to a neurodevelopmental follow-up examination at 2 years±3 months corrected age. All possible efforts were made	**Results** Outcome: Cerebral Palsy at ≥18 months of age or older (defined as GMFCS score ≥1)	**Limitations** Random sequence generation: See Thome 2015 Allocation concealment: See Thome 2015 Blinding of participants and personnel: Low risk

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Segerer, H., Teig, N., Blaser, A., Hentschel, R., Heckmann, M., Schlosser, R., Peters, J., Rossi, R., Rascher, W., Bottger, R., Seidenberg, J., Hansen, G., Zernickel, M., Bode, H., Dreyhaupt, J., Muche, R., Hummler, H. D., Neurodevelopmental outcomes of extremely low birthweight infants randomised to different PCO 2 targets: The PHELBI follow-up study, Archives of Disease in Childhood: Fetal and Neonatal Edition, 102, F376-F382, 2017 **Ref Id** 758895 **Country/ies where the study was carried out** Germany **Study type** Randomised controlled trial **Aim of the study**	n= 265 analysed (n= 130 high target level [14% loss to follow-up]; n=135 control level [15% loss to follow-up]) **Characteristics** See Thome 2015 **Inclusion criteria** See Thome 2015 **Exclusion criteria** See Thome 2015		to reach all families. The Psychomotor Developmental Index (PDI) and the Mental Developmental Index (MDI) were determined using Bayley Scales of Infant Development II (BSIDII) in their validated German translation. Scores were assessed relative to a standardised mean±SD of 100±15, with higher scores indicating better performance. The motor function was assessed by the modified Gross Motor Function Classification System (GMFCS), with scores ranging from level 0 (normal) to level 5 (most impaired).13 As well, parents were asked to complete a Child Development Inventory (CDI) questionnaire in its validated German translation, the 'Elternfragebogen zur kindlichen Entwicklung im Kleinkindalter'. The short form of the CDI with 70 questions concerning	high target: 66/130 ; standard ventilation: 66/135 Outcome: Severe cognitive impairement at ≥18 months of age or older MDI <70 high target: 37/122 ; standard ventilation: 41/127 PDI <70 high target: 36/109 ; standard ventilation: 39/117 Outcome: Moderate cognitive impairement at ≥18 months of age or older MDI <85 high target: 67/122 ; standard ventilation: 64/127 PDI <85 high target: 56/109 ; standard ventilation: 62/117 Outcome: Severe visual impairment at	(unmasked study, however performance of babies in tests would not be affected by knowing the allocation of intervention) Blinding of outcome assessors: Low risk for cerebral palsy and cognitive impairment as strict criteria used; high risk for hearing and visual impairment as unblinded parents were used as assessors with more subjective criteria used for assessment Incomplete outcome data (attrition bias): High risk (15% of population lost to follow-up) Selective reporting: low risk (All outcomes specified in the methods were reported) **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Assess neurodevelopmental outcomes in infants randomised to two different pCO2 targets **Study dates** See Thome 2015 **Source of funding** See Thome 2015			general development was used. Blindness and deafness were assessed by parent interviews. Cerebral Palsy defined as a GMFCS score of ≥1	≥18 months of age or older high target: 24/127 ; standard ventilation: 26/133 Outcome: Severe hearing impairment at ≥18 months of age or older high target: 8/127 ; standard ventilation: 5/132	
Full citation Thome, U. H., Genzel-Boroviczeny, O., Bohnhorst, B., Schmid, M., Fuchs, H., Rohde, O., Avenarius, S., Topf, H. G., Zimmermann, A., Faas, D., Timme, K., Kleinlein, B., Buxmann, H., Schenk, W., Segerer, H., Teig, N., Gebauer, C., Hentschel, R., Heckmann, M., Schlosser, R., Peters, J., Rossi, R., Rascher, W., Bottger, R., Seidenberg, J., Hansen, G., Zernickel, M.,	**Sample size** n= 362 randomised (n=179 high target group; n=180 control target group; n=3 dropouts) **Characteristics** Gestational age in weeks (SD in parentheses): high target group= 25.6 (1.4); control group= 25.7 (1.3) Birthweight in grams (SD in parentheses): high	**Interventions** High target group: $PaCO_2$ 55-65 mmHg from 1-3 days of life (0-72 hours post-natal age), 60-70 mmHg from days 4-6 (73-177 hours), and 65-75 mmHg from days 7-14 (145-336 hours) Control targt group: PaCO2 40-50	**Details** Methods: randomised controlled trial Blood pCO_2 was to be measured in at least 12-hr intervals or more frequently if clinically indicated or when measurement reuslts outside the target range occurred. Both arterial and capillary pCO2 measurements were accepted, because routine care in several of the study centres did not include arterial line placement in all	**Results** Outcome: Mortality prior to discharge high target group: 25/179 ; control group: 11/180 Outcome: BPD at 36 weeks PMA (defined as moderate or severe) high target group: 40/179 ; control group: 35/180	**Limitations** Random sequence generation: Low risk (The patients were assigned with a secure web-based randomisation system [e-randomiser, IZKS]) Allocation concealment: Unclear risk (no details provided on allocation concealment) Blinding of participants and personnel: Low risk (Because this study could not have been masked, to

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Alzen, G., Dreyhaupt, J., Muche, R., Hummler, H. D., Phelbi Study Group, Permissive hypercapnia in extremely low birthweight infants (PHELBI): a randomised controlled multicentre trial, The Lancet Respiratory MedicineLancet Respir Med, 3, 534-43, 2015 **Ref Id** 561299 **Country/ies where the study was carried out** Germany **Study type** Randomised controlled trial **Aim of the study** To study whether a higher pCO_2 target range would reduce the rate of moderate to severe bronchopulmonary dysplasia or death in extremely low birthweight infants needing invasive ventilation.	target group= 714 (156); control group= 709 (153) Boys: high target group= 59%; control group= 55% Antenatal steroids (any): high target group= 91%; control group= 87% Apgar score at 5 min (range in parentheses): high target group= 7 (1-9); control group= 8 (1-9) Intubation age >1h: high target group= 31%; control group= 32% Surfactant replacement: high target group= 96%; control group= 97% Methylxanthine treatment: high target group= 94%; control group= 94% **Inclusion criteria** Infants with a gestational age of between 23 weeks 28 weeks plus 6 days, weighing 400-1000g and receiving endotracheal intubation and invasive ventilation within 24 hours of birth were eligible.	mmHg from days 1-3 of life (0-72 hours post-natal age), 45-55 mmHg from days 4-6 (73-177 hours), and 50-60 mmHg from days 7-14 (145-336 hours)	infants, and there was consensus that arterial lines should not routinely be left in place for 14 days. To minimise volutrauma, a high ventilation rate (60–80 per min) was favoured over high tidal volumes in both groups. Initial ventilator settings comprised a rate of 60–80 per min or greater, inspiratory time of 0·25–0·35 s, positive end-expiratory pressure 3–6 mbar, and a peak inspiratory pressure resulting in minimal to moderate chest rise. The rate was allowed to be decreased only if the peak inspiratory pressure was 14 mbar or lower. Synchronised ventilation or forms of volume control were allowed to be used at the discretion of the clinicians in charge of patient care. Because the administration of sodium bicarbonate has been linked to increased lung damage,22,23 its use was discouraged.	Outcome: Periventricular leukomalacia high target group: 16/179 ; control group: 11/180 Outcome: Severe IVH (grade III or IV) high target group: 26/179 ; control group: 21/180 Outcome: pneumothorax high target group: 8/179 ; control group: 13/180	decrease the influence of any potential bias on duration of assisted ventilation, we defined and followed strict extubation and reintubation criteria). Blinding of outcome assessors: Low risk (objective outcomes unblinded; subjective outcomes were assessed by radiologists masked to treatment allocation) Incomplete outcome data (attrition bias): Low risk (all babies followed-up for clinical outcomes) Selective reporting: low risk (All outcomes specified in the methods were reported) **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Furthermore, to find out whether hypercapnia would be most beneficial to the infants requiring the most ventilatory support. **Study dates** March 1, 2008 to July 31, 2012 **Source of funding** Deutsche Forschungsgemeinschaft	**Exclusion criteria** Exclusion criteria were birth outside the prenatal centre's delivery ward, chromosomal anomalies, congenital malformations requiring early surgery or otherwise compromising respiratory care or outcome, hydrops fetalis, air leaks before randomisation, severe birht asphyxia, or a decision to provide compassionate care only.		Furthermore, we attempted to prevent inconsistent use between the two study groups to avoid it becoming a confounder. Therefore, bicarbonate administration to correct a low pH in combined acidosis was linked to the base defi cit rather than the pH or pCO_2 and allowed only if the base defi cit exceeded an arbitrary level of -8 mmol/L, independent of pH and pCO_2 Extubation could be attempted if the $PaCO_2$ was maintained within or below the target range assigned with a rate of less than 30 breaths per min and FiO_2 was less than 0·5. After extubation, no pCO_2 targets were defi ned by the study protocol. In the case of re-intubation before day 14, the target range according to the randomised group assignment and actual postnatal age was resumed. Outcomes: The primary outcome of the trial was		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			death or bronchopulmonary dysplasia before 36 weeks PMA according to the physiological definition of bronchopulmonary dysplasia—ie, requiring mechanical pressure support or supplemental oxygen at 36 weeks PMA within ±2 days, including an oxygen reduction test for infants requiring less than 0·3 FiO_2 (bronchopulmonary dysplasia or death). The bronchopulmonary dysplasia part of this definition also represents moderate to severe bronchopulmonary dysplasia according to the National Institute of Child Health and Development (NICHD) consensus definition. Major secondary outcomes included the severity of bronchopulmonary dysplasia according to the consensus definition and the incidence and severity of intracranial haemorrhage.		

Clinical evidence tables for question 4.4 What blood pressure monitoring strategies are associated with improved outcomes in preterm babies requiring respiratory support?

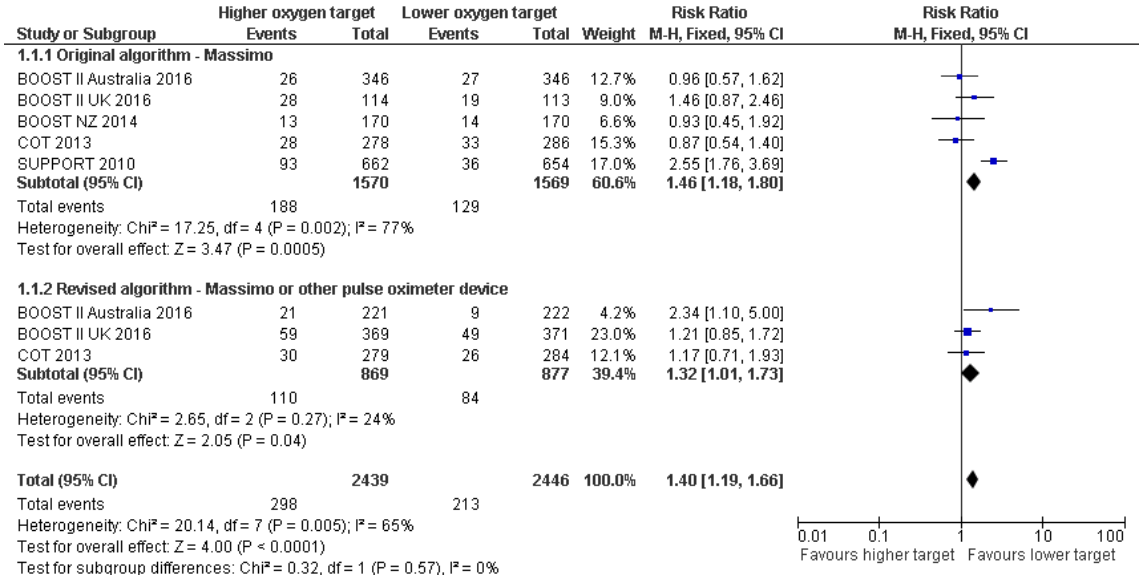
No evidence was identified for this review.

Appendix E – Forest plots

Forest plots for question 4.1 What oxygen levels are optimal in the management of preterm babies?

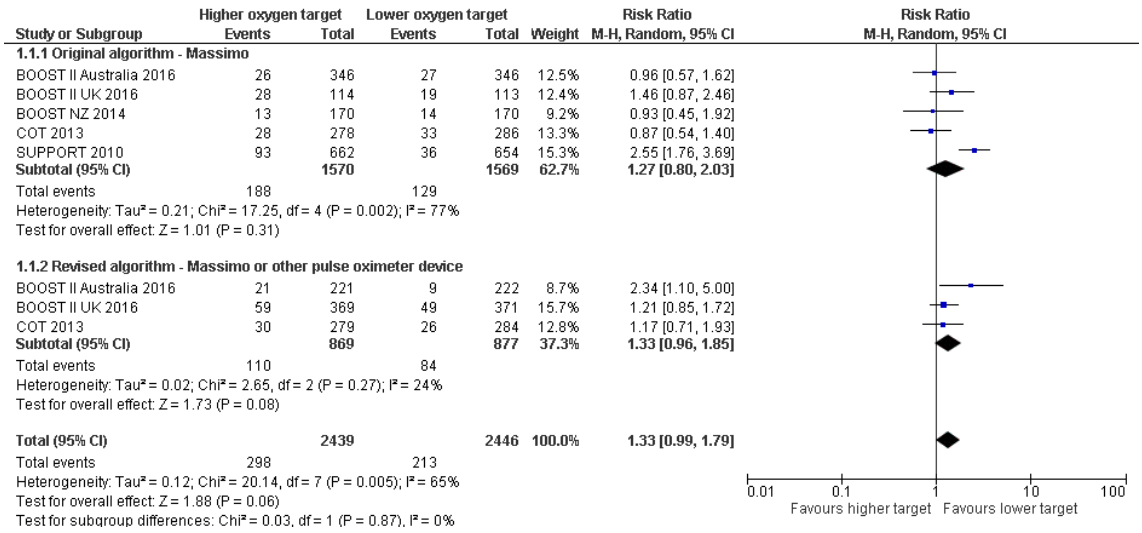
Comparison 1. Higher oxygen target saturation levels versus lower oxygen target saturation levels –

Figure 1: Severe ROP (enrolled at birth or soon after) – fixed effects model



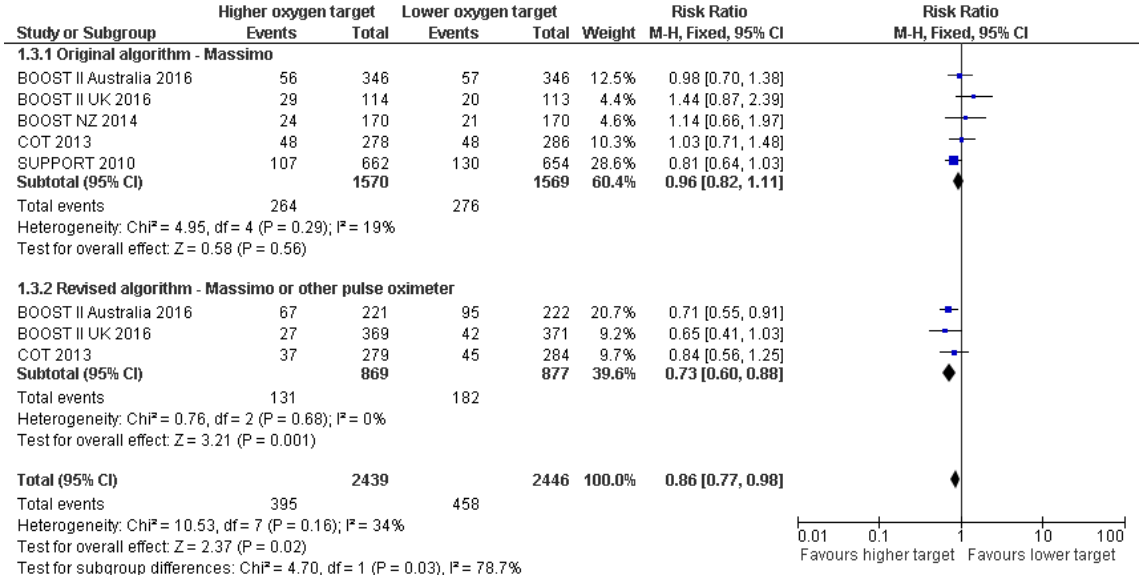
CI: confidence interval; M-H: Mantel-Haenszel; ROP: retinopathy of prematurity

Figure 2: Severe ROP (enrolled at birth or soon after) – random effects model



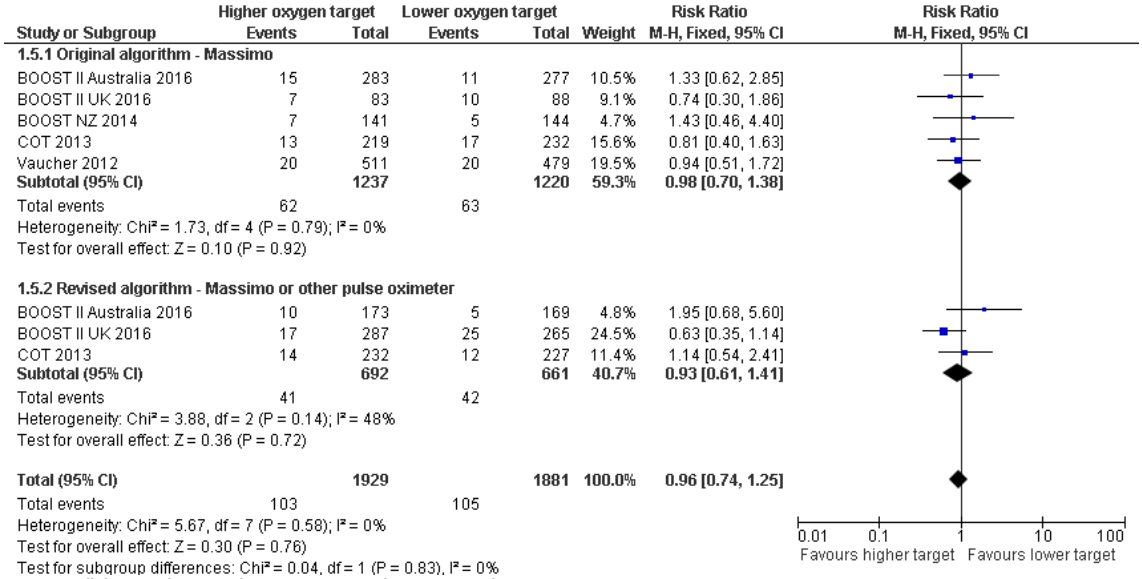
CI: confidence interval; M-H: Mantel-Haenszel; ROP: retinopathy of prematurity

Figure 3: Mortality prior to discharge (enrolled at birth or soon after)



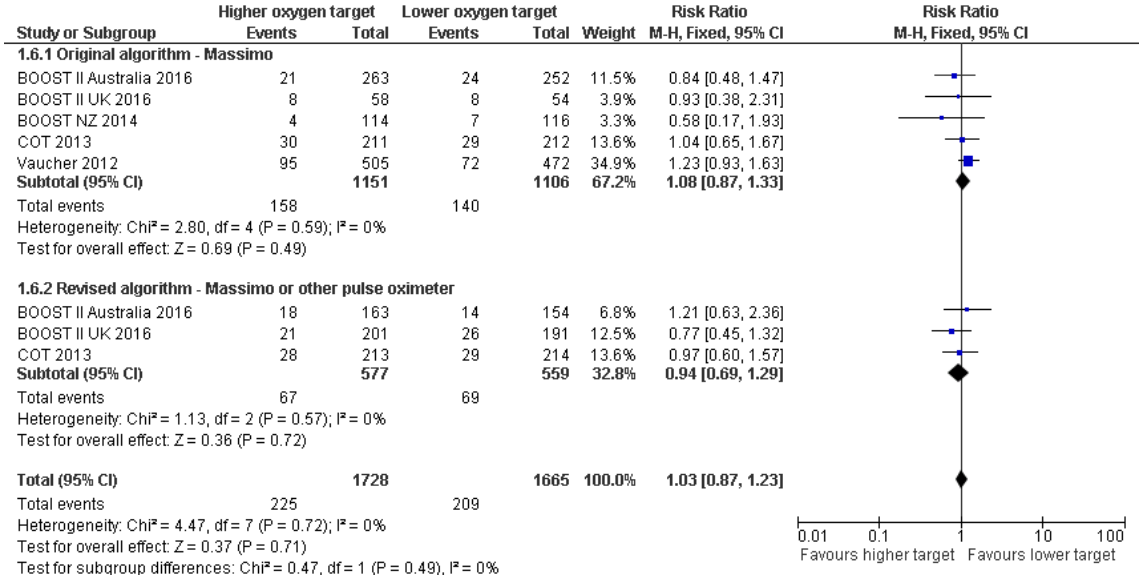
CI: confidence interval; M-H: Mantel-Haenszel

Figure 4: Neurodevelopmental outcomes: cerebral palsy at 18 months of age or older (enrolled at birth or soon after)



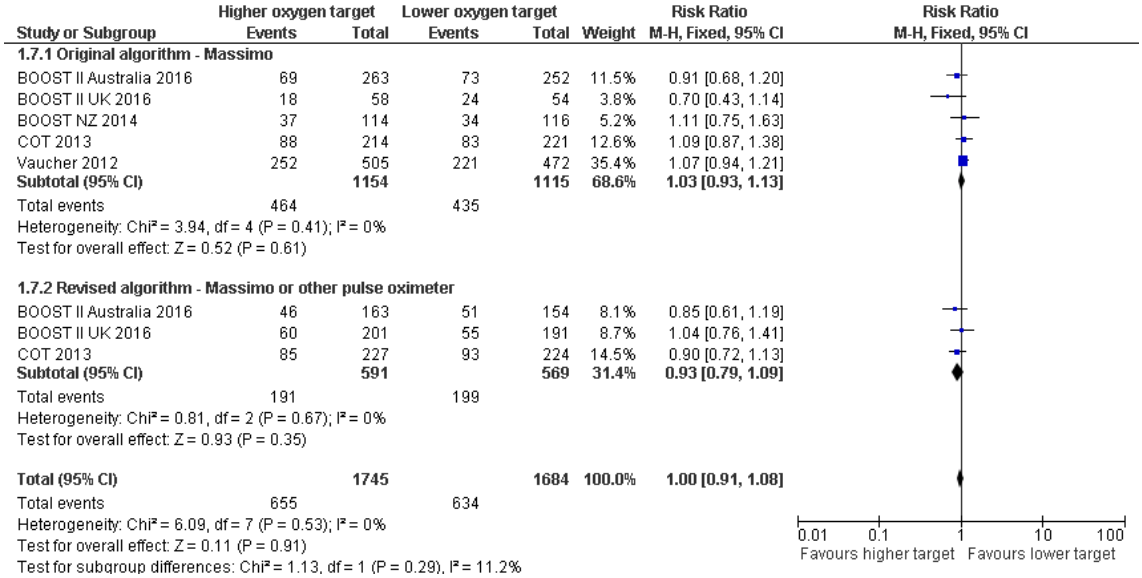
CI: confidence interval; M-H: Mantel-Haenszel

Figure 5: Neurodevelopmental outcomes: severe cognitive impairment at 18 months of age or older (enrolled at birth or soon after)



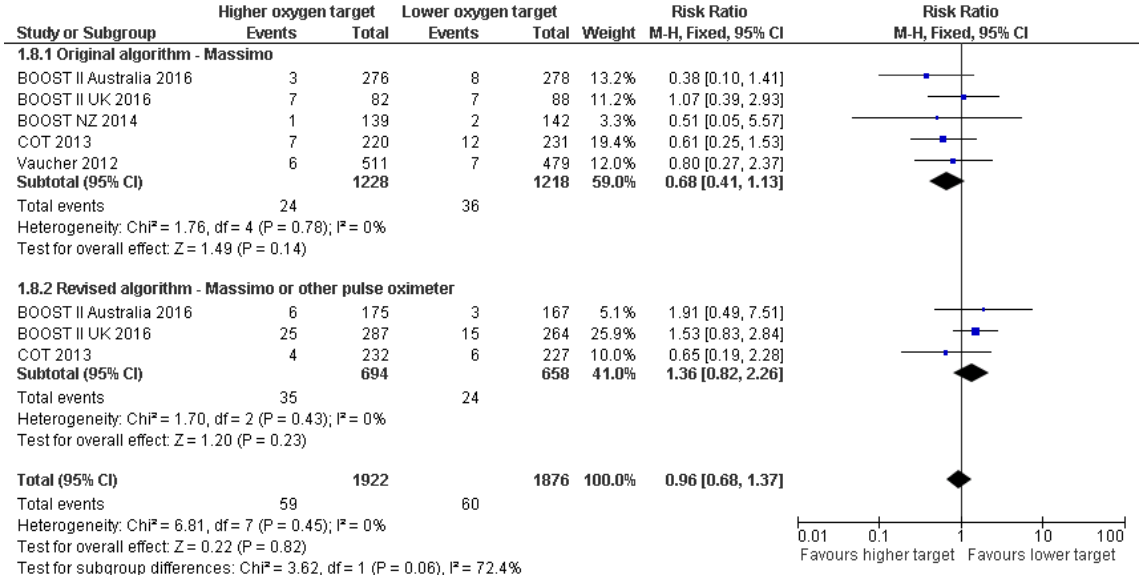
CI: confidence interval; M-H: Mantel-Haenszel

Figure 6: Neurodevelopmental outcomes: moderate cognitive impairment at 18 months of age or older (enrolled at birth or soon after)



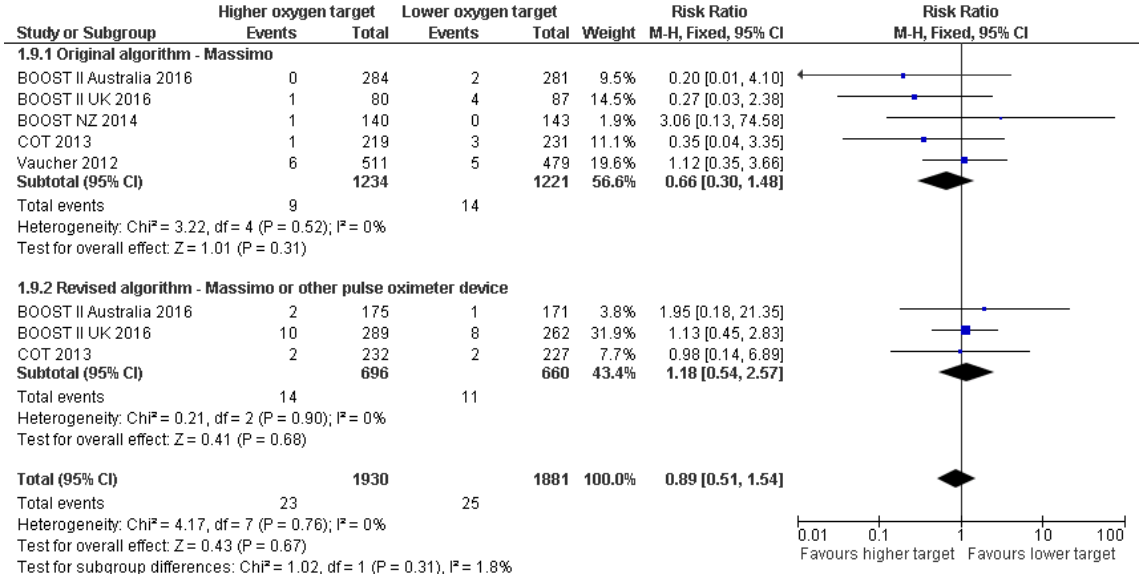
CI: confidence interval; M-H: Mantel-Haenszel

Figure 7: Neurodevelopmental outcomes: severe hearing impairment at 18 months of age or older (enrolled at birth or soon after)



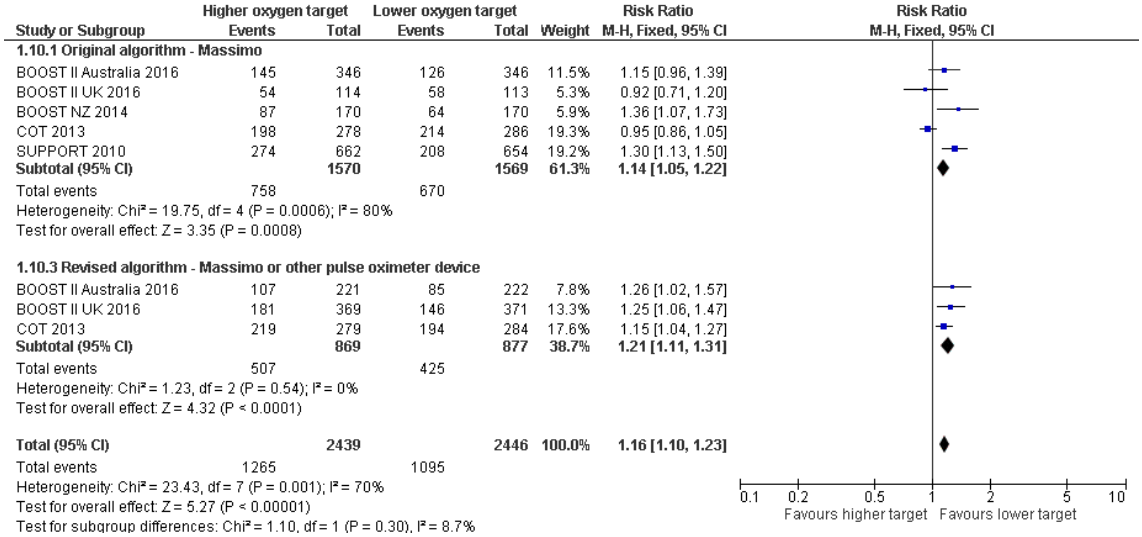
CI: confidence interval; M-H: Mantel-Haenszel

Figure 8: Neurodevelopmental outcomes: severe visual impairment at 18 months of age or older (enrolled at birth or soon after)



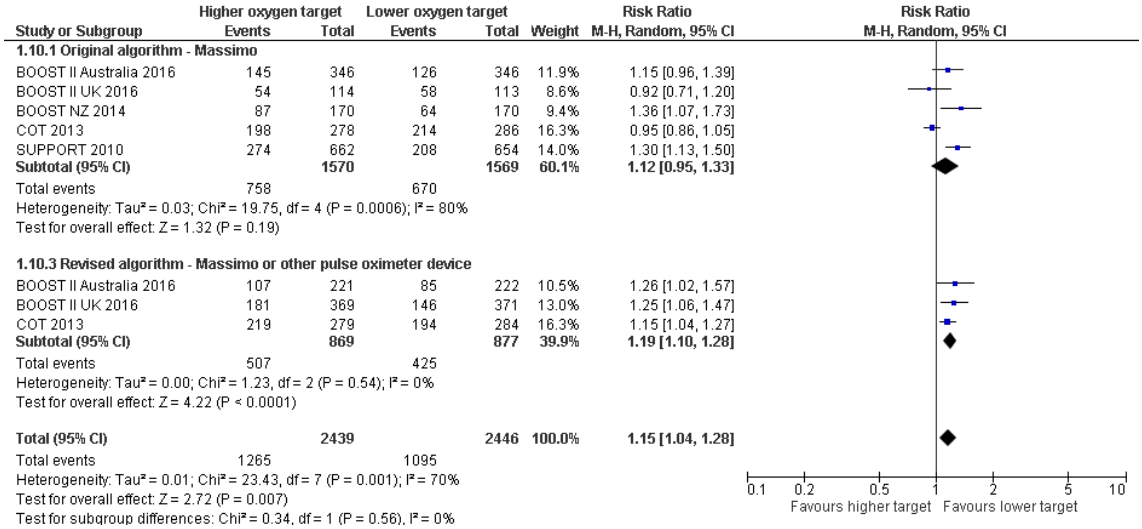
CI: confidence interval; M-H: Mantel-Haenszel

Figure 9: BPD at 36 weeks PMA (enrolled at birth or soon after) – fixed effects model



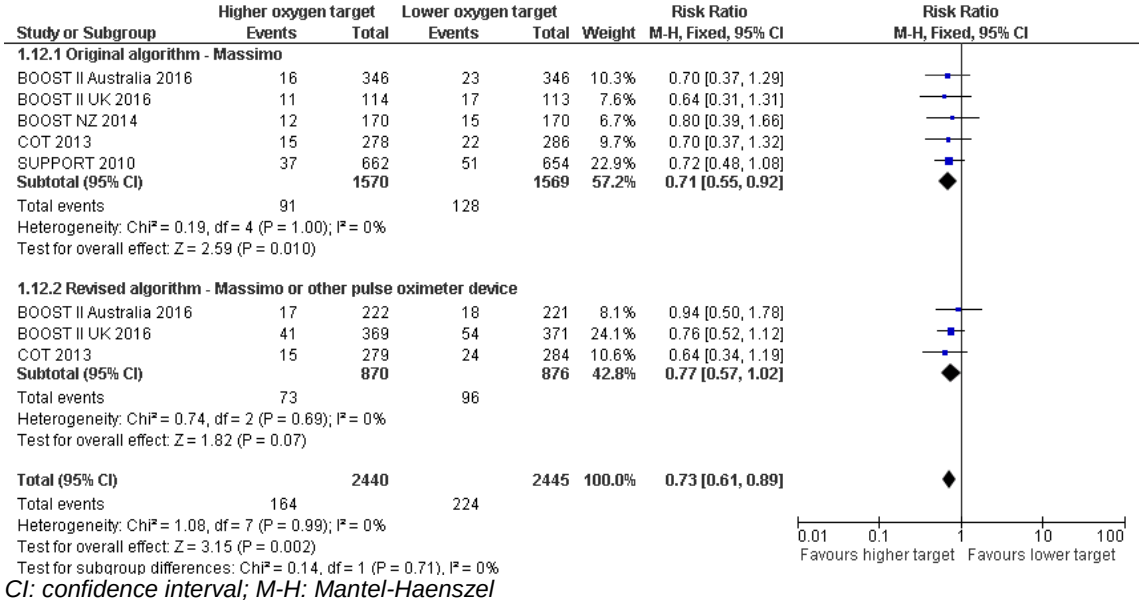
BPD: bronchopulmonary dysplasia; CI: confidence interval; M-H: Mantel-Haenszel

Figure 10: BPD at 36 weeks PMA (enrolled at birth or soon after) – random effects model



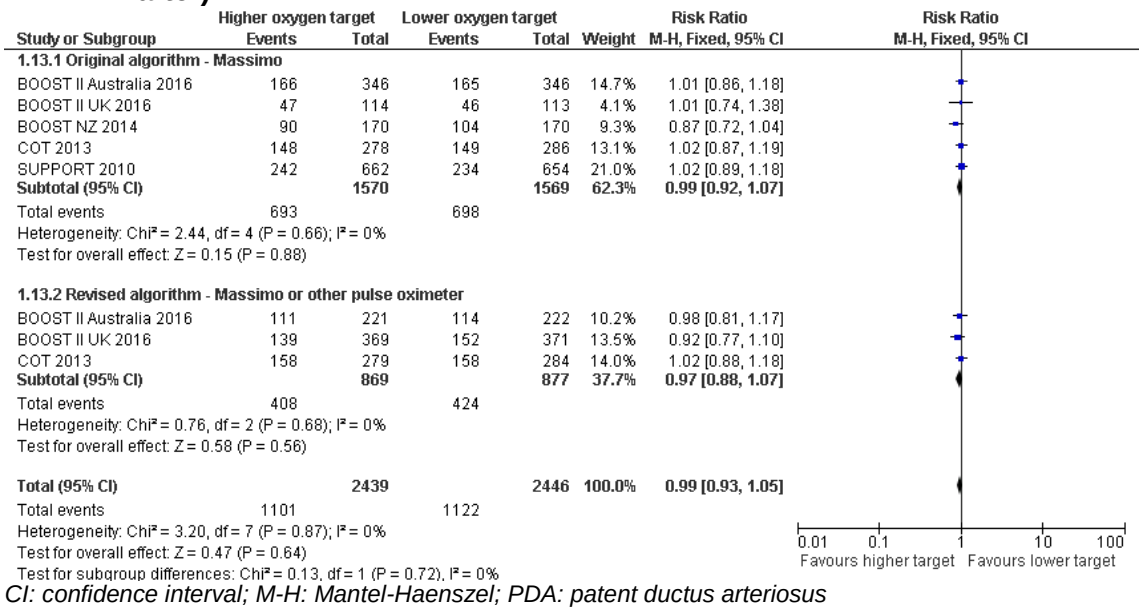
BPD: bronchopulmonary dysplasia; CI: confidence interval; M-H: Mantel-Haenszel

Figure 11: Necrotising enterocolitis (enrolled at birth or soon after)



CI: confidence interval; M-H: Mantel-Haenszel

Figure 12: PDA requiring medical or surgical intervention (enrolled at birth or soon after)



CI: confidence interval; M-H: Mantel-Haenszel; PDA: patent ductus arteriosus

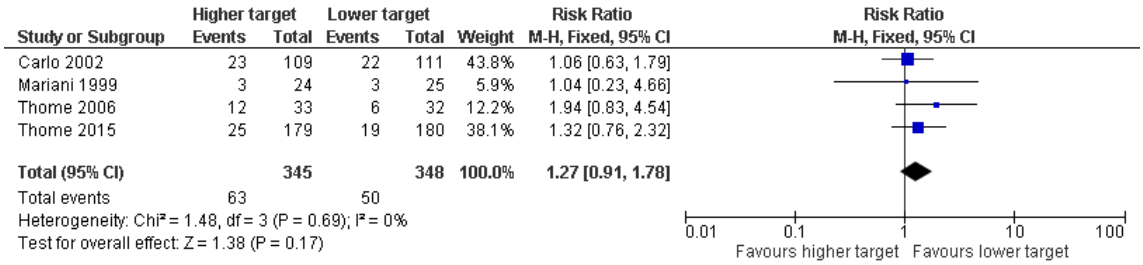
Forest plots for question 4.2 What is the best method for measuring oxygen levels in diagnosing hyperoxia or hypoxia in preterm babies?

No meta-analyses were conducted for this review question

Forest plots for question 4.3 What carbon dioxide levels are optimal in the management of preterm babies?

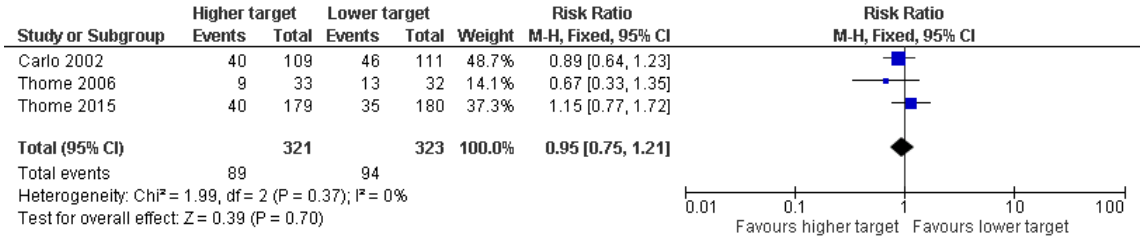
Comparison 1. Higher target range for partial pressure of carbon dioxide versus lower target range for partial pressure of carbon dioxide

Figure 13: Mortality prior to discharge



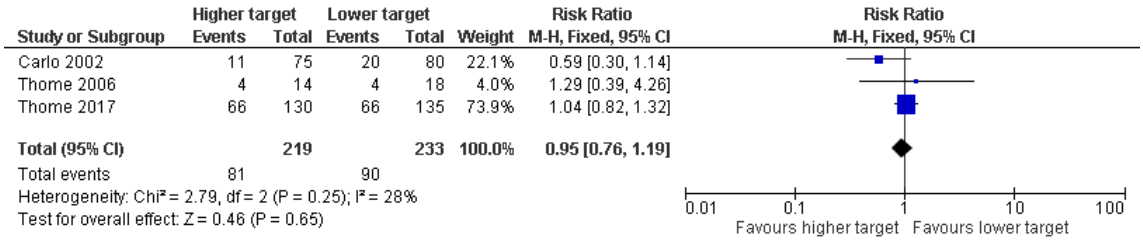
CI: confidence interval; M-H: Mantel-Haenszel

Figure 14: BPD at 36 weeks PMA



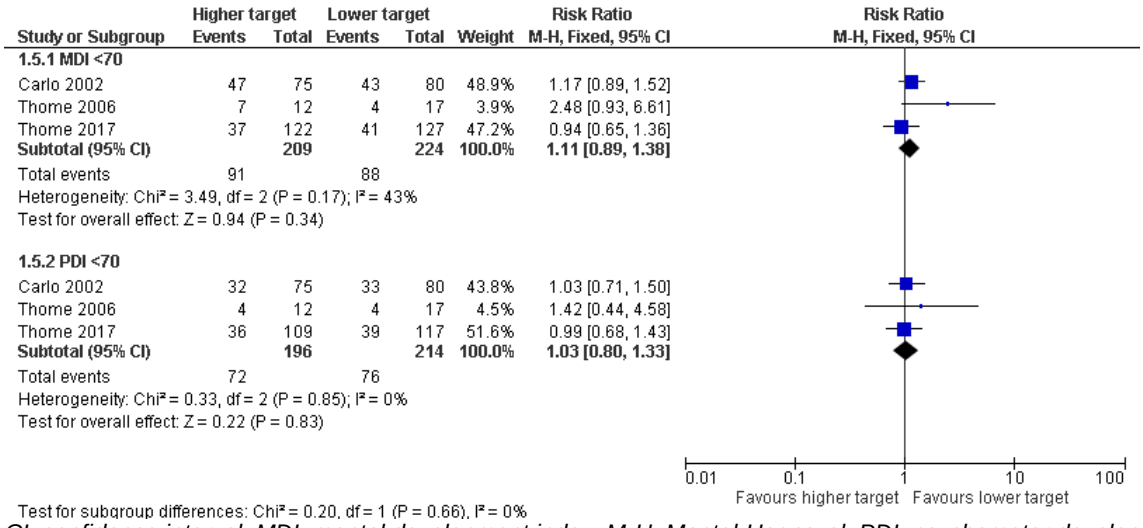
CI: confidence interval; M-H: Mantel-Haenszel

Figure 15: Neurodevelopmental outcomes: cerebral palsy at 18 months of age or older



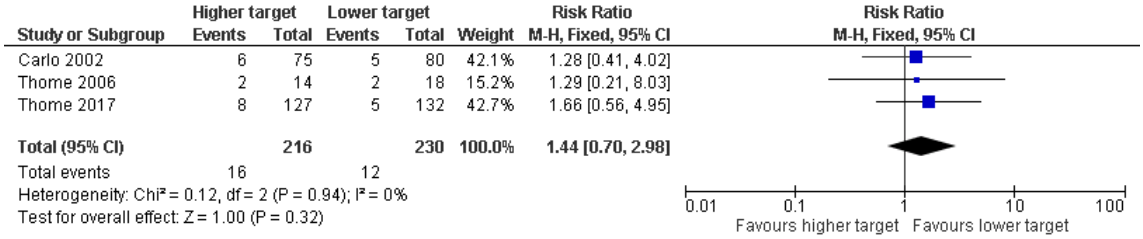
CI: confidence interval; M-H: Mantel-Haenszel

Figure 16: Neurodevelopmental outcomes: severe cognitive impairment at 18 months of age or older



CI: confidence interval; MDI: mental development index; M-H: Mantel-Haenszel; PDI: psychomotor development index

Figure 17: Neurodevelopmental outcomes: severe hearing impairment at 18 months of age or older

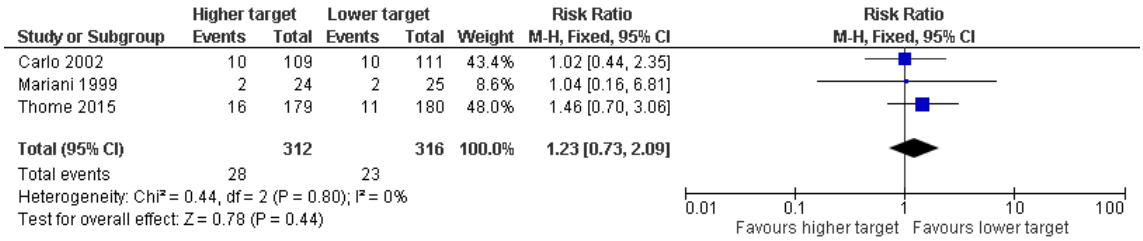


CI: confidence interval; M-H: Mantel-Haenszel

Figure 18: Neurodevelopmental outcomes: severe visual impairment at 18 months of age or older

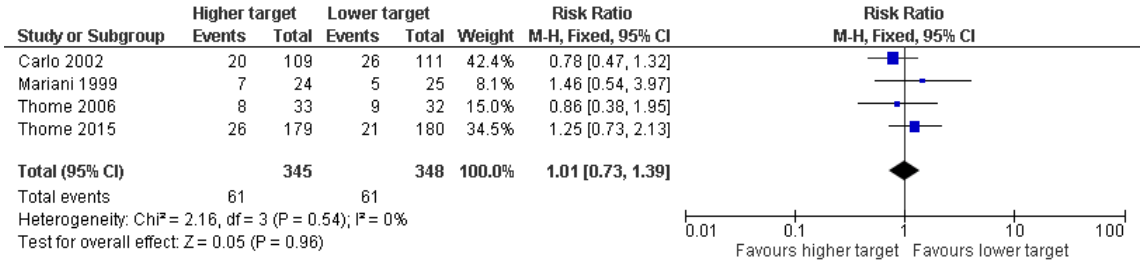
CI: confidence interval; M-H: Mantel-Haenszel

Figure 19: Periventricular leukomalacia



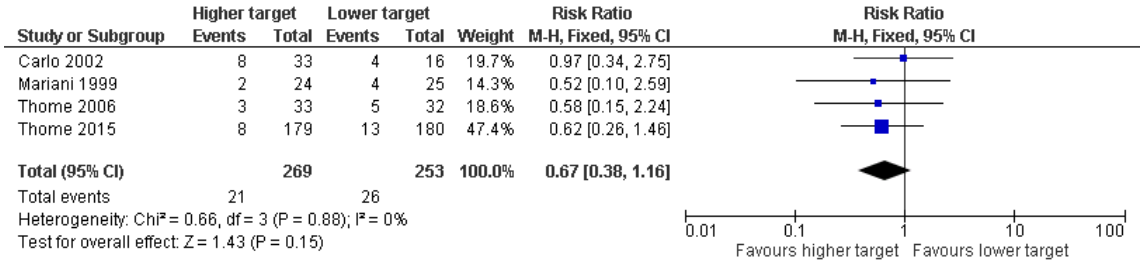
CI: confidence interval; M-H: Mantel-Haenszel

Figure 20: Severe IVH (grade III or IV)



CI: confidence interval; M-H: Mantel-Haenszel

Figure 21: Pneumothorax



CI: confidence interval; M-H: Mantel-Haenszel

Forest plots for question 4.4 What blood pressure monitoring strategies are associated with improved outcomes in preterm babies requiring respiratory support?

No clinical evidence was identified for this review and so there are no forest plots.

Appendix F – GRADE tables

GRADE tables for question 4.1 What oxygen levels are optimal in the management of preterm babies?

Table 10: Clinical evidence profile: Comparison 1. Higher oxygen target level versus lower oxygen target level

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Higher oxygen target	Lower oxygen target	Relative (95% CI)	Absolute	Quality	Importance
Severe Retinopathy of Prematurity - enrolled at birth or soon after												
5	randomised trials	no serious risk of bias	serious[1]	no serious indirectness	serious[2]	none	298/2439 (12.2%)	213/2446 (8.7%)	RR 1.33(0.99 to 1.79)	29 more per 1000 (from 1 fewer more to 69 more)	LOW	CRITICAL
Severe Retinopathy of Prematurity - enrolled at birth or soon after - Original algorithm – Massimo												
5	randomised trials	no serious risk of bias	serious[1]	no serious indirectness	serious[2]	none	188/1570 (12%)	129/1569 (8.2%)	RR 1.27 (0.80 to 2.03)	22 more per 1000 (from 16 fewer to 85 more)	LOW	CRITICAL
Severe Retinopathy of Prematurity - enrolled at birth or soon after - Revised algorithm - Massimo or other pulse oximeter device												
3	randomised trials	no serious risk of bias	no serious inconsistency[5]	no serious indirectness	serious[2]	none	110/869 (12.7%)	84/877 (9.6%)	RR 1.32 (1.01 to 1.73)	31 more per 1000 (from 1 more to 70 more)	MODERATE	CRITICAL
Severe Retinopathy of Prematurity - enrolled at 32 weeks PMA dependent on supplemental oxygen - Stage 3 or 4												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	22/180 (12.2%)	28/178 (15.7%)	RR 0.78 (0.46 to 1.31)	35 fewer per 1000 (from 85 fewer to 49 more)	LOW	CRITICAL
Severe Retinopathy of Prematurity - enrolled at 32 weeks PMA dependent on supplemental oxygen - Ablative retinal surgery												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Higher oxygen target**	**Lower oxygen target**	**Relative (95% CI)**	**Absolute**		
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	11/180 (6.1%)	20/178 (11.2%)	RR 0.54 (0.27 to 1.1)	52 fewer per 1000 (from 82 fewer to 11 more)	MODERATE	CRITICAL
Mortality prior to discharge - enrolled at birth or soon after												
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	395/2439 (16.2%)	458/2446 (18.7%)	RR 0.86 (0.77 to 0.98)	26 fewer per 1000 (from 4 fewer to 43 fewer)	MODERATE	CRITICAL
Mortality prior to discharge - enrolled at birth or soon after - Original algorithm – Massimo												
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	264/1570 (16.8%)	276/1569 (17.6%)	RR 0.96 (0.82 to 1.11)	7 fewer per 1000 (from 32 fewer to 19 more)	HIGH	CRITICAL
Mortality prior to discharge - enrolled at birth or soon after - Revised algorithm - Massimo or other pulse oximeter												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	131/869 (15.1%)	182/877 (20.8%)	RR 0.73 (0.6 to 0.88)	56 fewer per 1000 (from 25 fewer to 83 fewer)	MODERATE	CRITICAL
Mortality before discharge - enrolled at 32 weeks PMA dependent on supplemental oxygen												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	9/180 (5%)	5/178 (2.8%)	RR 1.78 (0.61 to 5.21)	22 more per 1000 (from 11 fewer to 118 more)	LOW	CRITICAL
Cerebral Palsy at 18 months of age or older - enrolled at birth or soon after												
5	randomised trials	no serious	no serious inconsistency	no serious indirectness	very serious[3]	none	103/1929 (5.3%)	105/1881 (5.6%)	RR 0.96 (0.74 to 1.25)	2 fewer per 1000 (from 15	LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Higher oxygen target**	**Lower oxygen target**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
		risk of bias								fewer to 14 more)		
Cerebral Palsy at 18 months of age or older - enrolled at birth or soon after - Original algorithm – Massimo												
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	None	62/1237 (5%)	63/1220 (5.2%)	RR 0.98 (0.7 to 1.38)	1 fewer per 1000 (from 15 fewer to 20 more)	LOW	CRITICAL
Cerebral Palsy at 18 months of age or older - enrolled at birth or soon after - Revised algorithm - Massimo or other pulse oximeter												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	None	41/692 (5.9%)	42/661 (6.4%)	RR 0.93 (0.61 to 1.41)	4 fewer per 1000 (from 25 fewer to 26 more)	LOW	CRITICAL
Severe cognitive impairment at 18 months of age or older - enrolled at birth or soon after												
5	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	None	225/1728 (13%)	209/1665 (12.6%)	RR 1.03 (0.87 to 1.23)	4 more per 1000 (from 16 fewer to 29 more)	MODERATE	CRITICAL
Severe cognitive impairment at 18 months of age or older - enrolled at birth or soon after - Original algorithm - Massimo												
5	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[2]	None	158/1151 (13.7%)	140/1106 (12.7%)	RR 1.08 (0.87 to 1.33)	10 more per 1000 (from 16 fewer to 42 more)	LOW	CRITICAL
Severe cognitive impairment at 18 months of age or older - enrolled at birth or soon after - Revised algorithm - Massimo or other pulse oximeter												
3	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[3]	None	67/577 (11.6%)	69/559 (12.3%)	RR 0.94 (0.69 to 1.29)	7 fewer per 1000 (from 38 fewer to 36 more)	VERY LOW	CRITICAL
Moderate cognitive impairment at 18 months of age or older - enrolled at birth or soon after												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Higher oxygen target**	**Lower oxygen target**	**Relative (95% CI)**	**Absolute**		
5	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	655/1745 (37.5%)	634/1684 (37.6%)	RR 1 (0.91 to 1.08)	0 fewer per 1000 (from 34 fewer to 30 more)	MODERATE	CRITICAL
Moderate cognitive impairment at 18 months of age or older - enrolled at birth or soon after - Original algorithm – Massimo												
5	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	464/1154 (40.2%)	435/1115 (39%)	RR 1.03 (0.93 to 1.13)	12 more per 1000 (from 27 fewer to 51 more)	MODERATE	CRITICAL
Moderate cognitive impairment at 18 months of age or older - enrolled at birth or soon after - Revised algorithm - Massimo or other pulse oximeter												
3	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[2]	none	191/591 (32.3%)	199/569 (35%)	RR 0.93 (0.79 to 1.09)	24 fewer per 1000 (from 73 fewer to 31 more)	LOW	CRITICAL
Severe hearing impairment at 18 months of age or older - enrolled at birth or soon after												
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	59/1922 (3.1%)	60/1876 (3.2%)	RR 0.96 (0.68 to 1.37)	1 fewer per 1000 (from 10 fewer to 12 more)	LOW	CRITICAL
Severe hearing impairment at 18 months of age or older - enrolled at birth or soon after - Original algorithm – Massimo												
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	24/1228 (2%)	36/1218 (3%)	RR 0.68 (0.41 to 1.13)	9 fewer per 1000 (from 17 fewer to 4 more)	MODERATE	CRITICAL
Severe hearing impairment at 18 months of age or older - enrolled at birth or soon after - Revised algorithm - Massimo or other pulse oximeter												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	35/694 (5%)	24/658 (3.6%)	RR 1.36 (0.82 to 2.26)	13 more per 1000 (from 7 fewer to 46 more)	MODERATE	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Higher oxygen target**	**Lower oxygen target**	**Relative (95% CI)**	**Absolute**		
Severe visual impairment at 18 months of age or older - enrolled at birth or soon after												
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	23/1930 (1.2%)	25/1881 (1.3%)	RR 0.89 (0.51 to 1.54)	1 fewer per 1000 (from 7 fewer to 7 more)	LOW	
Severe visual impairment at 18 months of age or older - enrolled at birth or soon after - Original algorithm – Massimo												
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	9/1234 (0.73%)	14/1221 (1.1%)	RR 0.66 (0.3 to 1.48)	4 fewer per 1000 (from 8 fewer to 6 more)	LOW	CRITICAL
Severe visual impairment at 18 months of age or older - enrolled at birth or soon after - Revised algorithm - Massimo or other pulse oximeter device												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	14/696 (2%)	11/660 (1.7%)	RR 1.18 (0.54 to 2.57)	3 more per 1000 (from 8 fewer to 26 more)	LOW	CRITICAL
Bronchopulmonary dysplasia at 36 weeks PMA - enrolled at birth or soon after												
5	randomised trials	no serious risk of bias	serious[1]	no serious indirectness	serious[2]	none	1265/2439 (51.9%)	1095/2446 (44.8%)	RR 1.15 (1.04 to 1.28)	67 more per 1000 (from 18 more to 125 more)	LOW	IMPORTANT
Bronchopulmonary dysplasia at 36 weeks PMA - enrolled at birth or soon after - Original algorithm – Massimo												
5	randomised trials	no serious risk of bias	serious[1]	no serious indirectness	serious[2]	none	758/1570 (48.3%)	670/1569 (42.7%)	RR 1.12(0.95to 1.33)	51 more per 1000 (from 21 fewer to 141 more)	LOW	IMPORTANT
Bronchopulmonary dysplasia at 36 weeks PMA - enrolled at birth or soon after - Revised algorithm - Massimo or other pulse oximeter device												

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Higher oxygen target**	**Lower oxygen target**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
3	randomised trials	no serious risk of bias	no serious inconsistency[5]	no serious indirectness	serious[2]	none	507/869 (58.3%)	425/877 (48.5%)	RR 1.21 (1.11 to 1.31)	102 more per 1000 (from 53 more to 150 more)	MODERATE	IMPORTANT
Bronchopulmonary dysplasia at 36 weeks PMA - enrolled at 32 weeks dependent on supplemental oxygen												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	116/180 (64.4%)	82/178 (46.1%)	RR 1.4 (1.15 to 1.7)	184 more per 1000 (from 69 more to 322 more)	MODERATE	IMPORTANT
Necrotising enterocolitis - enrolled at birth or soon after												
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	164/2440 (6.7%)	224/2445 (9.2%)	RR 0.73 (0.61 to 0.89)	25 fewer per 1000 (from 10 fewer to 36 fewer)	MODERATE	IMPORTANT
Necrotising enterocolitis - enrolled at birth or soon after - Original algorithm – Massimo												
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	91/1570 (5.8%)	128/1569 (8.2%)	RR 0.71 (0.55 to 0.92)	24 fewer per 1000 (from 7 fewer to 37 fewer)	MODERATE	IMPORTANT
Necrotising enterocolitis - enrolled at birth or soon after - Revised algorithm - Massimo or other pulse oximeter device												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	73/870 (8.4%)	96/876 (11%)	RR 0.77 (0.57 to 1.02)	25 fewer per 1000 (from 47 fewer to 2 more)	MODERATE	IMPORTANT
Patent ductus arteriosus requiring medical or surgical intervention - enrolled at birth or soon after												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Higher oxygen target**	**Lower oxygen target**	**Relative (95% CI)**	**Absolute**		
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1101/2439 (45.1%)	1122/2446 (45.9%)	RR 0.99 (0.93 to 1.05)	5 fewer per 1000 (from 32 fewer to 23 more)	HIGH	IMPORTANT
Patent ductus arteriosus requiring medical or surgical intervention - enrolled at birth or soon after - Original algorithm - Massimo												
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	693/1570 (44.1%)	698/1569 (44.5%)	RR 0.99 (0.92 to 1.07)	4 fewer per 1000 (from 36 fewer to 31 more)	HIGH	IMPORTANT
Patent ductus arteriosus requiring medical or surgical intervention - enrolled at birth or soon after - Revised algorithm - Massimo or other pulse oximeter												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	408/869 (47%)	424/877 (48.3%)	RR 0.97 (0.88 to 1.07)	15 fewer per 1000 (from 58 fewer to 34 more)	HIGH	IMPORTANT

CI: confidence interval; MID: minimal important difference; PMA: postmenstrual age; RR: relative risk
1 The quality of evidence was downgraded by 1 because heterogeneity; stratified analysis according to type of algorithm did not reduce heterogeneity in the "original Masimo" subgroup - so a random effects model was used for the "original Masimo" subgroup and for the overall pooled effect. Exploration of gestational age as a source of heterogeneity was not possible.
2 The quality of evidence was downgraded by 1 because the 95% CI crosses 1 MID
3 The quality of evidence was downgraded by 2 because the 95% CI crosses 2 MIDs
4 The quality of evidence was downgraded by 1 as there was >10% attrition (BOOST NZ 2014 and BOOST II Australia 2016)
5 Fixed effects model used

Modified GRADE for Diagnostic Test Accuracy studies tables for question 4.2 What is the best method for measuring oxygen levels in diagnosing hyperoxia or hypoxia in preterm babies?

Table 11: Clinical evidence profile: Summary of clinical evidence profile for tcPO2 in the identification of hyperoxia (defined as PaO2 > 100 mm Hg)

Index test	Number of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (95%CI)	Specificity (95%CI)	LR+	LR-	Quality
TcPO2	1	26 (335 blood samples)	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Serious imprecision[2]	79% (63 – 90%)	97% (94-99%)	26 (13-50)	0.22 (0.12-0.39)	Low

[1] *The quality of the evidence was downgraded by 1 as the population of infants with hyaline membrane disease includes infants up to 38 weeks PMA*
[2] *The quality of evidence was downgraded by 1 as the lower 95% CI crosses 75% boundary for sensitivity*

Table 12: Clinical evidence profile: Summary of clinical evidence profile for tcPO2 in the identification of hypoxia (defined as PaO2 <50 mm Hg)

Index test	Number of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (95%CI)	Specificity (95%CI)	LR+	LR-	Quality
TcPO2	1	26 (335 blood samples)	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	79% (63 – 90%)	97% (94-99%)	26 (13-50)	0.22 (0.12-0.39)	Very low

[1] *The quality of the evidence was downgraded by 1 as the population of infants with hyaline membrane disease includes infants up to 38 weeks PMA*
[2] *The quality of evidence was downgraded by 2 as the 95% CI crosses the 75% and 90% boundary for sensitivity*

GRADE tables for question 4.3 What carbon dioxide levels are optimal in the management of preterm babies?

Table 13: Clinical evidence profile: Comparison 1. Higher target range for partial pressure of carbon dioxide versus lower target range for partial pressure of carbon dioxide

Quality assessment							Number of babies		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Higher carbon dioxide target	Lower carbon dioxide target	Relative (95% CI)	Absolute	Quality	Importance
Mortality prior to discharge												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	63/345 (18.3%)	50/348 (14.4%)	RR 1.27 (0.91 to 1.78)	39 more per 1000 (from 13 fewer to 112 more)	MODERATE	CRITICAL
Bronchopulmonary dysplasia at 36 weeks PMA												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	89/321 (27.7%)	94/323 (29.1%)	RR 0.95 (0.75 to 1.21)	15 fewer per 1000 (from 73 fewer to 61 more)	MODERATE	CRITICAL
Bronchopulmonary dysplasia at 28 days PMA												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	9/24 (37.5%)	14/25 (56%)	RR 0.67 (0.36 to 1.25)	185 fewer per 1000 (from 358 fewer to 140 more)	LOW	CRITICAL
Cerebral Palsy at 18 months of age or older												
3	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[1]	none	81/219 (37%)	90/233 (38.6%)	RR 0.95 (0.76 to 1.19)	19 fewer per 1000 (from 93 fewer to 73 more)	LOW	CRITICAL
Severe cognitive impairment at 18 months of age or older - MDI <70												
3	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[1]	none	91/209 (43.5%)	88/224 (39.3%)	RR 1.11 (0.89 to 1.38)	43 more per 1000 (from 43	LOW	CRITICAL

Quality assessment							Number of babies		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Higher carbon dioxide target	Lower carbon dioxide target	Relative (95% CI)	Absolute	Quality	Importance
										fewer to 149 more)		
Severe cognitive impairment at 18 months of age or older - PDI <70												
3	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[2]	none	72/196 (36.7%)	76/214 (35.5%)	RR 1.03 (0.8 to 1.33)	11 more per 1000 (from 71 fewer to 117 more)	VERY LOW	CRITICAL
Moderate cognitive impairment at 18 months of age or older - MDI <85												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[1]	none	67/122 (54.9%)	64/127 (50.4%)	RR 1.09 (0.86 to 1.38)	45 more per 1000 (from 71 fewer to 191 more)	LOW	CRITICAL
Moderate cognitive impairment at 18 months of age or older - PDI <85												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[1]	none	56/109 (51.4%)	62/117 (53%)	RR 0.97 (0.76 to 1.24)	16 fewer per 1000 (from 127 fewer to 127 more)	LOW	CRITICAL
Severe hearing impairment at 18 months of age or older												
3	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[2]	none	16/216 (7.4%)	12/230 (5.2%)	RR 1.44 (0.7 to 2.98)	23 more per 1000 (from 16 fewer to 103 more)	VERY LOW	CRITICAL
Severe visual impairment at 18 months of age or older												
3	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[2]	none	28/216 (13%)	31/231 (13.4%)	RR 0.97 (0.62 to 1.54)	4 fewer per 1000 (from 51 fewer to 72 more)	VERY LOW	CRITICAL
Periventricular leucomalacia												

Quality assessment							Number of babies		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Higher carbon dioxide target**	**Lower carbon dioxide target**	**Relative (95% CI)**	**Absolute**		
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	28/312 (9%)	23/316 (7.3%)	RR 1.23 (0.73 to 2.09)	17 more per 1000 (from 20 fewer to 79 more)	LOW	IMPORTANT
Severe IVH (Grade III or IV)												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	61/345 (17.7%)	61/348 (17.5%)	RR 1.01 (0.73 to 1.39)	2 more per 1000 (from 47 fewer to 68 more)	LOW	IMPORTANT
Days on invasive ventilation (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	109	111	-	MD 4.00 lower (10.22 lower to 2.22 higher)	HIGH	IMPORTANT
1	randomised trials	no serious risk of bias	No serious inconsistency	no serious indirectness	serious[4]	none	n=24 Median (IQR) 2.5 days (1.5 to 11.5)	n=25 Median (IQR) 9.5 days (2 to 22.5)	-	Median 7 days fewer (p=0.17)	MODERATE	IMPORTANT
Pneumothorax												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	21/269 (7.8%)	26/253 (10.3%)	RR 0.67 (0.38 to 1.16)	34 fewer per 1000 (from 64 fewer to 16 more)	MODERATE	IMPORTANT

CI: confidence interval; IVH: intraventricular haemorrhage; IQR: interquartile range; MDI: mental development index; MID: minimal important difference; PDI: psychomotor development index; PMA: postmenstrual age; RR: relative risk

[1] The quality of the evidence was downgraded by 1 as the 95% CI crossed 1 MID

[2] The quality of the evidence was downgraded by 2 as the 95% CI crosses 2 MIDs

[3] The quality of the evidence was downgraded by 1 as there was a high level of attrition (>10%)

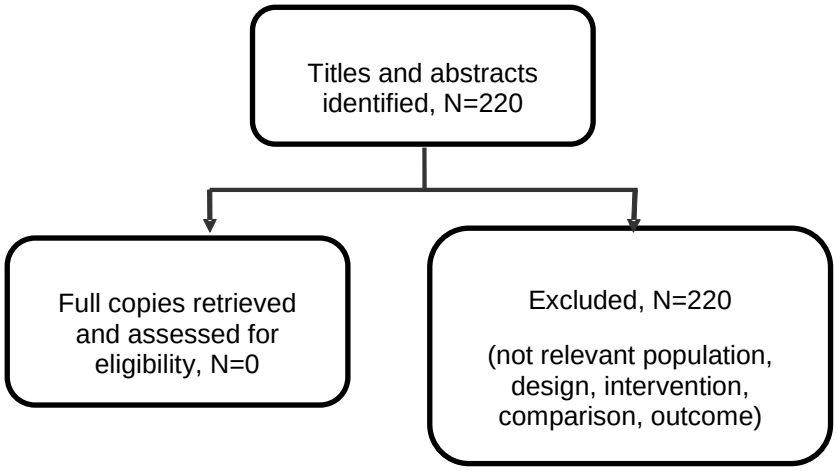
[4] The quality of the evidence was downgraded by 1, imprecision was not calculable because results were presented as medians

GRADE tables for question 4.4 What blood pressure monitoring strategies are associated with improved outcomes in preterm babies requiring respiratory support?

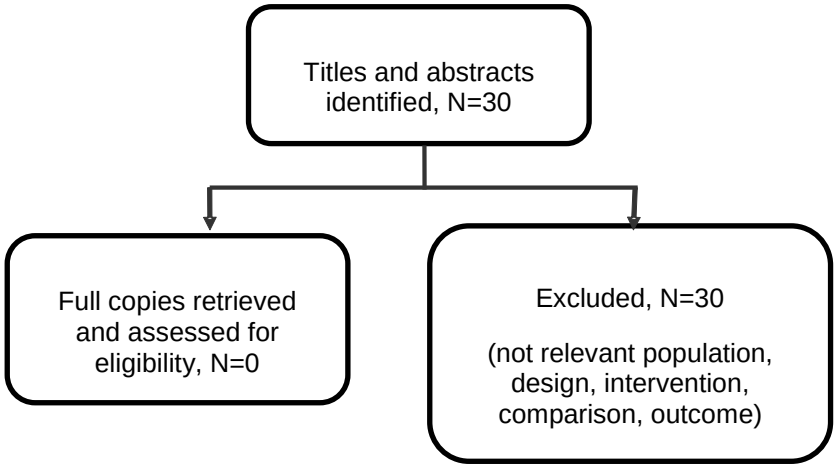
No clinical evidence was identified for this review so there are no GRADE tables.

Appendix G – Economic evidence study selection

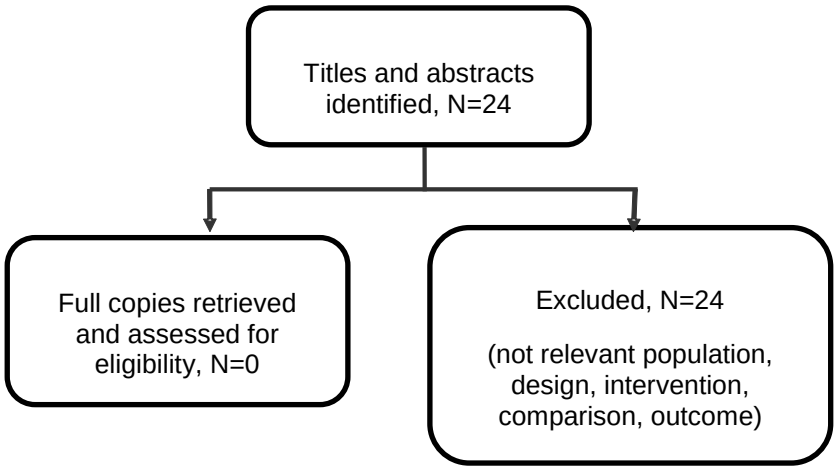
Economic evidence study selection for question 4.1 What oxygen levels are optimal in the management of preterm babies?



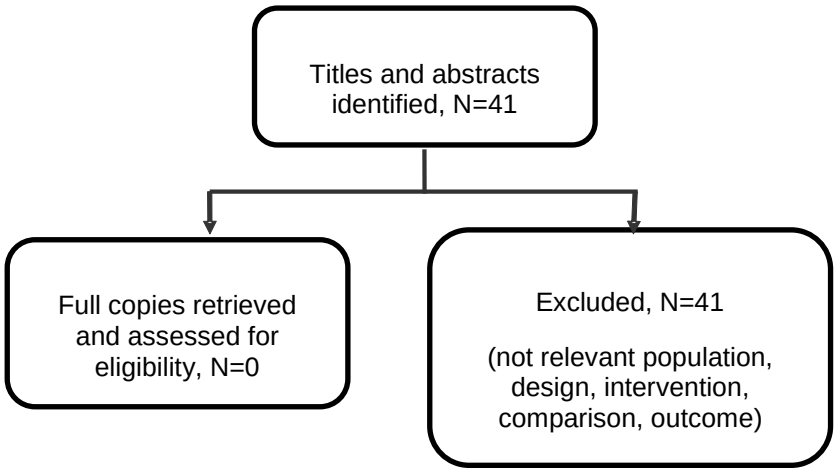
Economic evidence study selection for question 4.2 What is the best method for measuring oxygen levels in diagnosing hyperoxia or hypoxia in preterm babies?



Economic evidence study selection for question 4.3 What carbon dioxide levels are optimal in the management of preterm babies?



Economic evidence study selection for question 4.4 What blood pressure monitoring strategies are associated with improved outcomes in preterm babies requiring respiratory support?



Appendix H – Economic evidence tables

Economic evidence tables for question 4.1 What oxygen levels are optimal in the management of preterm babies?

No economic evidence was identified for this review.

Economic evidence tables for question 4.2 What is the best method for measuring oxygen levels in diagnosing hyperoxia or hypoxia in preterm babies?

No economic evidence was identified for this review.

Economic evidence tables for question 4.3 What carbon dioxide levels are optimal in the management of preterm babies?

No economic evidence was identified for this review.

Economic evidence tables for question 4.4 What blood pressure monitoring strategies are associated with improved outcomes in preterm babies requiring respiratory support?

No economic evidence was identified for this review.

Appendix I – Economic evidence profiles

Economic evidence profiles for question 4.1 What oxygen levels are optimal in the management of preterm babies?

No economic evidence was identified for this review.

Economic evidence profiles for question 4.2 What is the best method for measuring oxygen levels in diagnosing hyperoxia or hypoxia in preterm babies?

No economic evidence was identified for this review.

Economic evidence profiles for question 4.3 What carbon dioxide levels are optimal in the management of preterm babies?

No economic evidence was identified for this review.

Economic evidence profiles for question 4.4 What blood pressure monitoring strategies are associated with improved outcomes in preterm babies requiring respiratory support?

No economic evidence was identified for this review.

Appendix J – Economic analysis

Economic analysis for question 4.1 What oxygen levels are optimal in the management of preterm babies?

No economic analysis was undertaken for this review.

Economic analysis for question 4.2 What is the best method for measuring oxygen levels in diagnosing hyperoxia or hypoxia in preterm babies?

No economic analysis was undertaken for this review.

Economic analysis for question 4.3 What carbon dioxide levels are optimal in the management of preterm babies?

No economic analysis was undertaken for this review.

Economic analysis for question 4.4 What blood pressure monitoring strategies are associated with improved outcomes in preterm babies requiring respiratory support?

No economic analysis was undertaken for this review.

Appendix K – Excluded studies

Excluded studies for question 4.1 What oxygen levels are optimal in the management of preterm babies?

Clinical studies

Study	Reason for Exclusion
Ambalavanan, N, Carlo, Wa, Wrage, La, Das, A, Laughon, M, Cotten, Cm, Kennedy, Ka, Laptook, Ar, Shankaran, S, Walsh, Mc, Higgins, Rd, PaCO2 in surfactant, positive pressure, and oxygenation randomised trial (SUPPORT), Archives of disease in childhood. Fetal and neonatal edition, 100, F145-9, 2015	Intervention not of interest for review - PaCO2
Askie, L. M., Darlow, B. A., Davis, P. G., Finer, N., Stenson, B., Vento, M., Whyte, R., Effects of targeting lower versus higher arterial oxygen saturations on death or disability in preterm infants, Cochrane Database of Systematic Reviews, 2017 (4) (no pagination), 2017	No additional studies of interest for review than included Askie 2018 NEOPROM collaborative meta-analysis
Brown,J.V., Moe-Byrne,T., Harden,M., McGuire,W., Lower versus higher oxygen concentration for delivery room stabilisation of preterm neonates: systematic review, PLoS ONE [Electronic Resource], 7, e52033-, 2012	Intervention not of interest for review - oxygen concentrations used in the delivery room
Chen, M. L., Guo, L., Smith, L. E., Dammann, C. E., Dammann, O., High or low oxygen saturation and severe retinopathy of prematurity: a meta-analysis, Pediatrics, 125, e1483-92, 2010	Only 1 RCT relevant for review, extracted from primary paper
Finer, Nn, Carlo, Wa, Walsh, Mc, Rich, W, Gantz, Mg, Laptook, Ar, Yoder, Ba, Faix, Rg, Das, A, Poole, Wk, Donovan, Ef, Newman, Ns, Ambalavanan, N, Frantz, Id, Buchter, S, Sánchez, Pj, Kennedy, Ka, Laroia, N, Poindexter, Bb, Cotten, Cm, Meurs, Kp, Duara, S, Narendran, V, Sood, Bg, O'Shea, Tm, Bell, Ef, Bhandari, V, Watterberg, Kl, Higgins, Rd, Early CPAP versus surfactant in extremely preterm infants, New England Journal of Medicine, 362, 1970-1979, 2010	Outcomes stratified by method of ventilation not oxygen target level
Fiore, Jm, Walsh, M, Wrage, L, Rich, W, Finer, N, Carlo, Wa, Martin, Rj, Low oxygen saturation target range is associated with increased incidence of intermittent hypoxemia, The Journal of pediatrics, 161, 1047-52, 2012	No outcomes relevant for review - intermittent hypoxaemia
Fleck, B. W., Stenson, B. J., Retinopathy of Prematurity and the Oxygen Conundrum: Lessons Learned from Recent Randomized Trials, Clinics in Perinatology, 40, 229-240, 2013	Study design not of interest for review - editorial
Flint, A., Davies, M. W., The use of overnight oximetry in neonates: A literature review,	The included studies regarding preterm infants were not controlled trials.

Study	Reason for Exclusion
Journal of Paediatrics & Child HealthJ Paediatr Child Health, 15, 15, 2018	
Kayton, A., Timoney, P., Vargo, L., Perez, J. A., A Review of Oxygen Physiology and Appropriate Management of Oxygen Levels in Premature Neonates, Advances in Neonatal CareAdv Neonat Care, 18, 98-104, 2018	Not a systematic review
Lakshminrusimha, S., Manja, V., Mathew, B., Suresh, G. K., Oxygen targeting in preterm infants: A physiological interpretation, Journal of Perinatology, 35, 8-15, 2015	Study design not of interest for review - editorial
Lui, K., Jones, L. J., Foster, J. P., Davis, P. G., Ching, S. K., Oei, J. L., Osborn, D. A., Lower versus higher oxygen concentrations titrated to target oxygen saturations during resuscitation of preterm infants at birth, Cochrane Database of Systematic Reviews, 2018 (5) (no pagination), 2018	Outcome is the 'concentration of oxygen titrated' not level of saturation targeted
Manja, V., Lakshminrusimha, S., Cook, D. J., Oxygen saturation target range for extremely preterm infants: a systematic review and meta-analysis, JAMA Pediatrics, 169, 332-40, 2015	No additional RCTs identified in addition to Askie 2017 Cochrane Systematic review
Manja, V., Saugstad, O. D., Lakshminrusimha, S., Oxygen saturation targets in preterm infants and outcomes at 18-24 months: A systematic review, Pediatrics, 139 (1) (no pagination), 2017	No additional RCTs identified in addition to Askie 2017 Cochrane Systematic review
McGregor, M. L., Bremer, D. L., Cole, C., McClead, R. E., Phelps, D. L., Fellows, R. R., Oden, N., Retinopathy of prematurity outcome in infants with prethreshold retinopathy of prematurity and oxygen saturation >94% in room air: The High Oxygen Percentage in Retinopathy of Prematurity study, Pediatrics, 110, 540-544, 2002	Comparison of no interest for review - RCT vs RCT
Moreton, R. B., Fleck, B. W., Fielder, A. R., Williams, C. A., Butler, L., Wilson, C., Cocker, K., Juszczak, E., King, A., Stenson, B., Brocklehurst, P., Boost-Ii Uk Collaborative Group, The effect of oxygen saturation targeting on retinal blood vessel growth using retinal image data from the BOOST-II UK Trial, EyeEye, 30, 577-81, 2016	Outcomes of no interest for review - retinal blood vessel growth
Moya, M. P., Clark, R. H., Nicks, J., Tanaka, D. T., The effects of bedside blood gas monitoring on blood loss and ventilator management, Biology of the neonate, 80, 257-61, 2001	Study design not of interest to review - prospective cohort
Navarrete, C. T., Wrage, L. A., Carlo, W. A., Walsh, M. C., Rich, W., Gantz, M. G., Das, A., Schibler, K., Newman, N. S., Piazza, A. J., Poindexter, B. B., Shankaran, S., Sanchez, P. J., Morris, B. H., Frantz, I. D., 3rd, Van Meurs, K. P., Cotten, C. M., Ehrenkranz, R. A., Bell, E. F., Watterberg, K. L., Higgins, R. D., Duara, S.,	Outcomes not of interest for review - growth outcomes

Study	Reason for Exclusion
Eunice Kennedy Shriver National Institute of Child, Health, Human Development Neonatal Research, Network, Growth Outcomes of Preterm Infants Exposed to Different Oxygen Saturation Target Ranges from Birth, Journal of Pediatrics, 176, 62-68.e4, 2016	
Oei, J. L., Saugstad, O. D., Vento, M., Oxygen and preterm infant resuscitation: what else do we need to know?, Current Opinion in PediatricsCurr Opin Pediatr, 30, 192-198, 2018	Not a systematic review. Outcome is the concentration of oxygen titrated, not the level of saturation targeted.
Saugstad, O. D., Oxygenation of the Immature Infant: A Commentary and Recommendations for Oxygen Saturation Targets and Alarm Limits, NeonatologyNeonatology, 69-75, 2018	No additional RCTs identified in addition to Askie 2017 Cochrane Systematic review
Saugstad, O. D., Aune, D., In search of the optimal oxygen saturation for extremely low birth weight infants: A systematic review and meta-analysis, Neonatology, 100, 1-8, 2011	No additional RCTs identified in addition to Askie 2017 Cochrane Systematic review
Saugstad, O. D., Aune, D., Optimal oxygenation of extremely low birth weight infants: a meta-analysis and systematic review of the oxygen saturation target studies, Neonatology, 105, 55-63, 2014	No additional RCTs identified in addition to Askie 2017 Cochrane Systematic review
Schmid, M. B., Hopfner, R. J., Lenhof, S., Hummler, H. D., Fuchs, H., Cerebral desaturations in preterm infants: a crossover trial on influence of oxygen saturation target range, Archives of Disease in Childhood Fetal & Neonatal EditionArch Dis Child Fetal Neonatal Ed, 98, F392-8, 2013	Outcomes not of interest for review - cerebral desaturations
Stenson, B. J., Oxygen Saturation Targets for Extremely Preterm Infants after the NeOProM Trials, Neonatology, 109, 352-358, 2016	No additional RCTs identified in addition to Askie 2017 Cochrane Systematic review
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., Support Study Group of the Eunice Kennedy Shriver National Institute of Child Health, Human Development Neonatal Research, Network, 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 - Long term respiratory outcomes
van den Heuvel, M. E. N., van Zanten, H. A., Bachman, T. E., te Pas, A. B., van Kaam, A. H., Onland, W., Optimal Target Range of Closed-	Compares 'range width' rather than 'higher vs lower target range' for oxygen saturation levels

Study	Reason for Exclusion
Loop Inspired Oxygen Support in Preterm Infants: A Randomized Cross-Over Study, Journal of Pediatrics., 2018	
van Kaam, A. H., Hummler, H. D., Wilinska, M., Swietlinski, J., Lal, M. K., te Pas, A. B., Lista, G., Gupta, S., Fajardo, C. A., Onland, W., Waitz, M., Warakomska, M., Cavigioli, F., Bancalari, E., Claure, N., Bachman, T. E., Automated versus Manual Oxygen Control with Different Saturation Targets and Modes of Respiratory Support in Preterm Infants, Journal of pediatrics, 167, 545-50.e1-2, 2015	No outcomes of interest for review - time in pO2 targets

PCO2: partial pressure of carbon dioxide in arterial blood; PO2: partial pressure of oxygen; RCT: randomised controlled trial

Economic studies

All economic studies were excluded at the initial title and abstract screening stage.

Excluded studies for question 4.2 What is the best method for measuring oxygen levels in diagnosing hyperoxia or hypoxia in preterm babies?

Clinical studies

Study	Reason for Exclusion
Adams, J. M., Murfin, K., Gullikson, M., Detection of hyperoxemia in neonates by a new pulse oximeter, Neonatal intensive care : the journal of perinatology-neonatology, 7, 42-45, 1994	Population not relevant for review: preterm and term babies
Amin, A., Chowdhary, J., Showkat, H. I., Bhat, R. A., Wani, S., The role of pulse oximetry in resuscitation of asphyxiated neonates, European Journal of General Medicine, 11, 85-89, 2014	Population not of interest for review - asphyxiated newborns
Avery, G. B., Bancalari, E. H., Engler, A., Guilfoile, T. D., Hodgson, A. J., Hodson, W. A., Huch, A., Huch, R., Jay, A. W. L., Lucey, J. F., Martin, R. J., Gaffey, C., Lockhart, J. D., Task force on transcutaneous oxygen monitors, Pediatrics, 83, 122- 126, 1989	Study design not of interest for review - Narrative review
Bachman, T. E., Newth, C. J. L., Ross, P. A., Iyer, N. P., Khemani, R. G., Characterization of the bias between oxygen saturation measured by pulse oximetry and calculated by an arterial blood gas analyzer in critcally ill neonates, Lekar a Technika, 47, 130-134, 2017	Population is not relevant for review: not preterm infants
Baeckert, P., Bucher, H. U., Fallenstein, F., Fanconi, S., Huch, R., Duc, G., Is pulse oximetry reliable in detecting hyperoxemia in the neonate?, Advances in Experimental Medicine and Biology, 220, 165-169, 1987	Population not relevant for review: preterm and term babies

Study	Reason for Exclusion
Baquero, H., Alviz, R., Castillo, A., Neira, F., Sola, A., Avoiding hyperoxemia during neonatal resuscitation: time to response of different SpO2 monitors, Acta PaediatricaActa Paediatr, 100, 515-8, 2011	No relevant outcomes for review - time to response of different SpO2 monitors
Barr, P. A., Transcutaneous measurement of oxygen tension in infants with hyaline membrane disease, Australian Paediatric Journal, 15, 3-6, 1979	No outcomes of interest for review: r correlation analysis
Blanchette, T., Dziodzio, J., Harris, K., Pulse oximetry and normoxemia in neonatal intensive care, Respiratory Care, 36, 25-32, 1991	Population not relevant for review: preterm and term babies
Bohnhorst, B., Peter, C. S., Poets, C. F., Pulse oximeters' reliability in detecting hypoxemia and bradycardia: comparison between a conventional and two new generation oximeters, Critical Care Medicine, 28, 1565-8, 2000	Comparison not of interest for review - tcpo2 vs pulse oximetry (reference standard not used)
Bohnhorst, B., Peter, C. S., Poets, C. F., Detection of hyperoxaemia in neonates: data from three new pulse oximeters, Archives of Disease in Childhood Fetal & Neonatal EditionArch Dis Child Fetal Neonatal Ed, 87, F217-9, 2002	Population not of interest for review: preterm and term babies
Bossi, E., Meister, B., Pfenninger, J., Comparison between transcutaneous PO2 and pulse oximetry for monitoring O2-treatment in newborns, Advances in Experimental Medicine and Biology, 220, 171-176, 1987	Population not of interest for review: term and preterm babies
Brostowicz, H. M., Rais-Bahrami, K., Oxygen saturation monitoring in the neonatal intensive care unit (NICU): Evaluation of a new alarm management, Journal of Neonatal-Perinatal Medicine, 3, 201-205, 2010	Population not of interest for review: term and preterm babies
Carter, B. G., Carlin, J. B., Tibballs, J., Mead, H., Hochmann, M., Osborne, A., Accuracy of two pulse oximeters at low arterial hemoglobin-oxygen saturation, Critical Care Medicine, 26, 1128-33, 1998	Population not of interest for review: children
Carter, B., Hochmann, M., Osborne, A., Nisbet, A., Campbell, N., A comparison of two transcutaneous monitors for the measurement of arterial PO2 and PCO2 in neonates, Anaesthesia & Intensive CareAnaesth Intensive Care, 23, 708-14, 1995	Population not relevant for review: preterm and term babies
Castillo, A., Deulofeut, R., Critz, A., Sola, A., Prevention of retinopathy of prematurity in preterm infants through changes in clinical practice and SpO(2)technology, Acta Paediatrica, 100, 188-92, 2011	No outcomes relevant for review: retinopathy of prematurity
Cust, A. E., Donovan, T. J., Colditz, P. B., Alarm settings for the Marquette 8000 pulse oximeter to prevent hyperoxic and hypoxic episodes,	Population not of interest for review: preterm and term babies

Study	Reason for Exclusion
Journal of Paediatrics & Child HealthJ Paediatr Child Health, 35, 159-62, 1999	
Dingle, R. E., Grady, M. D., Lee, J. A., Paul, S., Continuous transcutaneous O2 monitoring in the neonate, American Journal of NursingAm, 80, 890-3, 1980	Study design not of interest for review: Narrative review
Fallenstein, F., Baeckert, P., Huch, R., Comparison of in-vivo response times between pulse oximetry and transcutaneous PO2 monitoring, Advances in Experimental Medicine & BiologyAdv Exp Med Biol, 220, 191-4, 1987	No relevant outcomes reported
Fanconi, S., Reliability of pulse oximetry in hypoxic infants, Journal of Pediatrics, 112, 424-427, 1988	No outcomes of interest for review: linear regression analysis. Unclear if population is of interest for review: patients with a mean age of 17 days with an acute life-threatening respiratory or circulatory condition
Fanconi, S., Sigrist, H., Transcutaneous carbon dioxide and oxygen tension in newborn infants: reliability of a combined monitor of oxygen tension and carbon dioxide tension, Journal of Clinical Monitoring, 4, 103-106, 1988	Population not of interest for review: preterm and term babies
Flint, R. B., Van Weteringen, W., Voller, S., Poppe, J. A., Koch, B. C. P., De Groot, R., Tibboel, D., Knibbe, C. A. J., Reiss, I. K. M., Simons, S. H. P., Big data analyses for continuous evaluation of pharmacotherapy: A proof of principle with doxapram in preterm infants, Current Pharmaceutical Design, 23, 5919-5927, 2017	Comparison not of interest: Not comparing to a reference/standard intervention
Foglia, E. E., Whyte, R. K., Chaudhary, A., Mott, A., Chen, J., Propert, K. J., Schmidt, B., The Effect of Skin Pigmentation on the Accuracy of Pulse Oximetry in Infants with Hypoxemia, Journal of Pediatrics, 182, 375-377.e2, 2017	Population not of interest for review: infants aged 37-40 weeks PMA
Gerstmann, D., Berg, R., Haskell, R., Brower, C., Wood, K., Yoder, B., Greenway, L., Lassen, G., Ogden, R., Stoddard, R., Minton, S., Operational evaluation of pulse oximetry in NICU patients with arterial access, Journal of Perinatology, 23, 378-83, 2003	No outcomes of interest for review: operator evaluation
Geven, W. B., Nagler, E., de Boo, T., Lemmens, W., Combined transcutaneous oxygen, carbon dioxide tensions and end-expired CO2 levels in severely ill newborns, Advances in Experimental Medicine and Biology, 220, 115-120, 1987	Population not of interest for review - mixed population of preterm and term babies
Gibson, L. Y., Pulse oximeter in the neonatal ICU: a correlational analysis, Pediatric nursing, 22, 511-515, 1996	No outcomes of interest for review: correlation analysis
Gomez-Rodriguez, G., Quezada-Herrera, A., Amador-Licona, N., Carballo-Magdaleno, D., Rodriguez-Mejia, E. J., Guizar-Mendoza, J. M.,	Population not of interest for review: term babies

Study	Reason for Exclusion
Pulse oximetry as a screening test for critical congenital heart disease in term newborns, Revista de Investigacion ClinicaRev Invest Clin, 67, 130-4, 2015	
Gong, A. K., Near-patient measurements of methemoglobin, oxygen saturation, and total hemoglobin: evaluation of a new instrument for adult and neonatal intensive care, Critical Care Medicine, 23, 193-201, 1995	Study design not of interest for review: In vitro study
Gorenberg, D. M., Pattillo, C., Hendi, P., Rumney, P. J., Garite, T. J., Fetal pulse oximetry: correlation between oxygen desaturation, duration, and frequency and neonatal outcomes, American Journal of Obstetrics & GynecologyAm J Obstet Gynecol, 189, 136-8, 2003	No outcomes relevant for review: correlation study
Gupta, R., Yoxall, C. W., Subhedar, N., Shaw, N. J., Individualised pulse oximetry limits in neonatal intensive care, Archives of Disease in Childhood Fetal & Neonatal EditionArch Dis Child Fetal Neonatal Ed, 81, F194-6, 1999	Population not of interest for review: preterm and term babies
Hay Jr, W. W., Rodden, D. J., Collins, S. M., Melara, D. L., Hale, K. A., Fashaw, L. M., Reliability of conventional and new pulse oximetry in neonatal patients, Journal of Perinatology, 22, 360-366, 2002	Population not of interest for review: preterm and term babies
Hay Jr, W. W., Thilo, E., Curlander, J. B., Pulse oximetry in neonatal medicine, Clinics in Perinatology, 18, 441-472, 1991	Study design not of interest for review: Narrative review
Hay, W. W., Jr., Rodden, D. J., Collins, S. M., Melara, D. L., Hale, K. A., Fashaw, L. M., Reliability of conventional and new pulse oximetry in neonatal patients, Journal of Perinatology, 22, 360-6, 2002	Comparison not of interest for review: conventional versus new pulse oximeters
Huch, A., Huch, R., Neumayer, E., Rooth, G., Continuous intra-arterial P O2 measurements in infants, Acta Paediatrica Scandinavica, 61, 722-723, 1972	No outcomes of interest relevant for review: no diagnostic outcomes
Huch, A., Lubbers, D. W., Huch, R., Continuous PO2 and heart rate recording in the human newborn, Advances in Experimental Medicine & BiologyAdv Exp Med Biol, 75, 737-45, 1976	No outcomes of interest relevant for review: no diagnostic outcomes
Iyer, P., McDougall, P., Loughnan, P., Mee, R. B., Al-Tawil, K., Carlin, J., Accuracy of pulse oximetry in hypothermic neonates and infants undergoing cardiac surgery, Critical Care Medicine, 24, 507-11, 1996	Population not of interest for review: preterm and term infants undergoing cardiac surgery
Jones, J. G., Lockwood, G. G., Fung, N., Lasenby, J., Ross-Russell, R. I., Quine, D., Stenson, B. J., Influence of pulmonary factors on pulse oximeter saturation in preterm infants, Archives of Disease in Childhood Fetal &	Comparison not of interest for review: relationship of gas exchange with BPD

Study	Reason for Exclusion
Neonatal EditionArch Dis Child Fetal Neonatal Ed, 101, F319-22, 2016	
Kamper, J, Nielsen, G, Erichsen, G, Filtenborg, Ja, Lillquist, K, Pedersen, Vf, Skjoldå, J, Stabell, I, Transcutaneous PO2 monitoring during treatment with continuous positive airway pressure in infants with idiopathic respiratory distress syndrome, Acta Anaesthesiologica Scandinavica, 27, 1-4, 1983	No outcomes of interest for review: clinical outcomes
Krouskop, R. W., Cabatu, E. E., Chelliah, B. P., McDonnell, F. E., Brown, E. G., Accuracy and clinical utility of an oxygen saturation catheter, Critical Care Medicine, 11, 744-749, 1983	Population not of interest for review: preterm and term babies
Lacerenza, S., De Carolis, M. P., Fusco, F. P., La Torre, G., Chiaradia, G., Romagnoli, C., An evaluation of a new combined Spo2/PtcCO2 sensor in very low birth weight infants.[Erratum appears in Anesth Analg. 2008 Oct;107(4):1389], Anesthesia & AnalgesiaAnesth Analg, 107, 125-9, 2008	No outcomes relevant for review: usability and reliability
Lafeber, H. N., Fetter, W. P., van der Wiel, A. R., Jansen, T. C., Pulse oximetry and transcutaneous oxygen tension in hypoxemic neonates and infants with bronchopulmonary dysplasia, Advances in Experimental Medicine & BiologyAdv Exp Med Biol, 220, 181-6, 1987	No outcomes relevant for review: r-coefficient
Lindemann, R., Haga, P., Bechensteen, A. G., Lossius, K., Langslet, A., Noninvasive monitoring of blood gases in the neonatal period, Scandinavian Journal of Clinical and Laboratory Investigation, 48, 33-36, 1988	No outcomes of interest for review: correlation study
Martin, R. J., Robertson, S. S., Hopple, M. M., Relationship between transcutaneous and arterial oxygen tension in sick neonates during mild hyperoxemia, Critical Care Medicine, 10, 670-672, 1982	No outcomes relevant for review - correlation study
Mense, L., Waitz, M., S<inf>po2</inf> histograms in preterm infants: A helpful tool for neonatologists?, Respiratory Care, 61, 569-570, 2016	Study design not of interest for review - Narrative review
Monin, P., Vert, P., Andre, M., Vibert, M., Transcutaneous PO2 monitoring (tcPO2) in the newborn during apneic spells, convulsions, cardiac catheterizations, and exchange transfusions, Birth Defects: Original Article Series, 15, 469-91, 1979	No outcomes of interest for review: no diagnostic outcomes
Moyle, J. T., Uses and abuses of pulse oximetry, Archives of Disease in Childhood, 74, 77-80, 1996	Study design not of interest for review: Narrative review
Niknafs, P, Norouzi, E, Bijari, Bb, Baneshi, Mr, Can we replace arterial blood gas analysis by pulse oximetry in neonates with respiratory distress syndrome, who are treated according to	Uncertainty around the diagnostic accuracy outcomes: no confidence intervals provided with outcomes and insufficient data to construct 2 x 2 tables

Study	Reason for Exclusion
INSURE protocol?, Iranian Journal of Medical Sciences, 40, 264-7, 2015	
Nitzan, M., Romem, A., Koppel, R., Pulse oximetry: Fundamentals and technology update, Medical Devices: Evidence and Research, 7, 231-239, 2014	Study design not of interest for review: Narrative review
Niu, C., Campbell, A., Larsen, P., Elder, D., Intermittent hypoxia in preterm and term infants up to 42 weeks postmenstrual age: Preliminary results of a 1-year longitudinal observational study, Journal of Paediatrics and Child Health, 54 (Supplement 1), 97, 2018	Comparison not of interest for review: Not testing a method of measuring oxygen levels
Nizami, S., Greenwood, K., Barrowman, N., Harrold, J. A., Performance Evaluation of New-Generation Pulse Oximeters in the NICU: Observational Study, Cardiovascular Engineering and Technology, 6, 383-391, 2015	Comparison not of interest for review: 2 different pulse oximeter brands
Paky,F., Koeck,C.M., Pulse oximetry in ventilated preterm newborns: reliability of detection of hyperoxaemia and hypoxaemia, and feasibility of alarm settings, Acta Paediatrica, 84, 613-616, 1995	No outcomes of interest for review: correlation study
Peabody, J. L., Jennis, M. S., Emery, J. R., Pulse oximetry--an alternative to transcutaneous PO2 in sick newborns, Advances in Experimental Medicine and Biology, 220, 145-150, 1987	Population not relevant for review: preterm and term babies
Poets, C. F., Southall, D. P., Noninvasive monitoring of oxygenation in infants and children: practical considerations and areas of concern, Pediatrics, 93, 737-46, 1994	Population not of interest for review: term and preterm babies References for sensitivity and specificity results reported for 100% preterm population checked in published paper - data for sensitivity and specificity extrapolated from correlation plots, papers excluded as accurate number of true positives, true negatives, false positives, and false negatives were not provided in the papers
Poets, C. F., Urschitz, M. S., Bohnhorst, B., Pulse oximetry in the neonatal intensive care unit (NICU): detection of hyperoxemia and false alarm rates, Anesthesia & AnalgesiaAnesth Analg, 94, S41-3, 2002	Study design not of interest: narrative review.
Poets, C. F., Wilken, M., Seidenberg, J., Southall, D. P., Von der Hardt, H., Reliability of a pulsed oximeter in the detection of hyperoxemia, Journal of Pediatrics, 122, 87-90, 1993	Population not of interest for review: preterm and term babies
Quine, D., Stenson, B. J., Arterial oxygen tension (Pao2) values in infants <29 weeks of gestation at currently targeted saturations, Archives of Disease in Childhood Fetal & Neonatal EditionArch Dis Child Fetal Neonatal Ed, 94, F51-3, 2009	No outcomes of interest for review: no diagnostic accuracy outcomes

Study	Reason for Exclusion
Quine, D., Stenson, B. J., Does the monitoring method influence stability of oxygenation in preterm infants? A randomised crossover study of saturation versus transcutaneous monitoring, Archives of Disease in Childhood: Fetal and Neonatal Edition, 93, f347-f350, 2008	No outcomes of interest for review: no diagnostic accuracy outcomes
Rosychuk,R.J., Hudson-Mason,A., Eklund,D., Lacaze-Masmonteil,T., Discrepancies between arterial oxygen saturation and functional oxygen saturation measured with pulse oximetry in very preterm infants, Neonatology, 101, 14-19, 2012	No outcomes of interest for review: mean difference
Solimano, A. J., Smyth, J. A., Mann, T. K., Albersheim, S. G., Lockitch, G., Pulse oximetry advantages in infants with bronchopulmonary dysplasia, Pediatrics, 78, 844-9, 1986	No outcomes of interest for review: correlation study
Whyte, R. K., Jangaard, K. A., Dooley, K. C., From oxygen content to pulse oximetry: Completing the picture in the newborn, Acta Anaesthesiologica Scandinavica, Supplement, 39, 95-100, 1995	No outcomes of interest for review: no diagnostic accuracy outcomes
Wimberley, P. D., Helledie, N. R., Friis-Hansen, B., Fogh-Andersen, N., Olesen, H., Pulse oximetry versus transcutaneous pO2 in sick newborn infants, Scandinavian Journal of Clinical and Laboratory Investigation SupplementScand J Clin Lab Invest Suppl, 188, 19-25, 1987	No outcomes of interest for review: correlation study
Ziehenberger, E., Urlesberger, B., Binder-Heschl, C., Schwaberger, B., Morris, N., Baik, N., Avian, A., Pichler, G., Is NIRS monitoring well tolerated in term and preterm neonates?, Signa Vitae, 12, 70-73, 2016	Population not of interest for review: Preterm infants not differentiated from term infants in any analysis

BPD: bronchopulmonary dysplasia; PMA: post-menstrual age; SpO2: pulse oximetry oxygen saturation

Economic studies

All economic studies were excluded at the initial title and abstract screening stage.

Excluded studies for question 4.3 What carbon dioxide levels are optimal in the management of preterm babies?

Clinical studies

Study	Reason for Exclusion
Relationship between PCO and unfavorable outcome in infants with moderate-to-severe hypoxic ischemic encephalopathy, Pediatric Research, 80, 204-208, 2016	Interventions not of interest for review: head cooling
Al-Matary, A., Kutbi, I., Qurashi, M., Khalil, M., Alvaro, R., Kwiatkowski, K., Cates, D., Rigatto, H., Increased peripheral chemoreceptor activity may be	Population not of interest for review: mixed population of neonates and adults

Study	Reason for Exclusion
critical in destabilizing breathing in neonates, Seminars in PerinatologySemin Perinatol, 28, 264-72, 2004	
Ambalavanan, N., Carlo, W. A., Hypocapnia and hypercapnia in respiratory management of newborn infants, Clinics in Perinatology, 28, 517-31, 2001	Study design not of interest for review: narrative review
Brown, M. K., Poeltler, D. M., Hassen, K. O., Lazarus, D. V., Brown, V. K., Stout, J. J., Rich, W. D., Katheria, A. C., Incidence of Hypocapnia, Hypercapnia, and Acidosis and the Associated Risk of Adverse Events in Preterm Neonates, Respiratory Care, 03, 03, 2018	Study design not of interest for review: An observational study with infants grouped by their PCO2
Ambalavanan, N., Carlo, W. A., Wrage, L. A., Das, A., Laughon, M., Cotten, C. M., Kennedy, K. A., Laptook, A. R., Shankaran, S., Walsh, M. C., Higgins, R. D., Support Study Group of the NICHD Neonatal Research Network, PaCO2 in surfactant, positive pressure, and oxygenation randomised trial (SUPPORT), Archives of Disease in Childhood Fetal & Neonatal EditionArch Dis Child Fetal Neonatal Ed, 100, F145-9, 2015	Study design not of interest for review: secondary exploratory analysis of an RCT
Carlo, W. A., Permissive hypercapnia and permissive hypoxemia in neonates, Journal of perinatology, 27, S64-S70, 2007	Study design not of interest for review - narrative review
Chawla, S., Natarajan, G., Shankaran, S., Carper, B., Brion, L. P., Keszler, M., Carlo, W. A., Ambalavanan, N., Gantz, M. G., Das, A., Finer, N., Goldberg, R. N., Cotten, C. M., Higgins, R. D., Eunice Kennedy Shriver National Institute of Child, Health, Human Development Neonatal Research, Network, Markers of Successful Extubation in Extremely Preterm Infants, and Morbidity After Failed Extubation, Journal of pediatrics, 06, 06, 2017	Study design not of interest for review: secondary exploratory analysis of an RCT
Gentner, S., Laube, M., Uhlig, U., Yang, Y., Fuchs, H. W., Dreyhaupt, J., Hummler, H. D., Uhlig, S., Thome, U. H., Inflammatory Mediators in Tracheal Aspirates of Preterm Infants Participating in a Randomized Trial of Permissive Hypercapnia, Frontiers in PediatricsFront, 5, 246, 2017	No outcomes of interest for review: inflammatory mediates in tracheal aspirates
Giannakopoulou, C., Korakaki, E., Manoura, A., Bikouvarakis, S.,	Study design not of interest for review: observational study

Study	Reason for Exclusion
Papageorgiou, M., Gourgiotis, D., Hatzidaki, E., Significance of hypocarbia in the development of periventricular leukomalacia in preterm infants, Pediatrics InternationalPediatr Int, 46, 268-73, 2004	
Hawkes,G.A., Kelleher,J., Ryan,C.A., Dempsey,E.M., A review of carbon dioxide monitoring in preterm newborns in the delivery room, Resuscitation, 85, 1315-1319, 2014	Study design not of interest for review: narrative review
Ma, J., Ye, H., Effects of permissive hypercapnia on pulmonary and neurodevelopmental sequelae in extremely low birth weight infants: a meta-analysis, SpringerplusSpringerplus, 5, 764, 2016	Data extracted from original RCTs included in the meta-analysis
Omer, M., Molloy, E. J., QUESTION 2: Is permissive hypercapnia beneficial to preterm infants?, Archives of Disease in Childhood, 102, 113-115, 2017	Study design not of interest for review: narrative review
Ou, X., Glasier, C. M., Ramakrishnaiah, R. H., Angtuaco, T. L., Mulkey, S. B., Ding, Z., Kaiser, J. R., Diffusion tensor imaging in extremely low birth weight infants managed with hypercapnic vs. normocapnic ventilation, Pediatric Radiology, 44, 980-986, 2014	No outcomes of interest for review: brain white matter development
Ryu, J., Haddad, G., Carlo, W. A., Clinical effectiveness and safety of permissive hypercapnia, Clinics in Perinatology, 39, 603-12, 2012	Study design not of interest for review: narrative review
Schumacher, E. M., Larsson, P. G., Pripp, A. H., Stiris, T. A., The effect of blood glucose and pCO2 on spectral EEG of premature infants during the first three days of life, Neonatology, 105, 297-305, 2014	Study design not of interest for review: cohort study
Thome, U. H., Ambalavanan, N., Permissive hypercapnia to decrease lung injury in ventilated preterm neonates, Seminars In Fetal & Neonatal MedicineSemin Fetal Neonatal Med, 14, 21-7, 2009	Study design not of interest for review - narrative review
Thome, U. H., Carlo, W. A., Permissive hypercapnia, Seminars in NeonatologySemin Neonatol, 7, 409-419, 2002	Study design not of interest for review - narrative review
Thome, U. H., Dreyhaupt, J., Genzel-Boroviczeny, O., Bohnhorst, B., Schmid, M., Fuchs, H., Rohde, O., Avenarius, S., Topf, H. G., Zimmermann, A., Faas, D., Timme, K., Kleinlein, B., Buxmann, H.,	Study design not of interest for review - An observational study with infants grouped by their PCO2

Study	Reason for Exclusion
Schenk, W., Segerer, H., Teig, N., Ackermann, B., Hentschel, R., Heckmann, M., Schlosser, R., Peters, J., Rossi, R., Rascher, W., Bottger, R., Seidenberg, J., Hansen, G., Bode, H., Zernickel, M., Muche, R., Hummler, H. D., Phelbi Study Group, Influence of PCO2 Control on Clinical and Neurodevelopmental Outcomes of Extremely Low Birth Weight Infants, Neonatology, 113, 221-230, 2018	
Woodgate, P. G., Davies, M. W., Permissive hypercapnia for the prevention of morbidity and mortality in mechanically ventilated newborn infants, Cochrane Database of Systematic Reviews, CD002061, 2001	Data extracted from original RCTs included in the meta-analysis
Zayek,M.M., Alrifai,W., Whitehurst,R.M.,Jr., Kua,K.L., Martino,A., Eyal,F.G., Acidemia versus hypercapnia and risk for severe intraventricular hemorrhage, American Journal of Perinatology, 31, 345-352, 2014	Study design not of interest for review: cohort study

Economic studies

All economic studies were excluded at the initial title and abstract screening stage.

Excluded studies for question 4.4 What blood pressure monitoring strategies are associated with improved outcomes in preterm babies requiring respiratory support?

Clinical studies

Study	Reason for Exclusion
Amoore, J. N., Propaq Neonatal monitor used with its own single- or with Critikon twin-hose cuffs: Does it matter?, 2, 41-45, 1997	Comparison not of interest for review: twin-hose cuff versus single-hose cuff
Amoore, J. N., Geake, W. B., An evaluation of three oscillometric non-invasive blood pressure simulators, Journal of Clinical Engineering, 22, 93-100, 1997	Comparison not of interest for review: comparison of different oscillometric non-invasive simulators
Amoore, J. N., Geake, W. B., Scott, D. H., Oscillometric non-invasive blood pressure measurements: the influence of the make of instrument on readings?, Med & Biol. Eng & Comput. 35, 131-4, 1997	Comparison not of interest for review: comparison of different oscillometric non-invasive simulators
Andriessen, P., Schoffelen, R. L. M., Berendsen, R. C. M., De Beer, N. A. M., Oei, S. G., Wijn, P. F. F., Blanco, C. E., Noninvasive Assessment of Blood Pressure Variability in Preterm Infants, Pediatric Research, 55, 220-223, 2004	No outcomes of interest for review: mean differences and correlation coefficient

Study	Reason for Exclusion
Northern Neonatal Nursing Initiative., Systolic blood pressure in babies of less than 32 weeks PMA in the first year of life. Northern Neonatal Nursing Initiative, Archives of Disease in Childhood Fetal & Neonatal Edition, 80, F38-42, 1999	No outcomes of interest for review: mean BP, mean difference, and correlation coefficient
Batisky, D. L., Neonatal Hypertension, Clin Perinatol, 41, 529-542, 2014	Study design not of interest for review: narrative review
Batton, B., Li, L., Newman, N. S., Das, A., Watterberg, K. L., Yoder, B. A., Faix, R. G., Laughon, M. M., Stoll, B. J., Higgins, R. D., Walsh, M. C., Early blood pressure, antihypotensive therapy and outcomes at 18-22 months' corrected age in extremely preterm infants, Archives of Disease in Childhood: Fetal and Neonatal Edition, 101, F201-F206, 2016	Comparisons not of interest for review: infants who did not receive an anti-hypotensive therapy in whom the BP rose as expected versus untreated infants in whom BP did not rise at the expected rate versus infants who received an anti-hypotensive therapy in the first 24 hours in whom BP rose as expected versus treated infants who did not experience the expected rise in BP. The expected rise in BP was defined a priori as an increase in the mean arterial BP (MABP) of 5 mmHg from postnatal hour four to postnatal hour 24
Batton,B., Zhu,X., Fanaroff,J., Kirchner,H.L., Berlin,S., Wilson-Costello,D., Walsh,M., Blood pressure, anti-hypotensive therapy, and neurodevelopment in extremely preterm infants, Journal of Pediatrics, 154, 351-357, 2009	Comparison not of interest for review: lower blood pressure (<25 mm Hg) versus higher blood pressure (>25 mm Hg)
Batton,B., Batton,D., Riggs,T., Blood pressure during the first 7 days in premature infants born at 23 to 25 weeks PMA, American Journal of Perinatology, 24, 107-115, 2007	Comparison not of interest for review: lower blood pressure (<25 mm Hg) versus higher blood pressure (>25 mm Hg)
Binder-Heschl, C., Urlesberger, B., Schwaberger, B., Koestenberger, M., Pichler, G., Borderline hypotension: how does it influence cerebral regional tissue oxygenation in preterm infants?, Journal of Maternal-Fetal & Neonatal Medicine, 29, 2341-6, 2016	Comparison not of interest for review: hypotensive (MABP < GA in mm Hg) versus normotensive (MABP equal to or more than GA in mm Hg)
da Costa, C. S., Czosnyka, M., Smielewski, P., Mitra, S., Stevenson, G. N., Austin, T., Monitoring of Cerebrovascular Reactivity for Determination of Optimal Blood Pressure in Preterm Infants, Journal of Pediatrics, 167, 86-91, 2015	Comparison not of interest for review: correlation between MABP with cerebrovascular activity
Dannevig, I, Dale, Hc, Liestøl, K, Lindemann, R, Blood pressure in the neonate: three non-invasive oscillometric pressure monitors compared with invasively measured blood pressure, Acta Paediatrica, 94, 191-196, 2005	No outcomes of interest for review: mean differences and correlation coefficient
de Jong, F., Monuteaux, M. C., van Elburg, R. M., Gillman, M. W., Belfort, M. B., Systematic review and meta-analysis of preterm birth and later systolic blood pressure, Hypertension, 59, 226-34, 2012	Study design not of interest for review: systematic review of prognostic studies
Dempsey, E. M., Al Hazzani, F., Barrington, K. J., Permissive hypotension in the extremely low	Comparison not of interest for review: normotensive (BP never less than GA) versus

Study	Reason for Exclusion
birthweight infant with signs of good perfusion, Arch dis. Child. Fetal Neonatology Ed., 94, F241-4, 2009	permissive hypotension (BP < GA, but signs of good perfusion) versus hypotension treated (BP < GA, signs of poor perfusion)
Dempsey, E. M., Barrington, K. J., Diagnostic criteria and therapeutic interventions for the hypotensive very low birth weight infant, Journal of Perinatology, 26, 677-681, 2006	Study design not of interest for review: survey of neonatology practice
Dgani,J., Arad,I., Measurement of systolic blood pressure in the follow-up of low birth weight infants, Journal of Perinatal Medicine, 20, 365-370, 1992	Study design not of interest for review: non-comparative study
Dionne, J. M., Abitbol, C. L., Flynn, J. T., Hypertension in infancy: Diagnosis, management and outcome, Pediatric nephrology, 27, 17-32, 2012	Study design not of interest for review: narrative review
Drouin, E., Gournay, V., Calamel, J., Mouzard, A., Roze, J. C., Feasibility of using finger arterial pressure in neonates, Archives of disease in childhood, 77, F139-F140, 1997	No outcomes of interest for review: mean difference and correlation coefficient
El-Khuffash, A., McNamara, P. J., Hemodynamic Assessment and Monitoring of Premature Infants, Clin Perinatol., 44, 377-393, 2017	Study design not of interest for review: narrative review
Emery, E. F., Greenough, A., Assessment of non-invasive techniques for measuring blood pressure in preterm infants of birthweight less than or equal to 750 grams, Early human development, 33, 217-222, 1993	No outcomes of interest for review: mean difference and correlation coefficient
Emery,E.F., Greenough,A., Non-invasive blood pressure monitoring in preterm infants receiving intensive care, European Journal of Pediatrics, 151, 136-139, 1992	No outcomes of interest for review: mean difference and correlation coefficient
Engle, W. D., Blood pressure in the very low birth weight neonate, Early Human Development, 62, 97-130, 2001	Study design not of interest for review: narrative review
Escourrou, G., Renesme, L., Zana, E., Rideau, A., Marcoux, M. O., Lopez, E., Gascoin, G., Kuhn, P., Tourneux, P., Guellec, I., Flamant, C., How to assess hemodynamic status in very preterm newborns in the first week of life? Journal of Perinatology, 37, 987-993, 2017	Study design not of interest for review: narrative review
Faust, K., Hartel, C., Preus, M., Rabe, H., Roll, C., Emeis, M., Wieg, C., Szabo, M., Herting, E., Gopel, W., Neocirculation, project, the German Neonatal, Network, Short-term outcome of very-low-birthweight infants with arterial hypotension in the first 24 h of life, Archives of Disease in Childhood Fetal & Neonatal, 100, F388-92, 2015	Comparison not of interest for review: hypotension (minMAP24 lower than gestational age [in weeks] or minMAP24 lower than median minMAP24 of all patients of the corresponding gestational age in completed weeks) versus normotensive
Gevers, M., Hack, M. W., van Genderingen, H. R., Lafeber, H. N., Westerhof, N., Calculated mean arterial pressure in the posterior tibial and	No outcomes of interest for review: mean difference and correlation coefficient

Study	Reason for Exclusion
radial artery pressure wave in newborn infants, Basic Res Cardiology, 90, 247-51, 1995	
Gevers, M., Van Genderingen, H. R., Lafeber, H. N., Hack, W. W. M., Accuracy of oscillometric blood pressure measurement in critically ill neonates with reference to the arterial pressure wave shape, Intensive Care Med, 22, 242-248, 1996	No outcomes of interest for review: mean difference and correlation coefficient
Greenough, A., Emery, E. F., Blood pressure levels of preterm infants in the first year of life, 82, Acta Paediatrica, 528-529, 1993	Study design not of interest for review: non-comparative study
Hegyi, T., Anwar, M., Carbone, M. T., Ostfeld, B., Hiatt, M., Koons, A., Pinto-Martin, J., Paneth, N., Blood pressure ranges in premature infants: II. The first week of life, Pediatrics, 97, 336-42, 1996	No outcomes of interest for review: mean, range, and correlation coefficient
Hegyi, T., Carbone, M.T., Anwar, M., Ostfeld, B., Hiatt, M., Koons, A., Pinto-Martin, J., Paneth, N., Blood pressure ranges in premature infants. I. The first hours of life, Journal of Pediatrics, 124, 627-633, 1994	No outcomes of interest for review: mean, range, and correlation coefficient
Jayasinghe, D., Gill, A. B., Levene, M. I., CBF Reactivity in Hypotensive and Normotensive Preterm Infants, Paediatric Research, 54, 848-853, 2003	Comparison not of interest for review: hypotension versus normotension No outcomes of interest for review: cerebral blood flow reactivity
Kent, A. L., Meskell, S., Falk, M. C., Shadbolt, B., Normative blood pressure data in non-ventilated premature neonates from 28-36 weeks gestation, 24, Pediatric Nephrology, 141-146, 2009	Study design not of interest for review: non-comparative study
Konig,K., Casalaz,D.M., Burke,E.J., Watkins,A., Accuracy of non-invasive blood pressure monitoring in very preterm infants, Intensive Care Medicine, 38, 670-676, 2012	No outcomes of interest for review: mean difference and correlation coefficient
Kunk, R., McCain, G. C., Comparison of upper arm and calf oscillometric blood pressure measurement in preterm infants, Journal of Perinatology, 16, 89-92, 1996	Comparison not of interest for review: upper arm versus calf oscillometric blood pressure measurements
Lalan, S. P., Warady, B. A., Discrepancies in the normative neonatal blood pressure reference ranges, Blood Pressure Monitoring, 20, 171-177, 2015	Studies included in systematic review not of interest for review: non-comparative studies
Lalan, S., Blowey, D., Comparison between oscillometric and intra-arterial blood pressure measurements in ill preterm and full-term neonates, Journal of the American Society of Hypertension, 8, 36-44, 2014	No outcomes of interest for review: mean difference and correlation coefficient
Lalan, S., Blowey, D., Corrigendum to "Comparison Between Oscillometric and Intra-arterial Blood Pressure Measurements in Ill Preterm and Full-term Neonates" Journal of American Society of Hypertension, January 2014, Volume 8, Issue 1, Pages 36-44.[Erratum	Study design not of interest for review: An amendment to an already excluded paper from 2014

Study	Reason for Exclusion
for J Am Soc Hypertens. 2014 Jan;8(1):36-44; PMID: 24503236], Journal of the American Society of Hypertension, 12, 479, 2018	
Lee, J., Rajadurai, V. S., Tan, K. W., Blood pressure standards for very low birthweight infants during the first day of life, Arch Dis Child Fetal Neonataology, 81, F168-F170, 1999	No outcomes of interest for review: mean differences and correlation coefficient
Leflore, J. L., Engle, W. D., Rosenfeld, C. R., Determinants of blood pressure in very low birth weight neonates: Lack of effect of antenatal steroids, Early Human Development, 59, 37-50, 2000	No outcomes of interest for review: mean difference and correlation coefficient
Lightburn,M.H., Gauss,C.H., Williams,D.K., Kaiser,J.R., Cerebral Blood Flow Velocities in Extremely Low Birth Weight Infants with Hypotension and Infants with Normal Blood Pressure, Journal of Pediatrics, 154, 824-828, 2009	Study design not of interest for review: non-comparative study
Limperopoulos, C., Bassan, H., Kalish, L. A., Ringer, S. A., Eichenwald, E. C., Walter, G., Moore, M., Vanasse, M., DiSalvo, D. N., Soul, J. S., Volpe, J. J., Du Plessis, A. J., Current definitions of hypotension do not predict abnormal cranial ultrasound findings in preterm infants, Pediatrics, 120, 966-977, 2007	Study design not of interest for review: non-comparative study
Liu, C. W., Chen, S. J., Hwang, B., Comparison of blood pressure in mature and premature neonates using direct and indirect methods of measurement, Clin Neonatology, 5, 1-6, 1998	No outcomes of interest for review: % of errors between different BP monitoring methods and mean difference
Low, J. A., Panagiotopoulos, C., Smith, J. T., Tang, W., Derrick, E. J., Validity of newborm oscillometric blood pressure, Clin Invest Med, 18, 163-167, 1995	No outcomes of interest for review: mean difference and correlation coefficient
Lyu, Y., Ye, X. Y., Isayama, T., Alvaro, R., Nwaesei, C., Barrington, K., Lee, S. K., Shah, P. S., Admission Systolic Blood Pressure and Outcomes in Preterm Infants of ≤ 26 Weeks' Gestation, American Journal of Perinatology, 34, 1271-1278, 2017	Comparisons not of interest for review: different ranges of admission to NICU systolic BPs
Meyer, S., Sander, J., Graber, S., Gottschling, S., Gortner, L., Agreement of invasive versus non-invasive blood pressure in preterm neonates is not dependent on birth weight or gestational age, Journal of Paediatrics & Child Health, 46, 249-54, 2010	No outcomes of interest for review: mean difference and correlation coefficient
Moniaci, V., Kraus, M., Determining the relationship between invasive and noninvasive blood pressure values, Neonatal Network, 16, 51-56, 1997	No outcomes of interest for review: mean difference and correlation coefficient
Nelson, R. M., Stebor, A. D., Groh, C. M., Timoney, P. M., Theobald, K. S., Friedman, B. A., Determination of accuracy in neonates for non-invasive blood pressure device using an	No outcomes of interest for review: mean difference and correlation coefficient

Study	Reason for Exclusion
improved algorithm, Data Analysis and Statistical Methods, 7, 123-129, 2002	
Neuman, M. R., Measurement of blood pressure, IEEE Pulse, 2, 39-44, 2011	Study design not of interest for review: narrative review
Nickavar, A., Assadi, F., Managing hypertension in the newborn infants, In J Prev Med, 5, S39-S43, 2014	Study design not of interest for review: narrative review
Nwankwo, M. U., Lorenz, J. M., Gardiner, J. C., A standard protocol for blood pressure measurement in the newborn, Pediatrics, 99, E10, 1997	No outcomes of interest for review: mean differences and correlation coefficient
O'Shea,J., Dempsey,E.M., A comparison of blood pressure measurements in newborns, American Journal of Perinatology, 26, 113-116, 2009	No outcomes of interest for review: mean differences and correlation coefficient
Papadopoulos, G., Mieke, S., Elisaf, M., Assessment of the performances of three oscillometric blood pressure monitors for neonates using a simulator, Devices and Technology, 4, 27-33, 1999	No outcomes of interest for review: mean differences and correlation coefficient
Pejovic, B., Peco-Antic, A., Marinkovic-Eric, J., Blood pressure in non-critically ill preterm and full-term neonates, Pediatric Nephrology, 22, 249-57, 2007	No outcomes of interest for review: mean differences and correlation coefficient
Pichler, G., Holler, N., Baik-Schneditz, N., Schwaberger, B., Mileder, L., Stadler, J., Avian, A., Pansy, J., Urlesberger, B., Avoiding Arterial Hypotension in Preterm Neonates (AHIP)-A Single Center Randomised Controlled Study Investigating Simultaneous Near Infrared Spectroscopy Measurements of Cerebral and Peripheral Regional Tissue Oxygenation and Dedicated Interventions, Frontiers in Pediatrics, 6, 15, 2018	Intervention not of interest for review: near infared spectroscopy
Pichler,G., Cheung,P.Y., Binder,C., O'Reilly,M., Schwaberger,B., Aziz,K., Urlesberger,B., Schmolzer,G.M., Time course study of blood pressure in term and preterm infants immediately after birth, PloS one, 9, -, 2014	No outcomes of interest for review: mean difference and correlation coefficient
Shead, S. L., Pathophysiology of the Cardiovascular System and Neonatal Hypotension, Neonatal Network, 34, 31-39, 2015	Study design not of interest for review: narrative review
Shimokaze, T., Akaba, K., Saito, E., Oscillometric and Intra-arterial Blood Pressure in Preterm and Term Infants: Extent of Discrepancy and Factors Associated with Inaccuracy, Am J Perinatol, 2014	No outcomes of interest for review: mean difference and correlation coefficients
Sun, M., Tien, J., Jones, R., Ward, R., A new approach to reproducibility assessment: Clinical evaluation of SpaceLabs medical oscillometric	No outcomes of interest for review: mean difference and correlation coefficient

Study	Reason for Exclusion
blood pressure monitor, Biomed Instrum Technol, 30, 439-448, 1996	
Takci, S., Yigit, S., Korkmaz, A., Yurdakok, M., Comparison between oscillometric and invasive blood pressure measurements in critically ill premature infants, Acta Paediatrica, 101, 132-5, 2012	No outcomes of interest for review: mean difference and correlation coefficient
Troy, R., Doron, M., Laughon, M., Tolleson-Rinehart, S., Price, W., Comparison of noninvasive and central arterial blood pressure measurements in ELBW infants, Journal of Perinatol, 29, 744-749, 2009	No outcomes of interest for review: mean difference and correlation coefficient
Vesoulis, Z. A., El Ters, N. M., Wallendorf, M., Mathur, A. M., Empirical estimation of the normative blood pressure in infants <28 weeks gestation using a massive data approach, Journal of Perinatol, 36, 291-295, 2016	Study design not of interest for review: non-comparative study
Wallenstein, M. B., Shaw, G. M., Yang, W., Stevenson, D. K., Failed umbilical artery catheterization and adverse outcomes in extremely low birth weight infants, Journal of Maternal-Fetal and Neonatal Medicine, 1-5, 2018	Study design not of interest for review: all received the same intervention, no comparison intervention or control
Yiallourou, S. R., Walker, A. M., Horne, R. S. C., Validation of a new noninvasive method to measure blood pressure and assess baroreflex sensitivity in preterm infants during sleep, SLEEP, 29, 1083-1088, 2006	No outcomes of interest for review: mean difference and correlation coefficient
Zubrow, A. B., Hulman, S., Kushner, H., Falkner, B., Determinants of blood pressure in infants admitted to neonatal intensive care units: a prospective multicenter study. Philadelphia Neonatal Blood Pressure Study Group, Journal of Perinatology, 15, 470-479, 1995	No outcomes of interest for review: mean differences and correlation coefficient

BP: blood pressure; GA: gestational age; MABP: mean arterial blood pressure; NICU: neonatal intensive care unit

Economic studies

All economic studies were excluded at the initial title and abstract screening stage.

Appendix L – Research recommendations

Research recommendations for question 4.1 What oxygen levels are optimal in the management of preterm babies?

Does targeting higher oxygen saturations of 92-97% in preterm babies lead to improved survival without significant complications?

Why this is important

Aiming for oxygen saturations of 91-95% instead of a lower saturation range in preterm babies receiving respiratory support has been shown to improve survival and reduce the incidence of necrotising enterocolitis. There are no studies looking at whether aiming for a saturation range of 92-97% in this group of babies has even better outcomes than a 91-95% saturation target range. It is plausible that targeting 92-97% may improve survival further; it is important to establish whether this can be achieved without increasing the risk of ROP or other complications.

Table 14: Research recommendation rationale

Research question	Does targeting higher oxygen saturations of 92-97% in preterm babies lead to improved survival without significant complications?
Importance to 'patients' or the population	There may be survival benefits with this higher oxygen saturation range.
Relevance to NICE guidance	There is no evidence from the NICE evidence review or this higher saturation range. I If this evidence were available it might be possible to make recommendations that would reduce mortality even further.
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 mortality, length of stay, reduce long term respiratory admissions, improve later health and therefore reduce costs to the NHS.
National priorities	To decrease morbidity and mortality related to prematurity.
Current evidence base	There is currently no evidence to demonstrate if use of a higher oxygen saturation range is beneficial
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 15: Research recommendation modified PICO table

Criterion	Explanation
Population	Preterm babies
Intervention	Oxygen saturation target = 92-97%
Comparator	Oxygen saturation target = 91-95%
Outcome	**Critical outcomes:** • Severe retinopathy of prematurity (defined as stage 3 or 4 retinopathy of prematurity, or retinopathy of prematurity requiring surgery or use of bevacizumab) • Mortality prior to discharge

Criterion	Explanation

	• Neurodevelopmental outcomes at ≥18 months:
	  ○ Cerebral palsy (reported as presence or absence of condition, **not** severity of condition)
	  ○ Neurodevelopmental delay (reported as dichotomous outcomes, **not** continuous outcomes such as mean change in score)
	  - Severe (score of >2 SD below normal on validated assessment scales, **or** on Bayley 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:
	• Bronchopulmonary dysplasia (oxygen dependency at 36 weeks corrected gestation or 28 days of age)
	• Necrotising enterocolitis
	• Patent ductus arteriosus requiring medical or surgical treatment

Study design	Multi-centre randomised controlled trial
Timeframe	Follow-up to 3 years

Research recommendations for question 4.2 What is the best method for measuring oxygen levels in diagnosing hyperoxia or hypoxia in preterm babies?

What is the accuracy of pulse oximetry and transcutaneous measurement of partial pressure of oxygen compared with arterial oxygen levels for detecting hyperoxia and hypoxia in preterm babies?

Why this is important

Both hypoxia and hyperoxia are known to be detrimental to preterm babies and an appropriate blood oxygen level should be maintained to avoid complications. Arterial measurements of oxygen levels are the most accurate method. Currently pulse oximetry is used in all neonatal units to measure oxygen saturations despite the knowledge that very high or very low values encompass a wide range of oxygen values due to the shape of the oxygen saturation curve. Transcutaneous monitoring is used in some neonatal units, and is believed to provide a more accurate indication of PaO_2 but there may be complications such as skin damage associated with its use.

Table 16: Research recommendation rationale

Research question	What is the accuracy of pulse oximetry and transcutaneous measurement of partial pressure of oxygen compared to arterial oxygen levels for detecting hyperoxia and hypoxia in preterm babies?
Importance to 'patients' or the population	There are potentially serious complications if preterm babies have oxygen levels that are either too low or too high, and therefore accurate assessment of oxygen levels in the blood is critical.
Relevance to NICE guidance	There is not currently sufficient evidence from the NICE evidence review to make evidence-based recommendations to optimise management in this area.
Relevance to the NHS	Correct assessment of oxygen levels would standardise clinical practice across neonatal units across NHS and might reduce length of stay, reduce long term respiratory admissions and improve later health, with a subsequent reduction in NHS costs.
National priorities	To decrease morbidity and mortality related to prematurity
Current evidence base	There are no relevant studies using modern equipment that provide this information.
Equality	Preterm babies have an equal right to safe and effective treatment to prevent BPD, thus reducing future complications and improving their quality of life.

Table 17: Research recommendation modified PICO table

Criterion	Explanation
Population	Preterm infants requiring respiratory support
Index test	Pulse oximetry or transcutaneous monitoring
Reference test	Arterial oxygen levels
Outcome	**Critical outcomes:** • Sensitivity • Specificity • Area under the receiver operating curve (AUROC) • Positive likelihood ratio (LR+) • Negative likelihood ratio (LR-) **Important outcomes:** • Adverse events • Infection • Burns • Ischaemic limbs • Emboli/thrombi • Blood loss due to excess sampling
Study design	Diagnostic test accuracy study – cohort study

Research recommendations for question 4.3 What carbon dioxide levels are optimal in the management of preterm babies?

What is the optimal carbon dioxide target range in preterm babies on non-invasive ventilation at different gestational ages?

Why this is important

Non-invasive ventilation settings in preterm babies are often chosen to target the CO_2 within a prescribed range. This may mean that the CO_2 is kept within a given range at the expense of causing volutrauma to the preterm lungs. Furthermore, decisions regarding changing from non-invasive to invasive respiratory support in preterm babies are made based on the CO_2 level, as well as clinical condition and oxygen requirements. There is a concern that CO_2 levels outside a prescribed range may cause complications. For example, the committee knew that low CO_2 levels in preterm babies are associated with white matter injury and in the past high CO2 levels were associated with the development of intraventricular haemorrhage. There is little up to date evidence on the upper safe level for CO_2 in this group.

Table 18: Research recommendation rationale

Research question	What is the optimal carbon dioxide target range in preterm babies on non-invasive ventilation at different gestational ages
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 also impact on long term neurodevelopmental outcome.
Relevance to NICE guidance	High Priority: Currently there is no evidence from the NICE evidence review for the optimal CO_2 target level in babies on non-invasive ventilation, and evidence in this area would allow recommendations on CO_2 target ranges to be made for babies on non-invasive ventilation.
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, and hence reduce costs to the NHS
National priorities	To decrease morbidity and mortality related to prematurity.
Current evidence base	Currently there is no evidence for the optimal CO_2 target level in babies on non-invasive ventilation.
Equality	Preterm babies have an equal right to safe and effective treatment to improve neurodevelopmental outcome and decrease BPD

Table 19: Research recommendation modified PICO table

Criterion	Explanation
Population	Infants <30 weeks gestation requiring non-invasive ventilation.
Intervention	Higher target range for partial pressure of carbon dioxide
Comparator	Lower target range for partial pressure of carbon dioxide
Outcome	**Critical outcomes:**

Criterion	Explanation

	• 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'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 the 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:
	• Periventricular leukomalacia
	• Severe intraventricular haemorrhage
	• Days on invasive ventilation
	• Pneumothorax

Study design	Multicentre randomised controlled trial; analysis by gestational age cohorts
Timeframe	Follow up to 3 years

Research recommendations for question 4.4 What blood pressure monitoring strategies are associated with improved outcomes in preterm babies requiring respiratory support?

What is the optimal method and frequency of measuring blood pressure for preterm babies requiring respiratory support?

Why this is important

The decision whether or not to monitor blood pressure in preterm babies, how this monitoring is undertaken (invasive or non-invasive blood pressure monitoring), and the frequency of monitoring varies greatly between neonatal units. There are no studies comparing different regimens in this patient population.

Table 20: Research recommendation rationale

Research question	What is the optimal method and frequency of measuring blood pressure for preterm babies requiring respiratory support?
Importance to 'patients' or the population	Which preterm neonates on respiratory support receive blood pressure monitoring varies between units. There is also variation in the type of monitoring used in these babies – invasive versus non-invasive monitoring- and the frequency of non-invasive measurements. Studies ascertaining which approach is associated with improved outcomes in this preterm population would standardise practice and improve outcome.
Relevance to NICE guidance	There was no evidence available from the NICE evidence review to inform recommendations on blood pressure monitoring, so research in this area would inform the development of future recommendations for NICE guidelines.
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 mortality, length of stay, reduce long term respiratory admissions and improve later health, and hence may reduce NHS costs.
National priorities	To decrease morbidity and mortality related to prematurity.
Current evidence base	There is currently no evidence to define the optimal blood pressure monitoring strategy in preterm babies
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 21: Research recommendation modified PICO table

Criterion	Explanation
Population	Preterm babies requiring respiratory support
Intervention	Different blood pressure monitoring methods and strategies, such as: • no blood pressure measurement unless significant concern regarding perfusion • non-invasive monitoring with different frequencies • continuous invasive blood pressure monitoring.
Comparator	Comparison of different intervention strategies with each other

Outcome	**Critical outcomes:**
	• Mortality prior to discharge
	• Blood pressure values
	• Different levels of interventions for blood pressure control.
	• Neurodevelopmental outcomes at ≥18 months:
	  ○ Cerebral palsy (CP) (reported as presence or absence of condition, **not** severity of condition)
	  ○ Neurodevelopmental delay (reported as dichotomous outcomes, **not** continuous outcomes such as mean change in score)
	  - Severe (score of >2 SD below normal on validated assessment scales, **or** on Bayleys assessment scale of mental developmental index (MDI) or psychomotor developmental index (PDI) <70 or complete inability to assign score due to CP or severe cognitive delay)
	  - Moderate (Score of 1-2 SD below normal on validated assessment scales, **or** on Bayleys assessment scale of MDI or PDI 70-84)

Criterion	Explanation
	○ 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) • Severe intraventricular haemorrhage (grade 3 or 4) **Important outcomes:** • Periventricular leukomalacia • Necrotising enterocolitis • Renal impairment • Vascular complications associated with invasive monitoring • • Bronchopulmonary dysplasia • Patent ductus arteriosus • Retinopathy of prematurity • Length of hospital stay • Cost analysis • Combination of above - disease free survival primary outcome
Study design	Multicentre randomised controlled trial Protocols should describe standard treatment protocols to allow the possible change in outcomes from the different monitoring methods. Blood pressure values and interventions for blood pressure support should be measured and recorded to allow interpretation of results.
Timeframe	Follow up to 3 years

What is the optimal target blood pressure range for preterm babies requiring respiratory support?

Why this is important

Blood pressure measurements are regularly taken in preterm babies on respiratory support as a surrogate marker of organ perfusion and haemodynamic stability. To date, there are no studies comparing different target blood pressure ranges in preterm neonates at different gestations to ascertain which range is associated with improved outcomes.

Table 22: Research recommendation rationale

Research question	What is the optimal target blood pressure range for preterm babies requiring respiratory support?
Importance to 'patients' or the population	There is currently no accepted, evidence-based blood pressure target range for preterm babies, and hence there are no reference ranges against which units can titrate blood pressure. The availability of an evidence-based optimal range may improve outcomes for babies
Relevance to NICE guidance	In the NICE evidence review, there was no evidence available to inform recommendations on blood pressure targets, so research in this area would inform the development of future recommendations for NICE guidelines.
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 mortality, length

Research question	What is the optimal target blood pressure range for preterm babies requiring respiratory support?
	of stay, reduce long term respiratory admissions and improve later health, and hence may reduce NHS costs.
National priorities	To decrease morbidity and mortality related to prematurity.
Current evidence base	There is currently no evidence to define the optimal blood pressure target range in preterm babies
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 23: Research recommendation modified PICO table

Criterion	Explanation
Population	Preterm babies requiring respiratory support
Intervention	Blood pressure treatment target ranges.
Comparator	Different blood pressure target ranges

Outcome	**Critical outcomes:**
	• Mortality prior to discharge
	• Blood pressure values
	• Different levels of interventions for blood pressure control.Neurodevelopmental outcomes at ≥18 months:
	  ○ Cerebral palsy (CP) (reported as presence or absence of condition, **not** severity of condition)
	  ○ Neurodevelopmental delay (reported as dichotomous outcomes, **not** continuous outcomes such as mean change in score)
	  - Severe (score of >2 SD below normal on validated assessment scales, **or** on Bayleys assessment scale of mental developmental index (MDI) or psychomotor developmental index (PDI) <70 or complete inability to assign score due to CP or severe cognitive delay)
	  - Moderate (Score of 1-2 SD below normal on validated assessment scales, **or** on Bayleys assessment scale of MDI or PDI 70-84)
	  ○ Neurosensory impairment (reported as presence or absence of condition, **not** severity of condition)
	  - Severe hearing impairment (for example, deaf)
	  - Severe visual impairment (for example, blind)
	• Severe intraventricular haemorrhage (grade 3 or 4)
	
	Important outcomes:
	• Periventricular leukomalacia
	• Necrotising enterocolitis
	• Renal impairment
	• Vascular complications associated with invasive monitoring
	• Bronchopulmonary dysplasia
	• Patent ductus arteriosus
	• Retinopathy of prematurity
	• Length of hospital stay
	•

Criterion	Explanation
Study design	Multicentre randomised controlled trial Protocols should describe blood pressure monitoring method, treatment thresholds and treatment regimens. Blood pressure values and Interventions for blood pressure support should be measured and recorded to allow interpretation of results.
Timeframe	Follow-up to 3 years