REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

The clinical and cost effectiveness of heated humidified high-flow nasal cannula vs usual care for preterm infants: systematic review and economic evaluation

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TITLE OF PROJECT

The clinical and cost effectiveness of heated humidified high-flow nasal cannula (HHHFNC) vs usual care for preterm infants: systematic review and economic evaluation

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Table of contents

List of tables

List of figures

LIST OF ABBREVIATIONS

BPD	bronchopulmonary dysplasia
CI	confidence interval
CLD	chronic lung disease
EDIN	Echelle Douleur Inconfort Nouveau-Né, neonatal pain and discomfort scale
FIO_2	fraction of inspired oxygen
GA	gestational age
HFNC	high-flow nasal cannula
HHHFNC	heated humidified high-flow nasal cannula
IVH	intraventricular haemorrhage
NCPAP	nasal continuous positive airways pressure
NEC	necrotizing enterocolitis
NICU	neonatal intensive-care unit
NIPPV	nasal intermittent positive pressure ventilation
O_2	oxygen
RDS	respiratory distress syndrome
RR	risk ratio
SD	standard deviation
UK	United Kingdom
US	United States

PLAIN LANGUAGE SUMMARY

What was the problem?

Respiratory problems may cause of short- and long-term ill health for babies who are born early (preterm). Preterm babies are often given mechanical ventilation to assist with breathing. This is an invasive where a tube is placed down the baby's breathing pipe. Non-invasive devices where prongs or tubes are placed in or near the baby's nose and mouth may also be used. One type of non-invasive device known as nasal continuous positive airways pressure (NCPAP) produces pressure to keep lungs open and assist with breathing. Another type of non-invasive device is known as heated humidified high flow nasal cannula (HHHFNC) which is believed to generate similar pressure. HHHFNC is also considered to increase comfort for baby and reduce side effects compared with NCPAP, and it does not require a face mask.

What did we do?

We reviewed the clinical evidence from available studies comparing HHHFNC with usual care. We also assessed the costs and benefits of HHHFNC compared with usual care.

What did we find?

We found no clear evidence that HHHFNC is clinically superior or inferior to other devices. Evidence from one small study suggested that parents of babies may prefer HHHFNC over alternative devices. We calculated that HHHFNC may also cost less but this depends on the lifespan and associated running costs of equipment.

What does this mean?

On the basis of currently available evidence, there is no reason to suggest that HHHFNC should not be used in clinical practice.

Word count: 246

ABSTRACT

Background: Respiratory problems are one of the most common causes of morbidity in preterm infants and may be treated with several modalities for respiratory support such as nasal continuous positive airways pressure (NCPAP) or nasal intermittent positive pressure ventilation (NIPPV). Heated humidified high-flow nasal cannula (HHHFNC) is gaining popularity in clinical practice.

Objectives: To address the clinical effectiveness of HHHFNC vs usual care for preterm infants we systematically reviewed the evidence of HHHFNC compared with usual care following ventilation (primary analysis) and with no prior ventilation (secondary analysis). The primary outcome was treatment failure defined as the need for re-intubation (primary analysis) or intubation (secondary analysis). We also aimed to assess the cost effectiveness of HHHFNC vs usual care if evidence permitted.

Data sources: The following databases were searched on 12 January 2015: Medline (2000 to 12 January 2015), Embase (2000 to 12 January 2015), The Cochrane Library (Issue 1, 2015) and seven trial and research registers. Bibliographies of retrieved citations were also examined.

Review methods: Two reviewers independently screened all titles and abstracts to identify potentially relevant studies for inclusion in the review. Full-text copies were assessed independently. Data were extracted and assessed for risk of bias. Summary statistics were extracted for each outcome and, where possible, data were pooled. Meta-analysis was carried out using fixed-effects models. An economic evaluation was planned.

Results: Clinical evidence was derived from seven randomised controlled trials (RCTs): 4 RCTs for the primary analysis and 3 RCTs for the secondary analysis. Only for nasal trauma leading to a change of treatment was there a statistically significant difference, favouring HHHFNC over NCPAP (risk ratio [RR] 0.21, 95% confidence intervals [CI] 0.10 to 0.42). For the following outcomes, there were no statistically significant differences between arms: treatment failure (re-intubation <7 days) (RR 0.76, 95% CI 0.54 to 1.09), bronchopulmonary dysplasia (RR 0.92, 95% CI 0.72 to 1.17), death (RR 0.56, 95% CI 0.22 to 1.44), pneumothorax (RR 0.33, 95% CI 0.03 to 3.12), intra-ventricular haemorrhage (IVH) (Grade 3+) (RR 0.41, 95% CI 0.15 to 1.15), necrotising enterocolitis (RR 0.41, 95% CI 0.15 to 1.14), apnoea (RR 1.08, 95% CI 0.74 to 1.57) and acidosis (RR 1.16, 95% CI 0.38 to 3.58). With no evidence to support the superiority of HHHFNC over NCPAP, a cost minimisation analysis was undertaken, the results suggesting HHHFNC to be less costly than NCPAP. However this finding is sensitive to the lifespan of equipment and the cost differential of consumables.

Limitations: There is a lack of published RCTs of relatively large sized populations comparing HHHFNC to usual care; this is particularly true for preterm infants who had received no prior ventilation.

Conclusions: To date, there is a lack of convincing evidence suggesting that HHHFNC is superior or inferior to usual care, in particular NCPAP. There is also uncertainty as to whether HHHFNC can be considered cost effective. Further evidence comparing HHHFNC to usual care is required.

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Funding: The National Institute for Health Research Health Technology Assessment programme.

Word count: 499

Key words: Meta-analysis, randomized controlled trial, heated humidified high-flow nasal cannula, infant, pre-term, premature

SCIENTIFIC SUMMARY

Background

Respiratory problems are one of the most common causes of morbidity in preterm infants. Clinically, respiratory distress syndrome (RDS) presents with early respiratory distress and infants are treated with several modalities for respiratory support. These include mechanical endotracheal ventilation, nasal continuous positive airways pressure (NCPAP), oxygen, nasal intermittent positive pressure ventilation (NIPPV) and heated humidified high-flow nasal cannula (HHHFNC). HHHFNC is gaining popularity in clinical practice, but to date, there is a lack of convincing evidence for the relative effectiveness of HHHFNC over any other modality.

Objectives

The aim of this systematic review and economic evaluation was to answer the question: What is the clinical and cost effectiveness of HHHFNC vs usual care for preterm infants? We conducted a primary analysis of HHHFNC to usual care following ventilation and a secondary analysis of HHHFNC to usual care with no prior ventilation. Usual care was considered to consist of NCPAP, oxygen or NIPPV. The primary outcome measure of the review was treatment failure as defined by a need for re-intubation.

Methods

The following databases were searched for relevant published literature on 8th September 2014:

- Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effectiveness, Health Technology Assessment database, NHS Economic Evaluation Database (for the cost effectiveness searches)
- ISI Web of Science- Science Citation Index Expanded
- ISI Web of Science- Proceedings (Index to Scientific & Technical Proceedings)
- Medline and Medline in Process (OvidSP)
- Embase (OvidSP)
- Pubmed (limited to the last 6 months)

In addition, we searched seven trial and research registers and bibliographies of previous reviews and retrieved articles. All databases were searched from the year 2000 to 8th September 2014. The searches were then updated on 12th January 2015.

Search terms included a combination of index terms (for the study population) and free-text words (for the technologies involved). No methodological filters or other limits were employed.

The citations identified by the search strategy were assessed for inclusion through two stages by two independent reviewers. First, all titles and abstracts were screened to identify all potentially relevant citations; and, second, inclusion criteria were applied to full-text articles.

The results of the data extraction and quality assessment for each study were presented in structured tables and as a narrative summary. All summary statistics were extracted for each outcome and, where possible, data were pooled and meta-analysis was carried out using a fixed-effects model.

Heterogeneity was explored through consideration of the study populations (e.g. differences in gestational age), interventions (e.g. starting flow rate for HHHFNC or starting pressure for NCPAP), outcome definitions (e.g. different definitions for re-intubation) and in statistical terms by the χ^2 test for homogeneity and the I^2 statistic

No studies were identified that explored the relative cost effectiveness of HHHFNC vs NCPAP so a de novo economic analysis was undertaken.

Results

Nine papers reporting on seven randomised controlled trials (RCTs) were included in the review. Four RCTs (735 infants) were relevant to the primary analysis and three RCTs (124 infants) were relevant to the secondary analysis. Overall the RCTs included in the review were of satisfactory methodological quality although it was not possible to blind administrators or participants in any study.

In the primary analysis (preterm infants treated following ventilation), three studies compared HHHFNC to NCPAP. It was possible to pool data for at least two trials comparing HHHFNC to NCPAP in a meta-analysis for three outcomes: need for re-intubation<7 days, bronchopulmonary dysplasia (BPD) and death. No significant differences were reported between arms (re-intubation: risk ratio [RR] 0.76, 95% confidence intervals [CI] 0.54 to 1. 09; BPD: RR 0.87, 95% CI 0.68 to 1.13 and Death: RR 0.66, 95% CI 0.24 to 1.82). No statistically significant differences were reported in individual trials between arms for any other outcomes. Regarding adverse events, one study reported a statistically significant lower rate of nasal trauma in the HHHFNC arm than in the NCPAP arm and another RCT reported a statistically significant lower nasal trauma score in the HHHFNC arm than in the NCPAP arm. No statistically significant differences were reported between arms for air leak syndromes (e.g. pneumothorax), nosocomial sepsis, intraventricular haemorrhage, necrotising enterocolitis, gastrointestinal perforation or apnoea. However, numerically, these adverse events were all

less common in the HHHFNC arm than in the NCPAP arm (with the exception of apnoea reported in two studies).

In the secondary analysis (infants who had not received prior ventilation), one study compared HHFNC to NIPPV, and two studies compared HHHFNC to NCPAP; one RCT was a cross-over trial (2 x 24 hours). Two studies reported the primary outcome of the review (re-intubation over an unspecified time period) but a statistically significant difference between arms was not found in either study (HHHFNC vs NIPPV, re-intubation rates of 28.9% vs.34.2% respectively; HHHFNC vs NCPAP 15.3% vs 13.3%). Neither of these studies reported a statistically significant difference for any of the secondary outcomes of interest to our review. The third study was the only study to report on quality of care where parents were more likely to favour HHHFNC over NCPAP for the following measures: (i) child satisfaction, (ii) contact and interaction and (iii) opportunities to take part in care. Only the study comparing HHHFNC to NIPPV reported on adverse events. These appeared to be numerically higher in the HHHFNC arm than in the NIPPV arm but no statistically significant differences between arms were reported.

For the primary analysis (preterm infants treated following ventilation), with no difference in primary outcomes being reported and the only difference in secondary outcomes being in rates of minor nasal trauma, a cost minimisation analysis was undertaken. For the secondary analysis (no prior ventilation) there is no evidence on the primary outcome (treatment failure as measured by the need for intubation) and as such no economic analysis was undertaken.

Costs for equipment were taken from the NHS Supply Chain. Assumptions were made about the lifespan of equipment and its rate of utilisation to estimate the costs of equipment per preterm infant. Weekly consumable costs were provided by a clinician working in a NHS neonatal unit.

Our analysis suggests that HHHFNC would cost less than NCPAP if:

- the capital equipment (flow generator or humidifier machines) for HHHFNC and NCPAP lasts 5 years
- the capital equipment is in use for 80% of the time and
- preterm babies require HHHFNC or NCPAP for an average of 43.5 days before discharge

This finding of HHHFNC being cost saving compared to NCPAP is sensitive to the assumed lifespan of equipment and the cost differential of consumables. If equipment lasts on average more than 6.8 years or the cost of consumable equipment is approximately £16 per week per preterm infant higher with HHHFNC than NCPAP, NCPAP will cost less than HHHFNC.

Conclusions

To date, there is a lack of convincing evidence to suggest that HHHFNC is superior or inferior to usual care, in particular NCPAP. This is true for preterm infants who have been treated following ventilation and for those who have received no prior ventilation. The results of one small trial suggest that parents do however prefer HHHFNC to NCPAP.

There is also uncertainty as to whether HHHFNC can be considered cost effective because the lack of clinical evidence precluded us from conducting an analysis of cost utility or cost effectiveness. The results of our cost minimisation analysis suggest that HHHFNC may cost less than NCPAP but there is much uncertainty around the assumptions employed and it is quite possible that HHHFNC costs more than NCPAP. As the overall cost of either HHHFNC or NCPAP is small compared to the cost of preterm neonatal care as a whole - and the potential cost differences between the systems are even smaller - the financial case for HHHFNC over NCPAP or vice versa is not compelling.

More RCT evidence comparing HHHFNC to usual care (in particular, NCPAP) is required to inform the evidence base for both the clinical and cost effectiveness for HHHFNC. Ideally, a large and adequately powered trial is required to compare HHHFNC to NCPAP in preterm infants previously ventilated and for preterm infants who have not received prior ventilation. Based on available evidence, it is possible that further research could include evidence derived from a non-inferiority trial.

Study registration

The study is registered as PROSPERO CRD42015015978

Funding

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Word count: 1316

1 BACKGROUND

1.1 Description of health problem

Respiratory problems are one of the most common causes of morbidity in preterm infants,[1] i.e. infants born before 37 completed weeks of gestation. Respiratory distress syndrome (RDS), also known as hyaline membrane disease is a serious medical condition where a new-born baby's lungs lack surfactant and are not functioning at a level that is able to provide their body with enough oxygen.[2-4] It is a particular problem for preterm infants since surfactant is usually produced between weeks 24 and 28 of pregnancy. European data for 2010 show an incidence of RDS of 92% at 24 to 25 weeks gestation, 88% at 26 to 27 weeks, 76% at 28 to 29 weeks and 57% at 30 to 31 weeks.[4] It has been reported that around a third of those born at 32 to 34 weeks will have RDS, falling to around 10% of those born at 34 weeks.[2]

Clinically, RDS presents with early respiratory distress comprising cyanosis, grunting, inter and subcostal retractions and tachypnoea and if left untreated, may result in death from progressive hypoxia and respiratory failure.[4] Consequences of RDS include:[3]

- Hypoxia, acidosis, hypothermia, and hypotension
- Bronchopulmonary dysplasia (BPD) also commonly known as chronic lung disease (CLD)
- Pulmonary haemorrhage
- Apnoea of prematurity/bradycardia
- Intraventricular haemorrhage (IVH)

Advances in care over the years have however resulted in significant decreases in mortality from RDS.[4,5] While data on RDS mortality is not routinely collected in the UK, the data from the US, show this has fallen from 2.89 per 1,000 live births between 1969 and 1973[6] (or 2.6 per 1,000 live births in 1970[7]) falling to 0.37 per 1, 000 live births between 1987 and 1995[8] (or 0.4 per 1,000 live births in 1994[7]). This decrease in RDS is also reflected by a decrease in mortality from all causes reported by a number of worldwide studies.[9]

1.2 Epidemiology

According to the UK Office for National Statistics (ONS),[10] there were 729,312 live births in England and Wales in 2012 and the gestational age was known and verified for 726,572 infants. Of these, 52,909 (7.3%) were born preterm, prior to 37 weeks. The majority (43,993 [83.1%]) were born between 32 to 36 weeks with 5,693 (10.8%) born between 28 and 31 weeks, 2,474 (4.7%) born between 24 and 27 weeks and 749 (1.4%) born before 24 weeks.

Birth weight is associated with gestational age. In England and Wales in 2012,[10] the vast majority of infants born before 24 weeks or those born between 24 and 27 weeks weighed under 1,500 grams (99.5% and 96.2% respectively). At 28 to 31 weeks, 85.6% weighed 1, 000 to 2,499 grams, 96.7% of those born between 32 and 36 weeks weighed 1,500 to 3,999 grams.[10]

Infant mortality is associated with gestational age and birth weight, decreasing with advanced gestational age and increasing birth weight (Table 1).[10]

Table 1 Infant mortality rate (per 1, 000 live births) by gestational age and birth weight in England and Wales, 2012

Gestational age	All	Birth weight				
		<1, 000g	1, 000 to 1,499g	1,500 to 2,499g	2,500 to 3,999g	≥4, 000g
All infants with known and verified gestational age	3.9	316.6	55.9	9.3	1.3	0.9
Under 24 weeks	877.2	885.1				
24 to 27 weeks	230.8	267.9	131.5	212.1		
28 to 31 weeks	48.3	110.7	49.3	28.2	20.0	
32 to 36 weeks	8.8	61.1	40.7	8.7	5.6	
Preterm to term	23.6	215.9	56.4	10.4	5.7	13.7
Term	1.4	9.6	35.3	7.8	1.2	0.8
Post to term	0.9			27.8	0.6	1. 0

Source: Office for National Statistics[10]

1.3 Current treatment options for preterm infants

Over the years, several modalities for respiratory support have been developed. The treatments which have arguably had the largest impact in reducing mortality are the administration of surfactant.[5,7] and antenatal corticosteroids.[11] Improved methods of mechanical ventilation, regionalised perinatal care, and continuous improvement in general neonatal care have also been highlighted as having an important impact, particularly in the period between 1970 and 1985, prior to the use of surfactant therapy in the 1990s.[5,7] Recently updated European Consensus Guidelines for the management of RDS in preterm infants[4] highlight that, in many instances, the risk of a preterm birth is known and this should enable preterm infants at risk of RDS to be born in centres where appropriate facilities are available for stabilisation and ongoing respiratory support, including intubation and mechanical ventilation, following birth.[4]

Once born, preterm infants require stabilisation. In practice, preterm infants who present with early respiratory distress may receive any one of the following interventions (described in more detail in sections 1.3.1 to 1.4):

1. Mechanical endotracheal ventilation

2. Nasal continuous positive airways pressure (NCPAP)
3. Oxygen
4. Nasal intermittent positive pressure ventilation (NIPPV)
5. HHHFNC

1.3.1 Mechanical endotracheal ventilation

Mechanical endotracheal ventilation assists breathing invasively via an endotracheal tube. This process is commonly referred to as intubation and was first introduced in the late 1950s.[5] While this has increased survival, lung injury has been recognised as an associated complication.[5] Lung injury in the short-term can lead to air leak.[12] Air leaks and increased pressures used to ventilate infants may result in pneumothorax, pneumomediastinum and pneumopericardium.[3] Lung injury in the longer term may result in BPD.[1, 12, 13] Largely for these reasons, the European Consensus Guidelines[4] recommend ventilation "for as short a time as possible" for extremely preterm infants if antenatal steroids have not been given to the mother and also for infants who have not responded to NCPAP.[4]

1.3.2 NCPAP

Devices which generate NCPAP can broadly be divided into two categories, continuous flow or variable flow devices.[14, 15] Continuous flow devices include conventional ventilators, jet ventilation systems and bubble NCPAP.[14] Common features of all NCPAP devices are:[12]

1. A gas source, which provides a continuous supply of air and/or oxygen
2. A pressure generator, which creates positive pressure in the circuit
3. A patient interface, which connects the NCPAP circuit to the infant's airway

The most commonly used interfaces between the NCPAP circuit and the preterm infant are nasal prongs and/or nasal masks. [22,2]The results of a meta-analysis[16] has shown that binasal prongs are more effective in preventing re-intubation compared to either single nasal or nasopharyngeal prongs. While there is evidence from meta-analyses that NCPAP may be more effective than headbox oxygen for reducing the incidence of respiratory failure (apnoea, respiratory acidosis and increased oxygen requirements) and the need for re-intubation,[17] there is no reliable evidence to suggest one NCPAP device is optimal over another NCPAP device.

Difficulties with the successful application of NCPAP are principally related to the relatively bulky interface with the infant which can result in problems maintaining proper position.[15] If leaks around the nares and via the mouth occur, this can result in inconsistent airway pressure generation and respiratory instability with increased oxygen requirements.[15] In particular, the bulky nature of most NCPAP interfaces can predispose to nasal irritation and trauma[15, 18] and

can restrict access to the head and face and have significant drawbacks with respect to integration of NCPAP with oral feeding.[19] Furthermore, face masks and standard nasal cannula associated with the prongs are uncomfortable and can cause irritation due to the use of dry, cold gas.[20] Finally, common to all variable flow NCPAP systems is a significant noise level; it is currently unknown what effect the continuous exposure to such levels of noise has on the development of preterm infants.[12]

1.3.3 Oxygen

Oxygen is the most widely used therapy in neonatology.[21] Aside from NCPAP, it may be administered via headbox, incubator or low flow nasal cannula. The European Consensus Guidelines[4] recommend a concentration of 21% to 30% oxygen to initiate stabilisation at resuscitation. Thereafter in the neonatal intensive-care unit (NICU) setting oxygen concentrations are closely monitored using oxygen saturation probes and targeting a narrow range of saturations to minimise effects of oxygen toxicity or hypoxia. As with ventilation, oxygen may lead to lung injury and the same short-term and long-term effects.

1.3.4 NIPPV

NIPPV is a development in non-invasive ventilatory support combining NCPAP with superimposed ventilator breathing at a set peak pressure.[12] NIPPV provides intermittent mandatory ventilation using nasal prongs[22] and may be synchronised (SNIPPV) or non-synchronised to the infant's breathing efforts.[23] NIPPV has been reported to achieve better gaseous exchange than simple oxygen therapy but has also been associated with significant head moulding, cerebral haemorrhage and gastric perforations.[24] Other complications related to nasal ventilation have been reported to be "essentially the same" as those for infants on NCPAP.[25] SNIPPV is argued to be preferable over NIPPV in order to minimise gastrointestinal perforations.[25]

1.4 The technology: HHHFNC

A number of differently branded HHHFNC devices exist including the Vapotherm 2000i and the Fisher &Paykel devices. Common to any HHHFNC device are three main features:[15]

1. A respiratory circuit with a means to maintain the temperature and, by extension, the humidity of the delivered gas until the distal end of the circuit
2. A humidifier to effectively warm and humidify respiratory gases
3. A nasal cannula with adapter that connects to the delivery circuit and which should allow little or no excess tubing between the end of the delivery circuit and the actual nasal prongs, thereby minimising further any potential for gas cooling and precipitation.

In addition to HHHFNC, variations of this technology exist in which gas flow is provided at a high rate but not heated (high-flow nasal cannula [HFNC]). Unheated gas cannot be adequately humidified even if it passes through a humidifier.[26]

With regard to gas flow rate, no optimal level exists.[15] One early study reported that the flow rate should vary from infant to infant depending on weight.[27] It has also been stated that gas flow rate should be adjusted according to clinical response, generally being increased for increasing respiratory distress or oxygen requirement and decreased for improving respiratory distress or decreasing oxygen requirement.[15] Unlike the nasal prongs for NCPAP (which fit tightly in the nares), the nasal cannulae for HHHFNC are smaller and looser-fitting. Nasal cannulae size varies from infant to infant, this being dictated by the size of the infant's nares.[18,20]

HHHFNC is gaining popularity and is increasingly used in clinical practice in many units in the UK and other countries, particularly in North America and Australasia.[28] This is largely due to the perceived greater ease of use of such devices as compared to NCPAP, allowing both practitioners and family members to more easily handle and care for infants.[15,20,29] In addition, it is considered that HHHFNC should improve patient tolerance and outcomes: heat and humidity should prevent airway water loss, airway cooling, thickened secretions and nasal irritation, allowing high flow rates without nasal drying or bleeding while comparably lighter and easier-to-apply interface may lessen nasal septal damage.[15,20] Other perceived advantages compared to NCPAP include a reduction in the number of ventilator days, an improvement in weight gain and being able to introduce oral feeding earlier.[18,20]

However, there are concerns about the unpredictability of the positive airway pressures generated by HHHFNC and the potential for infection. Unless the infant's mouth is closed and the leak around the nares minimised, it is unlikely that nasal cannula deliver a clinically relevant level of positive airway pressure[15] while in the absence of an effective way of controlling distending pressure, there is also the theoretical risk of lung over-distension and pneumothoraces;[18] pressure appears to be related to gas flow, prong size and patient size.[15] The potential for infection was discovered in 2005 when instances of gram-negative bacteria known as *Ralstonia* were reported from Vapotherm devices in the US. This led to the recall of all devices in January 2006 but the product returned to the market with US Food and Drug Administration (FDA) approval in January 2007, with new instructions for use, including the recommendation to utilise only sterile water in the system.[15]

1.5 Evidence for the effectiveness of HHHFNC from previous reviews

In 2011, a Cochrane review related to heated and non-heated HFNC by Wilkinson et al[30] concluded that there was "insufficient evidence to establish the safety or effectiveness of HFNC as a form of respiratory support in preterm infants. " Evidence was derived from two RCTs[31,32] comparing HHHFNC to NCPAP (including one RCT that was unpublished and halted early when the equipment was recalled[32]), an RCT comparing two types of HHHFNC (Vapotherm vs Fischer and Paykel)[33] and a crossover trial comparing HHHFNC to a non-humidified high flow device.[34] A whole range of efficacy and safety outcomes were considered by this review, none of which could be pooled for a meta-analysis. More recently a meta-analysis by Daishand Badurdeen[35] including three RCTs[36-38] that were published after the Cochrane review examined the effects of HHHFNC on extubation failure (i.e. need for re-intubation) and BPD. No significant differences were found between HHHFNC and NCPAP for either outcome. It is worth noting that one of the trials included in the meta-analysis (Yoder et al[38]) included both preterm and term infants.

1.6 Rationale for the current review

The wide variety of indications reported in studies included in systematic reviews,[30,35] surveys[28,29,39,40] and guidelines[20,41] support the need for updated evidence of the effectiveness of HHHFNC for a variety of indications, not simply following ventilation. While a recent meta-analysis has been published examining extubation failure and the incidence of BPD for HHHFNC compared to NCPAP,[35] there is also the need for a review of the evidence for other relevant outcomes and comparators.

1.7 Clarification of research question and scope

The aim of this project was to answer the question: What is the clinical and cost effectiveness of HHHFNC vs usual care for preterm infants? This was carried out by a systematic review of the available evidence and the subsequent assessment of the cost implications. We conducted a primary analysis of HHHFNC compared to usual care following ventilation and a secondary analysis of HHHFNC to usual care with no prior ventilation.

2 METHODS FOR SYNTHESISING CLINICAL EVIDENCE

Evidence for the clinical effectiveness of HHHFNC vs usual care for preterm infants was assessed by conducting a systematic review of published research evidence. The review was undertaken following the general principles published in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care.[42]

In order to ensure that adequate clinical input was obtained, an advisory panel comprising clinicians and a parent of children treated with a HHHFNC device was established. The role of this panel was to comment on the draft report and answer specific questions related to the care of preterm infants as the review progressed.

2.1 Search strategy

The following databases were searched for eligible studies:

- Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effectiveness, Health Technology Assessment database, NHS Economic Evaluation Database (for the cost effectiveness searches)
- ISI Web of Science- Science Citation Index Expanded
- ISI Web of Science- Proceedings (Index to Scientific & Technical Proceedings)
- Medline and Medline in Process (OvidSP)
- Embase(OvidSP)
- Pubmed (limited to the last 6 months)

Search terms included a combination of index terms (for the study population) and free-text words (for the technologies involved). No study design filters were applied. All databases were searched from the year 2000 to 8th September 2014. The searches were then updated on 12th January 2015.

Details of the search strategies can be found in the Appendix (section 9.1).

Trial and research registers were searched for ongoing trials and reviews including:

- Clinicaltrials. gov
- *meta*Register of Controlled Trials and ISRCTN Register
- WHO International Clinical Trials Registry Platform
- Prospero systematic review register
- National Institute for Health Research Clinical Research Network Coordinating Centre (NIHR CRN CC) Portfolio Database
- TRIP Database plus
- FDA

Bibliographies of previous reviews and retrieved articles were searched for further studies.

2.2 Study selection

A decision was made by the review authors to trial a new and freely available review software being developed for use in Cochrane reviews called Covidence.[43] The citations identified were independently assessed for inclusion through two stages by two reviewers (YD, RD). Firstly, the reviewers independently scanned all the titles and abstracts identified (and de-duplicated) through the searching exercise to identify the potentially relevant articles to be retrieved. Full text copies of the selected studies were subsequently obtained and assessed again for inclusion using the inclusion and exclusion criteria outlined in Table 2. Disagreements were resolved by discussion at each stage. There was no need to consult a third reviewer.

Table 2 Eligibility criteria

Criteria	Included	Excluded
Study design	Randomise controlled trials (RCTs)	Any study that is not an RCT
Patient population	Preterm infants requiring respiratory support	Not preterm infants
Interventions	Heated humidified high-flow nasal cannula (HHHFNC) of any type	A device not incorporating all elements associated with HHHFNC, e.g. a high-flow nasal cannula device which is non-humidified
Comparators	Usual care Usual care was considered to be NCPAP, NIPPV or oxygen for the primary analysis and NCPAP, NIPPV, oxygen or mechanical ventilation for the secondary analysis	Not usual care
Outcomes	**Primary outcome:** Failure of treatment as indicated by the need for re-intubation (treated following ventilation), or need for intubation (no prior ventilation) as measured at 3 time points: • Under 72 hours • Within 7 days • Ever **Secondary outcomes:** • death (prior to discharge from hospital) • chronic lung disease/bronchopulmonary dysplasia (BPD)(the need for supplemental oxygen at or greater than 36 weeks postmenstrual age for infants born before 32 weeks gestation; or the need for supplemental oxygen at 28 days of life) • composite outcome of death or BPD (as defined above) • duration in days of any form of respiratory support (mechanical ventilation, NCPAP, HHHFNC, oxygen) • length of stay in Neonatal intensive care unit(days) • length of stay in hospital (days) • adverse events/complications • quality of care • days to full feeds • failure to thrive (weight gain prior to discharge from hospital)	No study will be excluded based solely on outcomes measured

2.3 Data extraction strategy

Data relating to study design and findings were be extracted by one reviewer (VB) and independently checked for accuracy by a second reviewer (RD). Study details were extracted on pre-tested data extraction forms. Data from studies presented in multiple publications were extracted and reported as a single study with all other relevant publications listed. Where studies included preterm and non-preterm infants, only data for preterm infants were extracted and study authors were contacted for missing data as necessary.

2.4 Assessing the risk of bias

The plan for the conduct of risk of bias of the individual studies was originally based on the Cochrane risk of bias criteria[44] because the intention was to use the Covidence software for the entire review. However, it became clear that the data extraction tool used in Covidence did not allow us to easily produce tables for the review. We therefore opted to quality assess the included studies using criteria adapted from CRD at the University of York.[42] Criteria were assessed independently by one reviewer (VB) and then cross-checked by a second reviewer (YD). Disagreements were resolved through consensus and there was no need to consult a third reviewer.

2.5 Methods of analysis/synthesis

The results of the data extraction and quality assessment for each study were presented in structured tables and as a narrative summary for the primary analysis (preterm infants treated following ventilation) and secondary analysis (preterm infants with no prior ventilation). Where data permitted, we conducted a meta-analysis of primary and secondary outcomes using an appropriate software package (RevMan, The Cochrane Collaboration, and London, UK). We also conducted subgroup analyses based on gestational age. We planned to use the following categories: <30 weeks and ≥30 weeks (but the data did not permit us to use these specific thresholds once we had extracted the data). For dichotomous outcomes, we planned to use risk ratio (RR) and the corresponding 95% CIs to summarise results from each trial and for continuous outcomes, we planned to use the mean difference (or standardised mean difference where different scales are used). It was only possible to pool data for dichotomous outcomes. Where the data did not permit the conduct of a meta-analysis, data were presented in structured tables and as a narrative summary.

The decision to conduct a meta-analysis depended on there being sufficient data (at least two studies with the same interventions and comparators measuring the same outcome in the same way) and an assessment of heterogeneity. Heterogeneity was explored through consideration of the study populations (e.g. differences in gestational age), interventions (e.g.

starting flow rate for HHHFNC or starting pressure for NCPAP), outcome definitions (e.g. different definitions for re-intubation) and in statistical terms by the Chi^2 test for homogeneity and the I^2 statistic.[45] The I^2 statistic with a level of >50% was considered to indicate moderate levels of heterogeneity, and the Chi^2 test<0.10 to indicate statistically significant heterogeneity. Based on these assessments, a decision was made on whether to combine the results using a fixed-effects model (in the case of minimal heterogeneity), or a random effects model (in the case of substantial levels of heterogeneity).

If data had allowed, we would have conducted sensitivity analyses excluding trials deemed to be of low quality to assess the robustness of the findings. Had we included ten or more studies in a meta-analysis, an assessment of the risk of publication bias would have been conducted by constructing a funnel point and conducting a simple test of asymmetry to test for possible bias.[46]

3 METHODS FOR SYNTHESISING EVIDENCE OF COST EFFECTIVENESS

Scoping searches conducted in the preparation of the protocol identified no relevant published cost effectiveness studies. The search strategy is reported in the Appendix (section9.2). We therefore did not conduct another search of the literature for published cost effectiveness evidence but attempted to develop a de novo economic model if suitable data was available.

3.1 Modelling clinical pathway and outcomes

The definition of the patient pathway was determined through consultation between one of the authors who was a clinician (BS) and the economic modeller (JM). The pathway that was developed is shown in Figure 1. Data required to populate this patient pathway were taken from the studies included in the review (see section 4.2).

It was determined that the pathway was best modelled as a decision tree as there is no long-term progression of disease over time. It is assumed that any loss in utility from any of the primary outcomes is once and for all and that any short-term loss in utility from, for example, nasal injury, is a one-off utility decrement before a return to the long-term prior health state.

The model time horizon could in theory be lifetime provided there was evidence from the clinical review that the difference in outcomes between technologies had lifetime consequences.

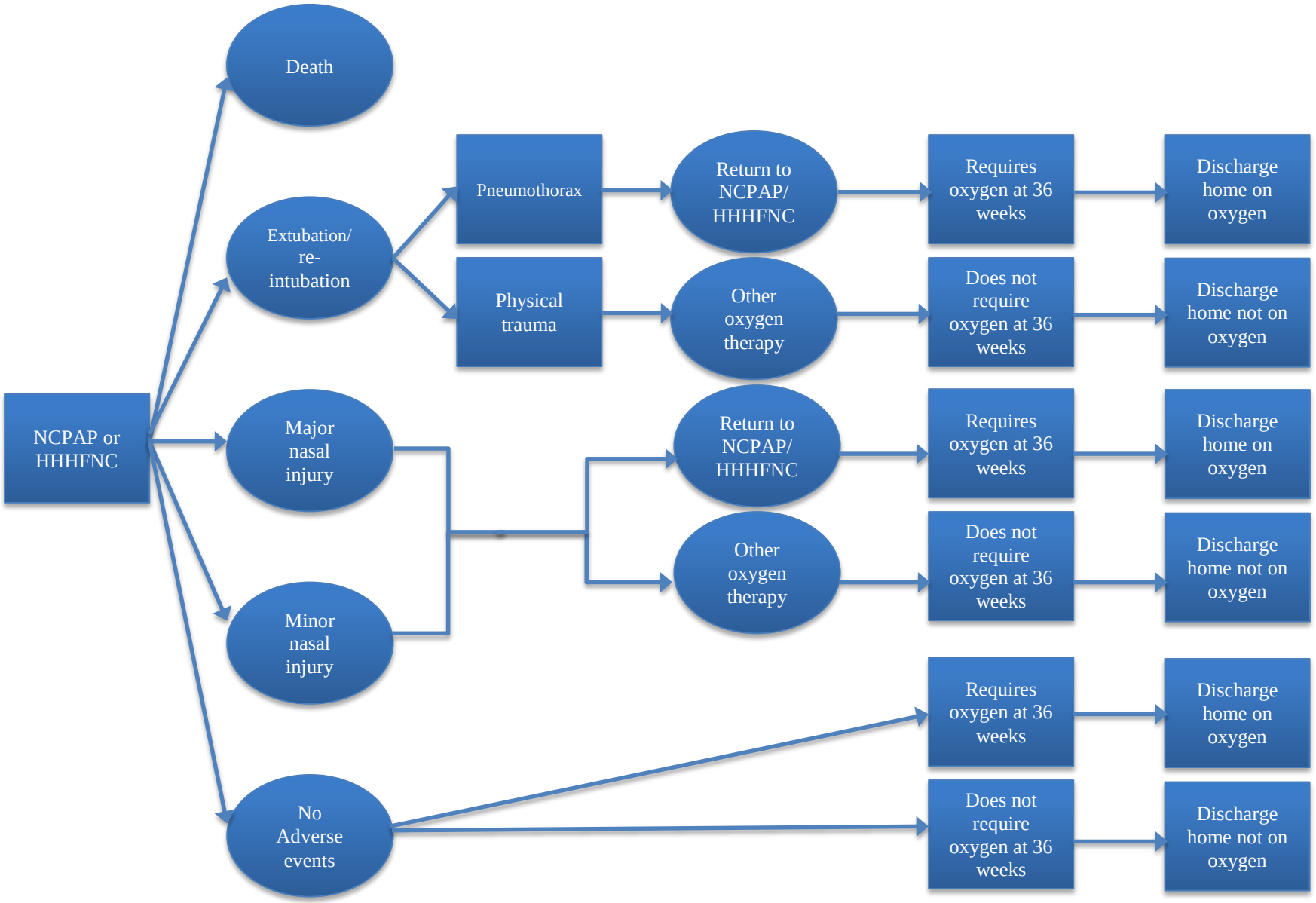

NCPAP or HHHFNC
Death
Extubation/ re-intubation
Pneumothorax
Physical trauma
Return to NCPAP/ HHHFNC
Other oxygen therapy
Requires oxygen at 36 weeks
Does not require oxygen at 36 weeks
Discharge home on oxygen
Discharge home not on oxygen
Major nasal injury
Minor nasal injury
Return to NCPAP/ HHHFNC
Other oxygen therapy
Requires oxygen at 36 weeks
Does not require oxygen at 36 weeks
Discharge home on oxygen
Discharge home not on oxygen
No Adverse events
Requires oxygen at 36 weeks
Does not require oxygen at 36 weeks
Discharge home on oxygen
Discharge home not on oxygen

Figure 1 Treatment pathway

3.2 Costs and utilities

Once the pathway and different clinical outcomes were determined, the appropriate treatment costs for the different technologies were identified through searching NHS Reference Costs[47] and the NHS Supply Chain[48] where available and appropriate.

Costing of the outcomes in the pathway was not undertaken until the conclusion of the clinical review, such that only outcomes where there was a difference identified in the review were costed. In all instances costs were to be taken from the perspective of the NHS.

Where costs were not available from published sources or where there was a menu of costs that could be chosen (such as from different manufacturers) then the costs were determined by resource use and costs in the neonatal units of the authors who are clinicians (BS, PS).

Patient elicited health states, with societal preference weights applied to those health states is the preferred method of utility derivation in health economics. Unfortunately in preterm infants this approach was not possible. Should there be a difference in outcomes identified in the clinical literature review, in selecting utility weights for different health states a pragmatic review of health utility literature in preterm babies and the clinical outcomes (including complications) identified in the pathway was to be undertaken. This would include searching for cost utility evaluations of other interventions for preterm babies to assess how utility values have been incorporated for this patient group by other researchers.

In the absence of any reliable utility information, then provided there was published clinical evidence on differences in outcomes from using HHHFNC or NCPAP we planned to model the full cost implications of using the technology taking into account the improved outcomes. If HHHFNC or NCPAP improves outcomes at lower cost than alternatives, then the absence of utility information would not then be important. If, on the other hand, the outcomes are improved with HHHFNC but at a higher cost than with NCPAP, a cost effectiveness analysis would be undertaken looking at ratios such as the cost per death averted.

A lack of evidence for difference in outcomes between HHHFNC and NCPAP would prevent undertaking of either cost utility or cost effectiveness analyses. If this was the case we planned to undertake a cost-minimisation analysis comparing HHHFNC with NCPAP. A cost minimisation analysis looks at the overall costs of the technologies per patient by comparing the resources required in capital goods, consumables and clinician time to administer each technology coupled with any evidence on adverse events and the resources required to treat these events. By applying suitable prices to these resources the analysis looks to identify the least expensive of the options – in this case from the perspective of the NHS. In such an

analysis where there is no clinical difference in outcomes that can be identified between technologies, it is the least expensive of the technologies that is the most cost effective.

3.3 Analysis of uncertainty

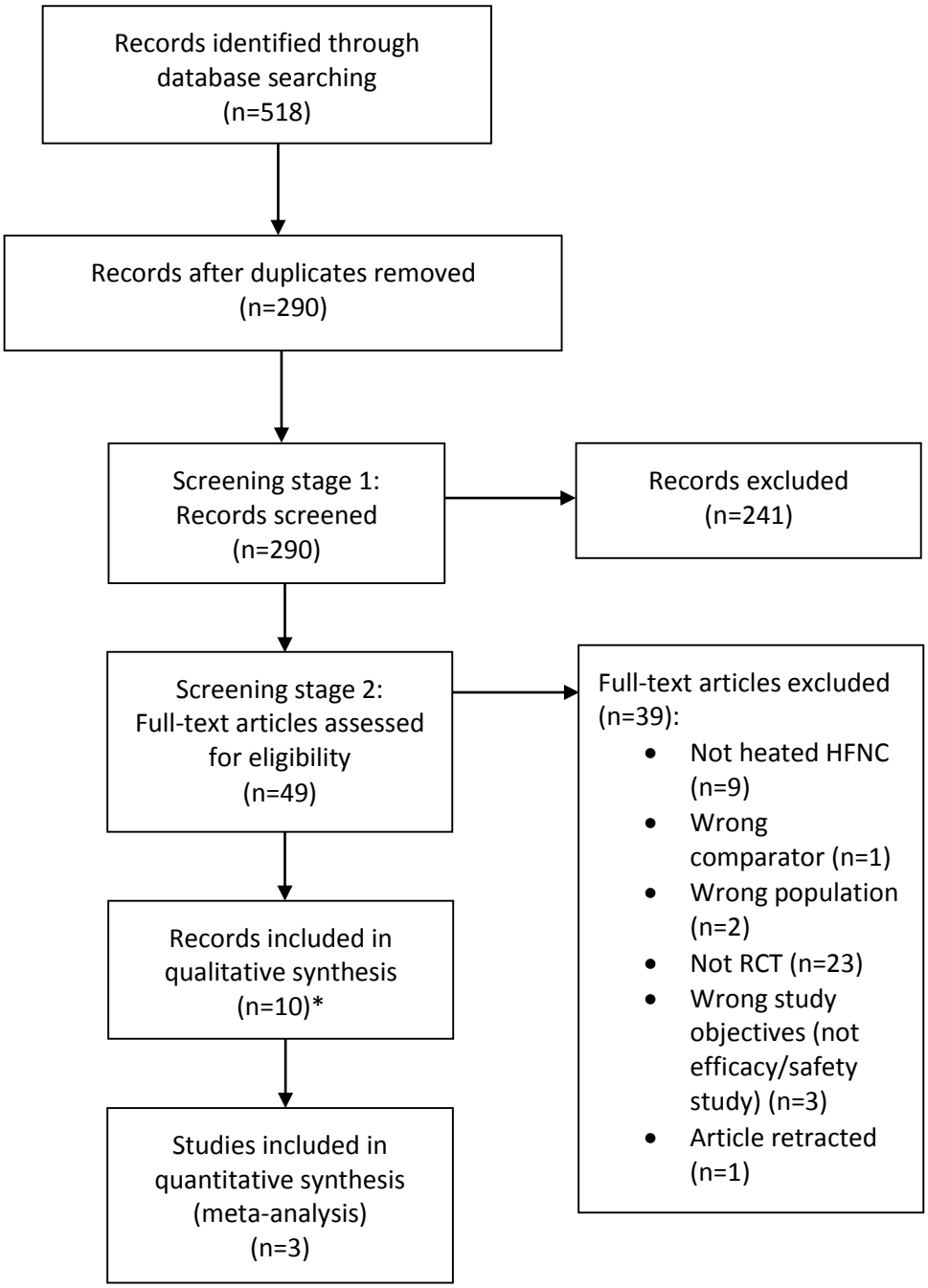
If a formal economic model could be constructed, appropriate sensitivity analyses were planned in order to assess the robustness of model results to realistic variations in the levels of the underlying data. Where the overall results are sensitive to a particular variable, the sensitivity analysis would analyse the exact nature of the impact of variations.

Imprecision in the principal model cost effectiveness results with respect to key parameter values was to be assessed by use of techniques compatible with the modelling methodology deemed appropriate to the research question and available evidence. This would include multi-way sensitivity analysis and cost effectiveness acceptability curves.

4 CLINICAL EFFECTIVENESS RESULTS

4.1 Initial searches and application of inclusion criteria

The results of the application of the study inclusion criteria are presented in Figure 2



* 10 papers report on 7 separate studies

Figure 2 PRISMA flow diagram

4.2 Included studies

In total 10records[32,36-38,49-54] were included. These report on seven separate Recasts summarised in Table 3. For the remainder of this report, only the primary paper for each of the studies will be referred to. In one instance, this was only an abstract.[32]

Three studies include preterm infants that had been previously ventialted,[36,37,49] (primary analysis). An additional study in which the majority received prior ventilation (see also section 4.4) was also included in this primary analysis.[38] The remaining three[32,51,52] included preterm infants requiring respiratory support following no prior ventilation (secondary analysis).

Table 3 Included studies

Study	Primary paper	Secondary paper	Study Sponsor
Primary analysis: preterm infants treated following ventilation			
Collaborative group 2014	Collaborative group 2014[49] (published in Chinese with English abstract)	Conference abstract: Ma 2014[53]	Supported by grants from Hebei Provincial Health Bureau GL2012013 and Talents Training Project of Hebei Province 2012‐334
Collins et al2013*	Collins et al2013[36]	Sub-study: Collins et al2014[50] *	Medical Research Foundation for Women and Babies, Melbourne, Australia
Manley et al 2013	Manley et al 2013[37]	Manley et al 2013[54]	Programme grant and Centre for Clinical Research Excellence grant from the National Health and Medical Research Council
Yoder et al 2013	Yoder et al 2013[38]	None	No external funding
Secondary analysis: infants who had received no prior ventilation			
Klingenberg et al 2014	Klingenberg et al 2014[51]	None	None stated
Kugelman et al 2014	Kugelman et al 2014[52]	None	None. Equipment supplied by Vapotherm Inc
Nair and Karna 2005	Abstract only Nair and Karna 2005[32] :	None	Equipment support from Vapotherm Inc

4.3 Study quality assessment

A summary of the quality assessment conducted is presented in Table 4 and a more detailed assessment is presented in the text below. Overall, the RCTs included in the review were of reasonable methodological quality although it was not possible to blind administrators or participants in any study. Studies included in the primary analysis (preterm infants treated following ventilation) were generally of better quality than those in the secondary analysis (infants who had received no prior ventilation). One of the studies included in this latter analysis, by Nair and Karna 2005, was not published but only presented as an abstract.[32]

4.3.1 Quality assessment of studies included in primary analysis

All four studies[36-38,49] were described as being randomised. However, for two studies, preterm infants were a non-randomised subgroup.[38,49] All studies[36-38,49] provided information on treatment allocation.[36-38,49 43-45,52 44-46,52] One study reported that assessors were blinded to treatment allocation.[36]

Baseline comparability was provided for allfourstudies.[36-38,49] However Collins et al[36] did not report achievement of comparability for all characteristics.

Allfourstudies[36-38,49] reported 100% completion of study participants and for all of these studies, analysis was conducted on an intention to treat (ITT) basis.

All four studies[36-38,49] provided details of eligibility criteria. However two of the studies[38,49] did not identify any co-interventions.

For all four studies,[36-38,49] a number of outcomes were reported and all of these outcomes appeared to be specified in the study methods.

4.3.2 Quality assessment of studies included in secondary analysis

All three studies were described as randomised.[32,51,52] Two of the studies did not state the randomisation process[32,51] and one study only partially described the method of randomisation.[52]

Two of the studies presented and achieved baseline comparability.[32,52] The study by Klingenberg et al[51] was a cross-over trial, hence there was only one group. Baseline characteristics were therefore presented for all participants and comparability (and whether it is achieved) is not applicable.

Two of the studies reported 100% completion of study participants and reported using ITT analysis.[32,52] Klingenberget al[51] reported >80% completion rate of participants and reasons for drop-outs were reported however, it was not stated whether ITT analysis was conducted.

One of the studies did not clearly identify their eligibility criteria[32] with only gestational age and requirement for respiratory support within the first 6 hours of life being specified. However, this study was only available as a conference abstract. Two of the studies did not identify any co-interventions.[32,51]

For all studies,[32,51,52] a number of outcomes were reported and all of these outcomes appeared to be specified in the study methods. One secondary outcome (salivary cortisol)in the study by Klingenberg et al[51] was omitted from statistical comparisons because the study authors

reported they only managed to collect enough saliva for cortisol measurement in 11 out of 80 attempts. This outcome measure was not, however, a pre-specified outcome for our review.

Finally, it should be noted that one of the studies was halted early.[32] This was because of the temporary recall of Vapotherm devices as a result of reports external to this trial of Ralstonia infections occurring with its use. This study has, to date, only been presented as an abstract.

Table 4 Study quality assessment

Studies	Randomisation			Baseline comparability		Eligibility criteria specified	Co-interventions identified	Blinding			Withdrawals			Intention to treat
	Truly Random	*Allocation concealment*	*Number stated*	*Presented*	*Achieved*			*Assessors*	*Administrators*	*Participants*	*Procedure assessed*	*>80% in final analysis*	*Reasons stated*	
Primary analysis: preterm infants treated following ventilation														
Collaborative Group2014[49] *	✓	✓	✓	✓*	✓*	✓	×	×	×	×	NA	×/✓*	NA*	✓
Collins et al 2013[36]	✓	✓	✓	✓	×/✓	✓	✓	✓	×	×	NS	✓	NA	✓
Manley et al 2013[37]	✓	✓	✓	✓	✓	✓	✓	×	×	×	NA	✓	NA	✓
Yoder et al 2013[38]	✓	✓	✓	✓*	✓*	✓	×	×	×	×	NA	×/✓*	NA*	✓
Secondary analysis: infants who had received no prior ventilation														
Kingenberg et al 2014[51]	NS	NS	✓	NA	NA	✓	×	×	×	×	NA	✓	✓	NS
Kuglemanet al 2014[52]	×/✓	×	✓	✓	✓	✓	✓	×	×	×	NA	✓	NA	✓
Nair and Karna 2005[32] †	NS	NS	✓	✓	✓	×/✓	×	NS	NS	×	NS	✓	NA	✓

×=no, ✓=yes, ×/✓=partially, ?=unclear, NS=Not stated, NA=not applicable

* The Collaborative Group2014[49] presented data for all study participants, a population of 255 infants who were both preterm (n=150) and term (n=105), hence baseline characteristics were only presented for this mixed population; furthermore, the analysis of interest was the subgroup of preterm infants which constituted 58.8% of all participants and hence <80% in final analysis although no drop outs were reported in the study

†Nair and Karna 2005[32] only reported their study as a conference abstract and so less information was available to assess study quality than in a fully published paper

4.4 Study characteristics

Study characteristics are presented in Table 5 and Table 6. A total of 859 infants were involved in the seven trials and the trial sizes ranged from 20[51] to 303.[37]

4.4.1 Study characteristics of studies included in primary analysis

As per the inclusion criteria, the four included studies[36-38,49] of infants who had been treated following ventilation were RCTs. A total of 735 infants were involved in the trials and the trial sizes ranged from 132[36] to 303.[37]

Three studies[37,38,49] were multi-centred; no study was carried out internationally with two studies conducted in Australia,[36,37] one in the US[38] and one in China.[49] The earliest study started enrolling participants in December 2007[38] and the most recent in 2012.[49] HHHNFC was compared to NCPAP in all four studies.[36-38,49]

The length of the study follow-up was only explicitly stated by Collins et al 2013[36] in which it is stated al 132 infants were followed for 7 days and 121 infants were followed until their discharge home; reasons for loss to follow-up after 7 days are provided. Yoder et al[38] also appear to have followed infants until discharge since they present a study flow chart presenting numbers of patients until discharge. It can be assumed that in the other two studies,[36,49] infants were followed up for a minimum of 7 days (since the primary outcomes in each study required follow-up for 7 days).

Study participants were generally similar across the studies (in terms of inclusion and exclusion criteria) although the two Australian studies[36,37] limited participation to infants with a gestational age <32 weeks and the US study[38] to ≥28 weeks. The US and Chinese studies[38,49] included preterm, term and post-term infants but only data for preterm infants has been synthesised in the remainder of this report (56.6% of participants in the Chinese study[49] and 32.4% in the US study[38]). In addition, the US study[38] also included infants who had not received prior ventilation (32.4% of all participants, including term and post-term babies, the proportion of preterm infants being unknown). The type of HHHFNC device and flow rate varied across studies as did the NCPAP devices and starting flow rates.

Table 5 Included study characteristics: primary analysis (preterm infants treated following ventilation)

Study	Study design, location and years conducted	Population studied	Excluded	Interventions	Outcomes
Collaborative group 2014[49]	Multi-centre RCT China 2012 to 2013	N=150* Infants who were admitted to NICU within 7 days after birth and were planned to extubate to non-invasive ventilation after endotracheal ventilation. No limitation on GA or birth weight.	Life-threatening congenital anomaly Congenital anomalies requiring surgical intervention, e.g. CDH, TEF, gastroschisis, omphalocele Congenital airway abnormalities, e.g. Robin syndrome, manidibulofacialdysostosis, oculo-auriculo-vertebral dysplasia syndrome, cleft lip or palate Uncontrolled air leak	HHHNFC (3L/min to 8L/min depending on birth weight) with Fisher-Paykel Heated Humidifier, Bird Blender or Optiflow nasal cannula n=79* NCPAP (6L/min to 10L/min, same PEEP with invasive ventilation) n=71*	Extubation failure*(re-intubation within 7 days)
Collins et al 2013[36]	Single centre RCT Australia 2009 to 2011	N=132 GA<32 weeks Previous endotracheal intubation with positive pressure ventilation Ready for extubation	Upper airway obstruction Congenital airway malformations Major cardiopulmonary malformations	HHHFNC (8L/min) with Vapotherm n=67 NCPAP (positive end-expiratory pressure (PEEP) of 8 cm water if the fraction of inspired oxygen (FiO_2)>0.3 or a PEEP of 7 cm H_2O if FiO2 <0.3 n=65	Extubation failure (composite outcome†) in next 7 days Nasal trauma BPD Duration of respiratory support Duration of supplemental oxygen requirement Pneumothorax after extubation Intraventicular haemorrhage Necrotizing enterocolitis Death Days to reach full enteral feeds
Manley et al 2013[37]	Multi-centre non-inferiority RCT Australia 2010 to 2012	N=303 GA<32 weeks Infants scheduled for extubation	GA>36 weeks Participation in concurrent study Major congenital anomalies	HHHFNC (5L/min to 6 L/min depending on prong size) with Fisher-Paykel Optiflow device n=152 NCPAP (bi-nasal midline prongs mechanical ventilation or underwater “bubble”.7 cm of water) n=151	Treatment failure (composite outcome†) within 7 days Re-intubation within 7 days Death before hospital discharge Require supplemental oxygen Duration of respiratory support Length of hospital admission Adverse events including BPD, nasal and septum trauma, necrotizing enterocolitis, intraventicular haemorrhage, nosocomial sepsis, gastrointestinal perforation and pneumothorax

Table 5 Included study characteristics: primary analysis (preterm infants treated following ventilation)

Study	Study design, location and years conducted	Population studied	Excluded	Interventions	Outcomes
Yoder et al 2013[38]	Multi-centre RCT US 2007 to 2012	N=150* GA ≥28 weeks Birth weight ≥1000g Intention to manage the infant with either non-invasive (no endotracheal tube) or mechanical ventilation (with an endotracheal tube) within first 24h of birth	Weight <1000g GA<28 weeks Presence of active air leak syndrome Concurrent participation in a study that prohibited HHHFNC Abnormalities of upper and lower airways Serious abdominal, cardiac, or respiratory malformations including tracheal esophagealfistula, intestinal atresia, omphalocele, gastroschisis, or diaphragmatic hernia	HHHFNC (3L/min to 8L/min depending on birth weight) with various devices n=75* NCPAP(various interfaces including bubble, Infant Flow NCPAP System and ventilator at 5 to 6 cm of water) n=75*	Extubation failure* (need for intubation within 72hours) BPD*

BPD=bronchopulmonary dysplasia; CDH=Congenital Diaphragmatic Hernia; FIO_2=fraction of inspired oxygen; GA=gestational age; NICU=neonatal intensive-care unit; PEEP=positive end-expiratory pressure; TEF=tracheoesophageal fistula

* Collaborative group 2014[49] and Yoder et al 2013[38] also included 105 term or post-term infants (HHHFNC, n=49 and NCPAP=56) and 282 term or post-term infants (HHHFNC, n=145 and NCPAP=137) respectively; additional outcomes were reported for the mixed population of preterm, term and post-term infants combined in both studies

† Collins et al 2013[36] defined extubation failure by composite criteria based on apnoea, acidosis and increase in fraction of inspired oxygen whereas Manley et al 2013[37] defined treatment failure by composite criteria based on apnoea, acidosis, increase in fraction of inspired oxygen and urgent need for intubation

4.4.2 Study characteristics of studies included in secondary analysis

Regarding the studies of infants who had not received prior ventilation, again as per the inclusion criteria the three included studies were RCTs, of which one was a crossover trial.[51] A total of 124 infants were involved in the trials and the trial sizes ranged from 20[51] to 76.[52]

All included studies[32,51,52] were single centre trials. One study was carried out in the USA,[32] one in Norway,[51] and one was a pilot study conducted in Israel.[52] All studies were single centre trials. The earliest study started enrolment from 2004[32] while the other two[51,52] were from 2010 onwards. HHHNFC was compared to NCPAP,[32,51] and NIPPV.[52]

The length of follow-up was not specified by any of the studies but may be assumed to be 48 hours (2 x 24 hours) in crossover trial[51] and a minimum of 7 days in Nair and Karna 2005[32] since the primary objective of this study was to compare the respiratory failure rate during the first 7 days of life. It is unclear how long preterm infants were followed up in the pilot study.[52]

Study participants were generally similar across the studies (in terms of inclusion and exclusion criteria) with all infants with a gestational age <35 weeks. However one study,[51] which was the cross-over study, included a minority (30%) of patients who had received prior ventilation. The type of HHHFNC device and flow rate varied across studies as did the NCPAP devices and starting flow rates.

Table 6 Included study characteristics: secondary analysis (infants who had received no prior ventilation)

Study	Study design, location and years conducted	Population studied	Excluded	Interventions	Outcomes
Klingenberg et al 2014[51]	Single centre cross-over trial (2×24h) Norway 2012 to 2013	N=20 GA <34 weeks Mild respiratory illness (treated with NCPAP for 72 hours)	Congenital anomalies Required high oxygen levels or frequent blood samples due to infection or hypoglycaemia	24h HHHFNC (5 L/min to 6L/min depending on birth weight) n=10 24h NCPAP (4 to 5cmH_2O) n=10	Patient comfort (EDIN scale) Respiratory parameters Ambient noise Salivary cortisol Parental assessments
Kugelman et al 2014[52]	Single centre RCT Israel 2010 to 2011	N=76 GA<35 weeks Birth weight >1, 000 g Infants with respiratory distress syndrome who need non-invasive respiratory support	Significant morbidity	HHHFNC (Vapotherm at flows between 1. 0 and 5. 0 L/min) n=38 NIPPV (SLE 2000 or 5000 via nasal prongs) n=38	Re-intubation Duration of nasal support Duration of endotracheal ventilation Time to full feeds Length of stay Air leaks Neonatal morbidities: pneumothorax BDP IVH necrotizing enterocolitis nasal trauma
Nair and Karna 2005[32]	Single centre RCT USA 2004	N=28 GA 27 to 34 weeks Required NCPAP in first 6 hours	No spontaneous respiration Major congenital anomalies Birth asphyxia (Apgar <3)	HHHNFC (Vapotherm mean flow rate 1.8 L/min) n=13 Variable flow NCPAP (infant-flow) at 5 to 6 cm H_2O n=15	Respiratory failure – 2 or more of: pH≤ 7.25 CO_2>60 (ABG) or >65 (CBG) FiO_2>70% Frequent apnoea or bradycardia

ABG=arterial blood gas; BPD=bronchopulmonary dysplasia; CBH=capillary blood gas; CO_2=carbon dioxide; EDIN=Echelle Douleur Inconfort Nouveau-Né, neonatal pain and discomfort scale; FIO_2=fraction of inspired oxygen; GA=gestational age; H_2O=water; IVH=intraventricular haemorrhage; SLE=Specialised Laboratory Equipment

4.5 Characteristics of the preterm infants included in the studies

Characteristics of the preterm infants that participated in the trials are presented in Table 7(primary analysis of preterm infants treated following ventilation) and Table 8 (secondary analysis of preterm infants with no prior ventilation). There is a lack of data for two studies[38,49] reporting on preterm infants treated following ventilation because both of these studies also included term or post-term infants and did not present baseline data for only preterm infants.

Where data on birth weight were provided, birth weight was generally lower in those studies relevant to the primary analysis (mean <1150 grams) than those in the secondary analysis (mean >1490 grams). Similarly, where data on mean gestational age were provided, this was generally lower in those studies relevant to the primary analysis (mean <28 weeks) than those in the secondary analysis (mean ≥30 weeks). Prior steroid use was only reported in three studies[36,37,52] and this was notably higher (≥88%) in the two studies relevant to the primary analysis[36,37] than in the study[52] included in the secondary analysis (50%). These differences in baseline findings suggest infants in the primary analysis to be heavier and with shorter gestational age than those in the secondary analysis is not unexpected as these are the infants who tend to most need mechanical ventilation as soon as they are born.

4.5.1 Participant characteristics of studies included in primary analysis

The participant characteristics across all four trials were broadly similar (Table 7).

4.5.2 Participant characteristics of studies included in secondary analysis

As evident from Table 8, infants in the Klingenberg et al 2014[51] study were notably lighter (<1250 grams) and slightly younger (≤29.3 weeks) than the other two studies[32,52] included in the secondary analysis (≥1493 grams and ≥31 weeks). This study[51] did in fact include a minority (30%) of patients who had received prior ventilation unlike the other two.[32,52] This may explain why mean birth weight and gestational age differed in this study compared with the other two studies[32,52] included in the secondary analysis as the data may be being skewed by the inclusion of preterm infants who had been treated following ventilation.

Table 7 Baseline characteristics: primary analysis (preterm infants treated following ventilation)

Study	Arm	Race, white, n (%)	Gestational age, mean (SD)	Birth weight, mean (SD)grams	Male, n (%)	Prior mechanical ventilation, n (%)	Intubation in delivery room, n (%)	Antenatal/ pre-study steroids, n (%)	5 min Apgar score (range)
Collaborative group 2014[49]	HHHNFC (n=79)	NR	NR*	NR*	NR*	79 (100)	NR	NR	NR
	NCPAP (n=71)	NR	NR*	NR*	NR*	71 (100)	NR	NR	NR
Collins et al2013[36]	HHHNFC (n=67)	NR	27.9 (1.95)	1123 (317)	33 (49)	67(100) Median (range) hrs 46 (24-98)	NR	59 (88)	7 (6 to 8)
	NCPAP (n=65)	NR	27.6 (1.97)	1105 (374)	41 (63)	65 (100) Median (range) hrs 57 (27-120)	NR	58 (89)	8 (6 to 9)
Manley et al 2013[37]	HHHNFC (n=152)	127 (83.6)	27.7 (2.1) N (%) <26 wks 32 (21.1)	1041 (338)	89 (59)	152(100) Median (range) hrs 36 (19.5-101.5)	102 (67.1)	142 (93.4)	7 (6 to 8)
	NCPAP (n=151)	120 (79.5)	27.5 (1.9) N (%) <26 wks 31 (20.5)	1044 (327)	72 (48)	151(100) Median (range) hrs 36 (20-93)	91 (60.3)	143 (94.7)	8 (6 to 8)
Yoder et al 2013[38]	HHHNFC (n=75)	NR	NR*	NR*	NR*	NR*	NR	NR*	NR
	NCPAP (n=73)	NR	NR*	NR*	NR*	NR*	NR	NR*	NR

Apgar=Appearance, Pulse, Grimace, Activity, Respiration
NR=not reported; SD=standard deviation
* Data were reported in the published paper only for preterm and term infants combined

Table 8 Baseline characteristics: secondary analysis(preterm infants who had received no prior ventilation)

Study	Arm	Gestational age, mean (SD)	Birth weight, mean (SD) grams	Male, n (%)	Antenatal/ pre-study steroids, n (%)	5 min Apgar score (range)
Klingenberg et al 2014[51]	HHHNFC (n=20)*	All infants: 29.3 (1.7)*	All infants: 1234 (353)*	All infants: 13(65)*	NR	NR
	NCPAP (n=20)*				NR	NR
Kugelman et al 2014[52]	HHHNFC (n=38)	31.8 (2.3)	1759 (488)	26(68)	19 (50)	9 (6 to 10)
	NIPPV (n=38)	32. 0 (2.3)	1835 (530)	24(63)	19 (50)	9 (7 to 10)
Nair and Karna 2005[32]	HHHNFC (n=13)	32 (0.5)	1675 (139)	NR	NR	NR
	NCPAP (n=15)	31 (0.5)	1493 (64)	NR	NR	NR

NR=not reported
* As this was a crossover study, data were identical for each arm

4.6 Efficacy findings from primary analysis

For pre-term infants treated following ventilation, it was possible to pool data in a meta-analysis for three outcomes. The primary outcome for our review was treatment failure as defined by the need for re-intubation at <72h, <7 days or ever. For the primary analysis, three studies[36,37,49] measured the need for re-intubation within the first 7 days. The data for these three studies[36,37,49] were pooled into a meta-analysis (Figure 3). Data were also pooled for BPD and death from three studies[36-38] (Figure 4 and Figure 5). For all analyses, a fixed-effects model was employed since there was no evidence of statistical heterogeneity (or indeed clinical heterogeneity based on the data presented in Table 5 and Table 7). The forest plots show that all the findings are in the direction of favouring HHHFNC. However no statistically significant differences were reported between arms for any of the outcomes. No significant statistical heterogeneity between studies were noted in any of the three meta-analyses (I^2=0% and Chi^2 test, p≥0.10).

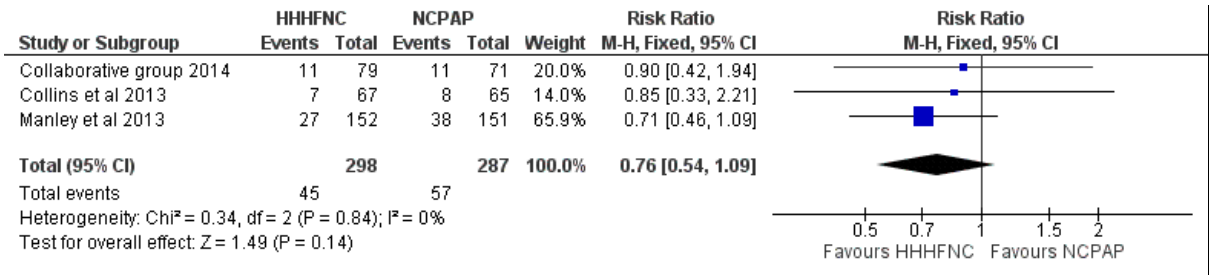


Figure 3: Meta-analysis for need for re-intubation<7 days

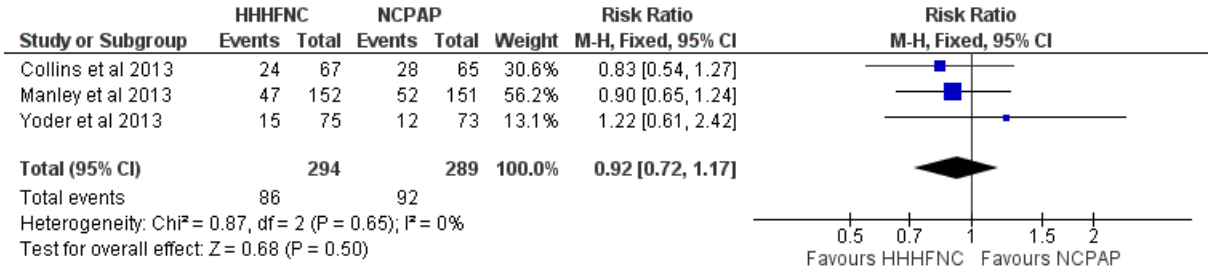


Figure 4: Meta-analysis for bronchopulmonary dysplasia

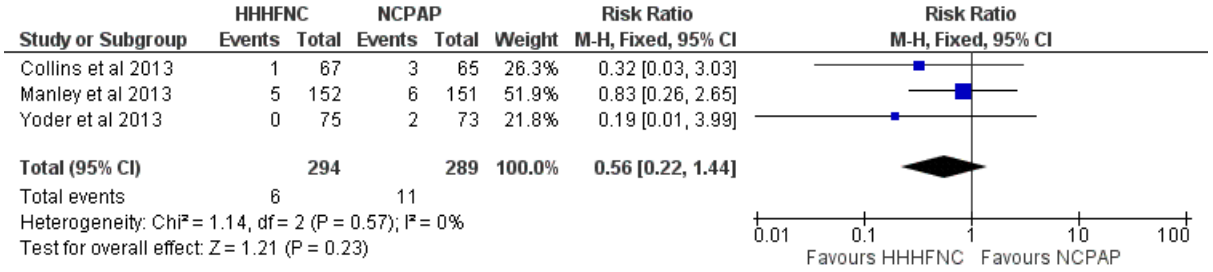


Figure 5: Meta-analysis for death

One trial[38] only reported re-intubation within 72 hours for preterm infants. As reported in Table 9, marginally fewer preterm infants required re-intubation in the HHHFNC arm than in the NCPAP arm. However, the proportions were small and no statistically significant difference between arms was reported.

All other outcomes reported in the trials are also presented in Table 9. No statistically significant differences were reported between arms in any of these studies[36,37] and so no study reported the superiority of HHHFNC over usual care. However, it should be noted that the Manley et al[37] study was a non-inferiority trial and so the aim of this trial was not to demonstrate superiority.

It should also be noted that the definition of extubation failure/treatment failure in two studies[36,37] differed to that used for our review; both studies[36,37] basing failure on a composite outcome including apnoea, acidosis and increase in fraction of inspired oxygen. In addition, Manley et al 2013[37] also included these three outcomes plus an urgent need for intubation in their composite outcome. Using these study definitions, it is noted that Manley et al[37] reported a numerically higher rate of treatment failure with HHHFNC than NCPAP (but the opposite was the case with regard to need for re-intubation). In contrast, Collins et al2013[36] reported a numerically lower rate of extubation failure with HHHFNC (and re-intubation rates were also numerically lower in the HHHFNC arm).

Hours on mechanical ventilation, days on oxygen support and length of hospital stay were reduced with HHHFNC compared with NCPAP in the study by Manley et al,[37] however the differences were not statistically significant. In the same study,[37] median weight gain also appeared to be higher in the HHHFNC arm than the NCPAP arm but again the difference was not statistically significant. Days to full feeds was only reported by Collins et al.[36] This was marginally higher in the HHHFNC arm by around half a day; the between-arm difference was not statistically significant.

A number of other secondary outcomes that we had planned to measure were not reported by any study, namely BPD/death (composite outcome), duration of respiratory support on NCPAP or HHHFNC, length of stay in NICU)or measures of quality of care.

Table 9 Study outcomes: primary analysis (preterm infants treated following ventilation)

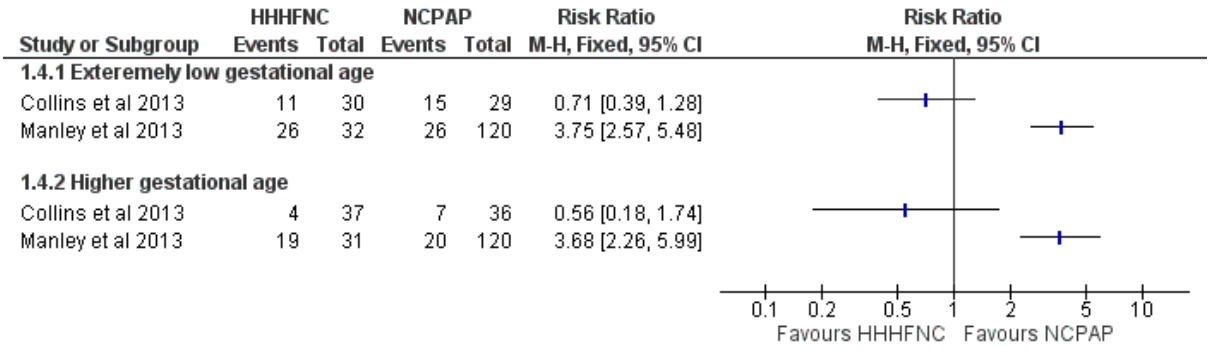
Study	Arm	Re-intubation n (%)	BPD/ Death, n (%)	Time on mechanical support, hours	Days on oxygen support	Length of hospital stay, days	Days to full feeds, mean (SD) / weight gain (grams)	Other, n (%)
Collaborative group 2014[49]	HHHNFC (n=79)	< 7 days: 11 (13.9)	NR¥	NR¥	NR¥	NR¥	NR¥	NR¥
	NCPAP (n=71)	11 (15.5)	NR¥	NR¥	NR¥	NR¥	NR¥	NR¥
Collins et al 2013[36]	HHHNFC (n=67)	< 7 days: 7 (10.4) Ever:14 (20.9)	BPD 24 (35.8) Death 1 (1.5)	NR	NR	NR	Days to full feeds 12.9 (0.73)	Failed extubation* 15 (22.4)
	NCPAP (n=65)	< 7 days: 8 (12.3) Ever: 16 (24.6)	BPD 28 (43.1) Death 3 (4.6)	NR	NR	NR	12.3 (0.65)	22 (33.8)
Manley et al 2013[37]	HHHNFC (n=152)	< 7 days: 27 (17.8)	BPD 47 (30.9) Death5 (3.3)	Median (range) days 34 (7 to 55)	Median (range) 38 (0 to 78)	Median (range) 79 (63 to 05)	Weight gain Median (range) 20 (-42 to 79.5)	Treatment failure† 52 (34.2)
	NCPAP (n=151)	38 (25.2)	BPD 52 (34.4) Death6 (4. 0)	38 (11 to 57)	49 (8 to 83)	84 (65 to 06)	10 (-54 to 75)	39 (25.8)
Yoder et al 2013[38]	HHHNFC (n=75)	< 72 hours: 3 (4. 0)	BPD 15 (20.0) Death 0	NR¥	NR¥	NR	NR¥	NR¥
	NCPAP (n=73)	5 (6.7)	BPD 12 (16.4) Death 2 (2.7)	NR¥	NR¥	NR	NR¥	NR¥

BPD=bronchopulmonary dysplasia; NR=not reported; SD=standard deviation

* Collins et al 2013[36] defined extubation failure by composite criteria based on apnoea, acidosis and increase in fraction of inspired oxygen, see also Table 11 for rates of apnoea and acidosis
†Manley et al 2013[37] defined treatment failure by composite criteria based on apnoea, acidosis, increase in fraction of inspired oxygen and urgent need for intubation, see also Table 11 for rates of apnoea and acidosis
§ Infants could be re-intubated, weaned to low flow therapy or stay on the same treatment within the first 24h and then crossover to the alternative mode of HHHFNC at 24h
¥Data were reported in the published paper only for preterm and term infants combined

4.6.1 Exploratory subgroup analyses

Extubation failure/treatment failure (as defined, differentially, in the individual studies[36,37]) was considered by gestational age in two trials.[36,37] In Manley et al 2013[37] it was considered in those born before 26 weeks completed gestation and those born from 26 weeks onwards and in Collins et al 2013[36] before/from 28 weeks. Unsurprisingly, the extubation failure/treatment failure rate was higher in infants with gestational age below 26/28 weeks (extremely low gestational age) than in infants born later. As shown in Figure 6, and as noted above for the whole trial population in section 4.6, the treatment effect was in opposite directions in the two included studies.[36,37]



Note:
Extremely low gestational age subgroup defined as <28 weeks GA in Collins et al 2013 and <26 weeks GA in Manley et al 2013
Higher gestational age subgroup defined as ≥28 weeks GA in Collins et al 2013 and ≥26 weeks GA in Manley et al 2013

Collins et al 2013[36] defined extubation failure by composite criteria based on apnoea, acidosis and increase in fraction of inspired oxygen whereas Manley et al 2013[37] defined treatment failure by composite criteria based on apnoea, acidosis, increase in fraction of inspired oxygen and urgent need for intubation

Figure 6: Extubation failure/treatment failure by subgroup

Re-intubation rates were only presented by subgroup in one study.[36] As reported in Table 10, re-intubation rates appeared to be higher in those treated with NCPAP compared with those treated with HHHFNC regardless of gestational age.

Table 10 Subgroup analysis of re-intubation rate by gestational age

Study	Arm	< 28 weeks GA, n (%)	≥ 28 weeks GA, n (%)
Collins et al 2013[36]	HHHNFC	5 (16.7)	4 (10.8)
	NCPAP	7 (24.1)	7 (19.4)

GA=gestational age

4.7 Adverse events reported for primary analysis

A summary of the adverse events reported in the included trials is presented in Table 11. Adverse event data were reported for preterm and term infants combined by the Collaborative Group[49] and Yoder et al[38] and so these data are not presented here.

Data were pooled into a meta-analysis for pneumothorax (Figure 7), nasal trauma leading to change of treatment (Figure 8), IVH (Grade 3+) (Figure 9), NEC (Figure 10), apnoea (Figure 11) and acidosis (Figure 12). With the exception of apnoea and acidosis, the forest plots show the findings are in the direction of favouring HHHFNC. Statistically significant differences were reported for nasal trauma leading to change of treatment with fewer pre-term infants changing treatment with HHHFNC than with NCPAP. No statistically significant differences between arms were reported for any other adverse events although for IVH (Grade 3+) and NEC, events were noticeably numerically fewer in the HHHFNC arm.

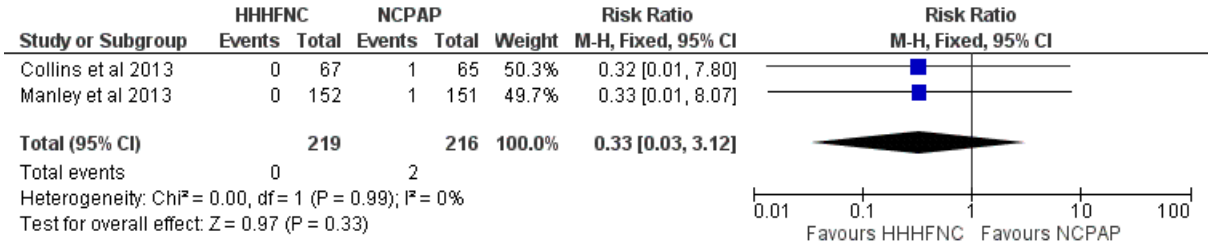


Figure 7: Meta-analysis for pneumothorax

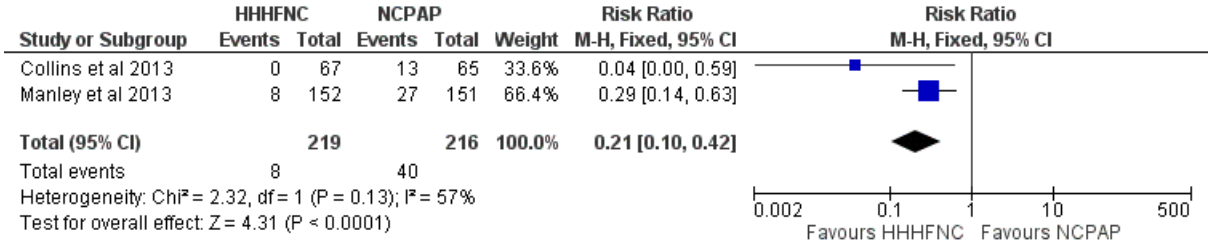


Figure 8: Meta-analysis for nasal trauma leading to change of treatment

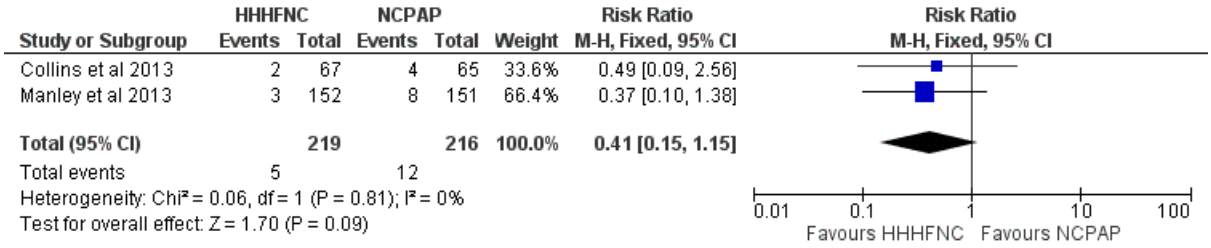


Figure 9: Meta-analysis for intraventricular haemorrhage (Grade 3+)

Figure 10: Meta-analysis for necrotizing enterocolitis

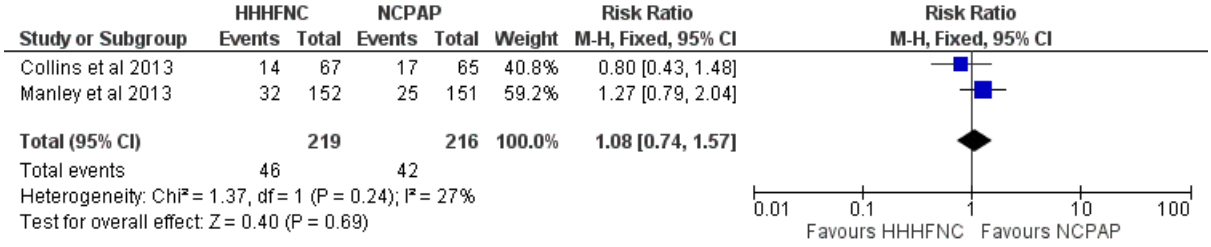


Figure 11: Meta-analysis for apnoea

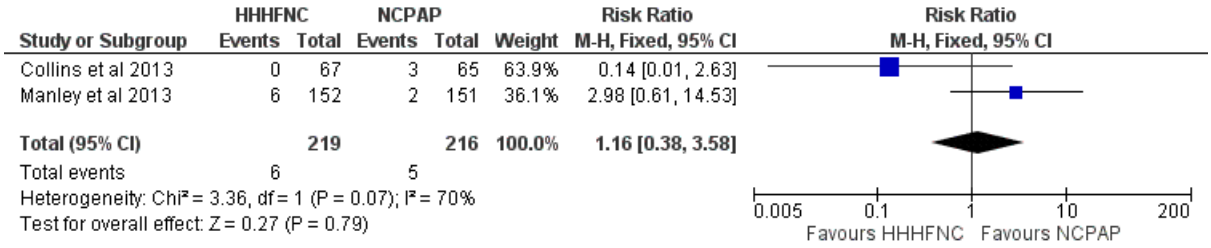


Figure 12: Meta-analysis for acidosis

In addition to data that could be pooled, differences in the nasal trauma score were statistically different favouring HHHFNC in Collins et al 2013.[36] In Manley et al 2013[37] the difference in the incidence of nasal trauma was statistically significant whether reported as any documented nasal trauma, nasal trauma leading to a change of treatment or nasal trauma caused by the assigned treatment. Manley et al 2013[37] was the only study to report on nosocomial sepsis and gastrointestinal perforation, both of which were numerically fewer in the HHHFNC arm than the NCPAP arm (17.1% vs 19.9% and 0.7% vs 1.3% respectively).

Table 11 Reported adverse events: primary analysis (preterm infants treated following ventilation)

Study	Arm	Air leak/ pneumothorax n (%)	Nasal trauma, n (%)	IVH, Grade 3+ n (%)	NEC, n (%)	Apnoea, n (%)	Acidosis, n (%)
Collaborative group 2014[49]	HHHNFC (n=79)	NR¥	NR¥	NR	NR	NR¥	NR¥
	NCPAP (n=71)	NR¥	NR¥	NR	NR	NR¥	NR¥
Collins et al 2013[36]	HHHNFC (n=67)	Pneumothorax 0 (0)	Leading to change of treatment 0 (0.0)** Nasal trauma score, mean (SD): 3.1 (7.2)	2 (2.9)	2 (2.9)	14 (20.9)	0
	NCPAP (n=65)	1 (1.5)	Leading to change of treatment 13 (20.0)** Nasal trauma score, mean (SD): 11.8 (10.7)	4 (6.2)	5 (7.7)	17 (26.2)	3 (4.6)
Manley et al 2013[37]	HHHNFC (n=152)	Pneumothorax 0 (0.0)	Any documented 60 (39.5)* Leading to change of treatment 8 (5.3)*** Caused by the assigned treatment 29 (19.1)****	3 (2. 0)	Stage 2/3 3 (2. 0)	32 (21.1)	6 (11.5)
	NCPAP (n=151)	1 (0.7)	Any documented 82 (54.3)* Leading to change of treatment 27 (17.9)*** Caused by the assigned treatment 80 (53. 0)****	8 (5.3)	7 (4.6)	25 (16.6)	2 (5.1)
Yoder et al 2013[38]	HHHNFC (n=75)	NR¥	NR¥	NR	NR¥	NR¥	NR
	NCPAP (n=73)	NR¥	NR¥	NR	NR¥	NR¥	NR

IVH=intra-ventricular haemorrhage; NEC=necrotizing enterocolitis; SD=standard deviation
¥ Data were reported in the published paper only for preterm and term infants combined
*Between arm differences were reported be statistically significant (p=0.01) ** (p<0.01) *** (p=0.001) **** (p<0.001)

4.8 Efficacy findings from secondary analysis

Findings for infants who had not received prior ventilation are summarised in Table 12. The primary outcome of our review, treatment failure as defined by the need for extubation, was reported in one study.[52] Respiratory failure defined by a composite outcome incorporating blood gas and another outcome such as fraction of inspired oxygen>70% or frequent apnoea or bradycardia was reported by one other.[32] Neither study[32,52] reported a statistically significant difference between arms for treatment failure/respiratory failure for either HHHFNC vs NIPPV[52] or HHHFNC vsNCPAP.[32]

In the study by Kugelman et al 2014,[52] compared to NIPPV, time on mechanical ventilation and length of hospital stay were reduced with HHHFNC and days on oxygen support were increased; however, the differences between trial arms were not statistically significant. In the same study,[52] days to full feeds also appeared to be greater in the HHHFNC arm than in the NIPPV arm, again the difference was not statistically significant. None of these outcomes were reported by either of the two other studies[32,51] comparing HHHFNC with NCPAP. A number of the other secondary outcomes that we had planned to measure were not reported by any study at all, namely BPD/death (composite outcome), duration of respiratory support on NCPAP or HHHFNC or length of stay in NICU.

4.9 Adverse events reported for secondary analysis

The authors of the study by Kugelman et al 2014[52] reported adverse events for infants who had not received prior ventilation. These were numerically higher with HHHNFC than with NIPPV (except for apnoea) but no statistically significant differences were reported. The following adverse events were reported for HHHFNC vs NIPPV: air leak (5.3% vs 0), nosocomial sepsis (10.5% vs 7.8%), IVH (5.3% vs 2.6%), NEC (5.3% vs 0) and apnoea (10.5% vs 13.1%). There were no incidences of nasal trauma in either arm.

Table 12 Study outcomes: secondary analysis(infants who had received no prior ventilation)

Study	Arm	Treatment failure, * n (%)	BPD/death, n (%)	Time on mechanical support, days, median (range)	Days on oxygen support, median (range)	Length of hospital stay, days, median (range)	Days to full feeds, median (range)
Klingenberg et al 2014[51]	HHHNFC (n=20)†	NA	NR	NR	NR	NR	NR
	NCPAP (n=20)†	NA	NR	NR	NR	NR	NR
Kugelman et al 2014[52]	HHHNFC (n=38)	11 (28.9)	BPD 1 (2.6) Death 0(0)	3. 0 (0.01 to 14)	5. 0 (0 to 69. 0)	35 (8 to 91)	13. 0(6 to 28)
	NIPPV (n=38)	13 (34.2)	BPD 2 (5.2) Death0 (0)	4. 0 (0.5 to 16)	3. 0 (0 to 90.0)	39.5 (9 to 113)	11. 0(5 to 49)
Nair and Karna 2005[32]	HHHNFC (n=13)	2 (15.3) 4 (12.1)§	NR	NR	NR	NR	NR
	NCPAP (n=15)	2 (13.3) 4 (11.8)§	NR	NR	NR	NR	NR

BPD=bronchopulmonary dysplasia; NA= not applicable (pre-term infants crossed-over treatment after 24 hours); NR=not reported

* Treatment failure defined as the need for need for endotrachealventilation by Kugelman et al 2014[52] and blood gas with ≥2 of the following: pH ≤7.25; pCO_2>60 (arterial blood gas) or >65 (capillary blood gas); fraction of inspired oxygen>70%; and frequent apnoea or bradycardia

†As this was a crossover study, data were identical for each arm

§Data extracted from that reported in the Wilkinson et al Cochrane review;[30] the total population of infants here was stated to be 67 (as opposed to n=28 in the conference abstract)

4.10 Quality of care

Klingenberg et al 2014[51] reported the results of a cross-over study comparing HHHFNC to NCPAP for preterm infants who had received no prior ventilation (secondary analysis); this was the only study to report on outcomes relevant to quality of care (within two 24h periods). The primary outcome of the study was patient comfort, defined as a state free of prolonged pain by a validated neonatal pain and discomfort scale (the EDIN [EDIN=Echelle Douleur Inconfort Nouveau-Né, neonatal pain and discomfort scale] scale).[55] No statistically significant differences between arms were reported for this outcome or for noise of equipment (measured by a handheld audiometer). There were however statistically significant differences for all parental assessment measures (from a visual analogue scale rated 1 to 10) with parents preferring HHHFNC to NCPAP (Table 13). In addition, it was noted by the study authors that infants had significantly lower respiratory rates in the HHHFNC arm than in the NCPAP arm in this study[51] but that all other respiratory parameters were similar.

Table 13 Quality of care outcomes

Study	Arm	EDIN score† mean (SD)	Noise, dBA, mean (SD)	Parental assessment, mean (SD)		
				Child satisfied¥	Contact and interaction¥	Participate in care¥
Klingenberg et al 2014[51]	HHHNFC (n=20)§	10.7 (3.3)	70 (10)	8.6 (1.1)**	9. 0 (1.1)**	9.1 (1.2)*
	NCPAP (n=20)§	11.1 (3. 0)	74 (10)	6.9 (1.6)**	6.7 (1.6)**	8. 0 (1.6)*

dBA=decibals; EDIN=Echelle Douleur Inconfort Nouveau-Né, neonatal pain and discomfort scale; SD=standard deviation; VAS=visual analogue scale

† EDIN score is a measure of patient comfort, defined as a state free of prolonged pain by a validated neonatal pain and discomfort scale

¥Visual analogue scale (scored from 1 to 10) with answers to the following questions: (1) How satisfied do you think your child has been over the last 24 h? (2) How do you assess your contact and interaction with your child over the last 24 h? (3) How do you assess your possibility taking part in nursing and care with your child over the last 24 h?

§ As this was a crossover study, data were identical for each arm

* Between arm differences were reported be statistically significant (p=0.03) ** (p<0.001)

5 COST EFFECTIVENESS RESULTS

For the primary analysis of preterm infants treated following ventilation, there were no statistically significant differences in any of the primary outcomes reported in the studies comparing HHHFNC and NCPAP that were included in the clinical review. The only difference identified was related to the rate of adverse events, notably in nasal injury in favour of HHHFNC. No long-term adverse events from nasal injury were identified from the studies included in the clinical review.

Given the absence of any differences in primary outcomes or in long-term adverse events, the time horizon of the economic model was limited to the period during which a preterm infant received oxygen therapy. With the only difference in outcome being short-term nasal injury, this can be the only difference in quality of life for the patient.

Utility value derivation from preterm infants cannot be done directly and in this case would likely result only in very small quality of life decrements related to skin irritation and infection. Treatment is rapidly administered and from the clinical experience of the authors who are clinicians (BS, PS), any irritation clears normally in 5to 7days. As such any utility loss was thought to be so small as to be inconsequential to include in the analysis although the treatment costs of this adverse event could be included. In the clinical experience of the authors who are clinicians (BS), nasal trauma from NCPAP can be so severe as to require plastic surgery. As this event was thought to be very rare and there was no evidence in the available literature of this event occurring, it has not been included in the analysis.

Given the absence of any difference in primary outcomes and utility between the technologies, a cost utility analysis could not be undertaken.

Also in the absence of any differences in primary outcomes, the only cost effectiveness analysis that could be undertaken would be based on the use of secondary outcome data; in this case, the incremental cost effectiveness ratio would defined as the cost per case of nasal injury avoided. As this is not a primary outcome in any of the studies included in the clinical effectiveness review, in our opinion it is unlikely that such an analysis would be meaningful and so cost effectiveness analysis was not undertaken.

Given the inability to undertake cost utility analysis or meaningful cost effectiveness analysis, coupled with there being evidence for no statistically significant difference between treatment arms for the primary clinical outcome, the need for re-intubation, a cost minimisation analysis for the primary analysis was undertaken comparing HHHFNC to NCPAP from the perspective of the NHS. For the secondary analysis of infants that had received no prior ventilation, there

was an absence of evidence on the difference in the primary outcome, the need for re-intubation; only one small study[52] examined this outcome with another that was halted early,[32] a similar outcome (respiratory failure) which was a composite endpoint; both compared HHHFNC to different devices (NIPPV[52] and NCPAP[32]) and so we considered there was an absence of evidence (as opposed to evidence of no difference from a meta-analysis for the primary outcome). Thus whilst considered for the secondary analysis, a cost-minimisation analysis was potentially misleading as it could lead decision makers towards a cheaper technology which has unknown relative effectiveness.

5.1 Treatment resource use and costs

Resource use of treatment included capital equipment, consumable costs and clinician time taken to establish a preterm infant onto either HHHFNC or NCPAP. All prices are in 2015 GBP unless otherwise stated. Given the time horizon is the period up to discontinuation of NCPAP or HHHFNC no discounting needed to be applied to costs.

5.1.1 Clinician time

From the clinical experience of two of the review authors (BS, PS), there is no difference in the time taken to set up a preterm infant on HHHFNC or on NCPAP and so this was not included in the analysis.

5.1.2 Capital equipment

NCPAP can be delivered either through mechanical ventilators or through dedicated NCPAP equipment. It is the opinion of the authors who are clinicians (BS, PS) that the preference is to use dedicated NCPAP equipment as this equipment is supposed to provide a nasal airflow that is more suitable for NCPAP than mechanical ventilation. In addition, the use of dedicated NCPAP equipment means that mechanical ventilators can be kept free for use elsewhere. Dedicated NCPAP equipment was therefore included as a resource in the evaluation rather than mechanical ventilators.

It is the opinion of the authors who are clinicians (BS, PS) that, not only is there a range of manufacturers with different devices that can be used, the prices quoted by the manufacturer can vary depending on the volume purchased.

From NHS Supply Chain information[48] the quoted price for a non-humidified NCPAP machine (the Maxblend NCPAP flow generator complete system by Armstrong Medical Ltd) was £6,122. Whilst there may be other devices available, this appeared to be the only fixed (rather than portable) system that can be used specifically on pre-term infants on NHS Supply Chain.[48] This compares with clinical experience of one the authors (BS) on the cost of a

NCPAP machine being in the region of £5,000 depending on make and volume purchased. As such the £6,122 figure for the Maxblend NCPAP machine seemed reasonable and was used in the analysis.

For HHHFNC, again there are several machines on the market that could potentially be used to deliver care. The Optiflow 850 is used in the Neonatal Unit where one of the authors (BS) is based. The NHS Supply Chain[48] cost of this device is £2,755 and this figure was used in the economic analysis.

To provide a unit cost per infant of each machine, we have assumed that each machine lasts 5 years and that any service costs for machines are equal and so do not need to be included in analysis. We have then assumed that the devices are in use for 80% of the time and that each preterm infant requires oxygen support for 43.5 days which is the midpoint of the medians for HHHFNC and NCPAP reported in Manley et al 2013.[37]

Putting these assumptions into a calculation suggests the unit cost of each machine per infant supported is equal to

- the cost of the machine (£6,122 for NCPAP and £2,755 for HHHFNC)
- *divided by* 80% (the machine utilisation rate)
- *divided by 365.2.5*5* (the number of days in the 5 year lifespan on the machines)
- *multiplied by 43.5* (the number of days on average an infant requires use of NCPAP or HHHFNC)

This suggests a unit cost of £182 per preterm infant for a NCPAP machine and £82 per preterm infant for a HHHFNC machine.

5.1.3 Consumables

As was the case for capital equipment, there are a range of suppliers and potential prices available from the NHS Supply Chain[48] for NCPAP and HHHFNC consumables, (i.e. equipment that is required as part of the treatment but which is disposed of and cannot be reused, such as nasal canulae or tubing).

Given the variation in potential prices for different systems and the potential difference in quoted prices and prices paid, the weekly cost of consumables used in the economic analysis was provided directly by the neonatal unit that had provided information on the NCPAP and HHHFNC capital equipment. This approach was undertaken to ensure consistency and that

any difference in the cost of consumables was that which was really experienced in a NHS setting.

For HHHFNC, the total cost of all consumables was estimated to be £67 per week and for NCPAP was estimated to be £55 per week.

5.1.4 Adverse events

The only evidence showing a statistically significant difference in the incidence of adverse events between infants on HHHFNC and NCPAP was nasal injury as reported in Manley et al 2013.[37] It was reported that 19.1% of infants on HHHFNC had septum injury from the treatment compared to 53. 0% of infants on NCPAP. There were no cases of nasal injury that were serious enough to require corrective surgery described in any of the studies included in the clinical review.

Based on the experience of two of the review's authors who are clinicians (BS, PS), the majority, if not all, nasal injury would be relatively minor with no long-term consequences. One author was unaware of damage that had led to corrective surgery whereas another could think of only one case in 5 years where nasal damage had resulted in the requirement for corrective surgery. Although it is recognised that there can be long-term aesthetic consequences from nasal injury, we are not aware of this as an issue nor are we aware of any literature that may point to this. As such, occurrences of serious and long-term nasal injury from either HHHFNC or NCPAP were not considered in the economic analysis, although the potential for long-term consequences from nasal injury should be considered as part of the overall analysis of the two technologies.

Treatment for nasal injury whilst the preterm infant is on oxygen therapy was described as being antiseptic/antibacterial cream 2 to 3 times a day for 5 to 7 days if it is ulcerated with rest to the infant's septum.

As the preterm infant will be in a high dependency care unit, Royal College of Nursing standards state a staff ratio of one nurse to two preterm infants will be required.[56] From a nurse time perspective, application of the cream would likely form part of the care routine for a preterm infant and there is no real opportunity cost of the time taken to apply the cream as the nurse would have to be on the unit in any event. As such, including the small amount of time it would take to apply the cream by a nurse is in our opinion not appropriate. The cost also of the antiseptic cream applied could vary by the preparation. It is assumed that the cream would contain chlorhexidine. Such creams are inexpensive even if bought privately. For example, 15g of neomycin 0.5%/chlorhexidine hydrochloride 0.1% cream can be purchased

for £2.85.[57] With such low costs there is no need to be too precise when measuring the volume of cream used or on the exact cream used and price paid. As such, we have assumed that over the 5 to 7 day treatment period there is a £2 cost for the cream used.

Manley et al 2013[37] and Collins et al 2013[36] reported changes in treatment because of nasal injury. It is not whether changes in treatment protocol reflects routine clinical practice in the NHS. Due to this, and since the changes in treatment did not result in longer lengths of stay (in Manley et al 2013[37]) or statistically significantly higher re-intubation rates (in Manley et al 2013[37] and Collins et al 2013[36]), changes in treatment because of nasal injury are not considered as being economically important.

5.1.5 Resource and cost summary

The costs per preterm infant for HHHFNC and NCPAP are summarised in Table 14. The data support the clinical opinion of the authors who are clinicians (BS, PS) that there is not likely to be a statistically significant difference between the costs of therapy whether NCPAP or HHHFNC is used. The higher capital equipment costs of NCPAP are not outweighed by the higher consumable costs of HHHFNC, with HHHFNC estimated to cost £26.37 less than NCPAP per each preterm infant treated.

Table 14 Costs per preterm infant for HHHFNC and NCPAP

Resource	HHHFNC		NCPAP	
	Cost per preterm infant	Source	Cost per preterm infant	Source
Capital equipment	£82. 02	NHS Supply Chain[48] for machine cost assumption of five year lifespan of machine and 80% utilisation. Manley et al 2013[37] for number of days per preterm infant on average on oxygen	£182.28	NHS Supply Chain[48] for machine cost assumption of five year lifespan of machine and 80% utilisation. Manley et al 2013[37] for number of days per preterm infant on average on oxygen
Consumables	£416.36	Clinical advice on weekly cost and Manley et al 2013[37] for number of days per preterm infant on average on oxygen	£341.79	Clinical advice on weekly cost and Manley et al 2013[37] for number of days per preterm infant on average on oxygen
Antiseptic cream for nasal injury	£0.38	Assumption of £2 cost of cream with rates of nasal injury from Manley et al 2013[37]	£1. 06	Assumption of £2 cost of cream with rates of nasal injury from Manley et al 2013[37]
Total costs per preterm infant	£498.76		£525.13	

5.2 Analysis of uncertainty

Ordinarily in an economic evaluation, scenario analysis and deterministic and probabilistic sensitivity analysis would be used to explore parameters where there was uncertainty in the economic model.

As we carried out a cost minimisation analysis, this analysis has focussed on the resources and costs associated with two treatments that the clinical evidence suggests are equally efficacious for the primary outcomes of interest. The only notable difference between the treatments was in nasal injury as an adverse event and this has a very low cost per patient.

No distributions on any of the costs or resource use are available and so any probabilistic analysis of uncertainty is not possible. However, assumptions were made on the life expectancy of NCPAP and HHHFNC machines. As the cost saving for HHHFNC is driven by the greater capital cost of NCPAP, these assumptions were explored with sensitivity analysis.

Table 15 below shows two way sensitivity analysis of the cost differential with HHHFNC vs NCPAP as the utilisation rates vary between 20% and 100% and the lifespan varies between 2 and 10 years.

Table 15 Two way sensitivity analysis of cost differential of NCPAP vs HHHFNC as machine lifespan and utilisation rates vary

Utilisation rates	Machine lifespan (years)					
	2	4	5	6	8	10
20%	£928.60	£427.36	£327.11	£260.27	£176.73	£126.61
40%	£427.36	£176.73	£126.61	£93.19	£51.42	£26.36
60%	£260.27	£93.19	£59.78	£37.50	£9.65	-£7. 06
80%	£176.73	£51.42	£26.36	£9.65	-£11.23	-£23.77
100%	£126.61	£26.36	£6.31	-£7. 06	-£23.77	-£33.79

Note: positive values represent a cost saving of HHHFNC over NCPAP and negative values represent a cost saving of NCPAP over HHHFNC

Threshold analysis shows that if the lifespan of the machines reaches 6.8 years then HHHFNC would no longer be cost saving compared with NCPAP. A machine lifespan above 6.8 years means that NCPAP becomes the less costly option.

Changes in machine life span and utilisation rate are positively related to the number of infants that can be used by each machine and therefore negatively related to the machine unit cost per infant (i.e. lower utilisation rates/machine lifespans lead to a lower number of infants that can use a machine over its lifespan and so therefore higher unit costs of the machine per infant). Whilst these changes in unit cost will be proportionally the same for each technology, the machine cost of NCPAP is higher than with HHHFNC. As such the change in the absolute

difference in unit cost per infant between the technologies is negatively related to the utilisation rate and machine lifespan (i.e. higher utilisation rates/machine lifespans lead to a smaller absolute difference in the machine unit costs per infant between NCPAP and HHHFNC.)

It is also possible that different neonatal units pay different costs for consumables depending on the NCPAP and HHHFNC systems employed. However, what is important for our economic analysis is the size of the cost differential in consumables rather than the consumable costs per se. As costs can vary between units, two way sensitivity analysis was also undertaken to show how the differential in consumable costs together with the lifespan of the different machines changes. The difference in consumable costs±£24 (200%) is shown in Table 16; in the initial analysis there is a cost difference of -£12 per week (consumable cost with NCPAP is £55 and with HHHFNC is £67).

The results presented in Table 16 demonstrate that the main finding of the economic analysis, i.e. HHHFNC is cost saving compared to NCPAP, is relatively sensitive to changes in the difference in weekly consumable costs of the two technologies. Assuming a 5 year lifespan for equipment as in the initial analysis, if the difference in consumable prices rises approximately by 35% from £12 to £16.24 then HHHFNC will no longer be cost saving compared to NCPAP.

Table 16 Two way sensitivity analysis of cost differential of NCPAP vs HHHFNC

Weekly consumable cost difference (NCPAP-HHHFNC) per preterm infant	**Machine lifespan (years)**					
	2	**4**	**5**	**6**	**8**	**10**
-£12	£325.88	£200.56	£175.50	£158.79	£137.91	£125.38
£0	£251.30	£125.99	£100.93	£84.22	£63.34	£50.80
£12	£176.73	£51.42	£26.36	£9.65	-£11.24	-£23.77
£24	£102.16	-£23.15	-£48.21	-£64.92	-£85.81	-£98.34
£36	£27.59	-£97.72	-£122.78	-£139.49	-£160.38	-£172.91

Note: positive values represent a cost saving of HHHFNC over NCPAP and negative values represent a cost saving of NCPAP over HHHFNC

6 DISCUSSION

6.1 Principal findings

We have conducted a systematic review of the literature to summarise the clinical effectiveness of HHHFNC vs usual care for preterm infants. Usual care was considered to consist of NCPAP, oxygen or NIPPV with five RCTs[32,36-38,49,51] comparing HHHFNC with NCPAP and one RCT[52] with NIPPV. Evidence was derived from four RCTs[36-38,49] for effectiveness of treatment following ventilation(primary analysis) and three RCTs[32,51,52] for effectiveness following no prior ventilation (secondary analysis) including a crossover trial by Klingenberg et al 2014.[51] The quality of the studies included in the primary analysis of treatment following ventilation could be considered to be superior to that of the studies included in the secondary analysis of treatment with no prior ventilation.

In the primary analysis, the primary outcome for our systematic review was treatment failure; we defined treatment failure to be the need for re-intubation within 72 hours, within 7 days or ever (i.e. time period not specified). There were proportionally fewer cases of re-intubation in the HHHFNC arm than in the NCPAP arm in all four RCTs[36-38,49] of preterm infants treated following ventilation although no statistically significant difference was found between treatment arms, either as reported in the individual studies[36,37,49] or in the meta-analysis of these three trials reporting re-intubation within 7 days. Two RCTs[36,37] used composite outcomes to define extubation failure/treatment failure rather than simply defining it as the need for re-intubation. Interestingly, despite the re-intubation rate being lower for those treated with HHHFNC than those treated with NCPAP, the largest RCT by Manley et al 2013[37] reported a higher rate of treatment failure for HHHFNC compared with NCPAP.

Extubation failure/treatment failure was the only outcome that was considered in a subgroup analysis where two trials[36,37] considered this outcome by gestational age. In our review protocol, we had proposed conducting subgroup analyses of gestational age prior to and from 30 weeks but the included studies reported these prior to and from 26 weeks[37] and prior to and from 28 weeks.[36] Unsurprisingly, infants with extremely low gestational age appeared to have higher rates of treatment failure in the individual studies[36,37] although the difference between subgroups was not statistically significant. The subgroup findings must be treated with extreme caution and can only be considered exploratory because different gestational age thresholds were used to define subgroups in the two studies and because extubation failure/treatment failure was also defined differently in the two studies;[36,37] as discussed above, both these studies[36,37] used composite outcomes as opposed to our definition, which was simply the need for re-intubation.

In the secondary analysis, with regard to preterm infants who had received no prior ventilation, treatment failure was defined by the need for endotracheal ventilation[52] or by a composite outcome.[32] Neither study[32,52] reported a statistically significant difference in treatment failure rates for HHHFNC vs NCPAP[32] or HHHFNC vs NIPPV.[52]

Secondary efficacy outcomes for the comparison of HHHFNC vs NCPAP were only reported in three studies;[36,37,38] all three studies were included in the primary analysis of treatment following ventilation. Meta-analyses found that the findings for both outcomes are in the direction of favouring HHHFNC but no statistically significant differences were found. The majority of other relevant secondary outcome data (e.g. days on mechanical support and length of hospital stay) also suggested an improvement for HHHFNC over NCPAP but these were not reported by two or more trials and no statistically significant differences were reported between arms.[36,37]

The authors of the study by Kugelman et al 2014[52] reported relevant secondary outcomes for HHHFNC vs NIPPV. In this study, no preterm infant had received prior ventilation (secondary analysis). Although the findings from this small study[52] appeared to marginally favour HHHFNC over NIPPV in terms of days on mechanical support and length of hospital stay and marginally favour NIPPV over HHHFNC in terms of days on oxygen support and days to full feeds, none of the between-arm differences were statistically significant.

Adverse event data for the comparison of HHHFNC vs NCPAP were only available from two studies[36,37] that were included in the primary analysis (preterm infants treated following ventilation). Importantly, nasal trauma was statistically significantly lower in the HHHFNC arm in the largest study by Manley et al 2013.[37] Meta-analysis of nasal trauma leading to change of treatment also showed statistically significantly fewer infants changing treatment from HHHFNC than with NCPAP. With the exception of apnoea and acidosis where mixed results were reported in the individual studies, pneumothorax, IVH (Grade 3+), NEC and acidosis appeared to be less common with HHHFNC than NCPAP but differences were not statistically significant.

Adverse event data for the comparison of HHHFNC vs NIPPV were only available from one study[52] that was included in the secondary analysis (patients with no prior ventilation). Generally, the adverse event profile appeared to marginally favour NIPPV over HHHFNC but there were no between-arm statistically significant differences.

Klingenberg et al 2014[51] reported outcomes from the smallest RCT included in our review (n=20) and was the only study to report quality of care outcomes. Although there were no

statistically significant differences between arms in terms of noise or neonatal pain and discomfort, there were statistically significant differences between study arms in terms of parental preferences for HHHFNC over NCPAP. Parental preferences were based on the belief that contact and interaction with the infant, participation in care and the satisfaction of their infant were all improved with HHHFNC compared with NCPAP. In this study,[51] preterm infants were not supposed to have been treated following ventilation although a minority of infants had in fact received prior ventilation (n=7; 30%).

In summary, therefore, following ventilation (primary analysis), there is a lack of convincing evidence for a difference in the need for re-intubation, BPD or death between HHHFNC and NCPAP; there is however some evidence for a decrease in nasal trauma. For preterm infants with no prior ventilation (secondary analysis), there is some suggestive evidence for parental preferences for HHHFNC over NCPAP but overall, an absence of any consistent evidence to suggest that HHHFNC is superior or inferior to usual care.

The lack of evidence supporting the clinical effectiveness of HHHFNC compared to usual care, or vice versa, precluded us from being able to conduct a cost utility or cost effectiveness analysis for either HHHFNC vs usual care following ventilation or for HHHFNC vs usual care with no prior ventilation. Instead, we were only able to conduct a cost minimisation analysis. Given the absence of evidence for infants who had no prior ventilation, cost-minimisation analysis was only performed for infants who had been treated following ventilation.

The results of our cost minimisation analysis suggest that HHHFNC would be cost saving over NCPAP for infants who have been treated following ventilation. However, the results of our economic analysis are sensitive to both the size of the machine lifespan and utilisation of equipment. When estimating and valuing resources for these two items in the analysis, it was necessary to make assumptions and so there is a degree of uncertainty associated with the results. If the HHHFNC and NCPAP machines last, on average, longer than 6.8 years and assuming an 80% utilisation rate for equipment, NCPAP is likely to become the less costly of the two technologies. Whilst the cost differential of consumables has a higher degree of certainty than the lifespan of the machines, since costs have been derived from an individual neonatal unit, it is not known how representative this difference might be across units in the UK. If HHHFNC consumables cost £16.24 or more than NCPAP consumables per week then NCPAP will become the less costly of the two technologies. Hence, whilst the best estimate from the economic analysis is that HHHFNC will cost just over £26 less per infant than NCPAP, the cost saving could be as high as £326 per infant with HHHFNC over NCPAP or NCPAP could save £173 compared to HHHFNC, depending on differences in the lifespan of machines, utilisation rates and cost differences in consumables.

In reality, the actual total cost differential between infants on either technology is relatively insignificant compared to the cost per day in a neonatal intensive care ward, regardless of the assumptions employed in the analysis. The NHS Reference Cost[47] for a day in a neonatal high dependency unit in 2013/14 was £839 per day or just under £36,500 for a 43.5 day stay. The cost of either treatment with HHHFNC or NCPAP during this period therefore costs less than 2% of the total care whilst the infant requires oxygen. The economic analysis therefore shows that cost does not seem to be a paramount consideration when deciding between the two technologies.

6.2 Similarities and differences with previous systematic reviews and meta-analyses

We are aware of two other published meta-analyses of HHHFNC vs NCPAP; one published alongside a systematic review by Daish and Badurdeen 2014[35] and another which accompanies a review of the literature by DeMauro et al 2014.[58] Both of these meta-analyses include the same three trials.[36-38] In addition, we are aware of an unpublished "pooled analysis" of HFNC vs NCPAP which has only been presented as an abstract by Rotta et al 2014[59] and which includes four trials; as data have only been presented in abstract form for this unpublished analysis,[59] it is unclear which trials were included and if the HFNC described in all four trials is heated.

All analyses reported no statistically significant differences between arms for extubation failure, although the RR exceeded one, suggesting the treatment effect may be in favour of NCPAP (RR 1.12, 95% CI 0.85 to 1.47[35] and RR 1. 05, 95% CI 0.79 to 1.39[58] in the published meta-analyses respectively; RR1.17, 95% CI0.90 to 1.51[59] in the unpublished analysis). Although our meta-analysis also reported no statistically significant differences, the RR was less than one suggesting the treatment effect may be in favour of HHHFNC (RR 0.76, 95% CI 0.54 to 1. 09).

The reasons for marginal differences in results arise from including different studies in the meta-analyses and from differences in how data were pooled in each of the meta-analyses. It is unclear from the unpublished abstract which four trials were included in the pooled analysis by Rhotta et al.[59] However, both the published meta-analyses[35,58] and our meta-analysis included three trials, including the same two Australian RCTs.[36,37] Whereas Daish and Badurdeen 2014[35] and DeMauro et al 2014[58] also included the US study by Yoder et al 2013,[38] we excluded this study from our meta-analysis since extubation failure reported for the subgroup of preterm infants was for re-intubation within 72 hours. Data from a subgroup analysis of preterm infants from the Chinese study[49] were also included in our meta-analysis but not in the others.

Crucially, we also used a standard definition of treatment failure across all studies included in our meta-analysis (re-intubation rates within 7 days). The other two published meta-analyses[35,58] however used the original study definitions of treatment failure/extubation failure which differed across all three studies[36-38] and importantly, were measured over different time points (within 7 days in the two Australian studies[36,37] and within 72 hours in the study by Yoder et al).[38] Finally, our meta-analysis included data describing only preterm infants who had received treatment following ventilation; the inclusion of the study by Yoder et al[38] in the other two published meta-analyses[35,58] resulted in a mixed population of infants, some of whom had received treatment following ventilation and some of whom had received no prior ventilation.

Differences in the choice of studies that were included in the meta-analyses and differences in how the data were pooled and analysed is reflected in the measures of statistical heterogeneity reported. A moderate level of statistical heterogeneity was identified for the meta-analysis of treatment failure (I^2=56% and Chi^2 test, p=0.11) by Daish and Badurdeen 2014.[35] Greater and statistically significant (p<0.10) levels of heterogeneity (I^2=59.5% and Chi^2 test, p=0.085) were reported in the meta-analysis by DeMauro et al 2014.[58] Our meta-analysis reported no statistical heterogeneity at all (I^2=0% and Chi^2 test, p=0.84).

As per our meta-analysis, Daish and Badurdeen 2014[35] also pooled data for BPD and found no statistically significant differences between treatment arms. Data were pooled from the same three RCTs[36-38] in both our meta-analysis and in the analysis conducted by Daish and Badurdeen 2014.[35] Hence, the findings of the meta-analyses were identical (RR 0.92, 95% CI 0.72 to 1.17) with no statistical heterogeneity evident (I^2=0% and Chi^2 test, p=0.87). In this instance, it should be noted that the inclusion of the study by Yoder et al[38] did result in a mixed population of infants in our meta-analysis, some of whom had received treatment following ventilation and some of whom had received no prior ventilation.

No previous meta-analysis of death has been previously published. The meta-analysis we conducted included only two trials[36,37] and again found no statistically significant differences between arms. However, as perhaps expected from a meta-analysis of only two trials with few events, CIs were wide (RR 0.66, 95% CI 0.24 to 1.82). No significant statistical heterogeneity between studies was reported (I^2=0% and Chi^2 test, p=0.42).

Prior to the publication of the meta-analyses by Daish and Badudeen[35] and de Mauro,[58] a Cochrane review[30] included narrative results from a systematic review of the effectiveness of HFNC (as opposed to HHHFNC) from four RCTs.[31-34] Four different analyses were presented, with one study included in each analysis: HFNC vs NCPAP for preterm infants who had received prior ventilation,[31] HFNC vs NCPAP with no prior ventilation,[32] HHHFNC vs 'standard'

HFNC[34] and a comparison of two different brands of equipment for HHHFNC.[33] It was not possible to conduct meta-analyses given each analysis only included one study. The review authors concluded that there was insufficient evidence to establish the safety or effectiveness of HFNC and that HFNC may be associated with a higher rate of re-intubation than NCPAP when used after ventilation. It should be noted that this latter conclusion was drawn from one study[34] comparing HFNC (not HHHFNC) to NCPAP and reporting a significantly worse outcome for HFNC (RR 4. 0, 95% CI 1.33 to 12. 05). No statistical differences were reported for HHHFNC vs HFNC in the study by Woodhead et al 2006[34] which examined re-intubation rates within the first 24hours. However, the study was small (n=40) and only two infants who received standard HFNC as opposed to HHHFNC required re-intubation, the data therefore suggest that HHHFNC may be superior to HFNC. Furthermore, infants were statistically significantly more likely to have a normal appearance of their nasal mucosa in the HHHFNC arm than in the HFNC arm in this study[34] ($p < 0.0005$). This arguably highlights the importance of distinguishing between HHHFNC and HFNC.

6.3 Strengths and limitations

One of the strengths of our systematic review is that we have limited the inclusion of our evidence to RCTs in which evidence has been presented for only preterm infants, as opposed to a mixed population of preterm and term infants. We have also limited our review to include only studies where it was clear that the intervention was HHHFNC; HFNC that is neither heated or humidified is now considered by many review authors[35,58] to be inconsistent with clinical practice. Finally, we have considered the clinical effectiveness of HHHFNC vs usual care both following ventilation and in preterm infants who have received no prior ventilation. This distinction is of importance given that the European Consensus Guidelines[4] recommend that NCPAP should be the preferred option for the stabilisation of preterm infants where possible, ventilation being preferred for less mature infants.

Whist we consider that limiting the inclusion of studies to only those where it was clear HFNC was heated to be a strength, this approach may also be considered to be a limitation; study authors do not always explicitly state that the interventions they are studying are heated. Therefore, it is possible we have excluded some studies that we should have included. Certainly, we have excluded three abstracts by Collins 2012[60] and Collins et al 2012[61,62] that report on the same study that we have included.[36] This is because it was not stated in these three abstracts[60-62] that the intervention was heated. Excluding these abstracts was however of no importance because we did include the fully published study with the relevant results. It does however suggest there is a need for common and consistent terminology when describing whether HFNC is heated or humidified. Of the other six papers[27,31,63-66] we excluded

for not being heated, three[27,31,63] explicitly stated they were unheated meaning three other papers[64-66] (of two studies, one[64] reported only as an abstract) may actually have been studies of HHHFNC.

An advantage of the data available for our primary analysis of infants who have received treatment following ventilation is that there is an element of consistency in how outcomes have so far been reported. This is particularly true for re-intubation, which has been reported within 7 days, enabling comparisons across trials, and also for BPD and death. However, it still remains unclear if re-intubation within 7 days is the optimal outcome and arguably, re-intubation should be reported at three different time-points, within 72 hours, within 7 days and ever. The only study we are aware of that has reported re-intubation at different time-points is the study by Yoder et al 2013.[38] Unfortunately, the findings at these two time periods are for a mixed population of preterm, term and post-term infants. This study[38] did however provide a subgroup analysis for some, but not all, preterm infants (gestational age <32 weeks [34.7% of the study population] as opposed to <37 weeks) but only for re-intubation within 72 hours. We contacted the principal author of the Yoder et al 2013[38] study to request further information about all preterm infants but to date we have not received a reply. It should also be noted that the study by Yoder et al 2013[38] also included infants who had received no prior ventilation alongside those who had been ventilated. However it is unclear how many of the preterm infants had received prior ventilation.

A limitation of our review is the lack of evidence regarding the quality of care delivered in the clinical studies. It is often cited that HHHFNC is preferred over NCPAP by staff and parents of preterm infants since it enables infants to be more easily handled and cared for than does NCPAP.[15,20,29] Only one of the RCTs[51] we identified examined outcomes relating to quality of care and data were available from only 20 participants and hence the generalisability of the findings should be treated with caution. Nevertheless, this study[51] did report that parents preferred HHHFNC over NCPAP. In terms of neonatal pain and discomfort and noise, there were no statistically significant differences between HHHFNC and NCPAP. However, RCTs are not necessarily the best types of study to evaluate such outcomes, with qualitative studies and surveys probably being better suited to studying such outcomes. For example, it would be illustrative to know whether improved parental contact which was reported with HHHFNC over NCPAP by Klingenberg et al 2014[51] included an increase in the amount of time spent in 'Kangaroo Care'. 'Kangaroo Care' entails skin to skin care between mother and infant. Previous studies have reported this practice to be beneficial to the development of infants[67,68] and to reduce mortality.[69,70] Nonetheless, the inclusion of outcomes such as those measuring parental preferences as secondary outcomes in RCTs is informative.

Another limitation of the evidence base is that it was not possible for investigators to blind health care staff or study participants to the treatment that they delivered or received in any of the RCTs. This is commonly cited as a major weakness of clinical trials[44] but when comparing an intervention such as HHHFNC to an intervention such as NCPAP, such blinding would be impossible to employ; realistically, only those responsible for the analysis of the results to be blinded. Only one study (included in the primary analysis) reported that assessors were blinded to treatment allocation.[36]

Arguably the largest limitation of our review, however, is the lack of published RCT data from relatively large sized populations where HHHFNC is compared to usual care. The lack of evidence is perhaps most stark when we present the secondary analysis of our review, assessing the effectiveness of interventions in preterm infants with no prior ventilation. As discussed, there were only 124 preterm infants from the three relevant trials[32,51,52] (although as also highlighted, seven of the participants in one trial[51] had in fact received treatment following ventilation); this figure (n=124)is smaller number than the number of participants in the smallest trial(n=132)[36] of preterm infants who had received treatment following ventilation (primary analysis). However, even for the primary analysis of those who received treatment following ventilation, more RCT evidence is required.

Finally, the lack of evidence describing treatment failure across trials and from our meta-analysis has also precluded us from being able to conduct a cost effectiveness or cost utility analysis, another limitation of our research. Instead we have only been able to conduct a cost minimisation analysis which is prone to levels of uncertainties around the costs and lifespan of different HHHFNC and NCPAP devices and associated consumables.

Uncertainty in the evidence base is evident from comparing the (statistically non-significant) findings for treatment failure from our meta-analysis to those of other authors;[35,58,59] the results of our meta-analysis suggest that the treatment effect may be in favour of HHHFNC over NCPAP whereas other authors[35,58,59] suggest the opposite effect. However, as discussed, other authors use different definitions of treatment failure and include mixed populations whereas we have limited the data in our meta-analysis to re-intubation within 7 days in a population limited to preterm infants who have previously been ventilated.

7 CONCLUSIONS

To date, there is a lack of convincing evidence to suggest that HHHFNC is superior or inferior to usual care, in particular NCPAP. This is true for preterm infants who have received treatment following ventilation and for those who have received no prior ventilation. The results of one small trial suggest that parents do however prefer HHHFNC to NCPAP.

There is also uncertainty as to whether HHHFNC can be considered cost effective because the lack of clinical evidence precluded us from conducting an analysis of cost utility or cost effectiveness. The results of our cost minimisation analysis suggest that HHHFNC may cost less than NCPAP but there is much uncertainty around the assumptions employed and it is quite possible that HHHFNC costs more than NCPAP. As the overall cost of either HHHFNC or NCPAP is small compared to the cost of preterm neonatal care as a whole -and the potential cost differences between the systems are even smaller - the financial case for HHHFNC over NCPAP or vice versa is not compelling.

More RCT evidence comparing HHHFNC to usual care (in particular, NCPAP) is required to inform the evidence base for both the clinical and cost effectiveness for HHHFNC. Ideally, a large and adequately powered trial is required to compare HHHFNC to NCPAP in preterm infants previously ventilated and for preterm infants who have not received prior ventilation. Based on available evidence from meta-analysis suggesting that the majority of outcomes (including re-intubation, BPD, death and many important adverse events) are in the direction of favouring HHHFNC, it is possible that further research could include evidence derived from a non-inferiority trial.

7.1 Recommendations for future research

Based on the available evidence to date, the following research recommendations are made:

1. There is a need for more RCT evidence comparing HHHFNC to usual care including, but not limited to, a comparison with NCPAP. Endpoints should include (re-)intubation, BPD, death and adverse events. In particular, there is a need for research into the need for (re-)intubation at both 72 hours and 7 days, both outcomes which should ideally be measured in individual trials. This is because to date, trials have utilised both outcome measures and results with respect to efficacy may differ at different follow-up times (as preterm infants may remain extubated for first 72 hours but then get re-intubated at 7 days).

2. Ideally, studies should only include preterm infants and where infants may have received either previous ventilation or no prior ventilation, RCTs should be stratified for these factors and subgroup analyses conducted.

3. Given the evidence to date has not shown HHHFNC to be statistically superior to NCPAP but the direction of the treatment effect appears to favour HHHFNC over NCPAP, a non-inferiority trial may be of particular value. As the primary outcome, BPD may be particularly clinically important and meaningful since it has been shown to be associated with long-term disability and morbidities. The sample size for such a trial would then depend on the significance level and desired statistical power as well as the rate of BPD and preferred non-inferior margin, as detailed in the Appendices (section 9.4, Table 23).

4. There is also a need for more research on quality of care in terms of staff and parental preferences and infant comfort. While these outcomes are arguably best researched via qualitative studies and surveys, including such outcomes in future RCTs will be informative.

8 REFERENCES

1. de Winter JP, de Vries MA, Zimmermann LJ. Clinical practice: noninvasive respiratory support in newborns. Eur J Pediatr. 2010; 169(7):777-82.
2. Miall L, Wallis S. The management of respiratory distress in the moderately preterm newborn infant. Arch Dis Child Educ Pract Ed. 2011; 96(4):128-35.
3. Pramanik A. Respiratory Distress Syndrome 2012; Available from: http://emedicine.medscape.com/article/976034-overview#aw2aab6b2b4aa (Accessed 03/12/2014).
4. Sweet DG, Carnielli V, Greisen G, Hallman M, Ozek E, Plavka R*, et al.* European consensus guidelines on the management of neonatal respiratory distress syndrome in preterm infants--2013 update. Neonatology. 2013; 103(4):353-68.
5. Kamath BD, MacGuire ER, McClure EM, Goldenberg RL, Jobe AH. Neonatal Mortality From Respiratory Distress Syndrome: Lessons for Low-Resource Countries. Pediatrics. 2011; 127(6):1139-46.
6. Malloy MH, Hartford RB, Kleinman JC. Trends in mortality caused by respiratory distress syndrome in the United States, 1969-83. Am J Public Health. 1987; 77(12):1511-4.
7. Lee K, Khoshnood B, Wall SN, Chang Y, Hsieh HL, Singh JK. Trend in mortality from respiratory distress syndrome in the United States, 1970-1995. J Pediatr. 1999; 134(4):434-40.
8. Malloy MH, Freeman DH. Respiratory distress syndrome mortality in the United States, 1987 to 1995. J Perinatol. 2000; 20(7):414-20.
9. Marlow N. Keeping up with outcomes for infants born at extremely low gestational ages. JAMA Pediatr. 2015; 169(3):207-8.
10. Office for National Statistics. Gestation-specific Infant Mortality, 2012. 2014; Available from: http://www.ons.gov.uk/ons/rel/child-health/gestation-specific-infant-mortality-in-england-and-wales/2012/index.html (Accessed 09/12/2014).
11. Roberts D, Dalziel S. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev. 2006; (3):Cd004454.
12. Mahmoud RA, Roehr CC, Schmalisch G. Current methods of non-invasive ventilatory support for neonates. Paediatr Respir Rev. 2011; 12(3):196-205.
13. Kugelman A. Optimal management of neonatal lung diseases using current technologies. Pediatr Pulmonol. 2014; 49:S26-S8.
14. Chowdhury O, Wedderburn CJ, Duffy D, Greenough A. CPAP review. Eur J Pediatr. 2012; 171(10):1441-8.
15. de Klerk A. Humidified high-flow nasal cannula: is it the new and improved CPAP? Adv Neonat Care. 2008; 8(2):98-106.
16. De Paoli Antonio G, Davis Peter G, Faber B, Morley Colin J. Devices and pressure sources for administration of nasal continuous positive airway pressure (NCPAP) in preterm neonates. Cochrane Database Syst Rev. 2008; (1):CD002977.
17. Davis PG, Henderson-Smart DJ. Nasal continuous positive airways pressure immediately after extubation for preventing morbidity in preterm infants. Cochrane Database Syst Rev. 2003; (2):CD000143.

18. Armfield M, West G. Use of Vapotherm for respiratory support with neonates. Paediatr Nurs. 2009; 21(1):27-30.

19. Jane Pillow J. Which continuous positive airway pressure system is best for the preterm infant with respiratory distress syndrome? Clin Perinatol. 2012; 39(3):483-96.

20. NHS Forth Valley Women & Children's Unit. Humidified High Flow Nasal Cannulae Guideline, Version 1. 2011; Available from: http://www.nhsforthvalley.com/__documents/qi/ce_guideline_wcdneonatal/humidifiedhighflownasalcannulaeguideline.pdf (Accessed 02/12/2014).

21. Cherian S, Morris I, Evans J, Kotecha S. Oxygen therapy in preterm infants. Paediatr Respir Rev. 2014; 15(2):135-41.

22. Bhandari V. The potential of non-invasive ventilation to decrease BPD. Semin Perinatol. 2013; 37(2):108-14.

23. Bhandari V. Nasal intermittent positive pressure ventilation in the newborn: review of literature and evidence-based guidelines. J Perinatol. 2010; 30(8):505-12.

24. Garg S, Sinha S. Non-invasive Ventilation in Premature Infants: Based on Evidence or Habit. J Clin Neonatol. 2013; 2(4):155-9.

25. Bhandari V. Noninvasive respiratory support in the preterm infant. Clin Perinatol. 2012; 39(3):497-511.

26. Dani C, Pratesi S, Migliori C, Bertini G. High flow nasal cannula therapy as respiratory support in the preterm infant. Pediatr Pulmonol. 2009; 44(7):629-34.

27. Sreenan C, Lemke RP, Hudson-Mason A, Osiovich H. High-flow nasal cannulae in the management of apnea of prematurity: A comparison with conventional nasal continuous positive airway pressure. Pediatrics. 2001; 107(5):1081-3.

28. Ojha S, Gridley E, Dorling J. Use of heated humidified high-flow nasal cannula oxygen in neonates: a UK wide survey. Acta Paediatr. 2013; 102(3):249-53.

29. Hough JL, Shearman AD, Jardine LA, Davies MW. Humidified high flow nasal cannulae: current practice in Australasian nurseries, a survey. J Paediatr Child Health. 2012; 48(2):106-13.

30. Wilkinson D, Andersen C, O'Donnell Colm PF, De Paoli Antonio G. High flow nasal cannula for respiratory support in preterm infants. Cochrane Database Syst Rev. 2011; (5):CD006405.

31. Campbell DM, Shah PS, Shah V, Kelly EN. Nasal continuous positive airway pressure from high flow cannula versus Infant Flow for Preterm infants. J Perinatol. 2006; 26(9):546-9.

32. Nair G, Karna P. Comparison of the effects of vapotherm and nasal CPAP in respiratory distress in preterm infants. PAS. 2005; 1(No:).

33. Miller SM, Dowd SA. High-flow nasal cannula and extubation success in the premature infant: a comparison of two modalities. J Perinatol. 2010; 30(12):805-8.

34. Woodhead DD, Lambert DK, Clark JM, Christensen RD. Comparing two methods of delivering high-flow gas therapy by nasal cannula following endotracheal extubation: a prospective, randomized, masked, crossover trial. J Perinatol. 2006; 26(8):481-5.

35. Daish H, Badurdeen S. Question 2: Humidified heated high flow nasal cannula versus nasal continuous positive airway pressure for providing respiratory support following extubation in preterm newborns. Arch Dis Child. 2014; 99(9):880-2.

36. Collins CL, Holberton JR, Barfield C, Davis PG. A randomized controlled trial to compare heated humidified high-flow nasal cannulae with nasal continuous positive airway pressure postextubation in premature infants. J Pediatr. 2013; 162(5):949-54.e1.

37. Manley BJ, Owen LS, Doyle LW, Andersen CC, Cartwright DW, Pritchard MA*, et al.* High-flow nasal cannulae in very preterm infants after extubation. N Engl J Med. 2013; 369(15):1425-33.

38. Yoder BA, Stoddard RA, Li M, King J, Dirnberger DR, Abbasi S. Heated, humidified high-flow nasal cannula versus nasal CPAP for respiratory support in neonates. Pediatrics. 2013; 131(5):e1482-90.

39. Desai P, Shetty S, Singh N, Kennea N. Current practice regarding the use of humidified high flow nasal cannulae (HHFNC) in uk neonatal units. Arch Dis Child. 2012; 97:A116.

40. Hochwald O, Osiovich H. The use of high flow nasal cannulae in neonatal intensive care units: Is clinical practice consistent with the evidence? J Neonatal Perinatal Med. 2010; 3(3):187-91.

41. Liverpool Women's NHS Foundation Trust. High Flow Therapy (HFT) (version 1-NICU204). 2014; Available from: http://www.liverpoolwomens.nhs.uk/Library/health_professionals/Neonatal_policy_library/High_Flow_Oxygen_Guideline.pdf (Accessed 02/12/2014).

42. Centre for Reviews and Dissemination (CRD). CRD's guidance for undertaking reviews in healthcare: Systematic Reviews (3rd Edition). York: CRD, University of York 2008.

43. Covidence Service Partners. Covidence. Melbourne, Australia 2014; Available from: https://www.covidence.org/ (Accessed 05/01/2015).

44. Higgins J P, T ., Green S. Cochrane handbook for systematic reviews of interventions. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration; 2011; Available from: www.cochrane-handbook.org (Accessed 17/12/2014).

45. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003; 327(7414):557-60.

46. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997; 315(7109):629-34.

47. Department of Health. NHS Reference costs: financial year 2013 to 2014. London 2015; Available from: https://www.gov.uk/government/publications/nhs-reference-costs-2013-to-2014 (Accessed 30/04/2015).

48. NHS Supply Chain. Available from: https://www.supplychain.nhs.uk/ (Accessed 16/04/2015).

49. Collaborative Group for the Multicenter Study on Heated Humidified High-flow Nasal Cannula V. [Efficacy and safety of heated humidified high-flow nasal cannula for prevention of extubation failure in neonates]. Zhonghua Er Ke Za Zhi. 2014; 52(4):271-6.

50. Collins CL, Barfield C, Horne RS, Davis PG. A comparison of nasal trauma in preterm infants extubated to either heated humidified high-flow nasal cannulae or nasal continuous positive airway pressure. Eur J Pediatr. 2014; 173(2):181-6.

51. Klingenberg C, Pettersen M, Hansen EA, Gustavsen LJ, Dahl IA, Leknessund A*, et al.* Patient comfort during treatment with heated humidified high flow nasal cannulae versus nasal continuous positive airway pressure: A randomised cross-over trial. Arch Dis Child Fetal Neonatal Ed. 2014; 99(2):F134-f7.

52. Kugelman A, Riskin A, Said W, Shoris I, Mor F, Bader D. A randomized pilot study comparing heated humidified high-flow nasal cannulae with NIPPV for RDS. Pediatr Pulmonol. 2014.

53. Ma L, Liu CQ, Gu XH, Liu XJ. The efficacy and safety of heated humidified high-flow nasal cannula for prevention of extubation failure in neonates. J Matern Fetal Neonatal Med. 2014; 27:208-9.

54. Manley BJ, Owen LS, Doyle LW, Andersen CC, Cartwright DW, Pritchard MA*, et al.* High-flow nasal cannulae vs. nasal cpap for post-extubation respiratory support of very preterm infants: A multicentre, randomised non-inferiority trial. J Paediatr Child Health. 2013; 49:41.

55. Debillon T, Zupan V, Ravault N, Magny J, Dehan M, Abu-Saad H. Development and initial validation of the EDIN scale, a new tool for assessing prolonged pain in preterm infants. Archives of Disease in Childhood Fetal and Neonatal Edition. 2001; 85(1):F36-F41.

56. Royal College of Nursing. Defining staffing levels for children and young people's services. London: Royal College of Nursing; 2013; Available from: http://www.rcn.org.uk/__data/assets/pdf_file/0004/78592/002172.pdf (Accessed 16/04/2015).

57. Clarity Pharmacy. Neomycin 0.5% / Chlorhexidine hydrochloride 0.1% cream Available from: http://www.claritypharmacy.com/product.php/14923/86/neomycin_0_5___chlorhexidine_hydrochloride_0_1__cream (Accessed 16/04/2015).

58. DeMauro SB, Millar D, Kirpalani H. Noninvasive respiratory support for neonates. Curr Opin Pediatr. 2014; 26(2):157-62.

59. Rotta A, Speicher R, Shein S, Speicher D.753: High flow nasal cannula therapy in preterm infants: A pooled analysis. Crit Care Med. 2014; 42 (Suppl 1):A1541.

60. Collins C. High flow nasal cannulae cause less nasal trauma compared to nasal continuous positive airway pressure in preterm infants. Arch Dis Child. 2012; 97:A116-A7.

61. Collins C, Holberton JR, Barfield C, Davis PG. High flow nasal cannulae (HFNC) or nasal continuous positive airway pressure (NCPAP) post-extubation in premature infants? A randomised controlled trial. Arch Dis Child. 2012; 97:A38-A9.

62. Collins CL, Holberton JR, Barfield C, Davis PG. Randomised controlled trial of high flow nasal cannulae (HFNC) versus nasal continuous positive airway pressure (NCPAP) post-extubation in preterm infants <32 weeks' gestation. J Paediatr Child Health. 2012; 48:66-7.

63. Campbell DM, Shah P, Shah V, Kelly E. High flow nasal cannula CPAP versus infant flow nasal CPAP in newly-extubated neonates < 1250 g (abstract). Pediatr Res. 2004; 56:472a.

64. Hua C, McEwan A, Callander I. Hiflow compared to cpap from 30 weeks gestation at liverpool hospital. J Paediatr Child Health. 2013; 49:131.

65. Iranpour R, Sadeghnia A, Hesaraki M. High-flow nasal cannula versus nasal continuous positive airway pressure in the management of respiratory distress syndrome. J Isfahan Med Sch. 2011; 29(143).

66. Iranpour R, Sadeghnia A, Hesaraki M. High-flow nasal cannula versus nasal continuous positive airway pressure in the management of respiratory distress syndrome. Arch Dis Child. 2012; 97:A115-A6.

67. Lawn JE, Mwansa-Kambafwile J, Horta BL, Barros FC, Cousens S. 'Kangaroo mother care' to prevent neonatal deaths due to preterm birth complications. Int J Epidemiol. 2010; 39 Suppl 1:i144-54.

68. Conde-Agudelo A, Belizan JM, Diaz-Rossello J. Kangaroo mother care to reduce morbidity and mortality in low birthweight infants. Cochrane Database Syst Rev. 2011; (3):CD002771.

69. Vesel L, Bergh AM, Kerber KJ, Valsangkar B, Mazia G, Moxon SG*, et al.* Kangaroo mother care: a multi-country analysis of health system bottlenecks and potential solutions. BMC Pregnancy Childbirth. 2015; 15 Suppl 2:S5.

70. Kc A, Wrammert J, Nelin V, Ewald U, Clark R, Malqvist M. Level of mortality risk for babies born preterm or with a small weight for gestation in a tertiary hospital of Nepal. BMC Public Health. 2015; 15(1):877.

71. Al-Alaiyan S. Erratum: A randomized controlled trial to compare heated humidified high-flow nasal cannulae with nasal continuous positive airway pressure postextubation in premature infants (Journal of Clinical Neonatology (2013) 2: 2). J Clin Neonatol. 2014; 3(4):241.

72. Andaya SC, Ramanathan R, Sardesai S, Cayabyab R, Garingo A, Seri I. Nasal respiratory support in preterm infants: A novel means of delivering time-cycled, pressure and flow limited intermittent mandatory ventilation via nasal cannula. J Investig Med. 2010; 58 (1):226.

73. Archer N, Cottis H, Ball S, Mills K, Hilliard T. A pilot randomised controlled study of oxygen delivery via vapotherm in infants with moderately severe acute bronchiolitis [Abstract]. 2009; [P4002]]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/731/CN-00758731/frame.html (Accessed 12/01/2015).

74. Beltramo F, Romero R, Chandler B, Soliz A. Successful extubation in low birth weight infants: A comparison of continuous positive airway pressure (CPAP) versus Vapotherm. Pediatric Academic Societies Annual Meeting. 2008; Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/469/CN-00838469/frame.html (Accessed 12/01/2015).

75. Bushell T, McHugh C, Meyer MP. A Comparison of two nasal continuous positive airway pressure interfaces - A randomized crossover study. J Neonatal Perinatal Med. 2013; 6(1):53-9.

76. Ciuffini F, Colnaghi M, Lavizzari A, Mercadante D, Musumeci S, Mosca F. [Therapy with high-flow nasal intubation in preterm infants]. Pediatr Med Chir. 2013; 35(3):118-24.

77. Daish H, Badurdeen S. Heated humidified high-flow nasal cannula versus nasal continuous positive airway pressure for postextubation ventilatory support in neonates: A meta-analysis. J Matern Fetal Neonatal Med. 2014; 27:208.

78. Dani C. High-flow nasal cannulae in very preterm infants after extubation. N Engl J Med. 2014; 370(4):385.

79. Dutta S. High-flow nasal cannula versus nasal continuous positive airway pressure in the management of apnea of prematurity. Pediatrics. 2002; 109(4):718-9; author reply -9.

80. Gagliardi L, Rusconi F. High-flow nasal cannulae in very preterm infants after extubation. N Engl J Med. 2014; 370(4):384-5.

81. Ignacio L, Alfaleh K. A randomized controlled trial to compare heated humidified high-flow nasal cannulae with nasal continuous positive airway pressure postextubation in premature infants. J Clin Neonatol. 2013; 2(2):75-7.

82. Ignacio L, Alfaleh K. High-flow nasal cannulae in very preterm infants after extubation. J Clin Neonatol. 2014; 3(1):11-3.

83. Kugelman A. NCPAP vs. NIPPV vs. heated humidified high-flow nasal cannula (HHHFNC) for the treatment of premature infants with RDS. J Matern Fetal Neonatal Med. 2014; 27:9.

84. Lavizzari A, Ciuffini F, Colnaghi M, Mercadante D, Vendettuoli V, Pierro M. High flow nasal cannula versus nasal CPAP in the management of respiratory distress syndrome: Preliminary data. Pediatric Academic Societies Annual Meeting. 2013; Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/965/CN-00997965/frame.html (Accessed 12/01/2015).

85. Lavizzari A, Veneroni C, Colnaghi M, Ciuffini F, Zannin E, Fumagalli M*, et al.* Respiratory mechanics during NCPAP and HHHFNC at equal distending pressures. Arch Dis Child Fetal Neonatal Ed. 2014; 99(4):F315-f20.

86. Lee EH, Park KH, Park C, Hwang MJ, Choi BM, Hong YS. Comparing humidified high flow nasal cannula versus nasal continuous positive airway pressure as respiratory supports after extubation in preterm infants. Pediatric Academic Societies Annual Meeting. 2011; Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/098/CN-00832098/frame.html (Accessed 12/01/2015).

87. Nagar S, Nanan R, Liu A. High-flow nasal cannulae in very preterm infants after extubation. N Engl J Med. 2014; 370(4):384.

88. Park KH, Lee EH, Chung BH, Choi YO, Lee JH, Choi BM*, et al.* Comparing usefulness of humidified high-flow nasal cannula and nasal continuous positive airway pressure for neonatal respiratory diseases in preterm infants. Pediatric Academic Societies Annual Meeting. 2011; Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/960/CN-00831960/frame.html (Accessed 12/01/2015).

89. Phadtare R, Joshi R, Rajhans A, Patil S, Dominic S, Devaskar U. High flow nasal cannula oxygen (Vapotherm) in premature neonates with respiratory distress syndrome: Is it better than the conventional nasal continuous positive airway pressure (NCPAP)? Perinatology. 2009; 11(1):1-8.

90. Roberts SA, Mitchell S, Victor S. High-flow nasal cannulae in very preterm infants after extubation. N Engl J Med. 2014; 370(4):385.

91. Saslow JG, Aghai ZH, Nakhla TA, Hart JJ, Lawrysh R, Stahl GE*, et al.* Work of breathing using high-flow nasal cannula in preterm infants. J Perinatol. 2006; 26(8):476-80.

92. Saslow JG, Aghai ZH, Nakhla TA, Hart JJ, Lawrysh R, Stahl GE*, et al.* Comparison of work of breathing (WOB) and changes in end-distending pressure (Pd) using nasal continuous positive airway pressure (NCPAP) and vapotherm (VAPO). PAS. 2006; 26(8 May 11):476-80.

93. Shetty S, Greenough A. Review finds insufficient evidence to support the routine use of heated, humidified high-flow nasal cannula use in neonates. Acta Paediatr. 2014; 103(9):898-903.

9 APPENDICES

9.1 Search strategies for evidence of clinical effectiveness

A draft search strategy for Medline was prepared and run on 8th September 2014 as part of the scoping searches. The search was updated on 12th January 2015 alongside a search of additional databases. The search strategies for each database are reported in Table 17 to Table 20.

Table 17 Search strategy conducted in Medline

Search terms	
1	((heat* or hot* or humid* or high-flow or "high flow" or highflow or "higher flow") adj5 (nasal adj3 (cannul* or prong*))). mp.
2	((high-flow or "high flow" or highflow or "higher flow") adj4 (therap* or treat*)). mp.
3	HFT. mp.
4	HHHFNC. mp.
5	HFNC. mp.
6	Fisher &Paykel Healthcare HHHFNC. mp.
7	Vapotherm 2000i. mp.
8	vapotherm*. mp.
9	"fisher and paykel". mp.
10	"fisher&paykel". mp.
11	or/1-10
12	exp Oxygen Inhalation Therapy/
13	(oxygen* adj4 inhalat* adj4 (therap* or deliver*)). mp
14	((low flow or low-flow) adj5 (nasal adj3 (prong* or cannul*))). mp.
15	exp Continuous Positive Airway Pressure/
16	exp Administration, Inhalation/
17	NCPAP. mp.
18	NCPAP. mp.
19	LFNC. mp.
20	exp High-Frequency Ventilation/
21	exp Positive-Pressure Respiration/
22	((oxygen* or high-freq*) adj4 (inhalat* or ventilat* or deliver* or admin*)). mp.
23	(continu* adj4 positiv* adj4 air* adj4 press*). mp.
24	(posit* adj4 press* adj4 (end-expirat* or respirat*)). mp.
25	or/12-24
26	exp Infant, Premature/
27	(infant* or child* or bab* or birth* or newborn* or neonat* or preterm* or prematur* or preterm*). mp.
28	infant/ or infant, newborn/ or infant, low birth weight/
29	infant care/ or intensive care, neonatal/
30	Infant, Newborn, Diseases/
31	Infant, Premature, Diseases/
32	or/26-31
33	11 and 25 and 32

Table 18 Search strategy conducted in PubMed (limited to last six months)

Search terms	
#1	((heat* or hot* or humid* or high-flow or "high flow" or highflow or "higher flow")) AND (nasal adj3 (cannul* or prong*)
#2	(((((HFT) OR HHHFNC) OR HFNC) OR fisher &paykel) OR (fisher and paykel)) OR vapotherm
#3	(#1 or #2)
#4	((oxygen*) AND inhalat*) AND (therap* or deliver*)
#5	(((low flow or low-flow)) AND nasal) AND (prong* or cannul*)
#6	((NCPAP) OR NCPAP) OR LFNC
#7	((oxygen* or high-freq*)) AND (inhalat* or ventilat* or deliver* or admin*)
#8	(((continu*) AND positiv*) AND air*) AND press*
#9	((posit*) AND press*) AND (end-expirat* or respirat*)
#10	(#4 or #5 or #6 or #7 or #8 or #9)
#11	(infant* or child* or bab* or birth* or newborn* or neonat* or preterm* or prematur* or preterm*)
#12	(#3 and #10 and #11)
#13	("2014/03/01"[Date - Entrez] : "2014/09/09"[Date - Entrez])
#14	(#12 and #13)

Table 19 Search strategy conducted in Embase

Search terms	
1	((heat* or hot* or humid* or high-flow or "high flow" or highflow or "higher flow") adj5 (nasal adj3 (cannul* or prong*))). mp.
2	((high-flow or "high flow" or highflow or "higher flow") adj4 (therap* or treat*)). mp.
3	(HFT or HHHFNC or HFNC). mp.
4	(Vapotherm 2000i or vapotherm*). mp.
5	("fisher&paykel" or "fisher and paykel"). mp.
6	or/1-5
7	exp oxygen therapy/
8	(oxygen* adj4 inhalat* adj4 (therap* or deliver*)). mp.
9	((low flow or low-flow) adj5 (nasal adj3 (prong* or cannul*))). mp.
10	exp positive end expiratory pressure/
11	exp inhalational drug administration/
12	(NCPAP or NCPAP or LFNC). mp.
13	exp high frequency ventilation/
14	((oxygen* or high-freq*) adj4 (inhalat* or ventilat* or deliver* or admin*)). mp.
15	(continu* adj4 positiv* adj4 air* adj4 press*). mp.
16	(posit* adj4 press* adj4 (end-expirat* or respirat*)). mp.
17	or/7-16
18	exp prematurity/
19	(infant* or child* or bab* or birth* or newborn* or neonat* or preterm* or prematur* or preterm*). mp.
20	exp low birth weight/ or exp extremely low birth weight/ or exp small for date infant/ or exp very low birth weight/
21	newborn disease/
22	newborn intensive care/
23	or/18-22
24	and/6, 17, 23

Table 20 Search strategy conducted in CDSR/Central/ DARE/HTA

Search terms	
#1	((heat* or hot* or humid* or high-flow or "high flow" or highflow or "higher flow") near/5 (nasal near/3 (cannul* or prong*)))
#2	((high-flow or "high flow" or highflow or "higher flow") near/4 (therap* or treat*))
#3	HFT
#4	HHHFNC
#5	HFNC
#6	Fisher &Paykel Healthcare HHHFNC
#7	Vapotherm 2000i
#8	vapotherm*
#9	"fisher and paykel"
#10	"fisher &paykel"
#11	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10
#12	MeSH descriptor: [Oxygen Inhalation Therapy] explode all trees
#13	(oxygen* near/4 inhalat* near/4 (therap* or deliver*))
#14	((low flow or low-flow) near/5 (nasal near/3 (prong* or cannul*)))
#15	MeSH descriptor: [Continuous Positive Airway Pressure] explode all trees
#16	MeSH descriptor: [Administration, Inhalation] explode all trees
#17	NCPAP
#18	NCPAP
#19	LFNC
#20	MeSH descriptor: [High-Frequency Ventilation] explode all trees
#21	MeSH descriptor: [Positive-Pressure Respiration] explode all trees
#22	((oxygen* or high-freq*) near/4 (inhalat* or ventilat* or deliver* or admin*))
#23	(continu* near/4 positiv* near/4 air* near/4 press*)
#24	(posit* near/4 press* near/4 (end-expirat* or respirat*))
#25	#12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24
#26	MeSH descriptor: [Infant, Premature] explode all trees
#27	(infant* or child* or bab* or birth* or newborn* or neonat* or preterm* or prematur* or preterm*)
#28	MeSH descriptor: [Infant] explode all trees
#29	MeSH descriptor: [Infant, Newborn] explode all trees
#30	MeSH descriptor: [Infant, Low Birth Weight] explode all trees
#31	MeSH descriptor: [Infant Care] explode all trees
#32	MeSH descriptor: [Intensive Care, Neonatal] explode all trees
#33	MeSH descriptor: [Infant, Premature, Diseases] explode all trees
#34	MeSH descriptor: [Infant, Newborn, Diseases] explode all trees
#35	#26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34
#36	#11 and #25 and #35

9.2 Search strategies for evidence of cost effectiveness

As part of the scoping searches, the following databases were searched to identify cost effectiveness studies:

- Medline (OVID)
- Medline In-Process Citations and Daily Update (OVID)
- Embase (Ovid)
- NHS Economic Evaluation Database (NHS EED) (The Cochrane Library)
- Heath Economics Evaluation Database (HEED) (Wiley)

The searches were run on 5th December 2014. The search strategy is reported in Table 21.

Table 21 Search strategy and results for identifying cost effectiveness studies

Search terms	
1	((heat* or hot* or humid* or high-flow or "high flow" or highflow or "higher flow") adj5 (nasal adj3 (cannul* or prong*))). mp.
2	((high-flow or "high flow" or highflow or "higher flow") adj4 (therap* or treat*)). mp.
3	HFT. mp.
4	HHHFNC. mp.
5	HFNC. mp.
6	Fisher &Paykel Healthcare HHHFNC. mp.
7	Vapotherm 2000i. mp.
8	vapotherm*. mp.
9	"fisher and paykel". mp.
10	"fisher&paykel". mp.
11	or/1-10
12	Economics/
13	"costs and cost analysis"/
14	Cost allocation/
15	Cost-benefit analysis/
16	Cost control/
17	Cost savings/
18	Cost of illness/
19	Cost sharing/
20	"deductibles and coinsurance"/
21	Medical savings accounts/

Table 21 (continued) Search strategy and results for identifying cost effectiveness studies

Search terms	
22	Health care costs/
23	Direct service costs/
24	Drug costs/
25	Employer health costs/
26	Hospital costs/
27	Health expenditures/
28	Capital expenditures/
29	Value of life/
30	exp economics, hospital/
31	exp economics, medical/
32	Economics, nursing/
33	Economics, pharmaceutical/
34	exp "fees and charges"/
35	exp budgets/
36	(lowadj cost). mp.
37	(highadj cost). mp.
38	(health?careadj cost$). mp.
39	(fiscal or funding or financial or finance). tw.
40	(costadj estimate$). mp.
41	(costadj variable). mp.
42	(unitadj cost$). mp.
43	(economic$ or pharmacoeconomic$ or price$ or pricing). tw.
44	or/12-43
45	11 and 44

9.3 Table of excluded studies with rationale

The list of citations excluded at stage 2 with reasons is presented in Table 22.

Table 22 List of citations excluded at stage 2 with reason

Study	Reason for exclusion
Al-Alaiyan2014[71]	Article retracted (RCT)
Andaya et al 2010[72]	Wrong population (mixed preterm, term and post-term)
Archer et al 2009[73]	Wrong population(acute bronchiolitis)
Beltramo et al 2008[74]	Wrong study design (not RCT)
Bushell et al 2013[75]	Not efficacy/safety study (mechanics of devices)
Campbell et al 2004[63]	Not heated HFNC (abstract)
Campbell et al 2006[31]	Not heated HFNC (RCT)
Chowdhurry et al 2012[14]	Wrong study design (review)
Ciuffini et al[76]	Wrong study design (not RCT)
Collins 2014[60]	Not heated HFNC (RCT [abstract])*
Collins et al 2014[61]	Not heated HFNC (RCT [abstract])*
Collins et al 2014[62]	Not heated HFNC (RCT [abstract])*
Daish and Badurdeen 2014[77]	Wrong study design (review)
Daish and Badurdeen 2014[35]	Wrong study design (review)
Dani 2014[78]	Wrong study design (letter)
Dani et al 2009[26]	Wrong study design (review)
DeMauro et al 2014[58]	Wrong study design (review)
Dutta 2002[79]	Wrong study design (letter)
Gagliardi and Ruscardi 2014[80]	Wrong study design (letter)
Hua et al 2013[64]	Not heated HFNC (RCT [abstract])
Ignacio and Alfaleh 2013[81]	Synopsis of another RCT (Collins et al 2013,[36])
Ignacio and Alfaleh 2014[82]	Synopsis of another RCT (Manley et al 2013[37])
Iranpour et al 2011[65]	Not heated HFNC (RCT [abstract])
Iranpour et al 2012[66]	Not heated HFNC (RCT)
Kugelman 2014[83]	Wrong study design (review)
Lavizzari et al 2013[84]	Not efficacy/safety study (mechanics of devices)
Lavizzari et al 2014[85]	Not efficacy/safety study (mechanics of devices)
Lee et al 2011[86]	Wrong study design (not RCT)
Nagar et al 2014[87]	Wrong study design (letter)
Park et al 2011[88]	Wrong study design (not RCT)
Phadtare et al 2009[89]	Wrong study design (not RCT)
Roberts et al[90]	Wrong study design (letter)
Rotta et al 2014[59]	Wrong study design (review [abstract])
Saslow et al 2006[91]	Wrong study design (not RCT) and not efficacy/safety study (mechanics of devices)
Saslow et al 2006[92]	Wrong study design (not RCT) and not efficacy/safety study (mechanics of devices)
Shetty and Greenough2014[93]	Wrong study design (review)
Sreenan et al 2001[27]	Not heated HFNC (RCT)
Wilkinson et al 2011[30]	Wrong study design (review)
Woodhead et al 2006[34]	Wrong comparator (HFNC, not usual care)

* It subsequently became apparent from subsequent fully published papers,[36,50] both of which were included in the review, that the intervention was HHHFNC – all papers relate to the same study

9.4 Required sample size for a non-inferiority trial

A research recommendation of this review is to conduct a non-inferiority trial, with BPD as the primary outcome. Table 23 shows the different sample sizes that would be required to conduct such a trial, always assuming a significance level (α) of 5% and statistical power (1-β) of 90% but with differences in the assumptions about the rate of BPD (which is always assumed to be equal in both arms of the trial) and desired non-inferiority margin.

Table 23 Sample size required for a non-inferiority trial, with different assumptions about the non-inferiority margin and rate of BPD*

Non-inferiority margin	Rate of BPD†	Total sample size required¥
10%	25%	644
	30%	720
	35%	780
7.5%	25%	1084
	30%	1280
	35%	1388
5%	25%	2572
	30%	2880
	35%	3120

BPD= bronchopulmonary dysplasia
*Assuming a significance level (α) of 5% and power (1-β) of 90%
† In total, our meta-analysis for BPD included 573 patients and 178 events, a BPD rate of 31%
¥ Assumes equal numbers of patients in each trial arm

The sample size has been calculated from the Sealed Envelope™ website at https://www.sealedenvelope.com/power/binary-noninferior/ (Accessed 24/11/2015).

The formula for the sample size calculation is:

$$n = f(\alpha, \beta) \times [\pi_s \times (100 - \pi_s) + \pi_e \times (100 - \pi_e)] / (\pi_s - \pi_e - d)^2$$

where:

π_s and π_e are the true percent 'success' in the standard and experimental treatment group respectively;

$$f(\alpha, \beta) = [\Phi^{-1}(\alpha) + \Phi^{-1}(\beta)]^2;$$

and Φ^{-1} is the cumulative distribution function of a standardised normal deviate.