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PROTOCOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

The clinical and cost effectiveness of heated humidified high-flow nasal cannula vs usual care for preterm infants Protocol

This protocol was commissioned by the NIHR HTA Programme as project number 14/151/03

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UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

1 TITLE OF PROJECT

The clinical and cost effectiveness of heated humidified high-flow nasal cannula (HHHFNC) vs usual care for preterm babies

2 TAR TEAM AND PROJECT 'LEAD'

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3 PLAIN LANGUAGE SUMMARY

Over the years, the chances of survival for babies born preterm (preterm infants) has been improving, largely due to improvements in treatment options available. Respiratory problems do however remain potential causes of short term and long term ill health and complications. Often preterm infants, particularly those born very early, are treated with a machine known as mechanical ventilation in which a tube is placed down the baby's throat, into the lungs, in order to assist with breathing. Help with breathing may also be given through a continuous positive airways pressure (CPAP) device in which prongs are positioned by the baby's nose or a mask is attached that covers the nose and mouth or a device known as nasal intermittent positive pressure ventilation. Alternative methods of respiratory support include providing oxygen via a head box where a clear hood surrounds the baby's head, via an incubator or via low flow cannula where oxygen is provided via smaller, thinner tubes and smaller, thinner prongs that sit just inside the baby's nose. Despite a lack of evidence for their effectiveness, heated humidified high-flow nasal cannula (HHHFNC) devices are increasingly being used in clinical practice. This is due to perceptions that they may increase comfort for both baby and mother while reducing some of the side effects with other devices, in particular nasal CPAP. We propose to conduct a systematic review and an economic evaluation to assess the clinical and cost effectiveness (costs and benefits) of the use of HHHFNC devices compared to usual care for preterm infants.

4 DECISION PROBLEM

4.1 Clarification of research question and scope

The aim is to address the following research question: What is the clinical and cost effectiveness of HHFNC vs usual care for preterm infants? This will be addressed by conducting a systematic review for evidence and, if the evidence permits, to assess the cost effectiveness through the development of a de novo economic model.

4.2 Preterm infants: epidemiology

According to the UK Office for National Statistics (ONS),[1] there were 729,312 live births in England and Wales in 2012. Of these the gestational age was known and verified for 726,572. Of these, 52,909 (7.3%) were born preterm, prior to 37 weeks. The majority (43,993 [83.1%]) were born at 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 under 24 weeks. Similar data are available from other countries. The rate of preterm birth varies between countries; however, proportional distribution of gestational age categories described above is similar.

Birth weight is associated with gestational age. In England a Wales in 2012,[1] the vast majority of infants born under 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.

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

Table 1 Infant mortality rate by gestational age and birth weight in England and Wales, 2012

		Birth weight				
Gestational age	**All**	**<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[1]

4.3 Morbidity and mortality associated with preterm birth

Respiratory problems are one of the most common causes of morbidity in preterm infants.[2] Respiratory distress syndrome (RDS), also known as hyaline membrane disease is a serious medical condition where a newborn baby's lungs cannot provide their body with enough oxygen due to a lack of surfactant in the lungs.[3-5] 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.[5] 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[3].

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.[5] Consequences of RDS include:[4]

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

Advances in care over the years have however resulted in significant decreases in mortality from RDS.[5,6] In the US, mortality has been estimated to be ~2.89 per 1,000 live births between 1969 and 1973[7] (or 2.6 per 1,000 live births in 1970 in another study[8]) falling to 0.37 per 1,000 live births between 1987 and 1995[9] (or 0.4 per 1,000 live births in 1994 in another study[8]). However, alongside increased survival, marginal increases in morbidities have been identified. The evidence for change in the long-term outcomes preterm infants is limited to early infancy and it has been the result of some advances in the respiratory care during neonatal period which need to be systematically evaluated.

4.4 Current treatment options for preterm infants

Over the years, several modalities for respiratory support have been developed. Surveys[10-12] cited in a review of available treatment options for RDS[13] show that science of providing best start to these babies is constantly evolving.

The treatment which has arguably had the largest impact in reducing mortality is the administration of surfactant from around 1990 onwards.[6,8] 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 surfactant therapy in the 1990s.[6,8] Recently updated European Consensus Guidelines for the management of RDS in preterm infants[5] 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.[5]

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 4.4.1 to 4.5):

1. Mechanical endotracheal ventilation
2. Oxygen
3. Continuous positive airways pressure (CPAP)
4. Nasal intermittent positive pressure ventilation (NIPPV)
5. HHHFNC

Any of the above interventions may precede or follow any other of the above interventions in the treatment pathway. Surfactant followed by brief ventilation then transferring the baby to CPAP (INtubation- SURfactant-Extubation - INSURE approach) is one approach reported to be effective from a Cochrane review published in 2007[14]. The European Consensus Guidelines[5] suggest that this could be considered for less mature infants and recommend that for most infants, CPAP should be the preferred option for stabilisation where possible. Two trials published in 2010[15,16] suggested that a significant number of infants (nearly half) can be managed on CPAP alone. However, there is still a role in treatment for ventilation and oxygen.

Although by no means used uncommonly, NIPPV is not thought to be used as frequently as the aforementioned devices. A survey published in 2008[17] found just less than half (48%) of all UK neonatal units used NIPPPV. In those units where it was used, it was most commonly (80%) used for “rescuing” infants for whom CPAP failed. It was routinely used after ventilation in 59% of units and as a first-line treatment in 16% of units.

Finally, in addition to all of the above, the use of HHHFNC is also increasing in clinical practice.[18-21]

4.4.1 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.[6] While this has increased survival, lung injury has been recognised as an associated complication.[6] Lung injury in the short term can lead to air leak.[13] Air leaks and increased pressures used to ventilate infants may result in pneumothorax, pneumomediastinum and pneumopericardium.[4] Lung injury in the longer term may result in BPD.[2,13,22] Largely for these reasons, the European Consensus Guidelines[5] 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 CPAP.[5]

4.4.2 CPAP

Devices which generate CPAP can broadly be divided into two categories, continuous flow or variable flow devices.[23,24] Continuous flow devices include conventional ventilators, jet ventilation systems and bubble CPAP.[23] Common features of all CPAP devices are:[13]

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 CPAP circuit to the infant's airway

The most commonly used interfaces between the CPAP circuit and the neonate are nasal prongs and/or nasal masks.[22,23] A meta-analysis[25] has shown that binasal prongs are more effective in preventing reintubation compared to either single nasal or nasopharyngeal prongs. While there is evidence from meta-analyses that CPAP may be more effective than headbox oxygen for reducing the incidence of respiratory failure (apnea, respiratory acidosis and increased oxygen requirements) and need for reintubation,[26] there is no reliable evidence to suggest one CPAP device is optimal over another CPAP device. Thus in practice, it may be more convenient to use a ventilator-generated constant CPAP because this method does not require a change of devices when mechanical ventilation and CPAP are employed for short periods.[13]

Difficulties with successful application of CPAP are principally related to the relatively bulky interface with the infant which can result in problems maintaining proper position.[24] 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.[24] In particular, the bulky nature of most CPAP interfaces can predispose to nasal irritation and trauma[24,27] and can restrict access to the head and face and have significant drawbacks with respect to integration of CPAP with oral feeding.[28] Furthermore, face masks and standard nasal

cannulae associated with the prongs are uncomfortable and can cause irritation due to the use of dry, cold gas.[29] Finally, common to all variable flow nasal CPAP 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.[13]

4.4.3 Oxygen

Oxygen is the most widely used therapy in neonatology.[30] Aside from CPAP, it may be administered via headbox, incubator or low flow nasal cannula. The European Consensus Guidelines[5] recommend a concentration of 21% to 30% oxygen to initiate stabilisation followed by increases or decreases in the concentration as appropriate (increasing only if persistently bradycardic or cyanosed). As with ventilation, oxygen may lead to lung injury and the same short term and long term effects.

4.4.4 NIPPV

NIPPV is a development in non-invasive ventilatory support combining CPAP with superimposed ventilator breathing at a set peak pressure.[13] NIPPV provides intermittent mandatory ventilation using nasal prongs[31] and may be synchronised (SNIPPV) or non-synchronised to the infant's breathing efforts.[32] NIPPV has been reported to achieve better gaseous exchange than simple oxygen therapy but has also been associated with significant head molding, cerebral hemorrhage and gastric perforations.[33] Other complications related to nasal ventilation have been reported to be "essentially the same" as those for infants on CPAP.[34] SNIPPV has been argued to be preferable over NIPPV in order to minimise gastrointestinal perforations.[34]

4.5 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:[24]

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.

With regard to gas flow rate, no optimal level exists.[24] One early study reported that this should vary from infant to infant depending on weight.[35] 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.[24] Unlike the nasal prongs for CPAP (which fit tightly in the nares), the nasal cannulae for HHHFNC are smaller and looser-fitting. Nasal cannulae size do nevertheless vary from infant to infant, this being dictated by the size of the infant's nares.[27,29]

HHHFNC is gaining popularity in clinical practice largely due to the perceived greater ease of use of such devices as compared to CPAP, allowing both practitioners and family members to more easily handle and care for infants.[20,24,29] 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.[24,29] Other perceived advantages compared to CPAP include a reduction in the number of ventilator days, an improvement in weight gain and being able to introduce oral feeding earlier.[27,29]

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[24] while in the absence of an effective way of controlling distending pressure, there is also the theoretical risk of lung over-distension and pneumothoraces;[27] pressure appears to be related to gas flow, prong size and patient size.[24] 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 FDA approval in January 2007, with new instructions for use, including the recommendation to utilise only sterile water in the system.[24]

4.6 Reported use of HHHFNC in clinical practice

The most recently published UK survey by Ojha et al 2013[21] reported HHHFNC was used in 77% of neonatal units, compared to 56% reported in 2012 by Desai et al.[18] In the US and Australasia the use of HHHFNC was reported to be 69%[19] and 63%[20] respectively. All surveys reported HHHFNC was used for different indications.[18-21] In the 2013 UK survey,[21] HHHFNC was commonly used as an alternative to CPAP (77%), weaning off CPAP (71%) and postextubation (53%).[21] In the 2012 UK survey,[18] HHHFNC was either used as standard respiratory support following extubation or following CPAP by 42% of units with the remainder (58%) using CPAP initially and then HHHFNC. In the most recent UK survey,[21] HHHFNC was used for infants of any gestational age (71%) or any birth weight (77%).

Ojha et al 2013[21] found that the Vapotherm 2000i was the most popular device used in the UK by 47% of neonatal units compared to 38% of units using the Fisher & Paykel device. In the US and Australasia the Fisher & Paykel device has been reported to be most commonly used: 59%[19] and 94%[20] respectively compared to 41% and 23% that respectively use the Vapotherm 2000i device. In both countries some units reported they use both devices and in addition, custom-built centre-specific devices also exist.[24] In the US survey,[19] these were reported to be used by 18% of units.

Surveys of practice all report flow rates to vary.[18-21] In the UK, flow rate was reported to depend on the size of the infant in ~30% of units, 5 L/min or 6 to 8 L/min in ~50% of units and >8 L/min in ~15% of units in a 2013 publication.[21] However, a separate UK survey presented as an abstract in 2012 found that 60% of units commenced HHHFNC at 8 L/min and 30% of units at 5 to 6L/min.[18] This survey also reported that flow rate was reduced in 0.5 to 1 L/min steps to wean and that "most units" weaned off HHHFNC once the flow rate was 2 to 3L/min.[18]

Unsurprisingly, nasal cannulae size was reported to differ across units in the most recent UK survey:[21] Size was reported to be 0.2cm or 0.3cm in 4% of responses which may also be equivalent to most common responses, namely the "size that best fits the nostrils" (56%) or a size that enables "space for a leak" (41%).

4.7 Guidelines for the use of HHHFNC in clinical practice

From a quick search of the Internet it is evident that guidelines for the use of HHHFNC produced by individual neonatal units recommend HHHFNC is used for a variety of indications. For example, NHS Forth Valley Women and Children's Unit [29] stipulate HHHFNC may be used in the following instances:

1. Infants with CLD
2. Weaning CPAP support
3. Alternative to CPAP in mild/moderate respiratory distress.
4. Post-op respiratory support
5. Infants with nasal trauma from CPAP
6. Treatment or prevention of apnoea of prematurity
7. Supportive growth optimisation (although the guidelines do question the appropriateness of this strategy)

The Liverpool Women's NHS Foundation Trust[36] on the other hand stipulates the following possible indications:

1. In infants with (evolving) BPD who are receiving CPAP, HHHFNC can be used if the baby is:

A. ≥28 weeks corrected gestational age AND
B. Receiving CPAP for ≥ 7 days (not likely to wean off in next few days) AND
C. In ≤ 50% oxygen

2. In infants with evolving BPD in ≤50% ambient oxygen, HHHFNC can be used if the baby is:
   A. ≥28 weeks corrected gestational age AND
   B. ≥7 days of age

3. Infants who are receiving CPAP support but have a nasal injury (after discussion with the attending consultant/ Advanced Neonatal Nurse Practitioner [ANNP]).

Liverpool's guidelines[36] also state that HHHFNC can be used for infants outside of these categories but only after discussion with the ward round consultant or ANNP (high flow therapy lead).

4.8 Evidence for the effectiveness of HHHFNC

To date, there is a lack of convincing evidence to support either the perceived benefits or concerns of using HHHFNC. In 2011, a Cochrane review[37] concluded that there was "insufficient evidence to establish the safety or effectiveness of HHHFNC as a form of respiratory support in preterm infants." Evidence was derived from two RCTs[38,39] comparing HHHFNC to CPAP (including one RCT that was unpublished and halted early[39]), an RCT comparing two types of HHHFNC (Vapotherm vs Fischer and Paykel)[40] and a crossover trial comparing HHHFNC to a non humidified high flow device.[41] 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 Daish et al[42] of three RCTs[43-45] published since the Cochrane review examined the effects of HHHFNC on extubation failure (i.e. need for reintubation) and BPD. No significant differences were found between HHHFNC and CPAP for either outcome.

Scoping searches conducted by LRiG in the preparation of this protocol identified two further RCTs and a crossover trial[46] comparing HHHFNC to CPAP. These RCTs from China[47,48] and Iran[49] have so far only been presented in abstract form. LRiG has also identified an RCT examining the effects of weaning from HHHFNC to CPAP[50] and an RCT presented only as an abstract examining both HHHFNC vs CPAP and also HHHFNC vs CPAP as a weaning strategy from CPAP.[51] In addition to comparisons with CPAP, LRiG identified an RCT comparing HHHFNC to NIPPV[52] and two others comparing different types of humidifiers for HHHFNC.[50,51]

4.9 Rationale for the current review

The wide variety of indications reported in studies included in systematic reviews,[37,42] surveys[18-21] and guidelines[29,36] 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 CPAP,[42] there is also the need for a review of the evidence for other relevant outcomes and comparators. Studies have also considered HHHFNC as a weaning strategy from CPAP[50,51] and compared different methods of providing HHHFNC; [40,41,53,54] these studies would fall outside the scope of our proposed review.

4.10 Key factors to be addressed

Issues to consider for all analyses in our review will include heterogeneity across studies, for example in terms of differences in gestational age, the length of previous ventilation, starting flow rate for HHHFNC (and starting pressure rate for CPAP) and types of devices/interfaces used as comparators (e.g. different types of CPAP devices and the use of prongs or masks).

5 METHODS FOR SYNTHESISING CLINICAL EVIDENCE

Systematic review methodology will be utilised to search for evidence of clinical effectiveness.

5.1 Search strategy

The following databases will be 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
- Embase
- ISI Web of Science- Proceedings (Index to Scientific & Technical Proceedings)
- Medline
- ISI Web of Science- Science Citation Index Expanded

No study design filters will be applied and non-English language reports will be excluded. All databases will be searched from the year 2000 until the latest available version.

Details of the draft search for Medline can be found in the Appendix (section 10.1).

Trial and research registers will be 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
- *meta*Register of Controlled Trials and ISRCTN Register
- National Research Register
- The Cochrane Library
- TRIP Database plus
- Google Scholar
- FDA

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

5.2 Study selection

The citations identified will be assessed for inclusion through two stages. Firstly, two reviewers will independently scan all the titles and abstracts identified by the searching exercise to identify the potentially relevant articles to be retrieved. Full text copies of the selected studies will subsequently be obtained and assessed independently by two reviewers for inclusion using the inclusion and exclusion criteria outlined below. Any disagreements will be resolved by discussion at each stage, and if necessary a third reviewer will be consulted.

Table 2 Eligibility criteria

Criteria	Included	Excluded
Study design	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:* • CPAP • Oxygen • NIPPV	Not usual care
Outcomes	**Primary outcome:** Failure of treatment as indicated by the need for reintubation, as measured at 3 time points: • Under 72 hours • Under 7 days • Ever **Secondary outcomes:** • death (prior to discharge from hospital) • chronic lung disease (CLD) / 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 CLD/BPD (as defined above) • duration in days of any form of respiratory support (mechanical ventilation, CPAP, HHHFNC, oxygen); • length of stay in NICU (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

* we intend to conduct a primary analysis of HHHFNC to usual care following ventilation and a secondary analysis of HHHFNC to usual care with no prior ventilation; mechanical ventilation may therefore be an additional comparator for the secondary analysis

† air leak syndromes (e.g. pneumothorax) reported either individually or as a composite outcome; nasal trauma (defined as erythema or erosion of the nasal mucosa, nares or septum); nosocomial sepsis (defined as positive blood or cerebrospinal fluid [CSF] cultures taken after five days of age; intraventricular hemorrhage (IVH) (however defined); necrotising enterocolitis (NEC) (defined according to modified Bell's criteria) and/or gastrointestinal (GI) perforation; apnea of prematurity (defined as pause in breathing of >20 seconds)/bradycardia (defined as heart rate <100 beats per minute in an infant <1,250 g or < 80 beats per minute in an infant ≥1,250g)

§ noise from device (however defined and measured); infant comfort (however defined and measured); acceptability of treatment to parents (however defined and measured); and acceptability of treatment to staff (however defined and measured)

5.3 Data extraction strategy

Data relating to study design and findings will be extracted by one reviewer and independently checked for accuracy by a second reviewer. Study details will be extracted on pre-tested data extraction forms (see Appendix, section 10.2 for the data we expect to extract). Data from studies presented in multiple publications will be extracted and reported as a single study with all other relevant publications listed.

5.4 Assessing risk of bias

The risk of bias of the individual studies will be assessed independently by two reviewers and then cross-checked for agreement. Disagreements will be resolved through consensus and, if necessary, a third reviewer will be consulted. The assessment of the risk of bias will be made according to the Cochrane Collaboration criteria[55] (see Table 3).

Table 3 Assessing the risk of bias of studies

Domain	Description	Judgment to be made
Sequence generation	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.	Was the allocation sequence adequately generated?
Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.	Was allocation adequately concealed?
Blinding of participants, personnel and outcome assessors *	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Was knowledge of the allocated intervention adequately prevented during the study?
Incomplete outcome data*	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.	Were incomplete outcome data adequately addressed?
Selective outcome reporting	State how the possibility of selective outcome reporting was examined by the review authors, and what was found.	Are reports of the study free of suggestion of selective outcome reporting?
Other sources of bias	State any important concerns about bias not addressed in the other domains in the tool. If particular questions/entries were pre-specified in the review's protocol, responses should be provided for each question/entry.	Was the study apparently free of other problems that could put it at a high risk of bias?

* Assessments should be made for each main outcome (or class of outcomes)
Source: Table 8.5.a from Cochrane Collaboration[55]

5.5 Methods of analysis/synthesis

We propose a primary analysis comparing HHHFNC to usual care following ventilation and a secondary analysis of HHHFNC to usual care with no prior ventilation. Usual care will be considered to consist of mechanical ventilation (secondary analysis only), CPAP, oxygen or NIPPV. Each of these different treatment modalities will be considered separately and no attempt will be made to compare usual care as a single homogeneous comparator.

The results of the data extraction and quality assessment for each study will be presented in structured tables and as a narrative summary. The possible effects of study quality (based on the assessment of risk of bias) on the effectiveness data and review findings will be considered.

For dichotomous outcomes, we will use relative risk (RR) and the corresponding 95% confidence interval (CI) to summarise results from each trial. For continuous outcomes, we will use the mean difference (or standardised mean difference where different scales are used) and corresponding 95% CI. Where possible, data will be pooled using a standard meta-analysis.[56]

For each comparator, meta-analysis of primary and secondary outcomes will be carried out using fixed or random effects models using an appropriate software package, depending on the assessment of heterogeneity. Heterogeneity will be 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 CPAP), outcome definitions (e.g. different definitions for reintubation) and in statistical terms by the χ^2 test for homogeneity and the I^2 statistic.[57] The I^2 statistic with a level of >50% will indicate moderate levels of heterogeneity, and the Chi^2 test with a P value of <0.10 will indicate statistically significant heterogeneity. Based on these assessments, a decision will be 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 the studies are deemed to vary so much that it would not be appropriate to combine results, then a meta-analysis will not be performed.

If the data allow, subgroups based on gestational age (<30 weeks and ≥30 weeks) will also be considered.

If appropriate and if data allows, sensitivity analyses will be conducted excluding trials deemed to be of low quality to assess the robustness of the findings. Trials of low quality will

be those considered to be of high risk of bias as determined using the criteria suggested by the Cochrane Collaboration[55] (see Table 4)

Table 4 Possible approach for summary assessments of the risk of bias for each important outcome (across domains) within and across studies

Risk of bias	Interpretation	Within a study	Across studies
Low risk of bias	Plausible bias unlikely to seriously alter the results.	Low risk of bias for all key domains	Most information is from studies at low risk of bias
Unclear risk of bias	Plausible bias that raises some doubt about the results	Unclear risk of bias for one or more key domains	Most information is from studies at low or unclear risk of bias
High risk of bias	Plausible bias that seriously weakens confidence in the results	High risk of bias for one or more key domains	The proportion of information from studies at high risk of bias is sufficient to affect the interpretation of the results

Source: Table 8.7.a from Cochrane Collaboration[55]

If ten or more studies are included in a meta-analysis, an assessment of the risk of publication bias will be made by constructing a funnel point and conducting a simple test of asymmetry to test for possible bias.[58]

6 METHODS FOR SYNTHESIZING EVIDENCE OF COST EFFECTIVENESS

Scoping searches conducted by LRiG in the preparation of this protocol identified no relevant published cost effectiveness studies. The search strategy is reported in the Appendix (section 10.3). We will not therefore conduct another search of the literature for published cost-effectiveness evidence but attempt to develop a de novo economic model if suitable data are available.

6.1 Modelling clinical pathway and outcomes

Data will be required to populate a patient pathway from the point that a preterm infant can first receive HHHFNC up until any clinically different outcomes can occur because of the choice to use HHHFNC or an alternative. The first step is therefore to construct this pathway with the assistance of clinical experts (for clinical expertise in this TAR team, see section 7).

Depending on the complexity of the pathway, transition probabilities to different clinical outcomes or health states may be fully provided by the clinical evidence review. This is likely to be the case if all clinically relevant differences occur in the very short term. If longer term transition probabilities are required, information will be gathered through a pragmatic literature review of existing relevant systematic reviews or though consultation with clinical experts. At this stage it is not possible to state whether the pathway would be better modelled as a Markov process or as a decision tree as it will depend on the final nature of the pathway and also on the availability of data.

6.2 Costs and utilities

Once the pathway and different clinical outcomes have been determined to produce results, the economic model will also require costs and utilities for preterm infants experiencing different outcomes.

Costs of different health outcomes, the intervention and comparators will be through the use of NHS reference costs where appropriate and available. Where reference costs are not available then the costs will be determined through clinical expert advice on resource use with unit costs for resource being taken from the Unit Costs of Health and Social Care published by the Personal Social Services Research Unit, the British National Formulary or, if we are able to obtain access, the NHS Supply Chain.

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 is not possible. 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 will be undertaken. This will include searching for cost-utility evaluations of other interventions for pre-term babies to assess how utility values have been incorporated for this patient group by other researchers.

If there is an absence of any reliable utility information, the model could examine whether outcomes from using HHHFNC are improved and then assess the full cost implications of using the technology taking into account the improved outcomes. If HHHFNC improves outcomes at lower cost than alternatives than the absence of utility information will not be material. In addition, the cost per death averted between HHHFNC could also be estimated as a means to determine cost-effectiveness. If neither cost-utility, cost-minimisation or cost-effectiveness analysis can be undertaken a narrative discussion will be presented in place of a formal economic model.

6.3 Sensitivity analyses

If a formal economic model can be constructed, appropriate sensitivity analyses will be undertaken 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 will analyse the exact nature of the impact of variations.

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

7 EXPERTISE IN THIS TAR TEAM AND COMPETING INTERESTS

The Liverpool Reviews and Implementation Group (LRiG) was established at the University of Liverpool in April 2001. It is a multi-disciplinary research group whose purpose, in the first instance, is to conduct Technology Assessment Reviews commissioned by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme. The team has substantial expertise in systematic reviewing, literature searching and assessing clinical outcomes and is well practised in applying this expertise to health technology evaluations. In addition, for the specific purposes of this review, LRiG has approached two clinical experts and in order to incorporate patient involvement, the mother of a baby born at Liverpool Women's Hospital. This TAR team will be made up of the individuals listed in Table 5

Table 5 TAR team for this project

Role	Person
Team lead /clinical systematic reviewer	Nigel Fleeman, LRiG
Economic modeller	James Mahon, Coldingham Economics
Systematic reviewer (clinical)	Vickie Bates, LRiG
Information specialist	Eleanor Kotas, LRiG
Medical statisticians	Kerry Dwan, LRiG Marty Richardson, LRiG
Director	Rumona Dickson, LRiG
Associate Director	Angela Boland, LRiG
Clinical advisors	Ben Shaw, Consultant in Neonatal and Respiratory Paediatrics Neonatal Unit, Liverpool Women's Hospital and Professor at Evidence-based Practice Research Centre, Edge Hill University, UK Prakesh Shah, Professor in the Departments of Paediatrics and HPME, Mount Sinai Hospital and University of Toronto and CIHR Applied Research Chair in Reproductive and Child Health Services and Policy Research Director, Canadian Neonatal Network
"Patient" advisor	Laura Ellis, parent of baby born at Liverpool Women's Hospital

The role of the team lead /clinical systematic reviewer will be to maintain day-to-day running of the review. He has compiled the study protocol (with input from other team members) and will carry out the study selection and data extraction (with assistance from the other systematic reviewer) and data synthesis (with assistance from the medical statisticians). It is also intended that he will draft the methods, narratives for included trials, and the results and discussion of the final report with other members of the TAR team contributing as

appropriate. In addition, the Director will provide assistance into all aspects of the review as and when necessary and the Associate Director will also provide feedback on drafts of the report.

No member of the LRiG research team has any competing interests to declare. Any competing interests relating to clinical advisors or reviewers will be identified and declared in the final report.

8 PROJECT TIMELINES

The proposed timelines for this project are summarised in Table 6

Table 6 Project timelines

Milestone	**Date**
Draft protocol submission	December 2014
Final protocol approval	January 2015
Beginning of review process	January 2015
Literature search and assessment of papers for review	January 2015
Data extraction	February 2015
Data synthesis and economic modelling	February 2015
Draft report for review	Beginning of March 2015
Report submitted	End of March 2015

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10 APPENDICES

10.1 Draft search strategy for MEDLINE

A draft search strategy for Medline has been prepared and run on 10th November 2014 as part of the scoping searches conducted in preparation of this protocol, as detailed in Table 7.

Table 7 Draft search strategy conducted in Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)

Search terms		Results
1	((heat* or hot* or humid* or high-flow or "high flow" or highflow or "higher flow") adj5 (nasal adj3 (cannul* or prong*))).mp.	146
2	((high-flow or "high flow" or highflow or "higher flow") adj4 (therap* or treat*)).mp.	294
3	HFT.mp.	120
4	HHHFNC.mp.	12
5	HFNC.mp.	55
6	Fisher & Paykel Healthcare HHHFNC.mp.	1
7	Vapotherm 2000i.mp.	10
8	vapotherm*.mp.	22
9	"fisher and paykel".mp.	69
10	"fisher & paykel".mp.	51
11	or/1-10	565
12	exp Oxygen Inhalation Therapy/	22147
13	(oxygen* adj4 inhalat* adj4 (therap* or deliver*)).mp.	12012
14	((low flow or low-flow) adj5 (nasal adj3 (prong* or cannul*))).mp.	15
15	exp Continuous Positive Airway Pressure/	4306
16	exp Administration, Inhalation/	25057
17	CPAP.mp.	5132
18	NCPAP.mp.	782
19	LFNC.mp.	1
20	exp High-Frequency Ventilation/	2530
21	exp Positive-Pressure Respiration/	21199
22	((oxygen* or high-freq*) adj4 (inhalat* or ventilat* or deliver* or admin*)).mp.	32461
23	(continu* adj4 positiv* adj4 air* adj4 press*).mp.	7928
24	(posit* adj4 press* adj4 (end-expirat* or respirat*)).mp.	17401
25	or/12-24	88725
26	exp Infant, Premature/	43630
27	(infant* or child* or bab* or birth* or newborn* or neonat* or preterm* or prematur* or pre-term*).mp.	2704139
28	infant/ or infant, newborn/ or infant, low birth weight/	970740
29	infant care/ or intensive care, neonatal/	12693
30	Infant, Newborn, Diseases/	35374

31	Infant, Premature, Diseases/	18574
32	or/26-31	2704139
33	**11 and 25 and 32**	**129**

10.2 Details of clinical data extraction

It is anticipated that clinical effectiveness data will be extracted and entered under the following headings:

Study details

- Author and Year of publication/abstract/data source (e.g. Jones et al 2012)
    - Endnote reference (endnote reference number)
    - Analysis included in (primary/secondary/exploratory):
- Inclusion/exclusion criteria (summary of trial inclusion/exclusion criteria)
- Follow-up duration
- Geographic location(s) of study
- Sponsor of study
- Sub-groups analysed (if any)

Intervention and comparator details

- Intervention (specify type of HHHFNC device(s) used, how long device is used for and starting flow rate)
- Comparator (specify type of comparator device(s) used, how long device is used for and starting pressure)

Participant characteristics

Mothers:

- Ethnicity (number, proportion)
- Primigravida (number, proportion)
- Exposure to antenatal glucocorticoids (number, proportion)
- Cesarean section (number, proportion)

All infants:

- Mean (standard deviation) / median (range) gestational age (weeks)
- Number (proportion) of infants by gestational age category
- Mean (standard deviation) / median (range) study start (postnatal) age (hours)
- Number (proportion) of infants with study start (postnatal) age of 7 days or less
- Mean (standard deviation) / median (range) birth weight (grams)
- Male sex (number, proportion)
- Singleton (number, proportion)
- Antenatal treatment with steroids (number, proportion)
- Received surfactant treatment (number, proportion)
- Received caffeine treatment before extubation (number, proportion)
- Number (proportion) of patients with RDS

Infants who received prior ventilation/oxygen/CPAP:

- Number (proportion) of patients who received prior ventilation/oxygen/CPAP (specify for each type)

- Mean (standard deviation) / median (range) duration of prior ventilation/oxygen/CPAP
- Time between ventilation and subsequent treatment with HHHFNC/usual care
- Intubated in the delivery room (number, proportion)
- Mean (standard deviation) / median (range) postnatal age at extubation
- Oxygen use at the time of extubation

Outcomes: Definitions and measures

- Primary outcome (description of outcome as reported)
- Secondary outcomes (description of outcomes as reported) including:
    - Adverse events/complications (description of outcomes as reported)
    - Quality of care (description of outcomes as reported)

Results

Primary outcome:

Failure of treatment as indicated by the need for reintubation, as measured at 3 time points:

- Under 72 hours
- Under 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)
- death or chronic lung disease (as defined above)
- duration in days of any form of respiratory support (mechanical ventilation, CPAP, HHHFNC, oxygen);
- length of stay in NICU (days)
- length of stay in hospital (days)
- adverse events/complications including:
    - air leak syndromes (e.g. pneumothorax) reported either individually or as a composite outcome
    - nasal trauma (defined as erythema or erosion of the nasal mucosa, nares or septum)
    - nosocomial sepsis (defined as positive blood or cerebrospinal fluid [CSF] cultures taken after five days of age
    - intraventricular hemorrhage (IVH)
    - necrotising enterocolitis (NEC) and/or gastrointestinal (GI) perforation
    - apnea of prematurity/bradycardia
    - failure to thrive (weight gain prior to discharge from hospital)
- quality of care in relation to:
    - infant comfort
    - acceptability to parents
    - acceptability to staff
- days to full feeds
- failure to thrive (weight gain prior to discharge from hospital)

10.3 Search strategy used for published evidence of cost effectiveness studies

As part of the scoping searches conducted in preparation of this protocol, 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)

These searches (detailed) in Table 8 were run on 5th December 2014 and yielded no additional relevant results to the previous search conducted on 10th November 2014.

Table 8 Search strategy and results for identifying cost effectiveness studies

Searches		Results
1	((heat* or hot* or humid* or high-flow or "high flow" or highflow or "higher flow") adj5 (nasal adj3 (cannul* or prong*))).mp.	146
2	((high-flow or "high flow" or highflow or "higher flow") adj4 (therap* or treat*)).mp.	294
3	HFT.mp.	120
4	HHHFNC.mp.	12
5	HFNC.mp.	55
6	Fisher & Paykel Healthcare HHHFNC.mp.	1
7	Vapotherm 2000i.mp.	10
8	vapotherm*.mp.	22
9	"fisher and paykel".mp.	69
10	"fisher & paykel".mp.	51
11	or/1-10	565
12	Economics/	27442
13	"costs and cost analysis"/	43264
14	Cost allocation/	1994
15	Cost-benefit analysis/	63470
16	Cost control/	20891
17	Cost savings/	9247
18	Cost of illness/	19167
19	Cost sharing/	2105
20	"deductibles and coinsurance"/	1502
21	Medical savings accounts/	487
22	Health care costs/	29299
23	Direct service costs/	1062
24	Drug costs/	12925
25	Employer health costs/	1093

Searches		Results
26	Hospital costs/	8210
27	Health expenditures/	14652
28	Capital expenditures/	1978
29	Value of life/	6025
30	exp economics, hospital/	20303
31	exp economics, medical/	14063
32	Economics, nursing/	4027
33	Economics, pharmaceutical/	2645
34	exp "fees and charges"/	28250
35	exp budgets/	12453
36	(low adj cost).mp.	22070
37	(high adj cost).mp.	7877
38	(health?care adj cost$).mp.	4434
39	(fiscal or funding or financial or finance).tw.	82865
40	(cost adj estimate$).mp.	1441
41	(cost adj variable).mp.	32
42	(unit adj cost$).mp.	1553
43	(economic$ or pharmacoeconomic$ or price$ or pricing).tw.	170878
44	or/12-43	473491
45	**11 and 44**	**8**