BMJ Open

A multi-centre, randomised controlled, non-inferiority trial, comparing high flow therapy with nasal continuous positive airway pressure as primary support for preterm infants with respiratory distress (The HIPSTER Trial): study protocol

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2015-008483
Article Type:	Protocol
Date Submitted by the Author:	14-Apr-2015
Complete List of Authors:	Roberts, Calum; The Royal Women's Hospital, Newborn Research Centre; The University of Melbourne, Department of Obstetrics and Gynaecology Owen, Louise; The Royal Women's Hospital, Newborn Research Centre; The University of Melbourne, Department of Obstetrics and Gynaecology Manley, Brett; The Royal Women's Hospital, Newborn Research Centre; The University of Melbourne, Department of Obstetrics and Gynaecology Donath, Susan; Murdoch Children's Research Institute, Clinical Epidemiology and Biostatistics Unit; The University of Melbourne, Department of Paediatrics Davis, Peter; The Royal Women's Hospital, Newborn Research Centre; The University of Melbourne, Department of Obstetrics and Gynaecology
Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Respiratory medicine, Intensive care
Keywords:	NEONATOLOGY, Neonatal intensive & critical care < INTENSIVE & CRITICAL CARE, Clinical trials < THERAPEUTICS

A multi-centre, randomised controlled, non-inferiority trial, comparing high flow therapy with nasal continuous positive airway pressure as primary support for preterm infants with respiratory distress (The HIPSTER Trial): study protocol

Calum T. Roberts[1,2], Louise S. Owen[1-3], Brett J. Manley[1,2], Susan M. Donath [3,4], and Peter G. Davis[1-3]

1. The Royal Women's Hospital, Melbourne, Australia
2. Department of Obstetrics and Gynaecology, The University of Melbourne, Australia
3. Murdoch Children's Research Institute, Melbourne, Australia
4. Department of Paediatrics, The University of Melbourne, Australia

Corresponding Author: Calum T. Roberts

Address: Newborn Research Centre
The Royal Women's Hospital
Locked Bag 300
Grattan St & Flemington Rd
Parkville 3052
Australia

Telephone: +61 3 83453773
Email: calum.roberts@thewomens.org.au

Word count: 3565
Abstract word count: 296

Keywords: preterm infants; non-invasive ventilation; continuous positive airway pressure; neonatal intensive care

ABSTRACT

Introduction: High flow (HF) therapy is an increasingly popular mode of non-invasive respiratory support for preterm infants. While there is now evidence to support the use of HF to reduce extubation failure, there have been no appropriately designed and powered studies to assess the use of HF as primary respiratory support soon after birth. Our hypothesis is that HF is non-inferior to the standard treatment, nasal continuous positive airway pressure (NCPAP) as primary respiratory support for preterm infants.

Methods and Analysis: The HIPSTER trial is an unblinded, international, multi-centre, randomised, non-inferiority trial. Eligible infants are preterm infants 28 to 36+6 weeks' gestational age (GA) who require primary non-invasive respiratory support for respiratory distress, in the first 24 hours of life. Infants are randomised to treatment with either HF or NCPAP. The primary outcome is treatment failure within 72 hours after randomisation, as determined by objective oxygenation, blood gas, and apnoea criteria, or the need for urgent intubation and mechanical ventilation. Secondary outcomes include the incidence of intubation, pneumothorax, bronchopulmonary dysplasia, nasal trauma, costs associated with hospital care, and parental stress. With a specified non-inferiority margin of 10%, using a two-sided 95% confidence interval and 90% power the study requires 375 infants per group (total 750 infants).

Ethics and Dissemination: Ethical approval has been granted by the relevant human research ethics committees at The Royal Women's Hospital (13/12), The Royal Children's Hospital (33144A), The Mercy Hospital for Women (R13/34), and the South-Eastern Norway Regional Health Authority (2013/1657). The trial is currently recruiting at nine centres in Australia and Norway. The trial results will be published in peer-reviewed international journals and presented at national and international conferences.

Trial Registration: Australian New Zealand Clinical Trials Registry ID: ACTRN12613000303741

Funding: National Health and Medical Research Council, Australia, Project Grant 1079089

Strengths and limitations of this study

- This is the first study that is appropriately designed and powered to assess the efficacy of high flow therapy as primary respiratory support for preterm infants.
- The use of a non-inferiority design is appropriate given the advantages of high flow over nasal continuous positive airway pressure. A narrow non-inferiority margin (10%) has been chosen to ensure the study results will be convincing to clinicians
- Blinding of the allocated respiratory support modes is not possible, but objective criteria are specified for the primary outcome of treatment failure.
- Some infants in the high flow group will have initially received a brief period of nasal continuous positive pressure prior to randomisation.
- The results of this trial, whether non-inferiority is demonstrated or not, will influence neonatal practice around the world.

INTRODUCTION

Background

Preterm birth is the leading cause of newborn death worldwide. Every year, 15 million infants are born preterm and >1 million die from complications[1]. Respiratory distress syndrome is one such complication, occurring in 44% of very low birthweight infants (<1500 grams)[2], therefore identifying the optimal method for providing breathing support is crucial for this group. Ventilation via an endotracheal tube (ETT) has improved preterm survival, but increased rates of lung damage[3]. As a result 'non-invasive' techniques (without an ETT) have been developed to minimise lung damage. Nasal continuous positive airway pressure (NCPAP) is an effective mode of support for newborn infants with respiratory distress. It reduces extubation failure in previously ventilated infants[4], and is an effective alternative to intubation and mechanical ventilation at birth for preterm infants with respiratory distress syndrome[5 6]. Published randomised trials have reported successful use of NCPAP without intubation and mechanical ventilation in 48-54% of infants born at 25-30 weeks[6 7]. NCPAP also significantly reduces the need for transfer in infants > 30 weeks' gestation with respiratory distress, born in non-tertiary neonatal units[8].

Unfortunately NCPAP has significant limitations; the need for the prongs to completely fill the nostrils can result in damage to the nasal mucosa and septum[9]. Excessive leak around the prongs and through the mouth can lead to inadequate support, whereas excessive pressure may result in pneumothoraces[6], both of which may require intubation and ventilation. Pressurised gas can cause abdominal distension[10], and the bulky fixation devices obscure the infant's face. Both of these problems interfere with feeding and positioning. These challenges are driving the search for alternative treatments.

In recent years, high flow (HF) therapy has become popular and is used in many neonatal intensive care units (NICUs) in the United States[11], as well as in NICUs and non-tertiary neonatal units within the UK, Australia and New Zealand[12-14]. HF refers to heated, humidified, blended oxygen delivered into the nose via loose fitting short bi-nasal prongs, at a flow of at least 1 L/minute[15 16].

While the use of commercially available HF systems has been adopted by many NICUs, there is relatively little evidence to support its efficacy as respiratory support in the neonatal population, in particular when used as the primary mode of respiratory support. The popularity of HF seems to be due to other perceived advantages; that the cannulae are easier to apply than NCPAP prongs, that it may be more comfortable for infants, that it may be associated with less nasal trauma and may enable easier access to babies' faces, allowing for greater opportunities for feeding and parental bonding[17]. If HF therapy was demonstrated to be as effective as NCPAP, these other factors might lead to it being preferred in clinical practice.

Evidence of Clinical Efficacy of HF

Pooled analysis of 9 randomised controlled trials (RCTs) has demonstrated that NCPAP prevents extubation failure, in comparison to ambient oxygen alone[4]. A 2011 Cochrane review of four randomised studies comparing NCPAP with HF in

177 infants found the trials unsuitable for meta-analysis, due to methodological differences, and concluded there was insufficient evidence to support the use of HF as post-extubation respiratory support in preterm infants[15].

In 2013 three RCTs were published, comparing NCPAP with HF as post-extubation respiratory support. Studies by Collins[18] and Manley[19] included 435 very preterm infants (< 32 weeks' gestation) randomised at extubation, and both trials demonstrated no significant difference in extubation failure within 7 days between the NCPAP and HF groups. Yoder[20] conducted a trial including 432 infants of ≥ 28 weeks' gestation (of whom 291 were randomised at extubation). There was no significant difference between the study groups for the primary outcome of intubation/re-intubation within the first 72 hours of treatment. These three trials suggest that HF is a viable alternative to NCPAP as post-extubation support.

While NCPAP is well established as a primary respiratory support mode for preterm infants, there is little evidence for HF in this setting. A retrospective review of infants initially treated with HF, compared with an earlier cohort managed with NCPAP, found fewer early intubations in the HF cohort[21]. The largest of the aforementioned RCTs included a subgroup of 141 infants who had not been previously intubated and ventilated. Although these infants were not analysed separately, the data are encouraging that HF may be a useful therapy for early respiratory distress. A small pilot RCT including 38 preterm infants managed with either early HF or nasal intermittent positive pressure ventilation demonstrated no difference in treatment failure. However there are no appropriately designed and powered RCTs comparing HF with NCPAP as primary treatment for early respiratory distress syndrome (RDS) in preterm infants.

Potential Advantages and Safety of HF

Concerns that airway pressures generated by HF could be very high have been allayed by an accumulation of data demonstrating that HF generates airway pressures at, or below, those resulting from NCPAP, especially when a leak is maintained around the prongs[22-25].

In late 2005, one of the commercially available HF devices was associated with bacterial infection[26] A worldwide brand recall took place before the device was re-introduced in early 2007, without further reported problems.

Preterm infants with RDS are at risk of pneumothorax, a recognised complication of NCPAP therapy[5 6]. Pneumothorax is also a potential risk of HF therapy. However, reports of pneumothoraces in preterm infants treated with HF are rare; only 2 cases were reported from the 431 infants randomised to receive HF in recent RCTs[18-20], compared with 10/436 infants randomised to receive NCPAP. However, most infants in those studies had previously been intubated and received surfactant replacement, meaning that pneumothorax rates would be expected to be low. Preterm infants treated with primary NCPAP from birth, who have not received surfactant, have much higher pneumothorax rates, up to 9%[6,8]; the risk of pneumothorax during primary HF support is unknown.

Three RCTs have convincingly demonstrated that HF results in less nasal trauma than NCPAP[18-20]. Further studies have shown HF is preferred by parents[27] and by

nursing staff[28]. Other perceived advantages of HF such as greater infant comfort and better establishment of feeding remain unproven.

Rationale and Aim

Neonatal HF use, including as primary support, is rapidly increasing around the world. It is crucial that HF therapy is applied without causing harm, by appropriate assessment of its use before it becomes widely accepted into neonatal practice. If HF does provide comparable support to NCPAP for preterm infants with early respiratory distress, then it is likely that it will be widely adopted in preference to NCPAP in neonatal intensive care units, as it is easier to use, more comfortable for infants[29] reduces nasal trauma, and is preferred by clinicians and parents[14 17 27].
The aim of this study is to assess whether HF is non-inferior to NCPAP in preventing treatment failure, when used as primary respiratory support for preterm infants.

METHODS

Study Design

HIPSTER is an international, multi-centre, randomised, non-inferiority trial, conducted in preterm infants ≥28 weeks' gestational age (GA) requiring primary non-invasive respiratory support for respiratory distress in the first 24 hours of life.

Blinding

The intervention in this study cannot be blinded. To limit bias, pre-defined, objective criteria for the primary outcome of treatment failure are specified, to provide clear direction to clinicians for the decision to escalate respiratory support.

Primary Outcome

The primary outcome is treatment failure within 72 hours after randomisation. Treatment failure is reached once an infant is receiving maximal therapy for their allocated treatment (NCPAP 8 cm H_2O or HF 8 L/min), plus at least one of:

1. Sustained increase in oxygen requirement above ≥40 %, to maintain oxygen saturation in the target range for that centre
2. Frequent apnoea: Six or more apnoeas requiring intervention in a 6-hour period, or two or more apnoeas requiring facemask positive pressure ventilation in a 24-hour period
3. Respiratory acidosis: Blood pH ≤7.20 and carbon dioxide >60 milimetres of mercury (mmHg) on capillary/arterial blood, taken at least an hour after commencing the assigned treatment

Treatment failure will also be adjudged to have occurred in any infant requiring urgent intubation and mechanical ventilation, as determined by the treating clinician.

Secondary outcomes

1. Reason(s) for 'treatment failure'
2. Intubation rate in first 72 hours, and at any time
3. Incidence of radiologically confirmed pneumothorax or other air leak
4. Incidence of significant nasal trauma (as measured using a validated nasal trauma scoring chart)
5. Incidence of bronchopulmonary dysplasia (supplemental oxygen requirement and/or need for respiratory support at 36 weeks' post-menstrual age)
6. Use of postnatal steroids for the treatment of lung disease
7. Discharged home with supplemental oxygen
8. Duration of admission, days of each respiratory support mode, death before discharge
9. Incidence of important neonatal morbidities including: late-onset sepsis, patent ductus arteriosus, necrotising enterocolitis, intestinal perforation, severe intraventricular haemorrhage, and treated retinopathy of prematurity
10. Days to reach full enteral feeds and full suck feeds, method of feeding at discharge, and weight gain until discharge
11. Economic analyses (overseen by a trial health economist)
12. Parental stress and perception of infant's treatment, as measured by a validated questionnaire: ('Parental Stress Scale: Neonatal Intensive Care Unit', PSS: NICU[30]).

Setting

The trial will be conducted in nine tertiary level neonatal intensive care units (four centres in Australia and five centres in Norway). All centres routinely care for preterm infants with respiratory distress, and use NCPAP as their standard mode of primary respiratory support.

Eligibility Criteria

Inclusion: Infants will be included if:

1. they are born at 28 – 36^{+6} weeks GA AND
2. they are admitted to a participating NICU (inborn or outborn) at <24 hours old, AND
3. the decision has been made by the attending clinician, to commence or continue (from stabilisation at birth) non-invasive respiratory support (this does not include the provision of supplemental oxygen alone), AND
4. they have not previously been intubated or received surfactant, AND
5. at randomisation, the infant has received <4 hours of NCPAP support (respiratory support may need to start prior to consent being obtained, if so this will be with NCPAP)

Exclusion: Infants will be excluded if:

1. they immediately require intubation and ventilation (determined by attending clinician), OR
2. they already satisfy 'treatment failure' criteria, OR
3. they have a known major congenital anomaly or air leak (pneumothorax)

Randomisation

Pre-randomisation stratification is by GA (<32 and ≥32 weeks') and by study centre. Multiple births will be randomised individually. The randomisation sequence is computer-generated with variable block sizes, assigned treatment is provided in consecutively numbered, sealed opaque envelopes.

Clinical Management

Eligible infants will be randomised to treatment with either HF or NCPAP. Infants with birth weight ≤1250 g will receive caffeine for apnoea prevention[31] at enrolment if not already given, to be continued at least during the primary outcome period. Apnoeic infants >1250 g may receive caffeine at clinician discretion. Infants in both groups will receive standard supportive care as per individual unit protocols, e.g. blood tests, x-rays, antibiotics, intravenous fluid/nutrition, and enteral feeds

Standard Care - Control group (NCPAP):

1. NCPAP will be delivered using any NCPAP delivery device and short bi-nasal prongs; pressure will start at 6-8 cm H_2O (clinician discretion). Pressure changes will be made in 1 cm H_2O increments/decrements in the range 5-8 cm H_2O. Weaning will be reviewed at least daily with cessation considered once the infant is stable on NCPAP 5 cm H_2O, in <30 % oxygen, for >24 hours. Subsequently, unconditioned 'low flow' oxygen may be given to maintain oxygen saturation.
2. Infants in the NCPAP group will not receive HF unless there is significant nasal trauma (defined as ≥ Stage 2 on the study Nasal Trauma Chart).
3. Infants who reach treatment failure criteria whilst receiving maximal NCPAP (8 cm H_2O) within the primary outcome period (72 hours) will be intubated and ventilated.

If non-invasive respiratory support is required later during admission (either post-extubation or for later deterioration), NCPAP should be used, unless there is significant nasal trauma.

Intervention Group (HF):

1. HF will be given using either Optiflow Junior (Fisher & Paykel Healthcare, New Zealand), or Vapotherm (Vapotherm, Exeter, USA). Gas flow will start at 6-8 L/min (clinician discretion), and flow changes will be made in 1 L/min increments/decrements in the range 4-8 L/min. Weaning will be reviewed at least daily with cessation considered once the infant is stable on 4 L/min, in <30 % oxygen, for >24 hours. Subsequently, unconditioned 'low flow' oxygen may be given to maintain oxygen saturation.

2. Infants who reach treatment failure criteria whilst receiving maximal HF (8 L/min) within the primary outcome period (72 hours) will receive NCPAP at 7-8 cm H_2O (clinician discretion).
3. Infants who again reach treatment failure criteria whilst receiving maximal NCPAP (8 cm H_2O), whilst still within the 72-hour primary outcome period, will be intubated and ventilated.
4. If further non-invasive respiratory support is required later during admission (e.g. for clinical deterioration) infants should receive HF. However, if they have previously reached treatment failure criteria during HF, they may be treated with NCPAP at clinician discretion.

Sample Size Calculation

A review of preterm infants >28 weeks' GA receiving NCPAP as their initial mode of respiratory support at the participating Australian centres (unpublished data) showed that 17 % of such infants were subsequently intubated and ventilated, within 72 hours of starting treatment. We therefore chose an expected NCPAP 'treatment failure' rate of 17%.

We have set the margin of non-inferiority for the trial at 10%. That is, HF will be considered non-inferior to NCPAP if the risk difference for treatment failure, and upper limit of its two-sided 95% confidence interval (CI) is <10%[32]. (e.g. if the NCPAP treatment failure rate is 17%, both the risk difference *and* upper limit of its 2-sided 95% CI must be <27%. To demonstrate this with 90% power, we require a sample size of 375 infants per group, 750 infants in total. We chose this margin of non-inferiority with consideration of the following factors:

- HF is already a widely accepted mode of respiratory support in many tertiary and non-tertiary neonatal units
- Infants in whom HF treatment fails will receive NCPAP, and we hypothesise that this will 'rescue' some of these infants from intubation
- The primary outcome of this study is treatment failure, as opposed to an outcome like death or severe disability, when a lower margin of non-inferiority would be necessary
- This non-inferiority margin was thought to be appropriate, and was agreed upon by all neonatologists in all participating centres, and by parent representatives consulted during the trial design phase.

Statistical Analysis

The incidence of the primary outcome will be compared using risk difference and 2-sided 95% CI. Planned subgroup analyses by GA strata will be performed for the primary outcome. Secondary outcomes will be compared using risk difference (95% CI) and Chi-squared tests, or the appropriate parametric (t-test) or non-parametric (Mann-Whitney U) tests. Statistical analyses will be by intention to treat, conforming to the Consort reporting guidelines.
Cost-effectiveness analysis will incorporate the costs of the device and of hospital care; a decision analysis will be constructed based on the primary outcome and associated hospital costs. Univariate and probabilistic sensitivity analyses will be conducted as a cost per additional treatment failure avoided for HF vs. NCPAP.

ETHICS AND DISSEMINATION

Research Ethics Approval

The HIPSTER Trial has received multi-site ethical approval from the relevant governing bodies for all participating centres.

Recruitment and Consent

Written parental consent is required for all infants participating in the trial. Consent will be sought in the antenatal period when possible, at all sites. When antenatal consent is in place, infants will be randomised as soon as possible after meeting eligibility criteria.
When antenatal consent has not been obtained, infants judged to require non-invasive respiratory support will receive standard treatment (NCPAP) until consent has been given. Families of infants meeting eligibility criteria will be approached at the earliest opportunity after birth, and before 4 hours of NCPAP has been given.
Additionally, at the lead centre (The Royal Women's Hospital, Melbourne), the Human Research Ethics Committee (HREC) has approved a retrospective consent process. Eligible infants who have not been consented antenatally can be randomised as soon as they meet eligibility criteria. Their parents will then be approached for consent in the first few days after trial entry, at which point the parents may choose to consent for their infant to remain in the trial, or remove them and opt for standard treatment.
The consent process, whether antenatal or postnatal, will include both a full verbal explanation of the trial and the use of the written patient information and consent form.

Data Collection and Storage

Outcome data, birth details and parental demographics will be collected from the infant's and mother's medical records, and by parental interview. Data will be de-identified and entered into a paper case record form. Data will subsequently

be entered into REDCap (Research Electronic Data Capture)[33] a secure, password-protected electronic database.

Monitoring and Safety

A data safety monitoring committee (DSMC) comprised of two independent neonatologists and an independent statistician has been appointed. Set DSMC review points on the progress and safety of the trial are after the primary outcome is known for 250 and 500 infants. Whilst no formal stopping rule will be used, the DSMC may recommend ceasing the trial if there is a statistically significant difference ($p<0.001$) in primary outcome between the treatment groups overall or within pre-specified GA subgroups[32], or in serious adverse events (identified as pneumothorax or other air leak from the lung whilst receiving the assigned treatment, and death before discharge). Cessation of the trial may also be recommended if there is equipment failure or recall, or if other evidence becomes available that would make continuing the trial unethical. All serious adverse events are be reported to the lead centre's Human Research and Ethics Committee, and will be reviewed by the DSMC at the pre-specified monitoring points. The first review point was reached in October 2014 and the DSMC recommended that the trial continue without modification.

Dissemination of Results

Trial results will be published in peer-reviewed international journals and presented at relevant national and international conferences. A plain language summary of the results will be sent to the parents of participants.

Current Status and Study duration

The trial began single site recruitment in May 2013, became multicenter in January 2014, extended to international sites in September 2014, and is currently recruiting in all nine participating centres. It is expected that recruitment will be completed in 2016.

Trial Registration

The HIPSTER Trial is registered with the Australian New Zealand Clinical Trials Registry (*ID:* ACTRN12613000303741).

Discussion

HF therapy has been widely adopted into neonatal practice due to due to its desirable qualities such as ease of use, reduced nasal trauma and parental and nursing preference[12 13]. However, it is of concern that HF is being used as primary respiratory support for preterm infants in the absence of good quality evidence of its efficacy in this setting. The HIPSTER Trial is the first appropriately powered and designed trial to assess HF as primary support for preterm infants.

Non-inferiority trials are relatively uncommon in neonatal practice, but appropriate in this case due to the advantages associated with HF, which would make it preferable to NCPAP, provided it is non-inferior in efficacy. The choice of non-inferiority margin is important in such a trial, and our margin of 10% was chosen in view of the fact that the primary outcome was treatment failure, and not a more critical outcome such as death, and that infants who have treatment failure on HF will be offered NCPAP, which may 'rescue' them from intubation and ventilation. This non-inferiority margin is half the size of that used in a previous post-extubation trial of HF published by our group[19], given that the expected rate of treatment failure in the population of The HIPSTER Trial, a study of primary respiratory support, is lower, and therefore the criteria for non-inferiority should be stricter.

A potential limitation to this trial is that blinding is not possible. We have attempted to minimise this by setting objective treatment failure criteria, which were agreed upon by all participating centres. Some infants randomised to HF will have received a brief period of NCPAP before randomisation, which conceivably could affect interpretation of the results. However, we have aimed to restrict the impact of this by making any infant who has received 4 or more hours of NCPAP ineligible for the trial, and by the use of antenatal consent when possible, and a retrospective consent process at the lead centre. Acceptance of such a process requires the approval of both the HREC and the treating clinical team, and this may vary from site to site. We feel retrospective consent is appropriate in this trial given that HF has already been adopted into standard practice as a mode of primary respiratory support by some neonatologists[12], and that along with the inclusion of 'rescue' NCPAP the HREC adjudged that infants in the HF group were not exposed to additional risk in comparison to those treated with NCPAP.

The use of HF in neonatal practice is now well established, but good quality evidence is required to determine in which clinical settings this is appropriate. If this trial demonstrates that HF is non-inferior to NCPAP as primary support, then this practice is likely to be widely adopted around the world. However, if HF is inferior to NCPAP then this study will ensure that preterm infants, who require non-invasive respiratory support, receive the optimal treatment.

Contributorship Statement

CR conceived and designed the trial protocol, wrote the first draft, and revised the manuscript for intellectual content. LO, BM and PD conceived and designed the trial protocol and revised the manuscript for important intellectual content. SD designed the protocol statistical analysis and revised the manuscript for important intellectual content. All authors have read and approved the final manuscript, and are accountable for its accuracy.

Competing Interests Statement

The authors have no competing interests to declare.

Data Sharing Statement

Further information on the study protocol may be requested from the corresponding author.

Research Ethics Approval

The trial is approved by: The Royal Women's Hospital Human Research Ethics Committee (Reference: 13/12), The Royal Children's Hospital Human Research Ethics Committee (Reference: 33144A), The Mercy Hospital for Women Human Research Ethics Committee (Reference: R13/34), and South-Eastern Norway Regional Health Authority Committee for Medical and Health Research (Reference: 2013/1657).

Funding

The HIPSTER trial is supported by a National Health and Medical Research Council (NHMRC, Australia) project grant (No. 1079089), a NHMRC Centre for Research Excellence grant (No. 1060733), and a grant from The Royal Brisbane and Women's Hospital (Australia) Foundation.

Acknowledgements

We wish to thank the following for their contribution to the trial:

HIPSTER investigators: TE Calisch, D Cartwright, C Collins, G Flagstad, D Fugelseth, DH Frøisland, M Grønn, C Klingenberg, A Leknessund, A Malhotra, B Nakstad, M Pritchard, A Ronnestad, AL Solevåg.
Research nurses/assistants: B Argus, MI Austgulen, A Brett, U Grepperud, KG Gustavsen, EA Hansen, B Høium, A Jørstad, G Lack, E Ludvigsen, PJ Lyseggen, L McKeown, B Mills, CS Nygaard, C Wong, E Yeomans.
Royal Women's Hospital Research Fellows: L McGrory, J O'Shea.
Data Safety Monitoring Committee: H Liley (chair), K Lee, K Wheeler.

REFERENCES

1. Blencowe H, Cousens S, Oestergaard MZ, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. Lancet 2012;**379**(9832):2162-72.
2. Fanaroff AA, Stoll BJ, Wright LL, et al. Trends in neonatal morbidity and mortality for very low birthweight infants. American journal of obstetrics and gynecology 2007;**196**(2):147 e1-8.
3. Chess PR, D'Angio CT, Pryhuber GS, et al. Pathogenesis of bronchopulmonary dysplasia. Seminars in perinatology 2006;**30**(4):171-8.
4. 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.
5. Finer NN, Carlo WA, Walsh MC, et al. Early CPAP versus surfactant in extremely preterm infants. The New England journal of medicine 2010;**362**(21):1970-9.
6. Morley CJ, Davis PG, Doyle LW, et al. Nasal CPAP or intubation at birth for very preterm infants. The New England journal of medicine 2008;**358**(7):700-8.
7. Dunn MS, Kaempf J, de Klerk A, et al. Randomized trial comparing 3 approaches to the initial respiratory management of preterm neonates. Pediatrics 2011;**128**(5):e1069-76.
8. Buckmaster AG, Arnolda G, Wright IM, et al. Continuous positive airway pressure therapy for infants with respiratory distress in non tertiary care centers: a randomized, controlled trial. Pediatrics 2007;**120**(3):509-18.
9. Robertson NJ, McCarthy LS, Hamilton PA, et al. Nasal deformities resulting from flow driver continuous positive airway pressure. Archives of disease in childhood Fetal and neonatal edition 1996;**75**(3):F209-12.
10. Jaile JC, Levin T, Wung JT, et al. Benign gaseous distension of the bowel in premature infants treated with nasal continuous airway pressure: a study of contributing factors. AJR American journal of roentgenology 1992;**158**(1):125-7.
11. Hochwald O, Osiovich H. High flow nasal cannulae in neonatal intensive care units: is clinical practice consistent with the evidence. Paper presented at: PAS Annual Meeting; 1-4 May 2010; Vancouver, British Columbia 2010.
12. Hough JL, Shearman AD, Jardine LA, et al. Humidified high flow nasal cannulae: current practice in Australasian nurseries, a survey. Journal of paediatrics and child health 2012;**48**(2):106-13.
13. Nath P, Ponnusamy V, Willis K, et al. Current practices of high and low flow oxygen therapy and humidification in UK neonatal units. Pediatrics international : official journal of the Japan Pediatric Society 2010;**52**:893-94.
14. Manley BJ, Owen L, Doyle LW, et al. High-flow nasal cannulae and nasal continuous positive airway pressure use in non-tertiary special care nurseries in Australia and New Zealand. Journal of paediatrics and child health 2012;**48**(1):16-21.

15. Wilkinson D, Andersen C, O'Donnell CP, et al. High flow nasal cannula for respiratory support in preterm infants. Cochrane Database Syst Rev 2011(5):CD006405.
16. Waugh JB, Granger WM. An evaluation of 2 new devices for nasal high-flow gas therapy. Respiratory care 2004;**49**(8):902-6.
17. Manley BJ, Dold SK, Davis PG, et al. High-flow nasal cannulae for respiratory support of preterm infants: a review of the evidence. Neonatology 2012;**102**(4):300-8.
18. Collins CL, Holberton JR, Barfield C, et al. A randomized controlled trial to compare heated humidified high-flow nasal cannulae with nasal continuous positive airway pressure postextubation in premature infants. The Journal of pediatrics 2013;**162**(5):949-54 e1.
19. Manley BJ, Owen LS, Doyle LW, et al. High-Flow Nasal Cannulae in Very Preterm Infants after Extubation. The New England journal of medicine 2013;**369**(15):1425-33.
20. Yoder BA, Stoddard RA, Li M, et al. Heated, humidified high-flow nasal cannula versus nasal CPAP for respiratory support in neonates. Pediatrics 2013;**131**(5):e1482-90.
21. Shoemaker MT, Pierce MR, Yoder BA, et al. High flow nasal cannula versus nasal CPAP for neonatal respiratory disease: a retrospective study. J Perinatol 2007;**27**(2):85-91.
22. Lampland AL, Plumm B, Meyers PA, et al. Observational study of humidified high-flow nasal cannula compared with nasal continuous positive airway pressure. The Journal of pediatrics 2009;**154**(2):177-82.
23. Sivieri EM, Gerdes JS, Abbasi S. Effect of HFNC flow rate, cannula size, and nares diameter on generated airway pressures: An in vitro study. Pediatr Pulmonol 2012.
24. Spence KL, Murphy D, Kilian C, et al. High-flow nasal cannula as a device to provide continuous positive airway pressure in infants. J Perinatol 2007;**27**(12):772-5.
25. Wilkinson DJ, Andersen CC, Smith K, et al. Pharyngeal pressure with high-flow nasal cannulae in premature infants. J Perinatol 2008;**28**(1):42-7.
26. Jhung MA, Sunenshine RH, Noble-Wang J, et al. A national outbreak of Ralstonia mannitolilytica associated with use of a contaminated oxygen-delivery device among pediatric patients. Pediatrics 2007;**119**(6):1061-8.
27. Klingenberg C, Pettersen M, Hansen EA, et al. Patient comfort during treatment with heated humidified high flow nasal cannulae versus nasal continuous positive airway pressure: a randomised cross-over trial. Archives of disease in childhood Fetal and neonatal edition 2014;**99**(2):F134-7.
28. Roberts CT, Manley BJ, Dawson JA, et al. Nursing perceptions of high-flow nasal cannulae treatment for very preterm infants. Journal of paediatrics and child health 2014.
29. Osman M, Elsharkawy A, Abdel-Hady H. Assessment of pain during application of nasal-continuous positive airway pressure and heated, humidified high-flow nasal cannulae in preterm infants. J Perinatol 2014.
30. Miles MS, Funk SG, Carlson J. Parental Stressor Scale: neonatal intensive care unit. Nursing research 1993;**42**(3):148-52.

31. Schmidt B, Roberts RS, Davis P, et al. Caffeine therapy for apnea of prematurity. The New England journal of medicine 2006;**354**(20):2112-21.
32. Piaggio G, Elbourne DR, Pocock SJ, et al. Reporting of noninferiority and equivalence randomized trials: extension of the CONSORT 2010 statement. JAMA : the journal of the American Medical Association 2012;**308**(24):2594-604.
33. Harris PA, Taylor R, Thielke R, et al. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. Journal of biomedical informatics 2009;**42**(2):377-81.

BMJ Open

A multi-centre, randomised controlled, non-inferiority trial, comparing high flow therapy with nasal continuous positive airway pressure as primary support for preterm infants with respiratory distress (The HIPSTER Trial): study protocol

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2015-008483.R1
Article Type:	Protocol
Date Submitted by the Author:	13-May-2015
Complete List of Authors:	Roberts, Calum; The Royal Women's Hospital, Newborn Research Centre; The University of Melbourne, Department of Obstetrics and Gynaecology Owen, Louise; The Royal Women's Hospital, Newborn Research Centre; The University of Melbourne, Department of Obstetrics and Gynaecology Manley, Brett; The Royal Women's Hospital, Newborn Research Centre; The University of Melbourne, Department of Obstetrics and Gynaecology Donath, Susan; Murdoch Children's Research Institute, Clinical Epidemiology and Biostatistics Unit; The University of Melbourne, Department of Paediatrics Davis, Peter; The Royal Women's Hospital, Newborn Research Centre; The University of Melbourne, Department of Obstetrics and Gynaecology
Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Respiratory medicine, Intensive care
Keywords:	NEONATOLOGY, Neonatal intensive & critical care < INTENSIVE & CRITICAL CARE, Clinical trials < THERAPEUTICS

A multi-centre, randomised controlled, non-inferiority trial, comparing high flow therapy with nasal continuous positive airway pressure as primary support for preterm infants with respiratory distress (The HIPSTER Trial): study protocol

Calum T. Roberts[1,2], Louise S. Owen[1-3], Brett J. Manley[1,2], Susan M. Donath [3,4], and Peter G. Davis[1-3]

1. The Royal Women's Hospital, Melbourne, Australia
2. Department of Obstetrics and Gynaecology, The University of Melbourne, Australia
3. Murdoch Children's Research Institute, Melbourne, Australia
4. Department of Paediatrics, The University of Melbourne, Australia

Corresponding Author: Calum T. Roberts

Address: Newborn Research Centre
The Royal Women's Hospital
Locked Bag 300
Grattan St & Flemington Rd
Parkville 3052
Australia

Telephone: +61 3 83453773
Email: calum.roberts@thewomens.org.au

Word count: 3565
Abstract word count: 296

Keywords: preterm infants; non-invasive ventilation; continuous positive airway pressure; neonatal intensive care

ABSTRACT

Introduction: High flow (HF) therapy is an increasingly popular mode of non-invasive respiratory support for preterm infants. While there is now evidence to support the use of HF to reduce extubation failure, there have been no appropriately designed and powered studies to assess the use of HF as primary respiratory support soon after birth. Our hypothesis is that HF is non-inferior to the standard treatment, nasal continuous positive airway pressure (NCPAP) as primary respiratory support for preterm infants.

Methods and Analysis: The HIPSTER trial is an unblinded, international, multi-centre, randomised, non-inferiority trial. Eligible infants are preterm infants 28 to 36+6 weeks' gestational age (GA) who require primary non-invasive respiratory support for respiratory distress, in the first 24 hours of life. Infants are randomised to treatment with either HF or NCPAP. The primary outcome is treatment failure within 72 hours after randomisation, as determined by objective oxygenation, blood gas, and apnoea criteria, or the need for urgent intubation and mechanical ventilation. Secondary outcomes include the incidence of intubation, pneumothorax, bronchopulmonary dysplasia, nasal trauma, costs associated with hospital care, and parental stress. With a specified non-inferiority margin of 10%, using a two-sided 95% confidence interval and 90% power the study requires 375 infants per group (total 750 infants).

Ethics and Dissemination: Ethical approval has been granted by the relevant human research ethics committees at The Royal Women's Hospital (13/12), The Royal Children's Hospital (33144A), The Mercy Hospital for Women (R13/34), and the South-Eastern Norway Regional Health Authority (2013/1657). The trial is currently recruiting at nine centres in Australia and Norway. The trial results will be published in peer-reviewed international journals and presented at national and international conferences.

Trial Registration: Australian New Zealand Clinical Trials Registry ID: ACTRN12613000303741

Funding: National Health and Medical Research Council, Australia, Project Grant 1079089

Strengths and limitations of this study

- This is the first study that is appropriately designed and powered to assess the efficacy of high flow therapy as primary respiratory support for preterm infants.
- The use of a non-inferiority design is appropriate given the advantages of high flow over nasal continuous positive airway pressure. A narrow non-inferiority margin (10%) has been chosen to ensure the study results will be convincing to clinicians
- Blinding of the allocated respiratory support modes is not possible, but objective criteria are specified for the primary outcome of treatment failure.
- Some infants in the high flow group will have initially received a brief period of nasal continuous positive pressure prior to randomisation.

INTRODUCTION

Background

Preterm birth is the leading cause of newborn death worldwide. Every year, 15 million infants are born preterm and >1 million die from complications[1]. Respiratory distress syndrome is one such complication, occurring in 44% of very low birthweight infants (<1500 grams)[2], therefore identifying the optimal method for providing breathing support is crucial for this group. Ventilation via an endotracheal tube (ETT) has improved preterm survival, but increased rates of lung damage[3]. As a result 'non-invasive' techniques (without an ETT) have been developed to minimise lung damage. Nasal continuous positive airway pressure (NCPAP) is an effective mode of support for newborn infants with respiratory distress. It reduces extubation failure in previously ventilated infants[4], and is an effective alternative to intubation and mechanical ventilation at birth for preterm infants with respiratory distress syndrome[5 6]. Published randomised trials have reported successful use of NCPAP without intubation and mechanical ventilation in 48-54% of infants born at 25-30 weeks[6 7]. NCPAP also significantly reduces the need for transfer in infants > 30 weeks' gestation with respiratory distress, born in non-tertiary neonatal units[8].

Unfortunately NCPAP has significant limitations; the need for the prongs to completely fill the nostrils can result in damage to the nasal mucosa and septum[9]. Excessive leak around the prongs and through the mouth can lead to inadequate support, whereas excessive pressure may result in pneumothoraces[6], both of which may require intubation and ventilation. Pressurised gas can cause abdominal distension[10], and the bulky fixation devices obscure the infant's face. Both of these problems interfere with feeding and positioning. These challenges are driving the search for alternative treatments.

In recent years, high flow (HF) therapy has become popular and is used in many neonatal intensive care units (NICUs) in the United States[11], as well as in NICUs and non-tertiary neonatal units within the UK, Australia and New Zealand[12-14]. HF refers to heated, humidified, blended oxygen delivered into the nose via loose fitting short bi-nasal prongs, at a flow of at least 1 L/minute[15 16].

While the use of commercially available HF systems has been adopted by many NICUs, there is relatively little evidence to support its efficacy as respiratory support in the neonatal population, in particular when used as the primary mode of respiratory support. The popularity of HF seems to be due to other perceived advantages; that the cannulae are easier to apply than NCPAP prongs, that it may be more comfortable for infants, that it may be associated with less nasal trauma and may enable easier access to babies' faces, allowing for greater opportunities for feeding and parental bonding[17]. If HF therapy was demonstrated to be as effective as NCPAP, these other factors might lead to it being preferred in clinical practice.

Evidence of Clinical Efficacy of HF

Pooled analysis of 9 randomised controlled trials (RCTs) has demonstrated that NCPAP prevents extubation failure, in comparison to ambient oxygen alone[4]. A 2011 Cochrane review of four randomised studies comparing NCPAP with HF in

177 infants found the trials unsuitable for meta-analysis, due to methodological differences, and concluded there was insufficient evidence to support the use of HF as post-extubation respiratory support in preterm infants[15].

In 2013 three RCTs were published, comparing NCPAP with HF as post-extubation respiratory support. Studies by Collins[18] and Manley[19] included 435 very preterm infants (< 32 weeks' gestation) randomised at extubation, and both trials demonstrated no significant difference in extubation failure within 7 days between the NCPAP and HF groups. Yoder[20] conducted a trial including 432 infants of ≥ 28 weeks' gestation (of whom 291 were randomised at extubation). There was no significant difference between the study groups for the primary outcome of intubation/re-intubation within the first 72 hours of treatment. These three trials suggest that HF is a viable alternative to NCPAP as post-extubation support.

While NCPAP is well established as a primary respiratory support mode for preterm infants, there is little evidence for HF in this setting. A retrospective review of infants initially treated with HF, compared with an earlier cohort managed with NCPAP, found fewer early intubations in the HF cohort[21]. The largest of the aforementioned RCTs included a subgroup of 141 infants who had not been previously intubated and ventilated. Although these infants were not analysed separately, the data are encouraging that HF may be a useful therapy for early respiratory distress. A small pilot RCT including 38 preterm infants managed with either early HF or nasal intermittent positive pressure ventilation demonstrated no difference in treatment failure. However there are no appropriately designed and powered RCTs comparing HF with NCPAP as primary treatment for early respiratory distress syndrome (RDS) in preterm infants.

Potential Advantages and Safety of HF

Concerns that airway pressures generated by HF could be very high have been allayed by an accumulation of data demonstrating that HF generates airway pressures at, or below, those resulting from NCPAP, especially when a leak is maintained around the prongs[22-25].

In late 2005, one of the commercially available HF devices was associated with bacterial infection[26] A worldwide brand recall took place before the device was re-introduced in early 2007, without further reported problems.

Preterm infants with RDS are at risk of pneumothorax, a recognised complication of NCPAP therapy[5 6]. Pneumothorax is also a potential risk of HF therapy. However, reports of pneumothoraces in preterm infants treated with HF are rare; only 2 cases were reported from the 431 infants randomised to receive HF in recent RCTs[18-20], compared with 10/436 infants randomised to receive NCPAP. However, most infants in those studies had previously been intubated and received surfactant replacement, meaning that pneumothorax rates would be expected to be low. Preterm infants treated with primary NCPAP from birth, who have not received surfactant, have much higher pneumothorax rates, up to 9%[6,8]; the risk of pneumothorax during primary HF support is unknown.

Three RCTs have convincingly demonstrated that HF results in less nasal trauma than NCPAP[18-20]. Further studies have shown HF is preferred by parents[27] and by

nursing staff[28]. Other perceived advantages of HF such as greater infant comfort and better establishment of feeding remain unproven.

Rationale and Aim

Neonatal HF use, including as primary support, is rapidly increasing around the world. It is crucial that HF therapy is applied without causing harm, by appropriate assessment of its use before it becomes widely accepted into neonatal practice. If HF does provide comparable support to NCPAP for preterm infants with early respiratory distress, then it is likely that it will be widely adopted in preference to NCPAP in neonatal intensive care units, as it is easier to use, more comfortable for infants[29] reduces nasal trauma, and is preferred by clinicians and parents[14 17 27].
The aim of this study is to assess whether HF is non-inferior to NCPAP in preventing treatment failure, when used as primary respiratory support for preterm infants.

METHODS

Study Design

HIPSTER is an international, multi-centre, randomised, non-inferiority trial, conducted in preterm infants ≥28 weeks' gestational age (GA) requiring primary non-invasive respiratory support for respiratory distress in the first 24 hours of life.

Blinding

The intervention in this study cannot be blinded. To limit bias, pre-defined, objective criteria for the primary outcome of treatment failure are specified, to provide clear direction to clinicians for the decision to escalate respiratory support.

Primary Outcome

The primary outcome is treatment failure within 72 hours after randomisation. Treatment failure is reached once an infant is receiving maximal therapy for their allocated treatment (NCPAP 8 cm H_2O or HF 8 L/min), plus at least one of:

1. Sustained increase in oxygen requirement above ≥40 %, to maintain oxygen saturation in the target range for that centre
2. Frequent apnoea: Six or more apnoeas requiring intervention in a 6-hour period, or two or more apnoeas requiring facemask positive pressure ventilation in a 24-hour period
3. Respiratory acidosis: Blood pH ≤7.20 and carbon dioxide >60 milimetres of mercury (mmHg) on capillary/arterial blood, taken at least an hour after commencing the assigned treatment

Treatment failure will also be adjudged to have occurred in any infant requiring urgent intubation and mechanical ventilation, as determined by the treating clinician.

Secondary outcomes

1. Reason(s) for 'treatment failure'
2. Intubation rate in first 72 hours, and at any time
3. Incidence of radiologically confirmed pneumothorax or other air leak
4. Incidence of significant nasal trauma (as measured using a validated nasal trauma scoring chart)
5. Incidence of bronchopulmonary dysplasia (supplemental oxygen requirement and/or need for respiratory support at 36 weeks' post-menstrual age)
6. Use of postnatal steroids for the treatment of lung disease
7. Discharged home with supplemental oxygen
8. Duration of admission, days of each respiratory support mode, death before discharge
9. Incidence of important neonatal morbidities including: late-onset sepsis, patent ductus arteriosus, necrotising enterocolitis, intestinal perforation, severe intraventricular haemorrhage, and treated retinopathy of prematurity
10. Days to reach full enteral feeds and full suck feeds, method of feeding at discharge, and weight gain until discharge
11. Economic analyses (overseen by a trial health economist)
12. Parental stress and perception of infant's treatment, as measured by a validated questionnaire: ('Parental Stress Scale: Neonatal Intensive Care Unit', PSS: NICU[30]).

Setting

The trial will be conducted in nine tertiary level neonatal intensive care units (four centres in Australia and five centres in Norway). All centres routinely care for preterm infants with respiratory distress, and use NCPAP as their standard mode of primary respiratory support.

Eligibility Criteria

Inclusion: Infants will be included if:

1. they are born at 28 – 36^{+6} weeks GA AND
2. they are admitted to a participating NICU (inborn or outborn) at <24 hours old, AND
3. the decision has been made by the attending clinician, to commence or continue (from stabilisation at birth) non-invasive respiratory support (this does not include the provision of supplemental oxygen alone), AND
4. they have not previously been intubated or received surfactant, AND
5. at randomisation, the infant has received <4 hours of NCPAP support (respiratory support may need to start prior to consent being obtained, if so this will be with NCPAP)

Exclusion: Infants will be excluded if:

1. they immediately require intubation and ventilation (determined by attending clinician), OR
2. they already satisfy 'treatment failure' criteria, OR
3. they have a known major congenital anomaly or air leak (pneumothorax)

Randomisation

Pre-randomisation stratification is by GA (<32 and ≥32 weeks') and by study centre. Multiple births will be randomised individually. The randomisation sequence is computer-generated with variable block sizes, assigned treatment is provided in consecutively numbered, sealed opaque envelopes.

Clinical Management

Eligible infants will be randomised to treatment with either HF or NCPAP. Infants with birth weight ≤1250 g will receive caffeine for apnoea prevention[31] at enrolment if not already given, to be continued at least during the primary outcome period. Apnoeic infants >1250 g may receive caffeine at clinician discretion. Infants in both groups will receive standard supportive care as per individual unit protocols, e.g. blood tests, x-rays, antibiotics, intravenous fluid/nutrition, and enteral feeds

Standard Care - Control group (NCPAP):

1. NCPAP will be delivered using any NCPAP delivery device and short bi-nasal prongs; pressure will start at 6-8 cm H_2O (clinician discretion). Pressure changes will be made in 1 cm H_2O increments/decrements in the range 5-8 cm H_2O. Weaning will be reviewed at least daily with cessation considered once the infant is stable on NCPAP 5 cm H_2O, in <30 % oxygen, for >24 hours. Subsequently, unconditioned 'low flow' oxygen may be given to maintain oxygen saturation.
2. Infants in the NCPAP group will not receive HF unless there is significant nasal trauma (defined as ≥ Stage 2 on the study Nasal Trauma Chart).
3. Infants who reach treatment failure criteria whilst receiving maximal NCPAP (8 cm H_2O) within the primary outcome period (72 hours) will be intubated and ventilated.

If non-invasive respiratory support is required later during admission (either post-extubation or for later deterioration), NCPAP should be used, unless there is significant nasal trauma.

Intervention Group (HF):

1. HF will be given using either Optiflow Junior (Fisher & Paykel Healthcare, New Zealand), or Vapotherm (Vapotherm, Exeter, USA). Gas flow will start at 6-8 L/min (clinician discretion), and flow changes will be made in 1 L/min increments/decrements in the range 4-8 L/min. Weaning will be reviewed at least daily with cessation considered once the infant is stable on 4 L/min, in <30 % oxygen, for >24 hours. Subsequently, unconditioned 'low flow' oxygen may be given to maintain oxygen saturation.

2. Infants who reach treatment failure criteria whilst receiving maximal HF (8 L/min) within the primary outcome period (72 hours) will receive NCPAP at 7-8 cm H_2O (clinician discretion).
3. Infants who again reach treatment failure criteria whilst receiving maximal NCPAP (8 cm H_2O), whilst still within the 72-hour primary outcome period, will be intubated and ventilated.
4. If further non-invasive respiratory support is required later during admission (e.g. for clinical deterioration) infants should receive HF. However, if they have previously reached treatment failure criteria during HF, they may be treated with NCPAP at clinician discretion.

Sample Size Calculation

A review of preterm infants >28 weeks' GA receiving NCPAP as their initial mode of respiratory support at the participating Australian centres (unpublished data) showed that 17 % of such infants were subsequently intubated and ventilated, within 72 hours of starting treatment. We therefore chose an expected NCPAP 'treatment failure' rate of 17%.

We have set the margin of non-inferiority for the trial at 10%. That is, HF will be considered non-inferior to NCPAP if the risk difference for treatment failure, and upper limit of its two-sided 95% confidence interval (CI) is <10%[32]. (e.g. if the NCPAP treatment failure rate is 17%, both the risk difference *and* upper limit of its 2-sided 95% CI must be <27%. To demonstrate this with 90% power, we require a sample size of 375 infants per group, 750 infants in total. We chose this margin of non-inferiority with consideration of the following factors:

- HF is already a widely accepted mode of respiratory support in many tertiary and non-tertiary neonatal units
- Infants in whom HF treatment fails will receive NCPAP, and we hypothesise that this will 'rescue' some of these infants from intubation
- The primary outcome of this study is treatment failure, as opposed to an outcome like death or severe disability, when a lower margin of non-inferiority would be necessary
- This non-inferiority margin was thought to be appropriate, and was agreed upon by all neonatologists in all participating centres, and by parent representatives consulted during the trial design phase.

Statistical Analysis

The incidence of the primary outcome will be compared using risk difference and 2-sided 95% CI. Planned subgroup analyses by GA strata will be performed for the primary outcome. Secondary outcomes will be compared using risk difference (95% CI) and Chi-squared tests, or the appropriate parametric (t-test) or non-parametric (Mann-Whitney U) tests. Statistical analyses will be by intention to treat, conforming to the Consort reporting guidelines.
Cost-effectiveness analysis will incorporate the costs of the device and of hospital care; a decision analysis will be constructed based on the primary outcome and associated hospital costs. Univariate and probabilistic sensitivity analyses will be conducted as a cost per additional treatment failure avoided for HF vs. NCPAP.

ETHICS AND DISSEMINATION

Research Ethics Approval

The HIPSTER Trial has received multi-site ethical approval from the relevant governing bodies for all participating centres.

Recruitment and Consent

Written parental consent is required for all infants participating in the trial. Consent will be sought in the antenatal period when possible, at all sites. When antenatal consent is in place, infants will be randomised as soon as possible after meeting eligibility criteria.
When antenatal consent has not been obtained, infants judged to require non-invasive respiratory support will receive standard treatment (NCPAP) until consent has been given. Families of infants meeting eligibility criteria will be approached at the earliest opportunity after birth, and before 4 hours of NCPAP has been given.
Additionally, at the lead centre (The Royal Women's Hospital, Melbourne), the Human Research Ethics Committee (HREC) has approved a retrospective consent process. Eligible infants who have not been consented antenatally can be randomised as soon as they meet eligibility criteria. Their parents will then be approached for consent in the first few days after trial entry, at which point the parents may choose to consent for their infant to remain in the trial, or remove them and opt for standard treatment.
The consent process, whether antenatal or postnatal, will include both a full verbal explanation of the trial and the use of the written patient information and consent form.

Data Collection and Storage

Outcome data, birth details and parental demographics will be collected from the infant's and mother's medical records, and by parental interview. Data will be de-identified and entered into a paper case record form. Data will subsequently

be entered into REDCap (Research Electronic Data Capture)[33] a secure, password-protected electronic database.

Monitoring and Safety

A data safety monitoring committee (DSMC) comprised of two independent neonatologists and an independent statistician has been appointed. Set DSMC review points on the progress and safety of the trial are after the primary outcome is known for 250 and 500 infants. Whilst no formal stopping rule will be used, the DSMC may recommend ceasing the trial if there is a statistically significant difference ($p<0.001$) in primary outcome between the treatment groups overall or within pre-specified GA subgroups[32], or in serious adverse events (identified as pneumothorax or other air leak from the lung whilst receiving the assigned treatment, and death before discharge). Cessation of the trial may also be recommended if there is equipment failure or recall, or if other evidence becomes available that would make continuing the trial unethical. All serious adverse events are be reported to the lead centre's Human Research and Ethics Committee, and will be reviewed by the DSMC at the pre-specified monitoring points. The first review point was reached in October 2014 and the DSMC recommended that the trial continue without modification.

Dissemination of Results

Trial results will be published in peer-reviewed international journals and presented at relevant national and international conferences. A plain language summary of the results will be sent to the parents of participants.

Current Status and Study duration

The trial began single site recruitment in May 2013, became multicenter in January 2014, extended to international sites in September 2014, and is currently recruiting in all nine participating centres. It is expected that recruitment will be completed in 2016.

Trial Registration

The HIPSTER Trial is registered with the Australian New Zealand Clinical Trials Registry (*ID:* ACTRN12613000303741).

Discussion

HF therapy has been widely adopted into neonatal practice due to due to its desirable qualities such as ease of use, reduced nasal trauma and parental and nursing preference[12 13]. However, it is of concern that HF is being used as primary respiratory support for preterm infants in the absence of good quality evidence of its efficacy in this setting. The HIPSTER Trial is the first appropriately powered and designed trial to assess HF as primary support for preterm infants.

Non-inferiority trials are relatively uncommon in neonatal practice, but appropriate in this case due to the advantages associated with HF, which would make it preferable to NCPAP, provided it is non-inferior in efficacy. The choice of non-inferiority margin is important in such a trial, and our margin of 10% was chosen in view of the fact that the primary outcome was treatment failure, and not a more critical outcome such as death, and that infants who have treatment failure on HF will be offered NCPAP, which may 'rescue' them from intubation and ventilation. This non-inferiority margin is half the size of that used in a previous post-extubation trial of HF published by our group[19], given that the expected rate of treatment failure in the population of The HIPSTER Trial, a study of primary respiratory support, is lower, and therefore the criteria for non-inferiority should be stricter.

A potential limitation to this trial is that blinding is not possible. We have attempted to minimise this by setting objective treatment failure criteria, which were agreed upon by all participating centres. Some infants randomised to HF will have received a brief period of NCPAP before randomisation, which conceivably could affect interpretation of the results. However, we have aimed to restrict the impact of this by making any infant who has received 4 or more hours of NCPAP ineligible for the trial, and by the use of antenatal consent when possible, and a retrospective consent process at the lead centre. Acceptance of such a process requires the approval of both the HREC and the treating clinical team, and this may vary from site to site. We feel retrospective consent is appropriate in this trial given that HF has already been adopted into standard practice as a mode of primary respiratory support by some neonatologists[12], and that along with the inclusion of 'rescue' NCPAP the HREC adjudged that infants in the HF group were not exposed to additional risk in comparison to those treated with NCPAP.

The use of HF in neonatal practice is now well established, but good quality evidence is required to determine in which clinical settings this is appropriate. If this trial demonstrates that HF is non-inferior to NCPAP as primary support, then this practice is likely to be widely adopted around the world. However, if HF is inferior to NCPAP then this study will ensure that preterm infants, who require non-invasive respiratory support, receive the optimal treatment.

Contributorship Statement

CR conceived and designed the trial protocol, wrote the first draft, and revised the manuscript for intellectual content. LO, BM and PD conceived and designed the trial protocol and revised the manuscript for important intellectual content. SD designed the protocol statistical analysis and revised the manuscript for important intellectual content. All authors have read and approved the final manuscript, and are accountable for its accuracy.

Competing Interests Statement

The authors have no competing interests to declare.

Data Sharing Statement

Further information on the study protocol may be requested from the corresponding author.

Research Ethics Approval

The trial is approved by: The Royal Women's Hospital Human Research Ethics Committee (Reference: 13/12), The Royal Children's Hospital Human Research Ethics Committee (Reference: 33144A), The Mercy Hospital for Women Human Research Ethics Committee (Reference: R13/34), and South-Eastern Norway Regional Health Authority Committee for Medical and Health Research (Reference: 2013/1657).

Funding

The HIPSTER trial is supported by a National Health and Medical Research Council (NHMRC, Australia) project grant (No. 1079089), a NHMRC Centre for Research Excellence grant (No. 1060733), and a grant from The Royal Brisbane and Women's Hospital (Australia) Foundation.

Acknowledgements

We wish to thank the following for their contribution to the trial:

HIPSTER investigators: TE Calisch, D Cartwright, C Collins, G Flagstad, D Fugelseth, DH Frøisland, M Grønn, C Klingenberg, A Leknessund, A Malhotra, B Nakstad, M Pritchard, A Ronnestad, AL Solevåg.
Research nurses/assistants: B Argus, MI Austgulen, A Brett, U Grepperud, KG Gustavsen, EA Hansen, B Høium, A Jørstad, G Lack, E Ludvigsen, PJ Lyseggen, L McKeown, B Mills, CS Nygaard, C Wong, E Yeomans.
Royal Women's Hospital Research Fellows: L McGrory, J O'Shea.
Data Safety Monitoring Committee: H Liley (chair), K Lee, K Wheeler.

REFERENCES

1. Blencowe H, Cousens S, Oestergaard MZ, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. Lancet 2012;**379**(9832):2162-72.
2. Fanaroff AA, Stoll BJ, Wright LL, et al. Trends in neonatal morbidity and mortality for very low birthweight infants. American journal of obstetrics and gynecology 2007;**196**(2):147 e1-8.
3. Chess PR, D'Angio CT, Pryhuber GS, et al. Pathogenesis of bronchopulmonary dysplasia. Seminars in perinatology 2006;**30**(4):171-8.
4. 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.
5. Finer NN, Carlo WA, Walsh MC, et al. Early CPAP versus surfactant in extremely preterm infants. The New England journal of medicine 2010;**362**(21):1970-9.
6. Morley CJ, Davis PG, Doyle LW, et al. Nasal CPAP or intubation at birth for very preterm infants. The New England journal of medicine 2008;**358**(7):700-8.
7. Dunn MS, Kaempf J, de Klerk A, et al. Randomized trial comparing 3 approaches to the initial respiratory management of preterm neonates. Pediatrics 2011;**128**(5):e1069-76.
8. Buckmaster AG, Arnolda G, Wright IM, et al. Continuous positive airway pressure therapy for infants with respiratory distress in non tertiary care centers: a randomized, controlled trial. Pediatrics 2007;**120**(3):509-18.
9. Robertson NJ, McCarthy LS, Hamilton PA, et al. Nasal deformities resulting from flow driver continuous positive airway pressure. Archives of disease in childhood Fetal and neonatal edition 1996;**75**(3):F209-12.
10. Jaile JC, Levin T, Wung JT, et al. Benign gaseous distension of the bowel in premature infants treated with nasal continuous airway pressure: a study of contributing factors. AJR American journal of roentgenology 1992;**158**(1):125-7.
11. Hochwald O, Osiovich H. High flow nasal cannulae in neonatal intensive care units: is clinical practice consistent with the evidence. Paper presented at: PAS Annual Meeting; 1-4 May 2010; Vancouver, British Columbia 2010.
12. Hough JL, Shearman AD, Jardine LA, et al. Humidified high flow nasal cannulae: current practice in Australasian nurseries, a survey. Journal of paediatrics and child health 2012;**48**(2):106-13.
13. Nath P, Ponnusamy V, Willis K, et al. Current practices of high and low flow oxygen therapy and humidification in UK neonatal units. Pediatrics international : official journal of the Japan Pediatric Society 2010;**52**:893-94.
14. Manley BJ, Owen L, Doyle LW, et al. High-flow nasal cannulae and nasal continuous positive airway pressure use in non-tertiary special care nurseries in Australia and New Zealand. Journal of paediatrics and child health 2012;**48**(1):16-21.

15. Wilkinson D, Andersen C, O'Donnell CP, et al. High flow nasal cannula for respiratory support in preterm infants. Cochrane Database Syst Rev 2011(5):CD006405.
16. Waugh JB, Granger WM. An evaluation of 2 new devices for nasal high-flow gas therapy. Respiratory care 2004;**49**(8):902-6.
17. Manley BJ, Dold SK, Davis PG, et al. High-flow nasal cannulae for respiratory support of preterm infants: a review of the evidence. Neonatology 2012;**102**(4):300-8.
18. Collins CL, Holberton JR, Barfield C, et al. A randomized controlled trial to compare heated humidified high-flow nasal cannulae with nasal continuous positive airway pressure postextubation in premature infants. The Journal of pediatrics 2013;**162**(5):949-54 e1.
19. Manley BJ, Owen LS, Doyle LW, et al. High-Flow Nasal Cannulae in Very Preterm Infants after Extubation. The New England journal of medicine 2013;**369**(15):1425-33.
20. Yoder BA, Stoddard RA, Li M, et al. Heated, humidified high-flow nasal cannula versus nasal CPAP for respiratory support in neonates. Pediatrics 2013;**131**(5):e1482-90.
21. Shoemaker MT, Pierce MR, Yoder BA, et al. High flow nasal cannula versus nasal CPAP for neonatal respiratory disease: a retrospective study. J Perinatol 2007;**27**(2):85-91.
22. Lampland AL, Plumm B, Meyers PA, et al. Observational study of humidified high-flow nasal cannula compared with nasal continuous positive airway pressure. The Journal of pediatrics 2009;**154**(2):177-82.
23. Sivieri EM, Gerdes JS, Abbasi S. Effect of HFNC flow rate, cannula size, and nares diameter on generated airway pressures: An in vitro study. Pediatr Pulmonol 2012.
24. Spence KL, Murphy D, Kilian C, et al. High-flow nasal cannula as a device to provide continuous positive airway pressure in infants. J Perinatol 2007;**27**(12):772-5.
25. Wilkinson DJ, Andersen CC, Smith K, et al. Pharyngeal pressure with high-flow nasal cannulae in premature infants. J Perinatol 2008;**28**(1):42-7.
26. Jhung MA, Sunenshine RH, Noble-Wang J, et al. A national outbreak of Ralstonia mannitolilytica associated with use of a contaminated oxygen-delivery device among pediatric patients. Pediatrics 2007;**119**(6):1061-8.
27. Klingenberg C, Pettersen M, Hansen EA, et al. Patient comfort during treatment with heated humidified high flow nasal cannulae versus nasal continuous positive airway pressure: a randomised cross-over trial. Archives of disease in childhood Fetal and neonatal edition 2014;**99**(2):F134-7.
28. Roberts CT, Manley BJ, Dawson JA, et al. Nursing perceptions of high-flow nasal cannulae treatment for very preterm infants. Journal of paediatrics and child health 2014.
29. Osman M, Elsharkawy A, Abdel-Hady H. Assessment of pain during application of nasal-continuous positive airway pressure and heated, humidified high-flow nasal cannulae in preterm infants. J Perinatol 2014.
30. Miles MS, Funk SG, Carlson J. Parental Stressor Scale: neonatal intensive care unit. Nursing research 1993;**42**(3):148-52.

31. Schmidt B, Roberts RS, Davis P, et al. Caffeine therapy for apnea of prematurity. The New England journal of medicine 2006;**354**(20):2112-21.
32. Piaggio G, Elbourne DR, Pocock SJ, et al. Reporting of noninferiority and equivalence randomized trials: extension of the CONSORT 2010 statement. JAMA : the journal of the American Medical Association 2012;**308**(24):2594-604.
33. Harris PA, Taylor R, Thielke R, et al. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. Journal of biomedical informatics 2009;**42**(2):377-81.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	11
	2b	All items from the World Health Organization Trial Registration Data Set	1-16
Protocol version	3	Date and version identifier	N/A for publication
Funding	4	Sources and types of financial, material, and other support	13
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	13
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	1, 13

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-6
	6b	Explanation for choice of comparators	4-6
Objectives	7	Specific objectives or hypotheses	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7, 13
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	6-9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	N/A
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	6-7
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	N/A

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	10
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10-11
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	10-11

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10-11
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	10
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N/A
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	11, 13
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	11
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	11
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	13
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	N/A

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	10-11
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	10-11
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	11
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	13
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/a for publication
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.