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Multicentre, randomised trial to investigate early nasal high—flow therapy in paediatric acute hypoxaemic respiratory failure: a protocol for a randomised controlled trial—a Paediatric Acute respiratory Intervention Study (PARIS 2)

Donna Franklin ,[1,2,3,4] Deborah Shellshear,[4,5,6] Franz E Babl ,[4,7,8,9] Luregn J Schlapbach ,[1,2,6] Ed Oakley,[4,7,8,9] Meredith L Borland,[4,10,11] Tobias Hoeppner,[4,10] Shane George,[1,2,4,12] Simon Craig,[4,13,14] Jocelyn Neutze,[4,15,16] Amanda Williams,[4,7,8] Jason Acworth,[2,4,5] Hamish McCay,[17] Alex Wallace,[17] Joerg Mattes,[18,19] Vinay Gangathimn,[4,20] Mark Wildman,[4,20] John F Fraser,[21,22] Susan Moloney,[23] John Gavranich,[24] John Waugh,[25] Sue Hobbins,[26] Rose Fahy,[26] Simon Grew,[27] Brenda Gannon,[28] Kristen Gibbons,[1,3] Stuart Dalziel,[4,16,29,30] Andreas Schibler,[1,2,3,4,6] on behalf of PARIS and PREDICT

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For numbered affiliations see end of article.

Correspondence to
Donna Franklin;
d.franklin2@uq.edu.au

ABSTRACT

Introduction Acute hypoxaemic respiratory failure (AHRF) in children is the most frequent reason for non-elective hospital admission. During the initial phase, AHRF is a clinical syndrome defined for the purpose of this study by an oxygen requirement and caused by pneumonia, lower respiratory tract infections, asthma or bronchiolitis. Up to 20% of these children with AHRF can rapidly deteriorate requiring non-invasive or invasive ventilation. Nasal high-flow (NHF) therapy has been used by clinicians for oxygen therapy outside intensive care settings to prevent escalation of care. A recent randomised trial in infants with bronchiolitis has shown that NHF therapy reduces the need to escalate therapy. No similar data is available in the older children presenting with AHRF. In this study we aim to investigate in children aged 1 to 4 years presenting with AHRF if early NHF therapy compared with standard-oxygen therapy reduces hospital length of stay and if this is cost-effective compared with standard treatment.

Methods and analysis The study design is an open-labelled randomised multicentre trial comparing early NHF and standard-oxygen therapy and will be stratified by sites and into obstructive and non-obstructive groups. Children aged 1 to 4 years (n=1512) presenting with AHRF to one of the participating emergency departments will be randomly allocated to NHF or standard-oxygen therapy once the eligibility criteria have been met (oxygen requirement with transcutaneous saturation <92%/90% (dependant on hospital standard threshold), diagnosis of AHRF, admission to hospital and tachypnoea ≥35 breaths/min). Children in the standard-oxygen group can receive rescue NHF therapy if escalation is required. The primary outcome is hospital length of stay. Secondary outcomes will include length of oxygen therapy, proportion of intensive care admissions, healthcare resource utilisation and associated costs. Analyses will be conducted on an intention-to-treat basis.

Ethics and dissemination Ethics approval has been obtained in Australia (HREC/15/QRCH/159) and New Zealand (HDEC 17/NTA/135). The trial commenced recruitment in December 2017. The study findings will be submitted for publication in a peer-reviewed journal and presented at relevant conferences. Authorship of all publications will be decided by mutual consensus of the research team.

Trial registration number ACTRN12618000210279

Strengths and limitations of this study

- ► This study is a pragmatic approach to test the efficacy of nasal high-flow therapy in children with acute hypoxemic respiratory failure.
- ► This study investigates if early use of nasal high-flow therapy compared with late or rescue nasal high-flow therapy is superior in regards to a patient-centred primary outcome; the hospital length of stay.
- ► The study is performed in a wide variety of hospital settings including regional, metropolitan and tertiary hospitals; hence results will be highly generalisable.
- ► Blinding of the intervention is not possible, due to the visual differences between the two trial interventions.

INTRODUCTION

Of the 6.3 million children under the age of 5 years worldwide who died in 2013, over 1 million deaths were caused by acute respiratory infections causing acute hypoxaemic respiratory failure (AHRF).[1] In limited-resource settings, children with severe pneumonia have a mortality rate between 13% to 20% and most deaths occurring with hypoxaemia before therapeutic benefit of antimicrobials.[2 3] While the paediatric mortality due to respiratory infections has decreased in high-income countries, AHRF is the most frequent cause of hospital admission resulting in major consumption of healthcare resources.[4–6] Asthma, pneumonia and bronchiolitis-associated hospitalisations in children in the USA are estimated to account for over US$3 billion of costs per year.[4] There is an emerging trend to improve respiratory gas exchange with methods other than oxygen, particularly in the early stage of disease process aiming to prevent the progression of the disease.[7]

However, to date, the provision of positive pressure ventilation has been restricted to intensive care settings, which remains costly, is a limited resource and requires technical expertise. In view of the global burden of respiratory disease the WHO recognises oxygen as a potential life-saving treatment and is advocating to develop low cost and low technology oxygen delivery methods that can be delivered in most healthcare settings.[8] Currently, standard oxygen therapy is delivered either using nasal prongs with low flow oxygen up to 4 L/min or using a face mask with oxygen flows of up to 8 L/min. Nasal high-flow (NHF) therapy is a new promising mode of respiratory support applied as an alternative to non-invasive ventilation, a potentially less tolerated respiratory support.[4 9] NHF therapy can be used very early in the disease process and requires little cooperation by the child. Several studies have shown that NHF therapy creates a distending pressure of the lung with a positive end-expiratory pressure (PEEP) effect of approximately 4 to 6 cm H_2O using flow rates of 1.5 to 2 L/kg/min in infants <12 months of age.[10] NHF therapy also decreases the work of breathing.[10–13] Because of its easy application and the fact that little cooperation of the patient is needed, NHF therapy in emergency departments (ED) has become increasingly popular.[14–18] However, the data remains equivocal. A recent randomised controlled trial (RCT) using NHF therapy in adult patients with AHRF showed that NHF therapy compared with standard-oxygen therapy or non-invasive ventilation resulted in reduced mortality in the intensive care unit (ICU) and at 90 days.[19] Yet meta-analysis, including this study, failed to show any definitive benefit for treatment failure or in-hospital mortality.[20]

The recent multicentre Paediatric Acute Respiratory Intervention Study (PARIS) RCT performed in Australia and New Zealand showed that NHF therapy in infants with bronchiolitis (aged <12 months) had a lower failure rate of 12% compared with standard-oxygen with 23% failure rate.[21 22] In this study performed in EDs and paediatric wards in general hospitals or tertiary children's hospitals, no difference in the overall hospital length of stay or ICU admission rate was observed. These results are supported by an earlier single-centre RCT in patients with bronchiolitis which also found a lower failure rate with NHF, but no difference in hospital length of stay or length of oxygen treatment.[23]

In a recent pilot study, we tested the feasibility of using NHF therapy in 552 children presenting with AHRF (excluded were infants with bronchiolitis <12 months of age). Included were children aged 0 to 16 years presenting with AHRF (SpO_2 <92%) to the ED and requiring hospital admission. The majority of children (79%) presenting with AHRF were aged between 1 to 4 years. Of these children allocated to early NHF therapy, 12% required escalation of care compared with 17% of children allocated to standard-oxygen therapy (data to be published). The data suggests that there is a beneficial role of NHF therapy in children with AHRF. Due to a lack of high-grade evidence we designed the PARIS 2 study, a randomised multicentre RCT to test the hypothesis that children with AHRF on NHF therapy as a first-line oxygen therapy have a reduced hospital length of stay compared with children on standard-oxygen therapy. We also aim to investigate whether this leads to a reduced requirement for escalation of care. A within trial health economics evaluation will be performed to determine the cost-effectiveness of the intervention, considering the heterogeneity of service users, health system, geographical and economical conditions and end implications for resource allocation from the payer's perspective. The modelling will account for the opportunity cost and affordability of the health system payer. In addition, a decision analytical model will be developed to account for longer term cost-effectiveness modelling.

Aim and objectives

The PARIS 2 trial will investigate if the use of NHF therapy in children presenting with AHRF will reduce the hospital length of stay. This will be achieved by comparing the use of early NHF therapy with standard-oxygen therapy.

The primary objective is to demonstrate if early use of NHF reduces the hospital length of stay.

The secondary objectives are to demonstrate if early use of NHF reduces the requirement to escalate therapy, reduces transfers to higher level of care such as intensive, reduces the proportion of adverse events, to demonstrate ex post within-trial and ex ante longer term cost-effectiveness of high-flow therapy, to show reduced length of oxygen therapy and to ascertain comfort levels of children on high-flow.

METHODS

Study design and settings

The PARIS 2 trial is a multicentre, randomised trial recruiting 1512 children aged 1 to 4 years requiring hospital admission for AHRF. The study will be performed in EDs and general paediatric wards of metropolitan

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Table 1 Clinical definitions for acute hypoxaemic respiratory failure diagnostic groups

Diagnostic groups: obstructive airway disease	Symptoms
► Asthma ► Reactive airways disease ► Bronchiolitis for children >12 months	Oxygen requirement *AND/OR* ► wheeze and/or cough ► +/- viral illness ► increased work of breathing and respiratory rate (>35/min) ► +/- fever
Diagnostic groups: non-obstructive airway disease	Symptoms
► Pneumonia – viral or bacterial ► Aspiration ► Acute lower respiratory tract infection ► Bronchopneumonia ► Acute respiratory distress syndrome ► Pneumonitis	Oxygen requirement *AND* ► cough ► +/- viral illness ► increased respiratory rate (≥35/min) ► +/- fever

hospitals and tertiary children's hospitals in Australia and New Zealand.

Definitions

AHRF is defined as children presenting to ED with increased work of breathing due to respiratory disease, having an ongoing oxygen requirement to maintain Transcutaneous Oxygen saturation (SpO_2) ≥90/92% (dependent on hospitals' current threshold for administering oxygen, which can either be 90% or 92%) with increased respiratory rate ≥35 breaths/min and requiring hospital admission. The syndrome of AHRF represents an array of clinical diagnoses such as pneumonia, pneumonitis, acute lower respiratory tract infection, reactive airways (asthma) including small numbers with bronchiolitis older than 12 months of age. For the purpose of this study there will be two groups of patients investigated with a ***pragmatic and point of care definition,*** which includes clinically diagnosed: (a) *wheeze (obstructive) and reactive airway disease* with an oxygen requirement and (b) *absent wheeze (non-obstructive) and parenchymal lung disease* with an oxygen requirement during hospital admission (table 1).

Participants

Children will be identified and recruited by treating clinicians in the ED of the participating hospitals. All patients with AHRF (acute respiratory disease and oxygen requirement) in these locations will be screened for inclusion criteria in the study. Patients meeting all inclusion criteria and no exclusion criteria (table 2) are eligible for randomisation.

Consent considerations

One of the primary challenges in performing research in an emergency setting is the inability to obtain true informed consent. Frequently, parents and guardians are not initially available when their child is brought into the ED. Furthermore, when parents or guardians are present, they are often too distressed by the situation to comprehend study procedures and there is not enough time to obtain informed consent.[24–26] In all participating centres, prospective consent will be obtained from the parent or guardian where possible. When prospective consent

Table 2 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
► Children aged 1–4 years plus 364 days presenting with AHRF ► *and* require hospital admission despite initial assessment and therapy ► *and* an ongoing oxygen requirement (SpO_2 <90/92%* in room air, dependent on hospital policy) ► *and* have a persistent tachypnoea of ≥35 breath/min for ≥10 mins at the time of randomisation	► Oxygen requirement and therapy in the emergency department existed for longer than 4 hours prior to inclusion (excludes oxygen given in ambulance or other hospital) ► Previous use of high-flow during this illness episode ► Upper airway obstruction ► Craniofacial malformations ► Critically ill infants requiring immediate higher level of respiratory support that is, non-invasive or invasive ventilation, low level of consciousness *OR* ► Critically ill with immediate need for intubation or non-invasive ventilation with the need of closer observation in ICU ► Basal skull fracture ► Trauma ► Cyanotic heart disease (eg, blue baby, expected normal saturation in room air <90/92%) ► Home oxygen therapy ► Palliative care ► Cystic fibrosis ► Oncology ► Child protection patients

AHRF, acute hypoxaemic respiratory failure; ICU, intensive care unit; SpO_2, oxygen saturation.

is not possible or practical, and local legislation allows, patients will be randomised to the study and written informed consent to remain in the study will be sought from parents and guardians at the earliest possible time after emergency stabilisation of the child (consent-to-continue). Data for children whose parents and guardians do not wish for their child to remain in the study will be handled according to local hospital policies, and the data will not be available for analysis.

This study has ethical approval for consent-to-continue for participating Australian sites by the Children's Health Queensland Human Research Ethics Committee (HREC/15/QRCH/159) and Ethics Committee of The University of Queensland (2016001491). For sites in New Zealand approval has been received for prospective consent (Health and Disability Ethics Committee, 17/NTA/135) as the legislation of New Zealand does not allow delayed consent.

Ethics and dissemination

Ethics was first obtained with Children's Health Queensland Human Research Ethics Committee (CHQ HREC) and Ethics Committee of The University of Queensland in Queensland, Australia. All participating centres in Australia were subsequently approved ethically by CHQ HREC, totalling 11 centres, and 3 New Zealand centres by Health and Disability Ethics Committee.

The primary outcome results will be published in a peer-reviewed journal with secondary outcomes having separate manuscripts submitted for publication in peer-reviewed journals. On completion of the trial, following the primary outcome manuscript, results will be presented locally, nationally and internationally at conferences and respiratory workshops.

Recruitment, randomisation and blinding

Children 1 to 4 (4 years and 364 days) years of age with respiratory disease will be screened at the time of admission to hospital for presence of inclusion criteria. Identified patients will be treated initially as per the treating clinician for suspected underlying potential cause of AHRF which may include bronchodilator therapy for reactive airway disease, fluid bolus and other medications such as antibiotics. If AHRF (SpO_2 <90/92% in room air) symptoms persist and hospital admission is required, then the patient will become eligible and will be randomised to standard-oxygen or NHF therapy. Excluded are children as per table 2. The study protocol prescribes the oxygen delivery and weaning method only (standard-oxygen or NHF therapy). A web-based randomisation schedule with a block size of 10 will be used with patients allocated 1:1 and stratified by site and by obstructive and reactive airway disease versus non-obstructive and parenchymal lung disease as defined by the admitting clinician.

Interventions and protocol

Treatment protocol for NHF therapy: NHF is set according to weight (table 3) using the AIRVO-2 system (Fisher & Paykel Healthcare, New Zealand). For children presenting with SpO_2 between 85% to 89/91% inclusive, the Fraction of Inspired Oxygen (FiO_2) is initially set at 0.21 and SpO_2 observed for 10 min. If SpO_2 remains <90/92% after 10 min then FiO_2 is increased and titrated to achieve SpO_2 ≥90/92%. If SpO_2 has improved to ≥90/92% then NHF therapy is continued in room air. For children presenting with SpO_2 <85% the FiO_2 is immediately increased in 5% increments to achieve SpO_2 ≥90/92%. FiO_2 is adjusted for all children to achieve and maintain SpO_2 of 90/92% to 98% avoiding long periods of hyperoxia with SpO_2 of 100%. For any flow rates >25 L/min the high-flow rates are increased gradually over 2 min and the patient observed in terms of his/her ability to tolerate NHF therapy. Age and flow specific nasal cannulas will be used.

Table 3 Applied nasal high-flow rates

Weight	High-flow rates
0–12 kg	2 L/kg/min Max 25 L/min
13–15 kg	30 L/min
16–30 kg	35 L/min
31–50 kg	40 L/min
>50 kg	50 L/min

Treatment protocol standard-oxygen: Standard subnasal 100% oxygen is offered at a rate of up to a maximum of 2-4 L/min (humidification according to standard hospital practice can occur) or via a face mask with a maximum of 8 L/min and oxygen flow rates titrated to achieve SpO_2 of 90/92% to 98%.

The study design is only prescriptive for the oxygen delivery method. For the remaining respiratory management, the individual hospital internal protocols will be followed, including pharmacological management such as antibiotic or antiviral therapy. Infants and children who are admitted because of increased work of breathing or feeding difficulty but develop an oxygen requirement after admission to the paediatric ward are still eligible for the study.

Step-by-step guide to commence treatment arm – NHF therapy or standard-oxygen

- At the time of randomisation the clinician must be reassured that the patient has SpO_2 <90/92% in room air for preferably up to 10 min of observational period
- NHF intervention arm: Appropriately sized high-flow nasal cannula will used with a gas mixture and flow according to the table 3. Initially the gas mixture is set at a FiO_2 of 21% and increased if SpO_2 remains <90/92% after 10 min of NHF therapy. If SpO_2 is <85% at enrolment then FiO_2 is immediately increased to achieve SpO_2 ≥90/92%. If the FiO_2 is greater than 40% (or up to 60% for no longer than 30 min and only used if needed from when NHF therapy first initiated) and increased work of breathing is present then a consultation with specialist paediatric centre

or local intensive care service must occur at this time. Increasing FiO_2 occurs in 5% increments at frequent intervals to maintain SpO_2 ≥90/92%. This can be 15 minutely to hourly according to local practice when performing observations, and depending on the patients requirements.

- The disposition of the study participant is dependent on local patient flow. No distinction in nursing ratio and care should be made between the two study arms.
- For the duration of bronchodilator administration, the NHF therapy is stopped and standard-oxygen therapy provided
- Control intervention arm: Standard subnasal oxygen (humidification optional) or face mask oxygen will be offered according to local practice. Maximal flow rates as follows: subnasal oxygen up to a maximum of 2-4 L/min and face mask oxygen up to 8 L/min. If SpO_2 remains <90/92% and/or the work of breathing is further increased since oxygen therapy commenced, then a consultation with a specialist paediatric centre or local intensive care service must occur at this time.
- Observations: Respiratory and heart rate and other clinical parameters hourly as a minimum (or according to hospital policy) and according to the Early Warning Tool (EWT) chart used in the participating study centre.
- Weaning off NHF therapy: Only FiO_2 is reduced to maintain SpO_2 ≥90/92% to 98%. FiO_2 can be reduced to room air (21%). Once stable on room air NHF therapy can be stopped. At least one set of observations showing stable in room air must occur prior to the NHF therapy being stopped. If SpO_2 drops to <90/92%, restart NHF therapy with room air initially for 10 min, and only increase FiO_2 when SpO_2 remains <90/92%. For the patient who starts and remains on room air only (21%) there are at least 2 hours of observations provided prior to stopping the NHF therapy. Again, if SpO_2 drops to <90/92%, restart NHF therapy with room air initially for 10 min, and only increase FiO_2 when SpO_2 remains <90/92%. Weaning of FiO_2 can occur 15 minutely to hourly according to local practice when performing observations, and depending on the patients requirements.

The study design is only prescriptive for the oxygen delivery method. For all other respiratory management, the individual hospital internal protocols will be followed, including pharmacological management.

Feeding while on NHF therapy: A nasogastric tube (NGT) is not mandatory in the use of NHF therapy but it is encouraged in the patients aged less than 2 to 3 years if clinically indicated. Insertion of a NGT remains at the discretion of the attending clinician. In patients who do not receive a NGT and are stable and wish to breastfeed/drink and/or eat, the NHF therapy should be reduced to 2 L/min (low flow therapy) via the same nasal cannula. This can be achieved by decreasing the flow to 2 L/min and increasing the oxygen to 95% FiO_2 for a maximum of up to 20 min and then return the patient to the previous NHF therapy settings. Patients who have had a NGT inserted should be assessed as to whether they can be fed. The use of the NGT over oral feeding while a nasogastric tube is in situ is preferred to prevent the risk of aspiration. Nasogastric feeding can be bolus or continuous at the discretion of the attending physician. Many of these patients will have an intravenous line in situ. Children who do not tolerate nasogastric feeds will have intravenous hydration.

Use of nebuliser and/or inhalation/burst therapy for NHF therapy patients: For the duration of inhalation/burst therapy, the NHF therapy will be stopped and nasal prongs removed (leaving wiggle pads in situ if applied) and administer the burst/inhalation therapy administered. This will allow for greater face-mask seal with the metered-dose inhaler via spacer if used. For nebulisers there is no need for additional oxygen via nasal prongs. After the inhalation/burst therapy is complete NHF therapy will be returned with previous settings.

Escalation of care with or without change in therapy in both intervention arms (figure 1): If at any time there is a change in oxygen therapy (standard-oxygen to NHF therapy or NHF therapy to standard-oxygen) data on reasoning for the change in therapy will be captured. Similarly, if there is an escalation of care to intensive care or high-dependency unit the clinical criteria will be recorded to inform the decision-making process.

Study outcomes and definitions

Primary outcome is defined as the hospital length of stay (days) defined from admission to hospital (time of randomisation) to the time of discharge.

The secondary outcomes are:

1. Length of oxygen therapy since randomisation.
2. Receiving a change in oxygen therapy in general ward settings from NHF to standard-oxygen therapy (non-tolerance) or from standard-oxygen to NHF therapy.
3. Intensive care/high dependency care admission.
4. Healthcare cost-effectiveness.
5. Transfer to a tertiary hospital.
6. Escalation of therapy such as non-invasive or invasive ventilation.
7. Tolerance level of NHF therapy compared with standard-oxygen therapy.
8. Clinical triggers that result in a change of therapy.
9. Complications, serious adverse events (death before hospital discharge, cardiac arrest, pneumothorax or air leak syndrome).

A preplanned subanalysis on the obstructive and non-obstructive groups to determine which, if any group responds differently to the two treatment arms and within the differing age groups (in 1 year steps).

Additionally, a preplanned sensitivity analysis will be performed using clinical criteria for the primary and secondary outcomes. They are as follows:

a. Heart rate remains >160/min for longer than 2 hours.
b. Respiratory rate remains >45/min for longer than 2 hours.

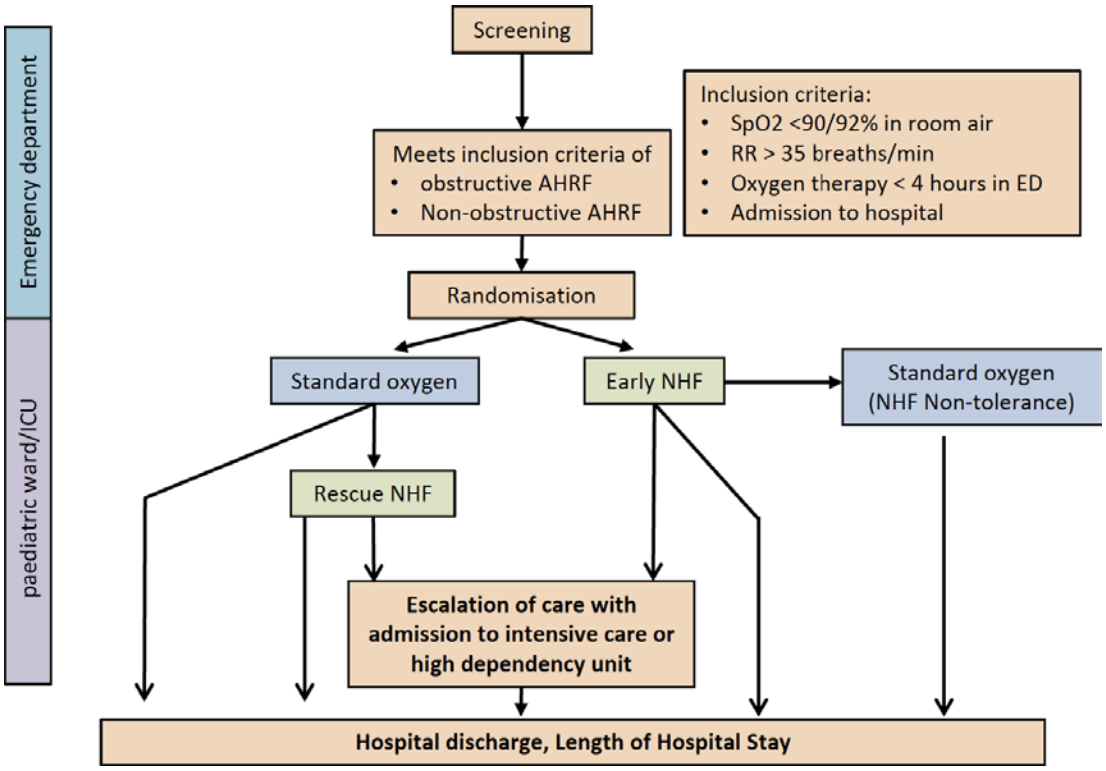

Figure 1 Study flow diagram. AHRF, acute hypoxaemic respiratory failure; ED, emergencydepartment; ICU, intensive care unit; NHF, nasal high-flow; RR, respiratory rate; SpO_2, oxygen saturation.

c. Oxygen requirement in NHF therapy arm exceeds FiO_2 >40/50% (dependant on hospital standard policy) to maintain SpO_2 ≥90/92% or oxygen requirement in control oxygen arm exceeds standard oxygen therapy (2-4 L/min by nasal prong, or 8 L/min by face mask) to maintain SpO_2 ≥90/92%.
d. The hospital internal EWT calls for medical review.

Data measures

Baseline demographics, age, weight, admission and discharge diagnosis, viral and bacterial testing and medical therapy such as antibiotics/antiviral, steroids, inhaled or intravenous bronchodilators and other drugs will be captured during the entire stay in hospital. Physiological parameters (heart rate, respiratory rate, body temperature, oxygen saturation, work of breathing, comfort scale, oxygen requirement) will be obtained at the time of randomisation and after initiation of the allocated intervention, at any time of change of respiratory support and at time of escalation of care including admission of intensive care. Data on respiratory support provided in intensive care will be obtained. Data on feeding during the study will be also captured.

Clinical tolerance for NHF therapy treatment arm: It is recognised that NHF therapy is a relatively new therapy for children with mild-to-moderate severity of respiratory illnesses. The tolerance level of placing nasal cannula with high flows in younger children, particularly the 1 to 4 year age group, is unknown. This RCT aims to additionally investigate the tolerance level of NHF therapy. A 100 mm unmarked visual analogue scale (VAS) will be used as a measurement instrument. Both the parent and the nurse caring for the patient will separately assess the intensity of respiratory patient-comfort level twice during admission: first, at 1 hour post commencement of oxygen therapy and second between 4 to 48 hours post commencement of oxygen therapy and document the comfort score that they believe the child is experiencing at that point in time. One end of the scale is marked with 'no discomfort' and the other end marked as 'maximal imaginable discomfort'. The VAS will measure both standard-oxygen therapy and NHF therapy treatment arms for level of comfort.

Data management

Study data will be obtained either directly from hospital records, electronic medical records or copies and entered after verification into the clinical research form (CRF). The investigators are responsible for ensuring the accuracy, completeness, legibility and timeliness of the data reported. All CRF and study documents will be completed in a neat, legible manner to ensure accurate interpretation of data. The document/forms will be stored and locked away as per site specific requirements and regulations for each individual hospital. Ongoing surveillance and adherence to the study protocol will be monitored by the Coordinating Principal Investigator and the steering committee, who are meeting via teleconference at 3-monthly interval. All serious adverse events, protocol deviations and protocol violations will be submitted to the chief investigator and all serious adverse events and protocol violations will be submitted to the

approving HREC and local Research Governance Offices (RGOs). All local regulatory process will be followed to ensure adherence to local governance requirements. An independent Data and Safety Monitoring Board (DSMB) that has been used in the past for other respiratory trials will be used. The DSMB will consist of an experienced Data and Safety Monitoring Chair (DSMC), clinical expert, statistician and a secretariat. An interim analysis will be undertaken by the DSMB after 100 participants have been enrolled into the study but only analysed for safety aspects. This had already occurred at the time of the publication of this protocol and the DSMB recommended to continue the trial.

SAMPLE SIZE AND STATISTICAL ANALYSIS PLAN

Sample size

The sample size calculation is based on a two-sided, randomised, parallel group trial design with total length of hospital stay as the primary outcome and survival analysis as the primary method of analysis. We consider a difference in length of hospital stay of at least half a day as clinically meaningful, however for the sample size calculation this will be reduced to 0.4 day to increase the sample size to adjust for the effect of clustering. Assuming a median length of hospital stay in the control therapy arm of 2 days (based on pilot data), compared with a median length of hospital stay in the NHF arm of 1.6 days, 5% level of significance and 90% power we require 1209 children. To allow for up to 20% non-compliance we require 1512 children in total; 756 in each treatment group. We estimate a 50% to 80% enrolment rate of eligible patients.

Statistical analysis plan

Descriptive statistics will be used to report on the baseline characteristics of the total study cohort stratified by treatment group. Kaplan-Meier plots will be used to graphically describe and compare the primary outcome (length of hospital stay) as well as duration of oxygen therapy. Analyses of secondary binary outcomes will be based on X^2 test for proportions and the absolute difference between treatment groups will be reported as the risk difference with a 95% CI. An independent samples t-test will be used for normally distributed continuous measures; Mann-Whitney U test for non-normally distributed continuous outcomes. Exploratory analyses will be conducted on the subset of patients who require escalation of treatment. These are conditional analyses that are not based on comparing complete randomised groups hence caution will be needed when interpreting the results. We plan to compare length of ICU stay between treatment groups for the subgroup of patients that are admitted to ICU. All analyses will be by intention-to-treat. Statistical significance is set at the 0.05 level.

Health economics evaluation

We will build an ex ante longer term decision analytical model and also undertake ex post within-trial modelling, to determine the cost-effectiveness of treatment compared with usual care. An appropriate bespoke health economics data collection tool will be developed to provide critical data for these models. Unit costs will be extracted from standard sources. To provide longer-term analysis, we will build a bespoke Decision Analytical Model to estimate cost-effectiveness under the horizon of 5 years. The model will be based on both aggregate resource, cost use and health state transitions data from literature, expert opinion, along with our newly collected data in the RCT. Models will include sensitivity analysis, and outputs will include cost-effectiveness acceptability curves – these will display the probability of cost-effectiveness at varying thresholds of net monetary benefit. Following a Markov chain modelling approach, we will use Monte Carlo simulation methods to incorporate the occurrence and timing of events. The main issue with such ex ante evaluation is uncertainty, and we will use standard bootstrap methods to account for this in our estimates. This will provide us with a sensitivity analysis of differences in potential costs depending on demographics and socioeconomic status. The model will be constructed and continuously updated with new data as it becomes available throughout the project. A standard within-trial cost utility analysis will be undertaken under the horizon of 5 days. This will compare costs and benefits in terms of resource use and quality adjusted life years gained. Resource use and travel data will be collected with the bespoke tool and the collated unit costs will be assigned to the resource utilisation to provide overall costs for both arms of the trial. Benefits will be assessed using appropriate quality of life instruments, for example EQ-5D-5L (developed by EuroQol) measuring Mobility; Self-care; Usual activity; Pain;Anxiety/depression and the PedsQL (Pediatric Quality of Life Inventory). The analysis will be from the healthcare provider perspective but with an additional societal perspective, to include for example, consumer travel costs. Probability sensitivity analysis will be provided to give the probability of cost-effectiveness at each threshold level of net monetary benefit. The data from this trial will then feed into our decision model, enhancing the model further with current and comparable data.

Outcomes and significance

Providing the hypothesis of the study can be proven, the following impact on future healthcare is expected: (i) Reduction in hospital length of stay for patients aged 1 to 4 years with AHRF, (ii) Reduction of transfers of patients aged 1 to 4 years with AHRF to specialist paediatric centres - 'keeps patients in their regional hospitals' and potentially gives the regional centres more autonomy in managing their patients with best respiratory practice, (iii) That early intervention reduces the number of patients requiring escalation of treatment, (iv) Reduction in healthcare costs and demonstration of cost-effectiveness of NHF therapy, (v) Potential to expand NHF therapy to older children with AHRF, (vi) Greater

expansion of knowledge for nursing and medical staff on the use of NHF therapy and the benefits and non-benefits in this population of children, (vii) Informing the use of NHF therapy in less developed countries in this population of children and (viii) Development of strategies to implement NHF therapy safely in the described study population.

Limitations

The intervention of high-flow therapy cannot be blinded and a certain clinician driven bias may occur. The escalation of care is driven by clinical criteria and judgement and there is the potential bias to favour one intervention over the other. However, our previous high-flow trial in bronchiolitis showed that this element was not cofounding the study outcomes.[22]

Data sharing

Data generated by this study will be shared and available in de-identified form on reasonable request, wherever legally and ethically possible.

Patient and public involvement

For the study protocol there was no direct patient or public involvement.

Current status of the trial

The study enrolment has commenced across 14 centres, with 1105 children recruited by August 2019. The expected end date of recruitment to this trial is December 2020.

Sites involved in the study include:

Australia

Queensland

- Queensland Children's Hospital
- Gold Coast University Hospital
- Caboolture Hospital
- Ipswich Hospital
- Redcliffe Hospital
- Townsville Hospital
- The Prince Charles Hospital

New South Wales

- John Hunter Children's Hospital

Victoria

- Royal Children's Hospital, Melbourne
- Monash Children's Hospital

Western Australia

- Perth Children's Hospital

New Zealand

- Starship Children's Health
- Kidz First, Middlemore Hospital
- Waikato Hospital

DISCUSSION

This large multicentre randomised trial will provide the much-needed high-grade evidence of the efficacy of NHF therapy compared with standard-oxygen in the ARHF children aged 1 to <5 years. This study will also provide a unique opportunity to investigate the safety profile off high-flow in children with acute hypoxaemic respiratory failure. We will capture data on health resource use and quality of life and the results can be utilised to inform best practice in use of high-flow outside intensive care settings.

Author affiliations
[1]Paediatric Critical Care Research Group, Child Health Research Centre, The University of Queensland, Brisbane, Queensland, Australia
[2]School of Medicine, The University Of Queensland, St Lucia, Queensland, Australia
[3]Mater Medical Research Institute, South Brisbane, Queensland, Australia
[4]Paediatric Research in Emergency Departments International Collaborative (PREDICT), Parkville, Victoria, Australia
[5]Emergency Department, Queensland Children's Hospital, South Brisbane, Queensland, Australia
[6]Queensland Children's Hospital, South Brisbane, Queensland, Australia
[7]Emergency Department, Royal Childrens Hospital, Parkville, Victoria, Australia
[8]Murdoch Children's Research Institute, Melbourne, Victoria, Australia
[9]Department of Paediatrics, Faculty of Medicine, Dentistry and Health Services, University of Melbourne, Melbourne, Victoria, Australia
[10]Emergency, Princess Margaret Hospital for Children, Subiaco, Western Australia, Australia
[11]University of Western Australia, School of Medicine, Divisions of Emergency Medicine and Paediatrics, Crawley, Western Australia, Australia
[12]Emergency Department, Gold Coast University Hospital, Southport, Queensland, Australia
[13]Emergency Department, Monash Medical Centre Clayton, Clayton, Victoria, Australia
[14]Department of Medicine, School of Clinical Science, Monash University, Clayton, Victoria, Australia
[15]KidzFirst Middlemore Emergency Department, Middlemore Hospital, Auckland, New Zealand
[16]University of Auckland, Auckland, New Zealand
[17]Paediatrics, Waikato Hospital, Hamilton, New Zealand
[18]Paediatrics, John Hunter Children's Hospital, Hunter Region Mail Centre, New South Wales, Australia
[19]University of Newcastle, Priority Research Centre GrowUpWell, Callaghan, New South Wales, Australia
[20]Emergency Department, Townsville General Hospital, Townsville, Queensland, Australia
[21]Adult Intensive Care Services, The Prince Charles Hospital, Brisbane, Queensland, Australia
[22]Critical Care Research Group, The Prince Charles Hospital and University of Queensland, Brisbane, Queensland, Australia
[23]Paediatric Department, Gold Coast University Hospital, Southport, Queensland, Australia
[24]Paediatrics, Ipswich Hospital, Ipswich, Queensland, Australia
[25]Paediatrics, Caboolture Hospital, Caboolture, Queensland, Australia
[26]Paediatrics, Prince Charles Hospital, Chermside, Queensland, Australia
[27]Paediatrics, Redcliffe Hospital, Redcliffe, Queensland, Australia
[28]The University of Queensland, Centre for Business and Economics of Health, St Lucia Qld, Queensland, Australia
[29]Starship Children's Health, Emergency Department, Newmarket, New Zealand
[30]Department of Surgery and Paediatrics, Child and Youth Health, University of Auckland, Auckland, New Zealand

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Collaborators Steering Committee: Each site is represented by at least one member for the steering group. Data and Safety Monitoring Board (DSMB): Phil Sargent, Scott Burgess, Kristen Gibbons (stat).

Contributors DF, AS, DS, SD and FEB were responsible for identifying the research question and contributing to the drafting of the protocol. All Authors, including DF,

AS, DS, FEB, LJS, EO, MLB, TH, SG, SC, JN, VG, MW, JA, HM, AW, JM, JFF, SM, JG, JW, SH, RF, SG, BG, KG have contributed to the development of the protocol and study design. DF was responsible for drafting this manuscript, with comments and feedback from all other authors. KG provided expert statistical advice and input, BG developed the health economic measures and analysis. All authors attest to having approved the final manuscript. DF and AS take responsibility for the manuscript as a whole.

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ORCID iDs
Donna Franklin http://orcid.org/0000-0003-1650-3270
Franz E Babl http://orcid.org/0000-0002-1107-2187
Luregn J Schlapbach http://orcid.org/0000-0003-2281-2598

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