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FIRST-line support for Assistance in Breathing in Children (FIRST-ABC): protocol for a multicentre randomised feasibility trial of non-invasive respiratory support in critically ill children

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ABSTRACT

Introduction Over 18 000 children are admitted annually to UK paediatric intensive care units (PICUs), of whom nearly 75% receive respiratory support (invasive and/or non-invasive). Continuous positive airway pressure (CPAP) has traditionally been used to provide first-line non-invasive respiratory support (NRS) in PICUs; however, high-flow nasal cannula therapy (HFNC), a novel mode of NRS, has recently gained popularity despite the lack of high-quality trial evidence to support its effectiveness. This feasibility study aims to inform the design and conduct of a future definitive randomised clinical trial (RCT) comparing the two modes of respiratory support.

Methods and analysis We will conduct a three-centre randomised feasibility study over 12 months. Patients admitted to participating PICUs who satisfy eligibility criteria will be recruited to either group A (primary respiratory failure) or group B (postextubation). Consent will be obtained from parents/guardians prior to randomisation in 'planned' group B, and deferred in emergency situations (group A and 'rescue' group B). Participants will be randomised (1:1) to either CPAP or HFNC using sealed, opaque envelopes, from a computer-generated randomisation sequence with variable block sizes. The study protocol specifies algorithms for the initiation, maintenance and weaning of HFNC and CPAP. The primary outcomes are related to feasibility, including the number of eligible patients in each group, feasibility of randomising >50% of eligible patients and measures of adherence to the treatment protocols. Data will also be collected on patient outcomes (eg, mortality and length of PICU stay) to inform the selection of an appropriate outcome measure in a future RCT. We aim to recruit 120 patients to the study.

Ethics and dissemination Ethical approval was granted by the National Research Ethics Service Committee North East—Tyne&Wear South (15/NE/0296). Study findings will be disseminated through peer-reviewed journals, national and international conferences.

Trials registration number NCT02612415; pre-results.

Strengths and limitations of this study

- This randomised trial aims to test the feasibility of comparing two modes of non-invasive respiratory support in critically ill children.
- If shown to be feasible, this study will inform the design and conduct of a future definitive randomised trial (RCT) comparing high-flow nasal cannula therapy with continuous positive airway pressure.
- In addition to testing feasibility, data will be collected on several secondary outcomes to inform the selection of an appropriate primary outcome measure for a future RCT.
- As a feasibility study run in three study sites, this study does not however have the power to show clinical effectiveness.
- This feasibility trial will not be assessing the cost effectiveness of the two treatments.

BACKGROUND

Each year, over 18 000 critically ill children are admitted to paediatric intensive care units (PICU) in the UK.[1] Irrespective of the primary reason for admission, respiratory support is the most common intervention undertaken in PICU; national audit data from the Paediatric Intensive Care Audit Network demonstrate that nearly 75% of admissions between 2011 and 2013 received either invasive (via an endotracheal tube or tracheostomy) and/or non-invasive respiratory support during their PICU stay.[1]

Although invasive ventilation can be life saving, concerns regarding its complications, such as ventilator-induced lung injury, need for prolonged sedation and nosocomial respiratory tract infections have encouraged the greater adoption of non-invasive

respiratory support (NRS) techniques in intensive care settings.[2–4] In critically ill adults and premature newborns, evidence from randomised clinical trials (RCT) supports the early use of NRS to reduce invasive ventilation and improve survival in specific patient subgroups.[5–8] In critically ill infants and children, there is a dearth of high-quality RCT evidence,[9] yet, the use of NRS has increased over the years in UK PICUs as well as internationally.[10]

Continuous positive airway pressure (CPAP) has traditionally been used as the first-line mode of NRS in the PICU setting, to either avoid intubation and invasive ventilation or to avoid reintubation after extubation, following a spell of invasive ventilation.[11 12] However, the widespread use of CPAP is limited by two main problems: (1) the need for a tight-fitting patient interface such as face mask, hood or nasal prongs to avoid leakage of gas from the ventilator circuit (which frequently causes patient discomfort/agitation as well as nasal and facial pressure sores with prolonged use, leading to treatment failure) and (2) the risk of serious complications such as pneumothorax or pneumomediastinum (which usually necessitates close monitoring and a high level of skilled nursing input).

Over the past decade, a novel mode of NRS, heated-humidified high-flow nasal cannula therapy (HFNC), has rapidly gained popularity despite the absence of RCT evidence to support its effectiveness in the PICU setting.[13 14] The main reason for its increasing use is related to patient comfort and ease of use.[15] HFNC does not require a tight seal and its patient interface (nasal prongs) is well tolerated by children. There is strong evidence from physiological and observational studies to support the use of HFNC in PICU—HFNC allows the delivery of heated and humidified medical gases to the patient at high-gas flow rates (matching or exceeding the patient's own peak inspiratory flow rate), which has been shown to confer a diverse range of beneficial effects such as reduction of airway resistance, reduction of dead space by nasopharyngeal washout with fresh gas, as well as delivery of positive airway pressure (similar to CPAP).[16 17] Studies in infants and children confirm that HFNC reduces the work of breathing and improves oxygenation and ventilation.[18 19] In single-centre observational studies, the use of HFNC has been shown to be associated with a dramatic reduction in the rate of intubation and invasive ventilation.[20–22] However, there have not yet been any RCTs comparing HFNC with other forms of NRS such as CPAP in the PICU setting.[23]

Before an expensive health technology such as HFNC is adopted more widely across the paediatric intensive care setting, it is crucial that evidence from a large pragmatic RCT is urgently available to support its clinical and cost effectiveness, especially since loss of clinical equipoise regarding the risks and benefits of HFNC is already occurring among clinicians.[24] Prior to a national RCT, however, it is imperative that the feasibility of conducting such an RCT is established. In this paper, we describe the protocol for a multicentre randomised feasibility trial to compare the two most commonly used modes of NRS (CPAP and HFNC) in critically ill children admitted to PICU (V.2.1, 17 March 2016).

STUDY AIM

The aim of this study is to conduct a feasibility study to inform the design and conduct of a future definitive multicentre RCT comparing two commonly used modes of non-invasive respiratory support (CPAP and HFNC) in the PICU setting.

STUDY OBJECTIVES

Primary objective: To determine the feasibility of an RCT of HFNC versus CPAP in critically ill children admitted to PICU.

Secondary objectives:

- to determine the rate of intubation and invasive ventilation (or reintubation) in each study arm
- to determine the rate of treatment failure in each study arm
- to assess the safety of the use of CPAP and HFNC
- to assess the physiological effects of CPAP and HFNC
- to assess the effect of CPAP and HFNC on patient outcomes.

STUDY DESIGN AND SETTING

This is a randomised, controlled, open-label clinical trial comparing HFNC with CPAP as the first-line non-invasive respiratory support modality in critically ill children. Patients will be recruited at three PICUs in London. Together, these PICUs admit around 2500 children annually. The frequency of NRS use is variable on the units (between 15% and 43% of admissions) owing to differences in availability of beds for high-dependency care. All three units have access to both modes of NRS (CPAP and HFNC).

INCLUSION CRITERIA

Pragmatic inclusion criteria will be used. To minimise variation in practice between and within centres, predefined, objective criteria are provided to clinicians to guide the decision on when to start NRS. Eligible patients aged between >36 weeks corrected gestational age and <16 years will fall into one of two groups:

Group A (step-up)

- Deemed by the treating clinician to require NRS for an acute illness;
- Satisfy one or more of the following criteria:
  - hypoxia (oxygen saturation <92% in fraction of inspired oxygen >0.40, or equivalent)
  - acute respiratory acidosis (pH <7.3 with a concomitant partial pressure of carbon dioxide >6.5 kPa)

- moderate respiratory distress (use of accessory muscles, subcostal and intercostal recession, tachypnoea for age, grunting).

Group B (step-down)

Deemed by the treating clinician to require NRS following a spell of invasive ventilation, either immediately after extubation as a planned procedure ('planned') or prompted by clinical deterioration within 72 hours after extubation ('rescue').

'Rescue' participants will be required to also satisfy one or more of the following criteria: hypoxia, acute respiratory acidosis or moderate respiratory distress (using the same definitions as above).

EXCLUSION CRITERIA

Patients will be excluded if they (1) are deemed by the treating clinician to require immediate intubation/invasive ventilation due to severe hypoxia, acidosis and/or respiratory distress, upper airway obstruction or recurrent apnoeas; (2) have a tracheostomy in place; (3) have a pre-existing air-leak syndrome (pneumothorax and/or pneumomediastinum); (4) have midfacial/craniofacial anomalies (unrepaired cleft palate, choanal atresia) or had recent craniofacial surgery; (5) have an agreed limitation of intensive care treatment plan in place ('not for intubation'); (6) have been on domiciliary NRS prior to PICU admission; (7) have been managed on either HFNC and/or CPAP (or other form of NRS such as bilevel positive airway pressure (BiPAP)) in the preceding 24 hours; (8) have been previously recruited to the study during the same PICU admission; (9) cannot be treated with HFNC due to unavailability of appropriate sized nasal prongs or HFNC device; or (10) cannot be treated with CPAP due to unavailability of right size of face mask, prong or other patient interface or CPAP device.

SCREENING FOR ELIGIBILITY

A Consolidated Standards for Reporting Trials (CONSORT) flow diagram is shown in figure 1. Clinical and/or the research nurse teams will assess patients admitted to study PICUs to identify potentially eligible study participants. Screening procedures will be different for Groups A and B. For Group B, all invasively ventilated patients on the PICU will be screened daily to identify children who are planned

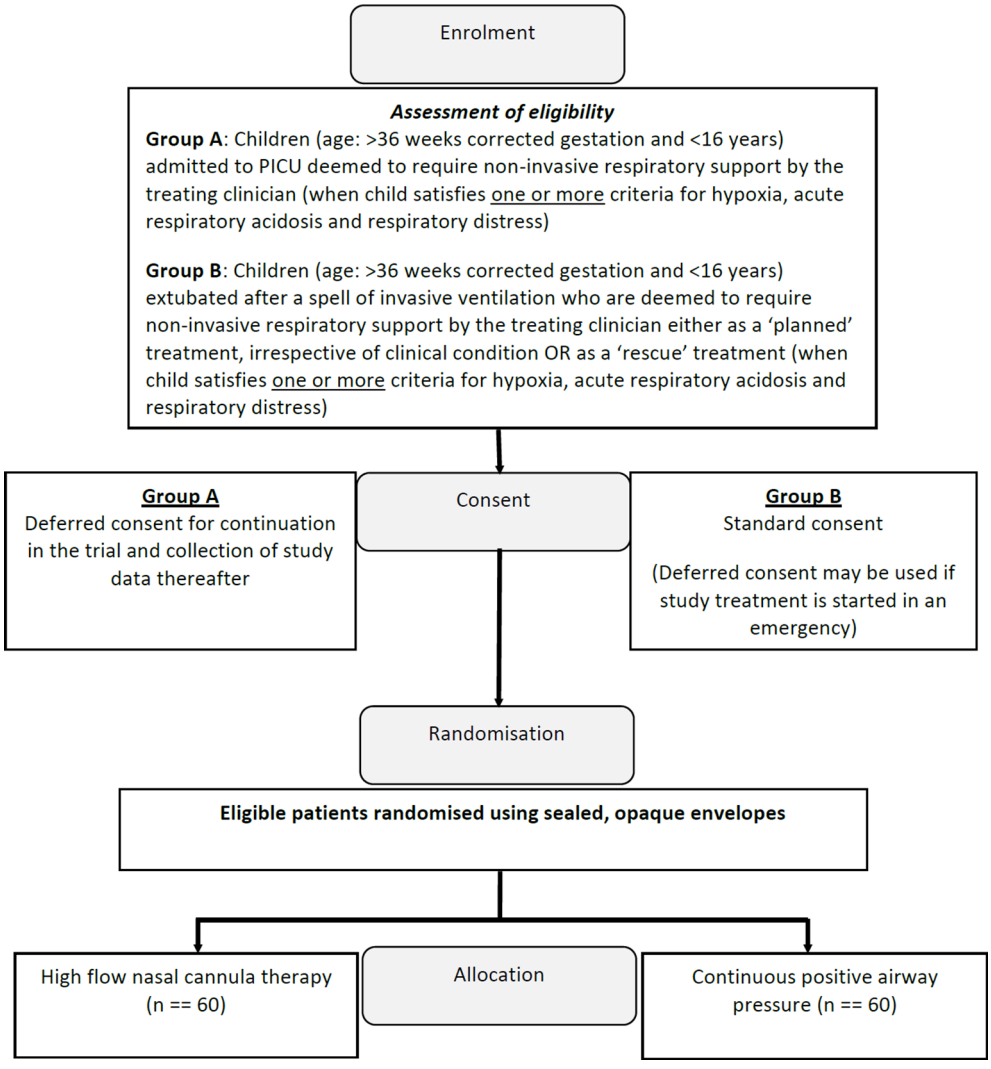

Figure 1 Planned flow of patients through the FIRST-line support for Assistance in Breathing in Children feasibility trial.

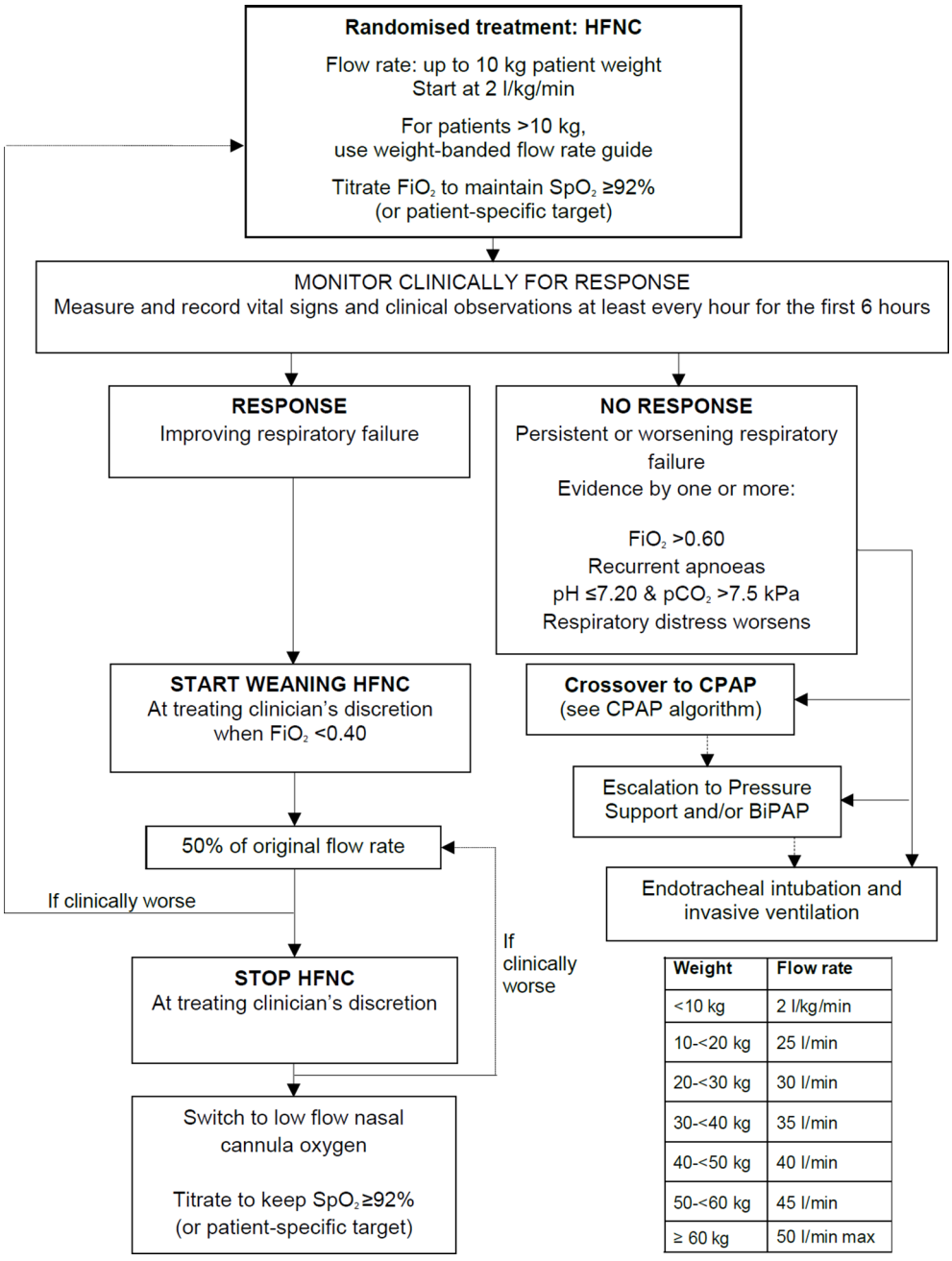

Figure 2 Study algorithm for the management of patients randomised to HFNC. BiPAP, bi-level positive airway pressure; CPAP, continuous positive airway pressure; FiO_2, fraction of inspired oxygen; HFNC, high-flow nasal cannula; PaO_2, partial pressure of arterial oxygen; pCO_2, partial pressure of carbon dioxide.

for extubation. The treating clinician will be approached to establish whether the patient would be placed on NRS immediately after extubation irrespective of clinical condition ('planned'), or whether NRS would only be used as a 'rescue' treatment after extubation. A screening log of all patients who fulfil inclusion criteria but meet exclusion criteria, as well as a log of eligible patients who are not recruited to the study, will be maintained.

PATIENT RECRUITMENT AND CONSENT

A mixed model of consent will be utilised (prospective and deferred) appropriate to the nature of the clinical situation (planned initiation of NRS or emergency initiation of NRS). Informed consent will be supported by providing information to parents/guardians at different stages of the patient pathway.

Group A: Patients requiring NRS as a 'step-up' treatment will most often need this started in a life-threatening emergency, where any delay in commencing treatment will be detrimental, making any attempt to obtain fully informed consent from parents/guardians during an emergency inappropriate and cause additional stress to families who are already distressed by their child's illness. Therefore, consent in this situation will be deferred.

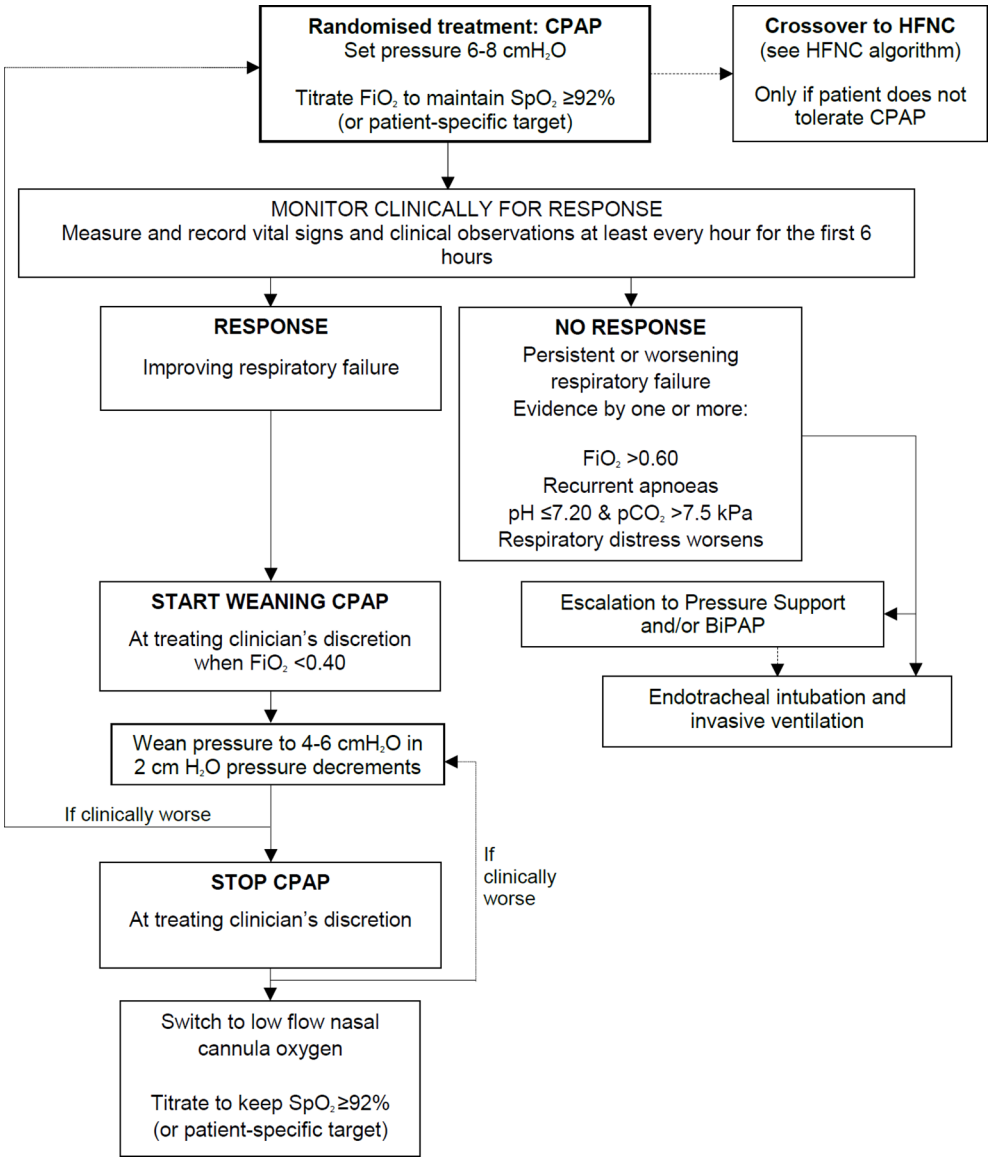

Figure 3 Study algorithm for the management of patients randomised to CPAP. BiPAP, bi-level positive airway pressure; CPAP, continuous positive airway pressure; FiO_2, fraction of inspired oxygen; HFNC, high-flow nasal cannula; pCO_2, partial pressure of carbon dioxide; SpO_2, normal blood oxygen saturation level.

Once notified of the recruitment of a patient to the study, the clinical/research nurse team will approach the parents/guardians as soon as practically possible after randomisation (usually within 24–48 hours) to discuss the study, provide written information and seek informed consent. Consent will be sought for continuation in the trial and for data collection from routine medical records. Both modes of NRS (CPAP and HFNC) are relatively safe, commonly used in clinical practice and in practice only determined by individual clinician preferences.

Group B: Patients requiring NRS as a 'step-down' treatment will be receiving invasive ventilation on PICU. Therefore, there will be sufficient time during which the clinical/research nurse team can discuss the study and provide detailed written information to the parents/guardians. Following this discussion, if parents/guardians refuse to participate in the research, no further involvement in the study will be considered. If NRS is 'planned' following extubation by the treating clinician, written consent will be obtained from parents/guardians by the clinical/research nurse team before randomisation. If NRS is initiated as a 'rescue' intervention following extubation, written consent may be deferred, depending on parental availability and the emergency nature of the situation. This was left at the discretion of the clinical team.

Due to the use of deferred consent, there may be rare situations where the patient is either: (1) discharged from hospital prior to consent being obtained from the parents/guardians or (2) the patient dies prior to consent being sought. In the former situation, we will aim to obtain postal consent as soon as possible after discharge, by sending parents/guardians study

Table 1 Schedule of events

	PICU admission OR prior to extubation	Study entry	Hourly for first 6 hours	At 12, 24, 36, 48 and 72 hours until end of treatment	Hospital discharge (or death)	At day 28
Screening for eligibility	x					
Informed consent and consent questionnaire		x		x*		
Randomisation		x				
Treatment (HFNC or CPAP)			x	x		
Physiology			x	x		
COMFORT score			x	x		
PSS:PICU Questionnaire (at 24 hours only)				x		
Hospital stay data					x	
Safety monitoring						x

*Deferred consent will be sought as soon as practically possible, usually within 48 hours.
CPAP, continuous positive airway pressure; HFNC, high-flow nasal cannula; PSS, Parental Stressor Scale; PICU, Paediatric Intensive Care Unit.

information on two separate occasions 4 weeks apart. If no consent form is received within 4 weeks of receipt of the letter, then the participants' data will be included in the study unless the family notify the site research team otherwise. In the latter situation, the parents/guardians will not be informed of their child's involvement in the trial as this may cause unnecessary and avoidable distress. Data up to the patient's death will still be collected and used as part of the study, as there may be a risk of bias if this was removed.

If prior consent is not provided for patients in group B, they will not be randomised to the trial. A minimal dataset will be collected for each patient approached but not randomised including study site, date/time approached and reason for non-consent. If deferred consent is not provided for patients in group A following randomisation, no further data will be collected from the child and the child will be recorded as not consented. Data collected up to the point of parental refusal of consent will be used. A minimal dataset will be collected for each patient randomised but not consented including study site, date/time randomised, randomised intervention (including whether started on assigned intervention or not) and reason for non-consent.

RANDOMISATION AND BLINDING

Randomisation will be performed as soon as possible after identifying the child as being eligible for the study (no later than 24 hours). Prerandomisation stratification will be by group (A or B) and by study site. Eligible patients will be randomised on a 1:1 basis to either CPAP or HFNC using sealed, opaque envelopes available at each centre. The randomisation sequence will be computer generated with variable block sizes to strengthen allocation concealment. The intervention in this study cannot be blinded, since both treatments (CPAP and HFNC) are already used in practice and recognisable by clinical staff. Study investigators, including those performing the final analysis, will be blinded to the allocation.

STUDY INTERVENTION

A commercially available and Conformité Européene (CE)-marked HFNC device will be used to deliver a prescribed gas flow rate for the duration that the patient needs NRS. The study protocol specifies clinical criteria and procedures for the initiation, maintenance and weaning of HFNC (see figure 2 for study algorithm). As per current practice, clinicians in the study will be able to stop HFNC and crossover to CPAP if clinically deemed necessary. Prespecified objective criteria will be provided in the study protocol as a guide for clinicians considering crossover from HFNC to CPAP to identify non-responders to HFNC. Reasons for crossover will be recorded. Crossover patients will remain in the study and continue to be monitored until they are off respiratory support.

CONTROL

A commercially available and CE-marked CPAP device will be used to provide a set expiratory pressure of 6–8 cm H_2O for the duration that the infant needs NRS. The study protocol specifies clinical criteria and procedures for the initiation, maintenance and weaning of CPAP (see figure 3 for study algorithm). As per current practice, clinicians will be able to stop CPAP and crossover to HFNC only if the patient has significant discomfort/intolerance to the CPAP. Crossover patients will remain in the study and continue to be monitored until they are off respiratory support.

CLINICAL MANAGEMENT

Recruited patients will be treated as per the study protocol with respect to the provision of NRS. Due to the pragmatic nature of the trial, all other treatment in both groups will be as per standard practice at the study sites. Infants who fail to improve on CPAP or HFNC may be escalated to other non-invasive modes of ventilation such as BiPAP or pressure support (before intubation and ventilation) as per the treating clinician's discretion.

DATA COLLECTION

A full schedule of assessments is provided in table 1. Patient demographics will be collected at randomisation (age, gender, primary reason for PICU admission, comorbidities). Routine clinical observations such as normal blood oxygen saturation level, fraction of inspired oxygen, potential of hydrogen, partial pressure of carbon dioxide, heart rate, respiratory rate and clinical signs of respiratory distress, a modified COMFORT score to indicate patient tolerance to the treatment (excluding the respiratory component) and use of sedative agents to improve tolerance to the treatment will be collected at the start of the randomised treatment and assessed on an hourly basis for the first 6 hours, then at 12, 24, 36, 48 and 72 hours until the end of the assigned treatment (or crossover, escalation or intubation/ventilation). A consent questionnaire used in other paediatric RCTs using deferred consent (CATCH trial, ISRCTN34884569 and EcLiPSE trial, ISRCTN22567894) will be administered to all parents/guardians (see online supplementary material 1) irrespective of whether consent is provided to participate in the trial or not.[25–27] Parents/guardians will also be asked to complete a validated instrument, the Parental Stressor Scale: Paediatric Intensive Care Unit (PSS:PICU) questionnaire, around 24 hours after initiation of NRS to assess parental stress (see online supplementary material 2).[28] Adverse events will be collected and assessed for duration, causality, expectedness, seriousness and severity.

DATA MANAGEMENT AND MONITORING

Study data, including serious adverse events, will be collected and managed using Research Electronic Data Capture (REDCap) electronic data capture tools managed by the Intensive Care National Audit and Research Centre (ICNARC) Clinical Trials Unit (CTU).[29] REDCap is a secure, web-based application designed to support data capture for research studies, providing (1) an intuitive interface for validated data entry, (2) audit trails for tracking data manipulation and export procedures, (3) automated export procedures for seamless data downloads to common statistical packages and (4) procedures for importing data from external sources. Study participants will be identified by a unique study specific number. The name and any other identifying detail will not be included in any study data electronic file. Research assistants and statisticians will carry out periodic data quality checks and clarify data errors with research sites.

This is a low-risk trial and major safety data are not anticipated. Serious adverse events (SAEs) will be reported to the ICNARC CTU unless otherwise defined in the protocol. Trends in SAEs will be monitored by the CTU, and unexpected SAEs will be notified to the Sponsor. The ICNARC CTU will conduct at least one monitoring visit to participating sites during the course of the trial. No formal data monitoring and ethics committee will be established since this is a feasibility study.

OUTCOME MEASURES

The primary outcomes are related to the primary study objective, namely determining the feasibility of a future RCT: (1) number of eligible patients in group A (step-up treatment) and group B (step-down treatment); (2) feasibility of randomising at least 50% of eligible patients; (3) acceptability of using a mixed model of consent (prospective and deferred); (4) adherence to the study protocol in terms of initiation, maintenance and weaning of the study treatments; (5) use of a modified COMFORT score to assess patient tolerance; and (6) use of the PSS:PICU questionnaire to measure parental stress 24 hours after the initiation of the treatment. Data will be collected on patient outcomes to inform the choice of an appropriate outcome measure for the definitive trial (rate of intubation, rate of treatment failure, rate of crossover/escalation, length of stay on PICU and in hospital, length of invasive and non-invasive ventilation and mortality in PICU and at hospital discharge).

DATA ANALYSIS

We will use intention-to-treat analysis to perform any comparisons between the groups, although as a feasibility study, this is not the main aim of the trial. Since crossover will be allowed, we will also perform a per-protocol analysis. We will calculate the rate of recruitment (number of patients randomised/number of eligible patients) for each group, the consent rate (number of patients consented/number of patients approached for consent) for prospective and deferred consent, rate of crossover (number of patients crossed over to the other treatment/number of patients randomised to the treatment) for each arm, the rate of intubation (number of patients needing intubation/number of patients randomised to the treatment) for each arm and the frequency of serious adverse events occurring in each treatment arm. As a feasibility study, no formal sample size calculations have been performed. Based on analysis of audit data, we expect around 250 eligible patients over the 6-month period at the three sites. Assuming a 50% recruitment rate, we will have recruited 120 study patients (around 40 patients in group A). Data from the literature suggests a 20% rate of intubation for group A (ie, we expect to see eight intubation events) and a 10% rate of reintubation for group B (ie, we expect to see eight reintubation events).

ETHICAL APPROVAL AND REGULATORY CONSIDERATIONS

Ethical approval was provided by the National Research Ethics Service Committee North East—Tyne and Wear South (ref: 15/NE/0296). Approval was obtained from all participating sites' research and development departments prior to the study initiation. The study protocol, patient information sheets, informed consent forms and other study-related documents were reviewed and approved by the Sponsor and Research Ethics Committee with respect to scientific content and compliance with applicable research regulations involving human subjects. Since the trial involves the use of CE-marked medical devices employed for their intended purpose, it is not considered to be a clinical investigation under the Medical Devices Regulations 2002, nor does it fall within the remit of the Medicines for Human Use (Clinical Trials) Regulations 2004. The study will comply with the Data Protection Act, 1998.

DISSEMINATION STRATEGY

The results of the study will be reported and disseminated via peer-reviewed scientific journals, conference presentations and written feedback to patient support groups.

DISCUSSION

Although CPAP has been used as a mode of non-invasive respiratory support for over two decades, its use in critically ill children is not supported by clinical trial evidence.[9] HFNC therapy has recently become a popular alternative to CPAP since it is better tolerated by patients and is easy to use.[30 31] Although observational studies indicate that the use of HFNC may reduce the need for intubation/invasive ventilation, there have been no RCTs comparing the clinical and cost-effectiveness of HFNC with CPAP in critically ill children.[20–22 32]

The design and conduct of a definitive RCT comparing HFNC and CPAP in critically ill children potentially involves several challenges. First, since the use of HFNC has superseded the use of CPAP in many paediatric settings, there is a risk that some clinicians (and/or parents) may be reluctant to randomise patients to one or the other treatment. Second, the lack of robust evidence to guide clinicians on when and which patients to select for NRS has resulted in variability in clinical practice; this makes it important that any study algorithms used for the initiation, maintenance and weaning of HFNC/CPAP are acceptable to clinicians and practical to use. Third, since RCTs involving the use of HFNC in premature newborns and adults have studied a range of clinical outcomes with varying results,[33–36] an important consideration for PICU patients is the choice of an appropriate and clinically relevant outcome measure. For all these reasons, it is crucial that a future definitive RCT is preceded by a feasibility trial. Findings from the FIRST-line support for Assistance in Breathing in Children feasibility trial will be used to inform the design and conduct of a future definitive trial.

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Contributors PR is the chief investigator of the study. He conceived the study and drafted the manuscript. PL, TD, PH, NE and MJP are study coapplicants and site principal investigators and made a significant contribution to the design and conduct of the study. RC is Study Manager at the ICNARC CTU responsible for day-to-day study management. PM is Senior Trial Manager at ICNARC CTU. Both have contributed to the design, inception and acquisition of data for the study. All authors commented critically on the manuscript and read and approved the final manuscript.

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Competing interests None declared.

Patient consent Not obtained.

Ethics approval Ethical approval for the study was provided by the National Research Ethics Committee (NRES) North East—Tyne and Wear South (ref:15/NE/0296). Management approvals were obtained from all study sites.

Provenance and peer review Not commissioned; externally peer reviewed.

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